European Medicines Agency*

Non-interventional registry-based Study – Study Report

A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs).

Protocol: EUPAS50476

FOUNDER: *European Medicines Agency
Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands

EU PAS REGISTER NUMBER: EUPAS50476

FWC CONTRACT NUMBER: EMA.2020.46.TDA.L5.01 - ROC11

PRINCIPAL INVESTIGATOR: Nicolas Deltour, VP Real World Strategy - Coordinating/Principal Investigator for Aetion; Pr Laurent Servais, Professor of Paediatric Neuromuscular Diseases, University of Oxford - Medical responsible party and Principal Investigator for TREAT-NMD

DATE STUDY INITIATED: Earliest registry start date was December 2007

DATE STUDY COMPLETED: Latest registry end date was May 2023

PASS INFORMATION

Title	**A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs)**
Protocol version identifier	Version 1.3
Date of last version of protocol	3 March 2023
EU PAS register number	EUPAS50476
Active substance	Not applicable
Medicinal product	Not applicable
Product reference	Not applicable
Procedure number	EMA/2020/46/TDA/11, Lot 5 (Pharmacoepidemiological research)
Marketing authorization holder(s)	Not applicable
Framework contractor	Aetion Germany GmbH
Framework contractor contact person	**Liz Garry** liz.garry@aetion.com
Joint PASS	No
Research question and objectives	To investigate SMA patients' course of disease and standards of care delivery over time in multiple European countries: ● Objective 1: To describe, by SMA type, the natural history of SMA (the disease and its progression) in the NEVER TREATED cohort and the TREATED cohort also stratified by DMT, including patient characteristics, disease progression based on motor function assessment as well as respiratory, nutritional, and skeletal deformities, post-diagnostic outcomes of interest, and serious adverse events of special interest.

	• Objective 2: To describe by SMA type the evolution of diagnosis methods and of medicinal and non-medicinal treatment over time, including adoption of DMTs in the "ALL" cohort and the DMTs patterns.
Country(-ies) of study	Belgium, Czech Republic and Slovakia, Germany and Austria, Spain, Sweden, United Kingdom and Ireland
Authors	Nicolas Deltour, Siyana Kurteva, Elizabeth Garry, Coralie Lecomte, Anabel Ferreras Seung Lee Prof. Laurent Servais

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorisation holder(s)	Not applicable
Framework contractor	Not applicable
MAH contact person	Not applicable

(Coordinating) Principal Investigator:

Name:	Nicolas Deltour
Signature:	[signature page provided at the end of this document]
Date:	[signature page provided at the end of this document]

Medical responsible party (Principal Investigator for TREAT-NMD):

Name:	Pr Laurent Servais
Signature:	[signature page provided at the end of this document]
Date:	[signature page provided at the end of this document]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

1. ABSTRACT

Name of Sponsor/Company	European Medical Agency
Name of Finished Product	Not applicable
Name of Active Ingredient(s)	Not applicable

Protocol No.: EUPAS50476

Title of Study: A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs)

Version and date: Version 5.1, 5 April 2024

Study Name: Not applicable

Sponsor's Responsible Party: Carla Jonker, EMA

Keywords: SMA, Natural History of Disease, Treatment Patterns, Disease Outcomes, Healthcare Management

EU PAS Register Number: EUPAS50476

NCT No.: Not applicable

Clinical Registry No.: Not applicable

Marketing Authorization Holder(s): Not applicable

Names and Affiliations of Principal Investigator(s): Laurent Servais, Professor of Paediatric Neuromuscular Diseases, University of Oxford (Principal investigator for TREAT-NMD), Nicolas Deltour, Vice President Real World Strategy (Coordinating-Principal investigator for Aetion)

Study Center(s): Belgium, Czech Republic and Slovakia, Germany and Austria, Spain, Sweden, United Kingdom and Ireland

Publication (Reference): None

Study Period: The study period began on each registry's start date, ranging from December 2007 for the UK and Ireland registry to January 2018 for the Belgium registry; and continued until the end of data availability, ranging from December 2021 for the Belgium registry to May 2023 for the Czech Republic & Slovakia, Germany and Austria, Spain, Sweden, and UK and Ireland registries. All data provided by the participating registries were used for analyses.

Rationale and background: Spinal muscular atrophy (SMA) is a rare recessive progressive neurodegenerative disorder. It results from the progressive loss of alpha motor neurons that leads progressive amyotrophy and hypotonia. Muscle weakness also affects respiratory and bulbar muscle in the most severe and frequent cases. The age of onset is highly variable from birth to adulthood, leading to a broad phenotypic spectrum. Secondary consequences of muscle weakness include respiratory, nutritional, or skeletal deformities.

Since the approval of new treatments for SMA, studies have reported disease trajectories that significantly differ from the known natural history of SMA. Considered together with the limited evidence on the long-term safety and efficacy available at drug approval, the EMA, to address the Committee for Advanced Therapies' needs, asked to investigate SMA patients' course of the disease, and the SMA standards of care delivery, as well as the disease progression given newly available disease-modifying therapies (DMTs), in real-world settings. Challenges and lessons learned from using disease-specific registries will also be discussed.

Research question and objectives: The specific research question is to investigate SMA patients' course of disease and standard of care delivery over time, in multiple European countries:

- Objective 1: to describe, by SMA type, the natural history of SMA (the disease and its progression) in the "NEVER TREATED" cohort and the "TREATED" cohort also stratified by DMT, including patient characteristics, disease progression based on motor function assessment as well as respiratory, nutritional and skeletal deformities, post-diagnostic outcomes of interest, and serious adverse events of special interest.
- Objective 2: to describe by SMA type the evolution of diagnosis methods and of medicinal and non-medicinal treatment over time, including adoption of DMTs in the "ALL" cohort and the DMTs patterns.

Study design: The study is a non-interventional, primarily descriptive, retrospective cohort study of SMA patients using 6 European registries (9 countries) federated in the TREAT-NMD network. The study period spanned from the registry start date, with the earliest start date being April 2008 to May 15, 2023. Patients were followed from registry entry to the date of latest available information. The study was conducted in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) principles and tools for scientific independence and transparency.

- Registry start date: Czech Republic &x Slovakia (May 2011), Belgium (Jan 2018), Germany and Austria (April 2008), Spain (Feb 2015), Sweden (Oct 2010), and United Kingdom (UK) and Ireland (Jan 2008)
- End of data availability: Czech Republic & Slovakia (May 2023), Belgium (Dec 2021), Germany and Austria (May 2023), Spain (April 2023), Sweden (April 2023), United Kingdom and Ireland (May 2023)

Setting: This study used data collected from patients enrolled across 6 patient- and clinician-based registries in 9 European countries (Belgium, Sweden, Czech Republic & Slovakia, Germany & Austria, Spain, and UK and Ireland).

Population and Study Size: The study population included all SMA patients with genetically confirmed 5q SMA enrolled in each of the registries selected for the study, with at least the month and year of birth date available. To assess the different objectives, three cohorts were studied:

- All patients ("ALL"): to study management care changes and differences across European countries
- Never treated patients ("NEVER TREATED"): to study the natural history of SMA
- Treated patients ("TREATED"): to study the natural history of SMA and to describe the use of available DMTs

Variables and Data Sources:

Exposure: The treated cohort (TREATED) consisted of patients who had been exposed to any DMT. Patients were classified as never treated (NEVER TREATED) if they had no record of DMT treatment at any point in their registry data and TREATED if they ever received a DMT. Based on a time-varying exposure approach, the patients could then contribute to more than one exposure category.

Outcomes: Natural history of SMA and SMA healthcare management were assessed with demographics, SMA history, genetic testing, nutritional status, motor function, scoliosis, pulmonary function, rehabilitative interventions, DMTs, co-medications, patient-reported outcomes, and hospitalisations. The following post-diagnosis outcomes were used to describe SMA natural history, and disease progression after DMT intake: motor function, skeletal deformities, pulmonary function, nutrition, hospitalisations, and deaths. The following outcomes were described for the assessment of DMT patterns: use of Spinraza /Zolgensma /Evrysdi, reasons for discontinuation, and treatment switch, age at first DMT, adequate dose administration, and treatment duration for Spinraza and Evrysdi. The incidence of the following serious adverse events of special interest (SAESI) was estimated among the causes of death and hospitalisation, even if they were not identified as DMT-related by the registries: thrombocytopenia and coagulation abnormalities, renal toxicity, hydrocephalus, meningitis, hypersensitivity reactions, cutaneous vasculitis, hepatotoxicity, and cardiac adverse event.

Data sources: Data from 6 registries in 9 European countries (Belgium, Sweden, Czech Republic & Slovakia, Germany & Austria, Spain, and UK and Ireland) were collected. Each registry provided data to the TREAT-NMD registry network. The German and Austrian registry provided aggregated data; all other registries provided de-identified patient-level data directly in the TREAT-NMD Central Data Warehouse (CDW) in a harmonised way, using a pre-defined import template to form the SMA Core dataset structure for analysis.

Statistical Methods: Descriptive analyses, mean, standard deviations, median and quartiles, minimum and maximum values were presented for continuous variables, and raw number and percentage of patients for categorical variables. Exploratory interrupted time series (ITS) were used to investigate trends in post-SMA diagnosis outcomes with respect to the availability of DMTs in each registry.

RESULTS:

A total of 2,188 patients were included in analyses across all registries (“ALL”), among whom 1,321 were classified as treated (“TREATED”), 847 were never treated (“NEVER TREATED”). In ALL, SMA type 1 represented 432 patients (19.7%), SMA type 2, 914 patients (41.8%) and SMA type 3, 779 (35.6%).

Preliminary objective: Description of registry specificities in terms of SMA population capture (in ALL, N=2,188):

- The greatest **number of patients** were identified from the Germany and Austria registry (31.9%), and the lowest from Sweden (8.0%); the breakdown for the other registries was 18.0% in the UK and Ireland, 15.9% in Czech Republic, 14.6% in Spain and 11.7% in Belgium.
- **Patients with SMA** Type 1 represented 19.7%, SMA Type 2 41.8% and SMA Type 3 35.6%, Across all registries, SMA type 1 ranged from 13.3% in Belgium to 27.6% in the Czech Republic and Slovakia; SMA type 2 ranged from 33.6% in the Czech Republic and Slovakia to 48.0% in Spain and SMA type 3 ranged from 29.2% in Spain to 40.6% in Sweden.
- **Registry time coverage** varied with Germany and Austria, and UK and Ireland registries covering 15 years (2008 to 2023) while Belgium covering only 4 years (2018 to 2021). The observed **duration of follow-up** ranged from 42 months (in Czech Republic and Slovakia) to 104.5 months (Sweden).
- There was an almost equal split between **male** (51.6%) and **female** (48.4%) across all registries, except in the Spain and the UK and Ireland registries with 54.5% male in both registries.
- The most common **age at onset of symptoms** was less than 6 months old for patients with SMA type 1, 6-18 months old for patients with SMA type 2, and 2-6 years old for SMA type 3, across all the registries.

- The MLPA was the most common method used for **genetic testing** across all SMA types and registries (24.1%).
- **Duration of the disease** across registries was on average 252.1 months.
- Overall, 24.5% of patients were **lost to follow-up** across all the country-specific registries, among which there were very few patients lost to follow-up in the Spain and Sweden registries.
- Patients treated with **at least one DMT** increased over time, from 2.2% in 2014-2016 to a peak of 68.4% in 2021 and 66.1% in 2022 (prior to 2017, this usage included only treatment intakes during clinical trials). Treatment with Spinraza was common across calendar periods, 2014-2023, across all registries with the highest distribution of patients treated with Spinraza in 2021 (51.1%). Treatment with Evrysdi did not begin until 2018 and the overall usage was less common, with the highest percentage observed in 2023 (23.1%). Treatment with Zolgensma did not begin until 2018 and was rare across all SMA types and across all registries. Treatment with more than 1 DMT was also rare across all SMA types.
- **Supportive strategies** like invasive, non-invasive ventilation and feeding tube usage were most commonly reported in patients with SMA type 1 across all the registries. Overall, more than 50% of patients had at least one episode of wheelchair use across registries and all the calendar periods.
- **PROs** were available in Belgium and Spain registries only, between 2018-2021 and 2020-2023 respectively. On average, patients across SMA types had approximately only one available record of PRO for each patient.

Objective 1: Natural history and impact of DMT treatments on disease progression (in "NEVER TREATED", N=847 and "TREATED", N=1,321):

In the SMA type 1 population, an improvement of "Best functional status" and "Best achieved motor milestones" was observed after patients started treatment, suggesting a positive effect of DMTs on the disease progression for SMA type 1 patients.

- **In never treated patients (N=154)**
    - **Best Motor function:**
        - Functional status and achieved motor milestones were not reported
        - The CHOP-INTEND best score median was non-estimable (<5 cases).
    - **Median event-free survival** (death or permanent ventilation) was 11.5 [5.2, 39.8] months.
    - **PRO** was non-estimable (< 5 cases) in both Spain and Belgium registries.

- **In treated patients (N=276)**
    - **Best Motor function:**
        - Missingness 27.9%, 101 patients (36.6%) achieved "sitter" and 33 (12%) "walker" status.
        - 75 patients (27.2%) achieved "sitting without support", 51 (18.5%) achieved "rolling onto their side", 7.2% were able to "stand with assistance", 6.5% to "walk with assistance", 2.9% to "walk without assistance" and 1.8% to "walk 10m without assistance".
        - The CHOP-INTEND best score median was 44 [33, 54].
    - **Median event-free survival** (death or permanent ventilation) was 10 [6, 24] months.

- **PRO** was 64.5 [48.8, 80.1] for the "Best score for Spain PROFuture Mobility and Independence PRO" and non-estimable for the "Best score for Belgium ACTIVLIM PRO".

In the SMA type 2 population, an improvement in "Best functional status" and "Best achieved motor milestones" was observed after patients started treatment, suggesting a positive effect of DMTs on the disease progression for SMA type 2 patients.

- **In never treated patients (N=361)**
  - **Best Motor function**:
    - Missingness 97.8%, 7 patients (1.9%) achieved "roll onto side", less than 5 patients achieved "Hold head without support".
    - CHOP-INTEND, RULM and HFMS(-E) best score median were non-estimable (<5 cases).
  - **Median event-free survival** (death or permanent ventilation) was 219 [156, 515] months.

  PRO was 56.9 [51, 64.9] for the "Best score for Spain PROFuture Mobility and Independence PRO" and -8.1 [-8.1, -8.1] for the "Best score for Belgium ACTIVLIM PRO".
- **In treated patients (N=540)**
  - **Best Motor function**:
    - Missingness 8.5%, 329 patients (60.9%) achieved "sitter", 133 (24.6%) "walker" status, and only 5.9% remained "non-sitters".
    - 205 patients (38.0%) achieved "sitting without support", 86 (15.9%) "walk with assistance", 13.9% "crawl", 7.8% "stand with assistance", 3% "walk 10m without assistance" and 3% "walk without assistance".
    - CHOP-INTEND, RULM and HFMS(-E) best score median were 46 [35, 57.5], 17 [10, 24] and 12.5 [4, 31.2], respectively.
  - **Median event-free survival** (death or permanent ventilation) was 143 [83, 246] months.
  - **PRO** was improved with 50 [28.2, 66.3] for the "Best score for Spain PROFuture Mobility and Independence PRO" and -6.6 [-8.1, -3.7] for the "Best score for Belgium ACTIVLIM PRO".

In the SMA type 3 population, an improvement in "Best functional status" and "Best achieved motor milestones" was observed after patients started treatment, suggesting a positive effect of DMTs on disease progression for SMA type 3 patients.

- **In never treated patients (N=299)**
  - **Best Motor function:**
    - Functional status and achieved motor milestones were not reported.
    - CHOP-INTEND, RULM and HFMS(-E) best score median were non-estimable, 33 [23.2, 37] and 51 [14.5, 60], respectively.
  - **Median event-free survival** (death or permanent ventilation) was 532 [393.5, 588.5] months.
  - **PRO** was 42 [27.4, 50] for the "Best score for Spain PROFuture Mobility and

Independence PRO" and -3.5 [-8.1, -2.6] for the "Best score for Belgium ACTIVLIM PRO".

- **In treated patients (N=476)**
  - **Best Motor function:**
    - Missingness 5.5%, 418 patients (87.8%) achieved "walker" and only 1.5% remained "non-sitters" status.
    - 302 patients (63.4%) were able to "climb stairs", 92 (19.3%) were able to "walk 10 metres without assistance", 22 (4.6%) to "walk without assistance".
    - CHOP-INTEND, RULM and HFMS(-E) best score median were 51 [28.5, 64], 35.5 [26.8, 37] and 50 [29.8, 58], respectively.
  - **No** event (death or permanent ventilation) was reported to estimate the **median event-free survival**.
  - **PRO** was improved with 10.9 [4.8, 27.7] for the "Best score for Spain PROFuture Mobility and Independence PRO" and 0.1 [-2.4, 2.8] for the "Best score for Belgium ACTIVLIM PRO".

From the exploratory ITS analyses, we observed that after the introduction of Spinraza (i.e., after 2017-07-01), the number of SMA type 1 and SMA type 2 patients first receiving full time ventilation was significantly reduced.

A total of 5 SAESI were observed across ALL 2,188 patients. The specific events include renal toxicity, hypersensitivity reactions, and hepatotoxicity.

Objective 2: Evolution of healthcare management (in ALL, N=2,188):

Patients taking at least one DMT increased steadily from 2.2% in 2014-2016 (clinical trials participation), to as high as 68.4%, in 2021. Spinraza and Zolgensma usage was often reported among patients with SMA type 1, whereas a higher distribution of patients with SMA type 2 were treated with Evrysdi. The number of patients treated with more than one DMT was low.

We observed an increase in the use of any ventilation across calendar periods spanning from 2011 to 2020 across SMA types. Ventilation usage in SMA type 1 has evolved from 18.8% in 2011/13 to 57.0% in 2020, in SMA type 2 from 10.3% in 2011/13 to 32.2% in 2020.

With respect to wheelchair **usage**, more than 50% of participants overall used it across all calendar periods. Wheelchair usage in SMA type 1 has evolved from 21.9% in 2011/13 to 62.2% in 2021, and in SMA type 2 increased slightly from 69.7% in 2011/2013 to 77.2% in 2021.

Muscular physiotherapy is similarly reported (36.9% overall) across all SMA types and others rehabilitative interventions (i.e., respiratory physiotherapy, contracture management, spinal brace, and speech therapy) have been more reported in SMA type 1 patients than in SMA type 2 and then in SMA type 3.

Feeding tube usage was most common in patients with SMA type 1. Usage in SMA type 1 increased from 25.0% in 2011/13 to 40.6% in 2021, and in SMA type 2 from 4.6% 2011/2013 to 6.0% in 2021.

DISCUSSION AND CONCLUSION:

DISCUSSION:

Preliminary objective: Description of registry specificities in terms of SMA population capture:

Registries have been implemented at different points in time, resulting in various lengths of history and data availability: from 2008 in Germany and UK and Ireland, 2010 in Sweden, 2011 in Czech republic, 2015 in Spain and 2018 in Belgium.

The features of registries were similar, and the data consistently reported across the 6 registries albeit some heterogeneities have been observed:

- The Czech Republic reported a higher proportion of SMA 1 (27.6%), Spain a higher proportion of SMA 2 (48%), and Sweden a higher proportion of SMA 3 (40.6%).
- Slightly more male than female patients included in the Spain, and UK and Ireland registries.
- Spain and Sweden registry had 100% patient retention.
- In Spain, a high proportion of SMA type 1 patients (19 patients, 26.8%) and SMA type 2 (55 patients, 35.9%) were classified as "Walkers" at their best functional status. *In this project, the definition of a "Walker", was a patient that: "walk with assistance", "walk without assistance", "walk 10 metres without assistance", or "climb stairs". However, the Spanish registry defined a walker as: "Someone who can walk at least 10 metres. Therefore, those who walk with assistance or without assistance but don't reach the 10 metres mark are not considered walkers".*
- The UK and Ireland registry had the highest amount of missing data for the genetic report data, followed by the Sweden registry while this variable was well recorded in all the other registries.
- PRO data were available only in Spain and Belgium, with very few records per patient.

Missingness for some variables was high across all registries, in particular for the "reason for and method of genetic testing" and the "duration of the disease".

Objective 1: Natural history and impact of DMT treatments on disease progression:

There was an improvement in "Best functional status" and "Best achieved motor milestones" observed once patients were under treatment, suggesting a positive effect of DMT on disease progression for SMA type 1, SMA type 2 and SMA type 3 patients. In addition, from exploratory ITS, after the introduction of Spinraza (i.e., after 2017-07-01), we observed that the number of SMA type 1 and SMA type 2 patients first receiving full time ventilation was significantly reduced.

In SMA type 1 patients:

Published studies showed that among untreated SMA type patients, none of them achieved independent sitting or other more advanced motor milestones. No functional status and no achieved motor milestones have been reported in the current study in SMA 1 patients who were never treated. In contrast, in SMA 1 patients who were treated, 36.6% achieved "sitter" status and 12% achieved "walker" status and more than a quarter (27.2%) of treated patients achieved "sitting without support", while 18.5% retained "rolling onto their side" as their best achieved motor milestone.

In SMA type 2 and 3 patients:

Other published observational research literature also shows that untreated patients with SMA type 2 could sit independently but not walk, whereas untreated patients with SMA type 3 develop independent

walking. In our study, very few functional status have been reported in SMA 2 and SMA 3 never treated patients. In contrast, in the treated SMA 2 patients, 60.9% achieved “sitter” status and 24.6% achieved “walker” status. Further, more than two thirds (38.0%) of treated patients achieved “sitting without support”. Higher motor milestones were also achieved by these SMA type 2 patients, including “walking with assistance” (15.9%), “crawl” (13.9%), “stand with assistance” (7.8%), “walking without assistance” (3.0%), and “walking 10 metres without assistance” (3.0%). In treated SMA 3 patients, 87.8% achieved “walker” status and 63.4% of treated patients were able to “climb stairs” and 19.3% were able to “walk 10 metres without assistance” and 4.6% to “walk without assistance”

Finally, the reduced proportion of SMA type 2 patients with scoliosis likely reflects that, in some registries, patients are no longer reported as having scoliosis after spinal fusion procedures.

SMA Pre-symptomatic patients: Results that do not match with existing literature.
Only 8 patients have been reported as pre-symptomatic or having been identified by NBS. However- Germans authors reported 47 patients identified by NBS in Germany and Belgian authors reported 16 cases. It is thus very likely that these patients have been reported in the different types following the number of SMN2 copies (patients with 2 copies = SMA1; patients with 3 copies = SMA2 and patients with 4 copies = SMA type 3). This could explain the high proportion of SMA type 1 walkers after treatment (12%) (which is nearly never reported in the literature) or the more intriguing proportion of non-sitters at genetic report in SMA type 3 (12.4%) - which normally never happens or very rarely.

Objective 2: Evolution of healthcare management:

Over the last decade, there has been increasing evidence of improvements in management of the disease progression of all SMA patients. Such findings have also been identified in the study, with a high rate of screening using MLPA or with more than 50% of participants using wheelchairs across the calendar period or also, we did see an increase in the use of any ventilation across calendar periods spanning from 2011 to 2020. Those results reflect the adapting strategies as standard of care across a wide range of clinical profiles of SMA patients.

CONCLUSIONS:

This large pan European/UK study is the first of its kind to evaluate natural disease progression, clinical, healthcare management and treatment patterns from multiple specific-disease registries across Europe, in the context of rare SMA disease. The study used data collected in SMA from patients enrolled across 6 patient- and clinician-based registries in 9 European countries (Belgium, Sweden, Czech Republic & Slovakia, Germany & Austria, Spain, and UK and Ireland) as part of the TREAT-NMD network.

The results were globally consistent with existing studies evaluating the natural history and progression of the SMA disease. Clinically relevant gains in motor function were observed in SMA 1, SMA 2 and SMA 3 treated patients per DMTs.

Improving the data accuracy and quality, reducing the missingness, identifying important data items - e.g., registry entry date, diagnosis date, presymptomatic and others - could help greatly answering key questions for the SMA community and for regulatory decision making. These different elements plead for a common dictionary for SMA Registries across Europe with Regulators for contributing to its definition.

Our study exemplified that the use of multiple registries in rare disease provides complementary information and new avenues to answer regulatory research questions.

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Description
6MWT	6-Minute Walk Test
AAV9	Adeno-associated virus serotype 9
ADR	Adverse Drug Reaction
AE	Adverse Event
AT	As Treated
ASD	Absolute Standardised Difference
BNMDR	Belgian Neuromuscular Diseases Registry
CDW	Central Data Warehouse
CGI-S/CGI-I	Clinician Global Impression of Severity / of Improvement
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP	Compound Muscle Action Potential
DEXA	Dual Energy X-ray Absorptiometry scan
DMT	Disease Modifying Therapy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EP	Endpoint
EU	European Union
FFP	Fit For Purpose
FundAME	Registro Nacional de Pacientes de la Fundación Atrofia Muscular Espinal
FVC	Forced Vital Capacity
GRP	Global Registry Platform
HINE	Hammersmith Infant Neurologic Examination
HFMSE	Expanded Hammersmith Functional Motor Scale
ICD	International Classification of Diseases
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISPE	International Society for Pharmacoepidemiology
ITS	Interrupted Time Series

ITT	Intention To Treat
JR	Jumping Rivers; the TREAT-NMD's subcontractor in charge of statistical analyses
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MFM	Motor Function Measure
MRI	Magnetic Resonance Imaging
PAS	Post-Authorization study
PCF	Peak Cough Flow
PGI-I	Patient Global Impression of Improvement
PPRL	Privacy-Preserving Record Linkage
PRO	Patient Reported Outcomes
QoL	Quality of Life
REQueST	Registry Evaluation and Quality Standards Tool
RSV	Respiratory Syncytial Virus
RULM	Revised Upper Limb Module
SAE	Serious Adverse Event
SAESI	Serious adverse events of special interest
SAP	Statistical Analysis Plan
SMA	Spinal Muscular Atrophy
SMN1	Survival of Motor Neuron 1
SMN2	Survival of Motor Neuron 2
SPIFD	Structured Process to Identify Fit-for-purpose Data
Swiss-Reg-NMD	Swiss Registry for Neuromuscular Disorders
TGDOC	TREAT-NMD Global Data Oversight Committee
UK	United Kingdom
VAS	Visual Analogue Scale

Definition of Term(s):

Registry	An organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.
Study	The term "study" indicates the collection of data for research purposes only. The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed.
Retrospective non-interventional study	A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information from the patient, although this may be required to address specific questions. Studies/Programs/Related Research Activities with only one visit can be considered prospective or retrospective bearing in mind this definition and the source of information.

3. INVESTIGATORS

Coordinating - Principal Investigator for Aetion: Nicolas Deltour, MSc

Principal investigator for TREAT-NMD: Laurent Servais, MD, PhD

Sponsor's responsible party - EMA: Carla Jonker, PhD

4. OTHER RESPONSIBLE PARTIES

Organisation	Key person	Position	Role
Aetion Germany GmbH	Nicolas Deltour*	VP, Real World Strategy, Pharmacoepidemiologist	Coordinating-Principal Investigator for Aetion
	Siyana Kurteva*	Senior Scientist, Pharmacoepidemiologist	Scientific lead
	Elizabeth Garry*	Head of Scientific Research	Scientific review
	Coralie Lecomte *	Senior Director Data Science, Pharmacoepidemiologist	Data feasibility assessment
	Elodie Boin	Scientist, Scientific Data Insights	Data feasibility assessment
	Anabel Ferreras*	Senior Project Director	Project management and results review
TREAT-NMD	Seung Lee*	Project Manager	Project management and results review

	Neil Bennett	Research and communication manager	Registry and communication support
	Marcel Heidemann	Data processor	Data management and analyst
	David Allison	CEO	Project director
	Pr. Laurent Servais*	Professor of Paediatric Neuromuscular Diseases, University of Oxford	Principal investigator for TREAT-NMD
Jumping Rivers	Theo Reo	Statistician	Data analyst/ project management
	Rhian Davies	Senior statistician	Data analyst
	Jack Kennedy	Senior statistician	Data analyst

* Considered an author of this report

5. MILESTONES

Milestones	**Planned date**	**Actual Date**	**Comments**
Study protocol submission to EMA	July 17, 2022	November 17, 2022	
Start of data collection (Data extraction from imported data)	September 2, 2022	December 5, 2022	
Planned study protocol validation	August 19, 2022	December 16, 2022	
Registration in the EU PAS register	September 19, 2022	December 19, 2022	
Statistical Analysis Plan	*Not planned*	April 27, 2023	
End of data collection (last derived dataset)	*Not planned*	May 15, 2023	

V1of report delivered to EMA	December 19, 2022	October 11, 2023	Draft version including key results
Final Version (V5.1) of report delivered to EMA	NA	March 14, 2024	Addressed EMA minor comments on V4

6. BACKGROUND AND RATIONALE

SMA is a rare recessive progressive neurodegenerative disorder with an estimated incidence of 1 in 6,000 to 1 in 10,000 live births and it is the leading genetic cause of mortality in infants and children (1). SMA is caused by the deletion or loss-of-function mutations of motor neuron 1 gene (SMN1), which results in insufficient levels of SMN1 protein (2). Around 95% of SMA cases are caused by homozygous deletions and less frequently point to mutations in *SMN1* gene (3). In humans, there is a paralogous gene, *SMN2*, that also codes for SMN protein.

Patients lacking a functional *SMN1* gene are dependent on their *SMN2* gene. However, the number of *SMN2* gene copies varies from one up to eight in some individuals, and children born with multiple copies of the *SMN2* gene usually have milder phenotypes.

A Spanish study published in 2009 showed that about 90% of SMA patients present homozygous exon 7-*SMN1* deletion, hybrid *SMN1–SMN2* genes were observed in 5% and small mutations in 4% (4). A Brazilian study published in 2020 showed that some of these small mutations (c.770_780dup and c.734_735insC) have a clinical phenotype correlated with *SMN2* copy number, whereas others (c.460C>T and c.5C>G) determine a milder phenotype independently of the *SMN2* copies (5).

Indeed, SMA encompasses a wide clinical continuum of disease severity and is categorised into several types, including: SMA type 0, SMA type 1, SMA type 2, SMA type 3 and SMA type 4, which are defined according to the age of symptom onset and maximum motor function achieved, as summarised by patient ability or not to sit or to walk (6).

SMA is a complex disorder with heterogeneous phenotypes of motor impairment and related comorbidities. It results from the progressive loss of alpha motor neurons that leads progressive amyotrophy and hypotonia. Muscle weakness also affects respiratory and bulbar muscle in the most severe and frequent cases with an immense majority developing symptoms before adulthood. The age of onset is highly variable from birth to adulthood, leading to a broad phenotypic spectrum. Secondary consequences of muscle weakness include respiratory, nutritional, or skeletal deformities (7). Neuromuscular and musculoskeletal evaluations should be performed regularly by trained examiners every six months. Physical rehabilitation may influence disease progression with specific goals being dependent on the functional status (non-sitters, sitters, and ambulants) and motor achievements of the patient. Similarly, orthopaedic management goals are dependent on the stage and needs of the patient, including the use of devices and surgery. Nutritional management is essential for all SMA types and requires regular assessments of growth, metabolic functions, and gastrointestinal symptoms.

A cohort study in the Netherlands recently assessed survival by more granular SMA subtypes (8). Based on this study, overall survival and / or mechanical ventilation seem to be relevant post-diagnosis outcomes for SMA type 1 and 2. For the least severe SMA types, and / or after DMT availability, these outcomes may be less relevant, notably as the exposure duration will be limited. Moreover, no studies in adults with SMA have yielded a robust, reliable measurement of study progress or treatment effectiveness. The considerable heterogeneity and slow disease progression in adults with SMA has contributed to the paucity of research and to the lack of treatment efficacy observed in the limited number of trials to date. Long durations and robust clinical outcome measures sensitive to changes in disease progression (or response to DMTs) are required in these specific populations. Identifying relevant outcome measures remains a key issue in SMA research, particularly in light of the significant benefit in quality of life derived from small functional changes in adults with SMA.

Several risk factors affecting survival have been identified (9). *SMN2* copy number is a strong prognostic factor for survival although the genotype-phenotype relationship of *SMN2* copy number depends also on the *SMN1* mutation variant (still, no perfect reliability; as it cannot predict disease severity or disability levels). Clinical disease severity is also a strong prognostic factor of survival, as measured by the SMA type, the age at onset of symptoms or the occurrence of severe symptoms (respiratory distress at birth,

reduced foetal movement, absence of head/trunk control). Supportive care including assisted ventilation or nutritional support may play an important role in survival as well. Increasing *SMN2* copy number is prognostic of improved motor function in individuals with type 1 SMA. This is less obvious in types 2 and 3 SMA, potentially due, as previously explained, to the large heterogeneity between individuals, an insufficient follow-up to capture differences in individuals who are declining more slowly or who are already severely disabled, or motor function scales that are inadequate to detect small changes that nonetheless would have significant benefit for the patient. Disease progression in types 2 and 3 SMA also typically depends on age. Younger age groups experience gains in motor function. The steepest declines in motor function occur during adolescence. Coratti et al. reported that age and baseline values were predictors of motor functional changes in type 2-SMA (10).

Moreover, a systematic newborn genetic screening has started in some countries like Germany (since October 2021) (11) and Belgium (since March 2021) which may render inappropriate or less relevant the SMA types as currently defined since pre-symptomatic patients may be treated before apparition of symptoms and have their natural course of disease modified.

Recently, the European Medicines Agency (EMA) approved three disease modifying therapies (DMT) for SMA: Nusinersen (Spinraza®) (12), Onasemnogene Abeparvovec-xioi (Zolgensma®) (13,14), and Risdiplam (Evrysdi®) (15,16). The year and type of approval by the EMA, mechanism of action, detailed indication and mode of administration are described in Table 1 below.

Table 1. Description of SMA disease-modifying therapy by year of approval, mechanism of action, indication and administration.

	Spinraza®.	**Zolgensma®**	**Evrysdi®**
Year/type of approval by EMA	2017/Full	2022/Full (conditional in 2020)	2021/Full
Mechanism of action	Synthetic anti-sense oligonucleotide that enables the *SMN2* gene to produce full length protein, which is able to work normally. This replaces the missing protein, thereby relieving the symptoms of the disease.	Gene therapy that contains a functional copy of the SMN1 gene. When injected, it passes into the nerves from where it provides the correct gene to make enough of the protein and thereby restore nerve function.	Corrects the splicing of *SMN2* leading to an increased production of functional and stable SMN protein, increasing and sustaining functional SMN protein levels.
Detailed indication (population)	For the treatment of 5q SMA	For the treatment of patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in	Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.

		the SMN1 gene and up to 3 copies of the *SMN2* gene.	
Administration	Solution for injection, intrathecal use by lumbar puncture. 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	Single-dose intravenous infusion.	Evrysdi is taken orally once a day after a meal at approximately the same time each day. <2 months of age: 0.15 mg/kg 2 months to <2 years: 0,20 mg/kg >2 years and <20 kg: 0.25 mg/kg ≥2 years and >20 kg: 5 mg

Since the approval of new treatments for SMA, studies have reported disease trajectories that significantly differ from the known natural history of SMA (1). Considered together with the limited evidence on the long-term safety and efficacy available at drug approval due to the rarity of disease, the EMA, to address the Committee for Advanced Therapies' needs, asked to investigate SMA patients' course of the disease and the standards of SMA care delivery in real-world settings.

This study using multiple specific-disease registries across Europe, with data collected by physicians or patients depending on the country, also served to better understand the challenges, limits or advantages of using such data-sources, notably in the framework of rare disease.

7. RESEARCH QUESTION AND OBJECTIVES

Research Question: The specific research question was to investigate SMA patients' course of disease, evolution of standard of care delivery over time, and use, effectiveness, and safety of DMTs, in multiple European countries, using data routinely collected by existing SMA registries.

A total of 6 European registries (covering 9 countries) were selected: 3 are physician-reported registries and 3 are patient-reported registries.

Objectives:

Preliminary objective aimed at assessing the heterogeneity of management of care or reporting over time within each registry and between registries (i.e., registry specificities in terms of SMA population capture). It was assessed in the ALL cohort.

Objective 1 aimed at describing the natural history of SMA (the disease and its progression), stratified by SMA type. It was assessed according to the patients' current age, by disease severity, in the NEVER TREATED cohort, and in the TREATED cohort, further stratified by DMT.
In addition to describing demographic and clinical characteristics of patients, outcomes of interest included (please refer to section 9.4 for more information):

- Disease management endpoints such as motor function assessment, respiratory, nutritional, and skeletal deformities
- Post-diagnostic outcomes of interest such as overall survival, the use of invasive ventilation, diagnosis of scoliosis, among others
- Serious adverse events such as thrombocytopenia, renal toxicity, hydrocephalus, among others
- Impact on quality of life (QoL) using patient-reported outcomes (PROs) where available.

Objective 2 aimed at describing patients' clinical management (i.e., health care management) and its evolution over time considering all available treatment options including use of DMTs. This second objective included two components:

Objective 2.1. Description of the evolution of diagnosis methods and of medicinal and non-medicinal treatment over time.

This component was assessed in the "ALL" cohort, by SMA type, as well as further stratified by calendar time in a few selected variables.

- Distribution of patients by methods used to diagnose SMA and their evolution over time
- SMA therapeutic options used overtime, including:
    - DMT adoption (percentage of patients treated by DMTs).
    - Percentage of patients with rehabilitative intervention (muscular or respiratory physiotherapy, orthoses including spinal brace, wheelchair use, speech therapy) over time

Objective 2.2. Description of the DMTs patterns:

This component was described in the TREATED cohort, stratified by SMA type. The outcomes included:

- Modality of treatment with DMT
- Mean age at initiation

Exploratory objective aimed at investigating trends in post-SMA diagnosis outcomes with respect to the availability of DMTs through the use of interrupted time-series (ITS) analyses, using the overall cohort "ALL"; selected post-diagnosis outcomes included death, full-time ventilation, and a composite outcome of these two outcomes of interest.

Hypothesis: This was an exploratory descriptive study to describe natural history and disease management of SMA patients. No hypotheses were specified or tested.

8. AMENDMENTS AND UPDATES

V1of report delivered to EMA	December 19, 2022	October 11, 2023	Draft version including key results
V2 of report delivered to EMA	NA	November 10, 2923	Addressed EMA comments on V1
V3 of report delivered to EMA	NA	December 14, 2023	Addressed EMA minor comments on V2
V4 of report delivered to EMA	NA	January 29, 2024	Addressed EMA minor comments on V3 Inclusion of the results of "Never Treated" cohort
Final Version (V5) of report delivered to EMA	NA	March 14, 2024	Addressed EMA minor comments on V4
Version 5.1	NA	April 5, 2024	Addressed EMA minor comments on V5

9. RESEARCH METHODS

9.1. Study Design

9.1.1. Overview of Study Design

The study was a non-interventional retrospective cohort study of SMA patients using 6 European registries federated in the TREAT-NMD network. The cohort design allowed the follow-up of patients over time to describe the natural history of SMA, as well as changes over time in patient care. Furthermore, ITS analyses were also implemented to explore SMA progression according to several post-diagnosis outcomes since the availability of DMTs.

9.1.2. Changes in Conduct

This is not applicable for this study.

9.2. Setting

After an in-depth feasibility assessment of 16 SMA-specific registries federated in the TREAT-NMD network that were interested in participating in this study, a total of 7 registries were initially selected and considered fit for the study purpose, mainly according to the availability of key data, data quality process in place and size of registry. Four clinician-reported registries were considered: Belgium, Sweden, Switzerland, and Czech Republic (collecting also data from Slovakia), as well as three patient-reported registries: Spain, Germany (collecting also data from Austria) and UK (collecting data from Ireland as well). However, due to the lag time in the contracting and data sharing process, Switzerland was excluded from the data analyses. The number of patients by selected registries that contributed to the final data analyses are as follows: Belgium - 256, Czech Republic and Slovakia - 348, Germany and Austria - 697, Spain - 319, United Kingdom and Ireland - 393, and Sweden - 175. All genetically confirmed SMA patients and available follow-up time was used for the descriptive analyses. Please refer to Appendix D "Feasibility Report", for a detailed description of the initial feasibility results.

9.2.1. Study Period

The study period started on each registry start date, with the earliest being the registry start date for UK and Ireland, December 2007, and ended on the last date of data availability, which corresponded to 15 May 2023 (end of data availability for UK and Ireland). Patients were followed from their entry in the registry until the earliest between the end of data availability in the registry, the death, or the censor at the last available information before loss to follow-up. In addition, in registries, the historical data of patients were reported at their baseline registration. This data corresponded to events or measures occurring or collected in the patient file before the date of registry implementation and thus, with dates prior the registry start date.

Table 2. Registry start date and end date of data availability for each of the registries included in the analyses.

	Registry start date	**End date of data availability**
Belgium	January 2018	December 2021
Czech Republic and Slovakia	May 2011	May 2023
Germany and Austria	April 2008	May 2023
Spain	February 2015	April 2023
United Kingdom and Ireland	December 2007	May 2023
Sweden	October 2010	April 2023

9.3. Patient Population

The primary study population included all SMA patients with genetically confirmed 5q SMA included in each of the registries selected for the study between the registry start date and 15 May 2023. No other inclusion or exclusion criteria were applied.

To assess the different objectives, three main cohorts were built and studied:

- Overall cohort of all patients (ALL): to study the SMA care management overtime and differences across European countries/registries
- Never treated patients (”NEVER TREATED”): to study the natural history of SMA
- Treated patients (TREATED): to study the natural history of SMA and to describe the pattern of DMTs use since their availability on the market

The treated cohort (TREATED) consisted of patients who had been exposed to any DMT. Patients were classified as never treated (NEVER TREATED) if never treated with any DMTs at any point of their journey and TREATED if they ever received a DMT. Based on a time-varying exposure approach, the patients could then contribute to more than one exposure category.

Patients entered the TREATED cohort when they received at least one of the following DMTs:

- Spinraza®
- Zolgensma®
- Evrysdi®

9.3.1. Study Subpopulations

Several subpopulations were defined to 1) assess the changes in prognostic factors such as type of SMA, age at symptom onset, best functional status and SMN2 copy number across patients with various disease severity, 2) describe healthcare management such as the use of DMTs or supportive care, as well as 3) assess and describe the heterogeneity of data across countries or registry. The subpopulations of clinical interest were defined as follows:

- **Class of age at symptom onset:** presymptomatic, prenatal, <1 month, [1-3 months), [3-6 months), [6-18 months), [1.5- 2 years), [2-6 years), [6-11 years), [11-18 years), 18 years+, missing

- **Type of SMA**: 1, 2, 3, 4, other

  When different types were reported for the same patient, the last reported type/subtype was considered to define the SMA type of a given patient.

- **SMN2 *c*opy number**: 0, 1, 2, 3, 4, > 4, unknown

- **Functional SMA status**: non-sitter, sitter, walker, unknown

- **Individual DMT**(s) **and overall combinations**

- **Achieved motor milestone**: climb stairs, walk 10 metres without assistance, walk without assistance, walk with assistance, stand without assistance, stand with assistance, crawl, sit without support, roll onto side, hold head without support, unknown

- **Registry:** Belgium, Czech Republic and Slovakia, Germany and Austria, Spain, Sweden, UK and Ireland

The definition of classes of age at onset of symptoms was based on a combination of categories presented in ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) E11 guideline (17) and clinical input confirming that the 2-year age limit is important, as it is used as a threshold for clinical trial inclusion and in differentiating treatment posology for Risdiplam. (18) Moreover, we used the 6-year cutoff as it presented a point in which effectiveness of certain DMTs significantly improves. (19) The 11-years of age was used as some DMTs are reimbursed using this limit.

9.4. Variables

9.4.1. Indicators and Characteristics For Preliminary Analysis (Description of registry specificities)

ID	Name	Description	Relevant columns in the TreatNMD dataset
1.01	Calendar year of registry entry (n, %)	Calendar year of registry entry	Derived
1.02	Calendar year of death (n, %)	Date of the death of the individual. The date of death *may* be provided as a year only, if the month is not known.	Date of death
1.03	Sex (n, %)	Current biological sex of the individual. Possible values: male, female, intersex, unspecified	Sex
1.04	Class of age at symptom onset (n, %)	Derived from the date of the onset of the first symptoms as defined in the item *Symptom onset*. Registries *may* ask for the onset age in their data collection form and calculate the date from the date of birth.	Derived from Symptom onset date
1.05	Best functional SMA status (n, %)	Based on the number of reported measures in the Motor ability columns. Possible values for motor ability include: roll onto side, sit without support, crawl, stand with assistance, stand without assistance, walk with assistance, walk without assistance, walk 10 metres without assistance, climb stairs, useful function of hands, reach overhead in a sitting position, raise hands to mouth in a sitting position.	Derived from Motor ability
1.06	Best achieved motor milestone (n, %)	Motor ability of the individual (best achieved) Possible values: hold head without support, roll onto side, sit without support, crawl, stand with assistance, stand without assistance, walk with assistance, walk without assistance, walk 10 metres without assistance, climb stairs, useful function of hands, reach overhead in a sitting position, raise hands to mouth in a sitting position)	Motor ability
1.07	SMN1 gene mutation type (n, %)	SMN1 gene mutation type of the individual. Possible values: homozygous deletion exon 7, compound heterozygous deletion exon 7, compound heterozygous substitutions, homozygous substitution)	SMN1 variant

ID	Name	Description	Relevant columns in the TreatNMD dataset
1.08	Number of SMN2 copies (n, %)	SMN2 copy number follows the following format: If the precise number is known, it is given as an integer, for example "3" If only a range is known, the lower and upper inclusive bounds are given and separated by a hyphen-minus. For example, if the copy number is known to be at least 3 and at most 5, it is specified as "3-5". If only a lower bound is known, it is specified with an appended plus sign. For example, if the copy number is known to be at least 4, it is specified as "4+".	SMN2 copy number
1.09	Methods used for genetic testing (n, %)	Testing method used to obtain the genetic result. Registries may add an additional free-text field in their data collections forms to capture possible methods other than the ones provided in this item; values in the free-text field should be checked by a curator and mapped to the provided values wherever possible. New methods may be added to the dataset by TREAT-NMD whenever appropriate. This item refers to the testing method used to obtain the result provided in *SMN1 variant* and *SMN1 variant HGVS*. Possible values: RFLP (Restriction Fragment Length Polymorphism), HRM (High Resolution Melting), MLPA (Multiplex Ligation-dependent Probe Amplification), DNA Sequencing, qrtPCR (Quantitative Real-Time PCR), ddPCR (Droplet Digital PCR)	SMN1 testing method
1.10	Duration of follow up (registry entry to death, end of data or loss to follow-up) (mean, sd, median, IQR)	Duration of follow up (registry entry to death, end of data or loss to follow-up)	Derived
1.11	Duration of SMA (from onset of symptoms to death, end of data or loss to follow-up, in months) (mean, sd, median, IQR)	Duration of SMA (from onset of symptoms to death, end of data or loss to follow-up, in months)	Derived
1.12	Duration between two consecutive visits collected in the registry (mean, sd, median, IQR)	Duration between two consecutive visits collected in the registry	Derived
1.13	Duration between genetic report date and registry entry (mean, sd, median, IQR)	Duration between genetic report date and registry entry	Derived
1.14	Reason for genetic testing (n, %)	Specifies whether the diagnosis was made as a result of screening. This item refers to a diagnosis of 5q SMA. Possible values: family screening (the diagnosis was made as a result of family screening), newborn screening (the diagnosis was made as a result of a newborn screening programme), prenatal screening (the diagnosis was made as a result of prenatal screening), no screening (the diagnosis was not made as a result of screening).	Screening

ID	Name	Description	Relevant columns in the TreatNMD dataset
1.15	Age at onset of SMA symptoms (mean, sd, median, IQR)	Derived from the date of the onset of the first symptoms as defined in the item *Symptom onset*. Registries may ask for the onset age in their data collection form and calculate the date from the date of birth.	Symptom onset date
1.16	Age at genetic report date (mean, sd, median, IQR)	Derived from the date of the genetic report confirming the individual's diagnosis.	Genetic report date
1.17	Age at registry entry (mean, sd, median, IQR)	Age at registry entry	Derived
1.18	Age at death (mean, sd, median, IQR)	Derived from the date of the death of the individual. The date of death *may* be provided as a year only, if the month is not known.	Date of death
1.19	Lost to follow-up (n, %)	Patients will be considered lost to follow-up if > 24 months has elapsed since their last available data, in absence of death.	Derived
1.20	Treated with at least one DMT (n, %)	Derived from *DMT,* which specifies the disease-modifying therapy the individual is receiving or has received at some point.	DMT
1.21	Treated with more than one DMT (n, %)		DMT
1.22	Treated with nusinersen (Spinraza®) (n, %)		DMT
1.23	Treated with Zolgensma (Zolgensma®) (n, %)		DMT
1.24	Treated with risdiplam (Evrysdi®) (n, %)		DMT
1.25	Invasive ventilation (n, %)	Episode that describes current or previous usage of invasive ventilation due to the individual's neuromuscular condition. Only periods of two weeks or more are to be added.	Invasive ventilation episode
1.26	Non-invasive ventilation (n, %)	Episode that describes current or previous usage of non-invasive ventilation due to the individual's neuromuscular condition. Only periods of two weeks or more are to be added.	Non-invasive ventilation episode
1.27	Feeding tube usage (n, %)	Episode that describes current or previous usage of a feeding tube due to the individual's neuromuscular condition. The start, stop and ongoing dates of this record apply to the feeding tube usage of the type specified in *Feeding tube usage type*. If the individual was switched from one type of usage to another, two record instances must be provided.	Feeding tube usage episode
1.28	Wheelchair usage (n, %)	Episode that describes when the individual used or has been using a manual or powered wheelchair or similar assisted mobility device due to their neuromuscular condition.	Wheelchair usage episode
1.29	At least one reported measure by available motor function scale or test, and by at least one PRO (n, %)	Based on the number of reported measures in the Motor ability and/or PRO columns. Possible values for motor ability include: roll onto side, sit without support, crawl, stand with	Motor ability & PRO

ID	Name	Description	Relevant columns in the TreatNMD dataset
1.30	At least three reported measure by available motor function scale or test, and by at least one PRO (n, %)	assistance, stand without assistance, walk with assistance, walk without assistance, walk 10 metres without assistance, climb stairs, useful function of hands, reach overhead in a sitting position, raise hands to mouth in a sitting position Possible PROs include: ACTIVLIM (Measurement of Activity Limitations), provide score between 0 and 36, and PROs as recorded in the Spanish PROFuture questionnaire. Please see sections 9.4.6 and Appendix B and C .	Motor ability & PRO
1.31	Available number of records of each motor function scale by patient (mean, sd, median, IQR)		Motor ability & PRO
1.32	Available number of records of each PRO by patients (mean, sd, median, IQR)		Motor ability & PRO

9.4.2. Indicators and Characteristics Used to Assess SMA Natural History and Disease Progression

ID	Name	Description	Relevant columns in the TreatNMD dataset
2.01	Sex (n, %)	Current biological sex of the individual. Possible values: male, female, intersex, unspecified	Sex
2.02	Registry (n, %)	Belgium, Spain, Czech Republic, etc.	Metadata
2.03	Age at symptom onset (mean, sd)	Derived from the date of the onset of the first symptoms as defined in the item *Symptom onset*. Registries *may* ask for the onset age in their data collection form and calculate the date from the date of birth.	Derived from Symptom onset date
2.04	Reason for genetic testing (n, %)	Specifies whether the diagnosis was made as a result of screening. Possible values include: Family screening, Newborn screening, Prenatal screening, No screening	Screening
2.05	Method used for genetic testing (n, %)	Testing method used to obtain the genetic result. Registries may add an additional free-text field in their data collections forms to capture possible methods other than the ones provided in this item; values in the free-text field should be checked by a curator and mapped to the provided values wherever possible. New methods may be added to the dataset by TREAT-NMD whenever appropriate. This item refers to the testing method used to obtain the result provided in *SMN1 variant* and *SMN1 variant HGVS*. Possible values: RFLP (Restriction Fragment Length Polymorphism), HRM (High Resolution Melting), MLPA (Multiplex Ligation-dependent Probe Amplification), DNA Sequencing, qrtPCR (Quantitative Real-Time PCR), ddPCR (Droplet Digital PCR)	SMN1 testing method
2.06	SMN1 variant (n, %)	Presence of SMN1 gene mutation.	SMN1 variant

ID	Name	Description	Relevant columns in the TreatNMD dataset
		Possible values: homozygous deletion exon 7, compound heterozygous deletion exon 7, compound heterozygous substitutions, homozygous substitution)	
2.07	Functional status at genetic report date (n, %)	Based on the number of reported measures in the Motor ability columns. Possible values for motor ability include: roll onto side, sit without support, crawl, stand with assistance, stand without assistance, walk with assistance, walk without assistance, walk 10 metres without assistance, climb stairs, useful function of hands, reach overhead in a sitting position, raise hands to mouth in a sitting position.	Derived from Motor ability episode
2.08	Achieved motor milestone at genetic report date (n, %)		Motor ability episode
2.09	Best functional status (n, %)		Derived from Motor ability episode
2.10	Best achieved motor milestone (n, %)		Motor ability episode
2.11	Best functional status before treatment (n, %)		Derived from Motor ability episode
2.12	Best functional status after treatment (n, %)		Derived from Motor ability episode
2.13	Best achieved motor milestone before treatment (n, %)		Motor ability episode
2.14	Best achieved motor milestone after treatment (n, %)		Motor ability episode
2.15	Height (mean, sd)	Height or length of the individual, as directly measured in centimetres.	Height
2.16	Weight (mean, sd)	Weight of the individual. measured in kilograms.	Weight
2.17	Age at first acquisition of -the best any of the motor ability episodes (mean, sd)	Age at first acquisition of -the best any of the motor ability episodes	Motor ability episode (early age record if multiple)
2.18	Age at first loss of the best any of the motor ability episodes (mean, sd)	Age at first loss of the best any of the motor ability episodes	Motor ability episode (early age record if multiple)
2.19	Full-time or part time wheelchair use (n, %)	Specifies the frequency of wheelchair usage. Possible values include: Part-time (the individual is sometimes able to get around without a wheelchair or similar device), Full-time (the individual is unable to get around at all without a wheelchair or similar device)	Wheelchair usage frequency
2.20	Age at first full-time or part-time wheelchair usage (mean, sd)	Age at first full-time or part-time wheelchair usage (mean, sd)	Wheelchair usage frequency
2.21	No contracture, one contracture, more than one contractures (n, %)	Combination of 8 contracture variables that Specifies whether the individual has location specific contractures	Contracture variables

ID	Name	Description	Relevant columns in the TreatNMD dataset
2.22	Score for CHOP-INTEND at genetic report date (mean, sd)	The list of measures included in the item Motor measure represents all validated motor measures that TREAT-NMD know to be currently in use for SMA. Selection of appropriate motor measure(s) is at the discretion of the clinician and/or preference of the individual. The Motor measure value description specifies the unit in which the outcome *must* be provided.	Motor Measures
2.23	Best score for CHOP-INTEND (mean, sd)		Motor Measures
2.24	Most recent score for CHOP-INTEND (mean, sd)		Motor Measures
2.25	Score for HFMS(-E) at genetic report date (mean, sd)		Motor Measures
2.26	Best score for HFMS(-E) (mean, sd)		Motor Measures
2.27	Most recent score for HFMS(-E) (mean, sd)		Motor Measures
2.28	Score for RULM at genetic report date (mean, sd)		Motor Measures
2.29	Best score for RULM (mean, sd)		Motor Measures
2.30	Most recent score for RULM (mean, sd)		Motor Measures
2.31	Score for HINE-2 at genetic report date (mean, sd)		Motor Measures
2.32	Best score for HINE-2 (mean, sd)		Motor Measures
2.33	Most recent score for HINE-2 (mean, sd)		Motor Measures
2.34	Score for MFM32 at genetic report date (mean, sd)		Motor Measures
2.35	Best score for MFM32 (mean, sd)		Motor Measures
2.36	Most recent score for MFM32 (mean, sd)		Motor Measures
2.37	Score for 6MWT at genetic report date (mean, sd)		Motor Measures
2.38	Best score for 6MWT (mean, sd)		Motor Measures
2.39	Most recent score for 6MWT (mean, sd)		Motor Measures
2.40	Change between scores in HFSM-E in consecutive age classes (mean, sd)	The list of measures included in the item Motor measure represents all validated motor measures that TREAT-NMD know to be currently in use for SMA. Selection of appropriate motor measure(s) is at the discretion of the clinician and/or preference of the individual. The Motor measure value description specifies the unit in which the outcome *must* be provided This record is longitudinal, for each record instance, a date stamp with month and year *must* be captured which can be used to compute change between scores in consecutive sage classes.	Transformation of Motor Measures
2.41	Change between scores in RULM in consecutive age classes (mean, sd)		Transformation of Motor Measures
2.42	Change between scores in 6MWT in consecutive age classes (mean, sd)		Transformation of Motor Measures
2.43	Age at report of (first) best CHOP-INTEND score (mean, sd)	The list of measures included in the item Motor measure represents all validated motor measures that TREAT-NMD know to be currently in use for SMA. Selection of appropriate motor measure(s) is at the discretion of the clinician and/or preference of the individual. The Motor measure value description specifies the unit in which the outcome *must* be provided This record is longitudinal, for each record instance, a date stamp with month and year *must* be captured	Motor Measures
2.44	Age at report of (first) best HFMS(-E) score (mean, sd)		Motor Measures
2.45	Age at report of (first) best RULM right side score (mean, sd)		Motor Measures
2.46	Age at report of (first) best HINE-2 score (mean, sd)		Motor Measures

ID	Name	Description	Relevant columns in the TreatNMD dataset
2.47	Age at report of (first) best MFM32 score (mean, sd)	based on which the age can be determined at report of (first) best score	Motor Measures
2.48	Age at report of (first) 6MWT best score (mean, sd)		Motor Measures
2.49	Ever diagnosed with scoliosis (n, %)	Specifies whether the individual has ever been diagnosed with scoliosis. Possible values for scoliosis diagnosis include: Yes or No	Scoliosis Diagnosis
2.50	Cobb angle value <30°, 30-45°, >45° (n, %)	Cobb angle according to radiology results. The unit of values is degrees.	Convert numeric cobb angle into categories
2.51	At least one use of spinal brace ever (n, %)	A list of Rehabilitative interventions the individual has received at some time during the period from Begin date to End date including spinal brace.	Rehabilitative Interventions
2.52	Surgery for scoliosis (n, %)	Specifies whether the individual has ever undergone surgery specifically to try and correct scoliosis. Possible values for scoliosis surgery include: Yes or No	Scoliosis surgery performed
2.53	Age at surgery for scoliosis (mean, sd)	Date of the scoliosis surgery based on which the age at the time of surgery for scoliosis can be determined.	Transformation of Scoliosis Surgery Date
2.54	Annual number of vertebral fracture by patient reported in cause of hospitalisation or as a comorbidity (mean, sd)		Hospitalisation acute reason code
2.55	Annual number of non-vertebral fractures by patient reported in cause of hospitalisation or as a comorbidity (mean, sd)	Main reason for acute hospitalisation as a ICD-10/ICD-11/MedDRA code	Hospitalisation acute reason code
2.56	Age at first reported vertebral fracture (mean, sd)	Age based on start date of episode for first reported vertebral fracture identified using ICD-10/ICD-11/MedDRA code	Hospitalisation acute reason code
2.57	Forced vital capacity percent (mean, sd)	Forced vital capacity as percentage of predicted value.	Forced vital capacity percentage
2.58	Forced vital capacity volume (n, %)	Forced vital capacity as absolute volume in litres.	Forced vital capacity volume
2.59	At least one episode of airway clearance assistance (n, %)	Specifies how often the individual currently uses assistance in airway clearance and/or secretion mobilisation, for example using suction, chest percussion or a cough assist device.	Airway Clearance Assistance
2.60	At least one episode of any non-invasive ventilation (n, %)	Episode that describes current or previous usage of non-invasive ventilation due to the individual's neuromuscular condition. Only periods of two weeks or more were added. Possible values include: Full-time, Part-time awake and sleeping, Part-time sleeping, Part-time	Non-invasive ventilation episode
2.61	At least one episode of full-time non-invasive ventilation (n, %)		Non-invasive ventilation episode
2.62	At least one episode of part-time awake and sleeping non-invasive ventilation (n, %)		Non-invasive ventilation episode

ID	Name	Description	Relevant columns in the TreatNMD dataset
2.63	At least one episode of part-time sleeping non-invasive ventilation (n, %)		Non-invasive ventilation episode
2.64	Age at start of first full-time non-invasive ventilation episode (mean, sd)	Age based on start date of first full-time non-invasive ventilation episode	Non-invasive ventilation episode
2.65	At least one episode of any invasive ventilation (n, %)	Episode that describes current or previous usage of invasive ventilation due to the individual's neuromuscular condition. Only periods of two weeks or more were added. Possible values include: Full-time, Part-time awake and sleeping, Part-time sleeping, Part-time	Invasive ventilation episode
2.66	At least one episode of full-time invasive ventilation (n, %)		Invasive ventilation episode
2.67	At least one episode of part-time awake and sleeping invasive ventilation (n, %)		Invasive ventilation episode
2.68	At least one episode of part-time sleeping invasive ventilation (n, %)		Invasive ventilation episode
2.69	Age at start of first full-time invasive ventilation episode (mean, sd)	Age based on start date of first full-time invasive ventilation episode	Invasive ventilation episode
2.70	Bronchopulmonary infections reported in cause of hospitalisation or as a comorbidity (n, %)	Main reason for acute hospitalisation as a ICD-10/ICD-11/MedDRA code	Hospitalisation acute reason code
2.71	At least one episode of respiratory physiotherapy (n, %)	A list of Rehabilitative interventions the individual has received at some time during the period from Begin date to End date including respiratory physiotherapy.	Rehabilitative Interventions
2.72	At least one episode of feeding tube usage (n, %)	Episode that describes current or previous usage of a feeding tube for feeding due to the individual's neuromuscular condition. Possible values include: Exclusive, Supplementary	Feeding tube usage episode
2.73	At least one episode of exclusive feeding tube usage (n, %)		Feeding tube usage episode
2.74	At least one episode of supplementary feeding tube usage (n, %)		Feeding tube usage episode
2.75	At least one gastronomy reported in cause of hospitalisation or as a comorbidity (n, %)	Main reason for acute hospitalisation as a ICD-10/ICD-11/MedDRA code	Hospitalisation acute reason code
2.76	Age at first gastrostomy (mean, sd)	Age based on admission date of hospitalisation.	Hospitalisation admission date
2.77	At least one hospitalisation (n, %)	Hospitalisation admission date.	Hospitalisation admission date
2.78	Annual number of hospitalisations (mean, sd)		Hospitalisation admission date
2.79	Event-free survival (death or permanent ventilation) (mean, sd)	Time to death or to permanent ventilation. (*Date of the death of the individual. The date of death may be provided as a year only, if the month is not known. Episode that describes current or previous usage of non-invasive/invasive ventilation due to the individual's neuromuscular condition. Possible values include: Full-time invasive or non-invasive ventilation, respectively*).	Date of death or first full-time invasive ventilation or full-time non-invasive ventilation
2.80	Causes of death (n, %)	Cause of death as code of the classification specified	Cause of death code

ID	Name	Description	Relevant columns in the TreatNMD dataset
		in Cause of death classification (ICD-10/ICD-11 codes).	
2.81	Causes of hospitalisation (n, %)	Main reason for hospitalisation as a code in the classification specified in Hospitalisation acute reason classification (ICD-10/ICD-11 codes/MedDRA).	Hospitalisation acute reason code
2.82	Comorbidity	Comorbidity as code of the classification specified in Comorbidity classification (ICD-10/ICD-11 codes/MedDRA).	Comorbidity code
2.83	Score for Spain PROFuture Mobility and Independence PRO at genetic report date (mean, sd)	Patient Global Impression of Severity (PGI-S) according to the individual, or according to a caregiver answering on behalf of the individual ("Select the option that best describes how affected you are now by your SMA"). The Patient-reported outcome measure value description specifies which type of score *must* be provided.	Patient-reported outcome measures
2.84	Best score for Spain PROFuture Mobility and Independence PRO (mean, sd)		Patient-reported outcome measures
2.85	Most recent score for Spain PROFuture Mobility and Independence PRO (mean, sd)		Patient-reported outcome measures
2.86	Score for Belgium ACTIVLIM PRO at genetic report date (mean, sd)		Patient-reported outcome measures
2.87	Best score for Belgium ACTIVLIM PRO (mean, sd)		Patient-reported outcome measures
2.88	Most recent score for Belgium ACTIVLIM PRO (mean, sd)		Patient-reported outcome measures

9.4.3. Indicators and Characteristics Used to Assess SMA Healthcare Management

ID	Name	Description	Relevant columns in dataset
3.01	SMN1 testing method (n, %)	Testing method used to obtain the genetic result. Registries may add an additional free-text field in their data collections forms to capture possible methods other than the ones provided in this item; values in the free-text field were checked by a curator and mapped to the provided values wherever possible. New methods may be added to the dataset by TREAT-NMD whenever appropriate. This item refers to the testing method used to obtain the result provided in *SMN1 variant* and *SMN1 variant HGVS*. Possible values: RFLP (Restriction Fragment Length Polymorphism), HRM (High Resolution Melting), MLPA (Multiplex Ligation-dependent Probe	SMN1 testing method

ID	Name	Description	Relevant columns in dataset
		Amplification), DNA Sequencing, qrtPCR (Quantitative Real-Time PCR), ddPCR (Droplet Digital PCR)	
3.02	SMN2 testing method (n, %)	Testing method used to obtain the genetic result. Registries may add an additional free-text field in their data collections forms to capture possible methods other than the ones provided in this item; values in the free-text field should be checked by a curator and mapped to the provided values wherever possible. New methods may be added to the dataset by TREAT-NMD whenever appropriate. This item refers to the testing method used to obtain the result provided in SMN2 copy number. Possible values: RFLP (Restriction Fragment Length Polymorphism), HRM (High Resolution Melting), MLPA (Multiplex Ligation-dependent Probe Amplification)	SMN2 copy number testing method
3.03	At least one DMT (n, %)	Specifies the disease-modifying therapy the individual is receiving or has received at some point.	DMT
3.04	Taken the drugs listed as comedications at least once from registry entry (n, %)	Prescribed allopathic drug or supplement the individual has taken.	Allopathic drug
3.05	Annual influenza vaccination (n, %)		Allopathic drug
3.06	At least one pneumococcal vaccination (n, %)		Allopathic drug
3.07	Pneumococcal vaccination at least once every 5 years (n, %)		Allopathic drug
3.08	At least one episode of any ventilation (n, %)	Episode that describes current or previous usage of non-invasive/invasive ventilation due to the individual's neuromuscular condition. Only periods of two weeks or more are added.	Invasive ventilation episode or Non-invasive ventilation episode
3.09	At least one episode of feeding tube usage (n, %)	Episode that describes current or previous usage of a feeding tube for feeding due to the individual's neuromuscular condition.	Feeding tube usage episode
3.10	At least one episode of wheelchair use (n, %)	Episode that describes when the individual used or has been using a manual or powered wheelchair or similar assisted mobility device due to their neuromuscular condition.	Wheelchair usage episode

ID	Name	Description	Relevant columns in dataset
3.11	Age at first episode of any ventilation (invasive or non-invasive) (mean, sd, median, IQR)	Age based on start date of first non-invasive/invasive ventilation episode	Invasive ventilation episode or Non-invasive ventilation episode
3.12	Age at first episode of invasive ventilation (mean, sd, median, IQR)	Age based on start date of first invasive ventilation episode	Invasive ventilation episode
3.13	Age at first episode of feeding tube usage (mean, sd, median, IQR)		Feeding tube usage episode
3.14	Age at first episode of gastrostomy (mean, sd, median, IQR)	Age based on start date of first gastrostomy episode	Hospitalisation acute reason code
3.15	At least one episode of muscular physiotherapy ever (n, %)	A list of rehabilitative interventions the individual has received at some time during the period from Begin date to End date including muscular physiotherapy.	Rehabilitative Interventions
3.16	At least one episode of respiratory physiotherapy ever (n, %)	A list of rehabilitative interventions the individual has received at some point during the period from Begin date to End date including respiratory physiotherapy.	Rehabilitative Interventions
3.17	At least one episode of contracture management using orthotics ever (n, %)	A list of rehabilitative interventions the individual has received at some point during the period from Begin date to End date including contracture management using orthotics .	Rehabilitative Interventions
3.18	At least one episode of spinal brace ever (n, %)	A list of rehabilitative interventions the individual has received at some point during the period from Begin date to End date including spinal brace.	Rehabilitative Interventions
3.19	At least one episode of speech therapy ever (n, %)	A list of rehabilitative interventions the individual has received at some point during the period from Begin date to End date including speech therapy.	Rehabilitative Interventions
3.20	Age at first DMT (mean, sd)	Date on which the individual received first therapy specified in DMT.	DMT
3.21	Patients who received more than one DMT (n,%)	Specifies the disease-modifying therapy the individual is receiving or has received at some point. Possible values include: Nusinersen, Onasemnogene abeparvovec, Risdiplam.	DMT
3.22	Treated with nusinersen (Spinraza®) (n, %)		DMT
3.23	Treated with Zolgensma (Zolgensma®) (n, %)		DMT
3.24	Treated with risdiplam (Evrysdi®) (n, %)		DMT

ID	Name	Description	Relevant columns in dataset
3.25	Treated with nusinersen (Spinraza®) & Zolgensma (Zolgensma®) (n, %)		DMT
3.26	Treated with nusinersen (Spinraza®) & risdiplam (Evrysdi®) (n, %)		DMT
3.27	Treated with Zolgensma (Zolgensma®) & risdiplam (Evrysdi®) (n, %)		DMT
3.28	Treated with nusinersen (Spinraza®) & Zolgensma (Zolgensma®) & risdiplam (Evrysdi®) (n, %)		DMT
3.29	Age at initiation of nusinersen (Spinraza®) (mean, sd, median, IQR)	Date on which the individual received nusinersen.	DMT
3.30	Age at initiation of Zolgensma (Zolgensma®) (mean, sd, median, IQR)	Date on which the individual received Onasemnogene abeparvovec.	DMT
3.31	Age at initiation of risdiplam (Evrysdi®) (mean, sd)	Date on which the individual received risdiplam.	DMT
3.32	Dose regarding weight at administration (n, %)	Value of the dosage, given in the unit specified in DMT dosage unit: Vector genomes per kilogram body weight, Milligrams per kilogram body weight, Milligrams	DMT dosage value
3.33	Co-administration of corticosteroids (n, %)	Duration in days of the administration of prophylactic systemic corticosteroids in relation to Zolgensma administration	DMT corticosteroid administration duration > 0
3.34	Anti-AAV9 antibody test before Zolgensam administration (n, %)	Anti-AAV9 antibody test date & Date on which the individual received a single administration of the therapy specified in DMT.	Anti-AAV9 antibody test date & DMT single administration date
3.35	Positive (>1:50) anti-AAV9 antibody test (n, %)	Antibody titre measured in this anti-AAV9 antibody test. Possible values include: <= 1:50, > 1:50	Anti AAV9 antibody test result
3.36	At least one adequate dose (12mg) (n, %)	Value of the dosage, given in the unit specified in DMT dosage unit: Vector genomes per kilogram body weight, Milligrams per kilogram body weight, Milligrams	DMT dosage value
3.37	Time between genetic report date and first administration (D0) (mean, sd)	This item currently only applies to nusinersen and risdiplam. Deviation definition for nusinersen: Specifies whether the interval between any two consecutive administrations of nusinersen differs by 14 days or more from that specified in the applicable prescription information. Deviation definition for risdiplam: Specifies whether the individual has ever	DMT administration schedule deviation

ID	Name	Description	Relevant columns in dataset
		failed to take the prescribed dosage of risdiplam for 7 consecutive days or more during this episode.	
3.38	Treatment duration defined as the time from initiation to last available administration date (discontinuation date, death, loss to follow-up, date of data-extraction if the last information indicates that nusinersen (Spinraza®) is ongoing) (mean, sd, median, IQR)	This is an episode record: For each record instance, the following dates *must* be captured: ● Start date: The month and year when the condition described by the record started to hold, if known ● Stop date: The month and year when the condition ceased to hold, if applicable and known ● Ongoing date: The month and year on which the condition was known to hold, if applicable	DMT episode
3.39	Ongoing nusinersen (Spinraza®) at their last reported dose (n, %)		DMT episode
3.40	Treatment discontinuation (n, %)	Specifies whether this therapy is ongoing or stopped. Stopped: The individual has stopped receiving the therapy since the date specified in Start date	DMT status
3.41	Reason for treatment discontinuation (n, %)	Reason the individual has stopped receiving the therapy specified in DMT (in the case of a continuous treatment), or has received a different disease-modifying therapy after receiving a single-administration therapy specified in DMT. Possible values include: Funding, Side effects from procedure, Side effects from drug, Scoliosis, Insufficient benefit, Insufficient initial improvement, Loss of response, Elective choice	DMT stopping reason
3.42	Treatment duration in patients with treatment discontinuation (mean, sd)	Specifies whether this therapy is ongoing or stopped. For each record start date and stop date must be captured.	DMT status
3.43	At least one adequate dose regarding age and weight (n, %)	Value of the dosage, given in the unit specified in DMT dosage unit: Vector genomes per kilogram body weight, Milligrams per kilogram body weight, Milligrams	DMT dosage value
3.44	Treatment duration defined as the time from initiation to last available administration date (discontinuation date, death, loss to follow-up, date of data-extraction if the last information indicates that risdiplam (Evrysdi®) is ongoing) (mean, sd, median, IQR)	This is an episode record: For each record instance, the following dates were captured: ● Start date: The month and year when the condition described by the record started to hold, if known ● Stop date: The month and year when the condition ceased to hold, if applicable and known	DMT episode

ID	Name	Description	Relevant columns in dataset
3.45	Ongoing risdiplam (Evrysdi®) at their last reported dose (n, %)	• Ongoing date: The month and year on which the condition was known to hold, if applicable	DMT episode
3.46	Treatment discontinuation (n, %)	Specifies whether this therapy is ongoing or stopped. Stopped: The individual has stopped receiving the therapy since the date specified in Start date	DMT status
3.47	Reason for treatment discontinuation (n, %)	Reason the individual has stopped receiving the therapy specified in DMT (in the case of a continuous treatment), or has received a different disease-modifying therapy after receiving a single-administration therapy specified in DMT. Possible values include: Funding, Side effects from procedure, Side effects from drug, Scoliosis, Insufficient benefit, Insufficient initial improvement, Loss of response, Elective choice	DMT stopping reason
3.48	Treatment duration in patients with treatment discontinuation (mean, sd)	Specifies whether this therapy is ongoing or stopped. For each record start date and stop date must be captured.	DMT status
3.49	At least one SAE reported in the registry related to any DMT (n, %)	Specifies whether the reason for hospitalisation specified in Hospitalisation acute reason code or was classified as a serious adverse event (SAE) in relation to a disease-modifying therapy. Or whether this comorbidity was classified as a serious adverse event (SAE) in relation to a disease-modifying therapy.	Hospitalisation SAE or Comorbidity SAE
3.50	At least one SAE reported in the registry related to nusinersen (Spinraza®) (n, %)	Disease-modifying therapy to which this SAE was related.	Hospitalisation SAE DMT or Comorbidity SAE DMT
3.51	At least one SAE reported in the registry related to Zolgensma (Zolgensma®) (n, %)		Hospitalisation SAE DMT or Comorbidity SAE DMT
3.52	At least one SAE reported in the registry related to risdiplam (Evrysdi®) (n, %)		Hospitalisation SAE DMT or Comorbidity SAE DMT
3.53	Incidence rate of listed SAESI	Main reason for hospitalisation as a code in the classification specified in Hospitalisation acute reason classification (ICD-10/ICD-11 codes/MedDRA).	Hospitalisation acute reason code matches defined ICD-10 list

9.4.4. Disease Modifying Treatment Usage

Exposure: Patient exposure was defined according to the information collected in the registry. The exposures of interest were as follows:

- Treated with at least one DMT (this served to create an overall exposure category representing all patients who were treated, regardless of the treatment or combination of treatments received during the follow-up).
- Treated with Spinraza®, and possible combinations with Spinraza®.
- Treated with Zolgensma®, and possible combinations with Zolgensma®.
- Treated with Evrysdi®, and possible combinations with Evrysdi®

Treated with at least one DMT or possible treatment combinations was defined using the following fields available within the TreatNMD network:

- The “DMT received field” indicator (e.g. “Yes”)
- A field indicating the name of the specific DMT taken Spinraza®, Zolgensma®, and Evrysdi®
- A field indicating the corresponding start date (or a single administration date for Zolgensma®)

All three fields were needed to be specified for the individual to be considered as exposed to a given DMT and flagged as a treated patient. The availability of individual DMTs in each participating country, according to information provided by the registries during the feasibility assessment are summarised in Appendix D (Provided a stand-alone document, submitted along with this report).

Exposure definition: In all the analyses, the treated cohort (TREATED) consisted of patients who had been exposed to any DMT. Based on a time-varying exposure approach, patients were categorised among monotherapy or/and treatment combination categories. Patients were classified as never treated (NEVER TREATED) if never treated with any DMTs at any point of their journey. For all patients, end of follow-up was the earliest of date of death or end of follow-up / end of data (censoring at last available information in lost-to follow-up patients).

9.4.5. Evaluation of Safety:

Serious adverse events of special interest (SAESI):

The following events were searched using ICD (International Classification of Diseases) codes among the causes of death and hospitalisation, even if they were not identified as DMT-related by the registries. Please refer to the Statistical Analysis Plan for the definition of the code lists.

- Thrombocytopenia and coagulation abnormalities
- Renal toxicity
- Hydrocephalus
- Meningitis
- Hypersensitivity reactions
- Cutaneous vasculitis
- Hepatotoxicity
- Cardiac adverse event

Adverse events of interest:

ICD codes among the causes of death and hospitalisation were used to identify the following events considered as adverse event of interest:

- Osteoporosis
- Fractures
- Pulmonary infections including bronchopulmonary infections
- Sleep apnea
- Pneumothorax
- Atrial or ventricular defect
- Diabetes
- Vertebral fracture
- Non-vertebral fractures

9.4.6. Evaluation of Effectiveness/Clinical Response and Patient Outcomes:

Post-SMA diagnosis outcomes:

Exploratory Interrupted Time Series (ITS) analysis has also been implemented to explore SMA progression according to specific post-diagnosis outcomes. ITS has been assessed over periods before / after DMT availability. The following outcomes have been assessed:

- Rates of death and permanent invasive/non-invasive ventilation (composite outcome)
- Rates of death
- Rates of permanent invasive/non-invasive ventilation

Patient-reported outcomes: PRO scores from data contained in the Spanish (PROFuture) and Belgium (ACTIVLIM) registries were included. Upon data availability, PRO scores were measured/reported: 1) at genetic report date, 2) as an overall best score, and 3) at the most recent score. Standard classifications were used as reported in the literature (24,25) for the PRO score's calculations. Specific registries' questionnaires used in the construction of each PRO score are included in the Appendix B & C. Scores were generated by converting raw data into a linear measure of activity limitation using a Rasch model.

PROFuture, used by the Spanish registry, has been validated in adults, but not yet children (26). ACTIVLIM has been validated in both children (6-15) and adults (16-80)(25).

The following PROs were measured and included in the analyses:

1) Spain PROFuture mobility and independence score as measured at genetic report date
2) Spain PROFuture mobility and independence best score measured over the entire follow-up period
3) Spain PROFuture mobility and independence most recent score as reported across various current age categories
4) Belgium ACTIVLIM PRO score as measured at genetic report date
5) Belgium ACTIVLIM PRO best score measured over the entire follow-up period
6) Belgium ACTIVLIM PRO most recent score as reported across various current age categories

9.4.7. Medical Resource Utilisation and Health Economics

These types of analyses were not applicable to this study report.

9.4.8. Sample Collection and Handling

No sample collection or handling occurred as a result of this non-interventional study.

9.5. Data Sources and Data Management

TREAT-NMD is a global registry network launched in 2007 for the neuromuscular field that provides an infrastructure to ensure the most promising new therapies reach patients as quickly as possible across multiple diseases. The global registry network is composed of Member Registry Curators including Patient Representatives and supported by the TREAT-NMD Ethic Board Representatives. The TREAT-NMD SMA core dataset containing 23 data items was established in 2008 when the main purpose of the registries was clinical trial readiness and recruitment. TREAT-NMD currently has 26 SMA registries (19 in Europe) as part of the network with an estimated 4,800 patients. The TREAT-NMD Registry Network is made up of SMA clinician, patient reported and dual reported registries.

The purpose of the TREAT-NMD Central Data Warehouse (CDW) is to collect data in a harmonised way by using the SMA Core dataset, to build a natural pool of data and allow for better data analysis. The core data model was developed through extensive stakeholder engagement with registry curators, physicians, physiotherapists, patient representatives and industry representatives. The final list of registries contributing data to this project has been determined after fit-for-purpose data assessment.

This study used data from multiple existing SMA registries across Europe. Data sources were selected after pre-feasibility and feasibility assessments based on the EMA guideline on registry-based studies (27), the REQueST tool (28), and a structured process to identify fit-for-purpose data (SPIFD - generating a ranking for data elements considered in the assessment) (29). The feasibility included assessment on registry characteristics, governance and quality assurance, data reliability, data relevance, data access, as well as minimum data needs (demographics, genetic diagnosis, clinical characteristics, treatments, disease outcomes and patient-reported outcomes). A total of 16 SMA registries across 18 European countries within the TREAT-NMD network were initially contacted for pre-feasibility assessment (Bulgaria, Croatia, Czech Republic & Slovakia, Georgia, Hungary, Latvia, Slovenia, Turkey Kukas, Turkey Lukam, Ukraine, Belgium, Germany & Austria, Spain, Sweden, Switzerland, United Kingdom & Ireland). Among

those, 10 were selected for feasibility assessment; main reasons for exclusion were low sample size, capturing only children, absence of data quality assurance process or audit practices, country-specific situation, and workload preventing participation. Variability in data availability was observed across registries assessed. Almost all patients had genetically confirmed SMA diagnosis (except for some patient-based registries); genetic testing methods were available in a few registries. Overall, treatments and disease outcomes were recorded with more details in clinician-based registries. Dosage of DMTs was not available across patient-based registries. Motor function test results were not collected in patient-based registries. Patient-reported outcomes data were generally limited. Based on overall registry ranking, European regional coverage, and registry type, 7 registries were recommended for the study conduct: 3 patient-based registries (Germany & Austria, Spain, UK & Ireland) and 4 clinician-based registries (Belgium, Sweden, Switzerland, Czech Republic & Slovakia). Switzerland was finally not included in the study due to lag time in the contracting process and data sharing. In Spain, the PROfuture questionnaire was in the validation phase at the time of registry assessment; nonetheless PRO data were used for the study. The final registries included in the study are described below. The detailed feasibility findings are presented in Appendix D.

Belgium

The Belgian Neuromuscular Diseases Registry (BNMDR)[5] is a national clinician-based registry which started in 2008 (and restructured in 2018), with 272 adults and children SMA patients included as of June 2022. This registry is funded by the National Health Insurance (Belgium National Institute for Health and Disability Insurance). The registry is governed by a Steering Committee that meets annually. This committee includes representatives of experts (physicians), patient organisations, one representative of the National Health Insurance and two representatives of Sciensano who manages the registry (a public research institution established in 2018). During the annual meeting, data collected, and evolution of the project are being discussed. A Scientific Committee composed by experts from participating centres (physicians) is also in place. This committee can meet more regularly to support decision making on scientific aspects.

A dedicated quality team is responsible for managing Sciensano's quality management system. They ensure that all services comply with quality standards in order to guarantee the accuracy of the analysis results that they issue and the reliability of the opinions or conclusions that they formulate. The quality standards applied within Sciensano are ISO 15189, 17025 and 17043.

At the beginning of each project, documents such as study protocol and report, statistical analysis plan and data management plan are created and regularly updated.

Registry patient-level data are de-identified and can be shared with TREAT-NMD. Patients followed over different centres can be identified, and most complete data are being kept in the registry. A data validation process is in place to avoid the entry of aberrant data within the form completed by data providers/physicians. In addition, statistics are being run on the registry data and compared to historical checks once a year (e.g., description such as counts, distribution, percentages of key characteristics). If discrepancies are identified, queries are being raised for aberrant data. Missing data are checked once a year and trends checked with data providers/physicians in order to improve completion (e.g., unavailability of source data or changing to mandatory fields).

Czech Republic & Slovakia

The REaDY is a national clinician-based registry which started in 2011 covering both Czech Republic and Slovakia. It was developed by the Institute of Biostatistics and Analyses, with 317 adults and children

SMA patients included as of May 2022. This registry is funded by the pharmaceutical industry. The registry has been endorsed by ethical committees and regulatory authorities in both Czech and Slovak Republics.
Quality documentation for the registry implementation is available: data management plan and data validation plan. In addition, a validation process is set up within the database with data quality control by the system. Each eCRF adjustment is discussed and approved by a study guarantor.
Registry patient-level data are de-identified and can be shared with TREAT-NMD. Data verification statistics are run on the data upon request such as checking date/integer ranges or checking correct data types. No specific actions are put in place to improve missingness.

Germany & Austria
The SMA-Patient registry for Germany and Austria (*DMD- und SMA-Patientenregister für Deutschland und Österreich*) is a patient-based registry which started in 2008, with 893 adults and children SMA patients included as of June 2022. This registry is operated by the Friedrich Baur Institut in Munich University Hospital (Germany)[6], dedicated to patient care and cutting-edge research in the field of neuromuscular disorders (NMD). This registry is funded by research project sponsors. The registry is governed by an independent oversight committee.
Registry patient-level data are de-identified and can only be shared with TREAT-NMD at an aggregated level. Registry participants provide a copy of human genetic findings which are reviewed at the centre and added to the participant's dataset. All participants are asked at least once per year to review and add genetic reports to the dataset for timeliness and completeness. Missing data are checked every 6 months and query raised to ask for completion.

Spain
The *Registro Nacional de Pacientes de la Fundación Atrofia Muscular Espinal* (FundAME) is a national patient-based registry which started in 2015, with 273 adults and children SMA patients included as of June 2022. This registry is funded by FundAME[7]. The registry governing bodies are as follows: 2 curators, 1 data manager who is responsible for the registry, 1 patient representative and 1 financial & administrative responsible.
The following information is being described into a protocol: curation method, responsibilities, instructions, and resources during the different phases including promotion and training activities within the patient registry.
Required data changes and dataset modifications are documented. Currently the data is migrating to a new platform, hence documentation will be updated.
Registry patient-level data are de-identified and can be shared with TREAT-NMD. The following items are being checked against medical records by a physician or a (research) nurse: SMN1 data, SMN2 data and forced vital capacity. All other items are curated by a SMA specialist healthcare professional. Data is being verified every time there’s a data modification or update in every patient. Patients are encouraged through contacts or phone calls to complete missing data or send medical reports.

Sweden
The Swedish National Registry for NMD (*Neuromuskulära sjukdomar i Sverige* - NMiS) is a national clinician-based registry which started in 2010, with 177 adults and children SMA patients included as of

September 2022. This registry is funded by the government. The registry is governed by a Steering Committee composed by 2 representatives of patient organisations.
The quality standards applied for the platform used by the NMiS-registry are following ISO 13485:2016. It covers NMiS-registry on a general level regarding platform development, risk analysis, maintenance, etc.
Registry patient-level data are de-identified and can be shared with TREAT-NMD. A data verification process is in place where all registry items are being checked against medical records by a physician or a (research) nurse once a year. Queries are being raised to ask for completion of missing information. In order to improve completion of missing data, helptext, automatic reminders and mandatory fields are also put in place in the registry.

UK & Ireland
The UK SMA Patient Registry[8] is a patient-based registry which started in 2007 covering the United Kingdom and Ireland, with 566 adults and children SMA patients included as of June 2022. This registry is funded by Biogen, through its funding of Adult SMA REACH. This registry is governed by an independent steering committee. This includes representation from three patient organisations, SMA UK, MDUK and TreatSMA. Enrolment is patient-initiated and achieved online through the registry website (www.sma-registry.org.uk). Patients become aware of the registry through patient organisations, through the clinical studies Adult SMA REACH and SMA REACH UK (paediatric) and through distribution of registry information leaflets from their neuromuscular clinic.
The patient registry has a study protocol in place but does not have a quality plan document. Registry patient-level data are de-identified and can be shared with TREAT-NMD. Data management is performed by the registry coordinator. Patients are requested to share a copy of their genetic report with the registry, enabling the registry coordinator or medical staff to verify their eligibility upon receipt. Duplicate registrations are routinely investigated and removed, following contact with the patient. Data is regularly reviewed by the curator and any anomalies are followed-up with the patient. Periodic follow-ups with patients are performed to request missing data, notably genetic reports. This is through both targeted and more general communications. All database entries and contacts are traceable through an audit trail. Self-audit is performed approximately every two years.

All data was collected via the TREAT-NMD Global Registry Platform (GRP), where it was validated and stored in the central data warehouse (CDW) ready for analysis. All the data was shared with the CDW by March 15th, 2023. Core Member Registries collected and processed data according to the national or international laws and best practices that apply to each of them respectively (in particular, accuracy and minimization of missing data; informed consent concerning use of the data for research; right of the patients to withdraw consent etc).

Several processes were put in place to ensure data quality:

- The TREAT-NMD Privacy-Preserving Record Linkage (PPRL) Generator is an online tool developed for use within the Global Registry Network to generate a unique record string based on demographic information. The purpose of the PPRL tool is twofold:
    - The process of de-identifying the patient data is completed by the PPRL tool within the registry databases. This allows patient level data to be shared without revealing any identifying information to TREAT-NMD.
    - Management of duplicate records: some patients may be registered in more than one single registry. The use of the TREAT-NMD PPRL generator will allow TREAT-NMD to alert the registry(s) of a potential duplicate PPRL.

For direct user registries, creation of an export file ready to transfer data will automatically include the patients' PPRLs. These are not visible to the user, but rather the system will identify and flag duplicate records. Indirect user registries will be provided with the TREAT-NMD PPRL generator tool for use in their own systems.

- Before data is transferred to TREAT-NMD all safety reporting instances are checked by a curator for accuracy and will be corrected before being transferred.
  The system has automated validation built into its functionality for direct user registries, to ensure that any fields that have missing data, fields that have a query raised against it (for example, outside of an agreed range)and any text added to a field where numbers are expected, are checked.
  The Curator has the responsibility to check through any validation flags raised by the system and either resolve the issue by sending the query back to the data provider or accept the validation error if it is deemed to be reasonable/appropriate. All of these checks are the responsibility of the Curator before transferring data to the CDW holding area.
  Whilst the de-identified data is in the holding area, the individuals' record will be checked via automatic process, for any validation errors and also by the TREAT-NMD data analyst. Any automatic validation errors that are not within a small tolerance will be returned to the registry curator for another check of the data content. If the data has passed the automatic process validation or the error is within a small tolerance, then the data will be approved by the data analyst and transferred into the CDW for storage and future analysis.
- Once the data is in the CDW the data analyst will then analyse the data for data quality-management purposes and future uses of the data, whether that is for enquiries or post marketing activities.

No auditing practices were in place between TREAT-NMD and the Registries. Registries were encouraged to collect data at regular intervals (every 6 or 12 months). However, how the data collection occurred in each registry depended on their internal data governance and management. TREAT-NMD did not have authority or right to govern registries' internal process, although advice and support were provided to registries for regular data collections.

Data items with reference period time included the data collection period: begin and end dates, reported at each visit /data-collection. Begin date specified the beginning of the period to which the question refers; end date specified the end of the period to which the question refers.

The data collection period covered:

- The year before registry entry for the first visit
- The period between the last update (last visit) to the date of data entry (current visit).

Historical data was also collected by registries, notably for longitudinal data or when data entry was not at diagnosis. The date stamp in this case was the date when the clinical examination or test was done.

Certain events were collected by the registries over the data collection period as "currently", "previously" or "never" occurred over the period of interest. These events were then mapped by TREAT-NMD as:

- "Currently" when the event is current,
- "Previously when it has been previously the case, but is not currently
- "Never" when it has never been the case
- Sometime when it has been the case at some time, but it is unknown whether it is currently the case
- Not currently when it is currently not the case, but it is unknown whether it has previously been the case.

9.6. Bias

There are several limitations derived from the use of specific disease registries that may result in specific biases. First, participation and involvement in these registries is voluntary, and therefore, not all SMA patients treated or not treated might be included in this study. This may introduce a selection bias if certain subgroups of patients are routinely included in or excluded from the registry or if participation in the registries is differential depending on the patient socioeconomic status (e.g., if participation is higher among more economically advantaged patients), on the health system in place in the country or any other factor. Also, there is a potential for healthy user effect, where patients who participate and agree to be part of the registry may differ in their health-related behaviour, having a direct impact on their willingness to participate in the data collection.

Second, while registries offer a unique opportunity to compare patients on a given treatment to those untreated, the inability to determine accurately the treatment duration preceding the study entry point, introduces the potential of including some prevalent users of the treatments of interest. The extent to which our participants could have used any of the DMTs prior to registry entry is unknown. Nevertheless, there may be a potential for selection bias, where patients who had been on the treatment for a while have survived the early high-risk period for drug-related adverse reactions following treatment initiation. This is especially exacerbated in the context of missing the start date of treatment and being unable to determine the duration of treatment. However, given the descriptive nature of this study and the lack of formal safety and/or comparative effectiveness analysis, this bias is less of a concern.

Thirdly, registry information is collected by physicians or directly entered by patients. A form of information bias, surveillance bias, may be introduced if routine follow-up of patients is influenced by the treatment they receive. Therefore, if the administration differs between DMTs, if closer monitoring is required for some DMT-treated patients, or if monitoring has evolved over time or differs between countries, there is potential for surveillance bias. Delay for diagnosis may be longer for milder phenotypes (type 3 and 4) which may lead to an underestimation of the burden of disease for those phenotypes and delay initiation of new therapies, while there is consistent evidence of the benefit of early treatment (30). In addition, the diagnosis date is not directly captured within the TREAT-NMD GRP. As a result, the genetic report date was used as a proxy. However, some issues with this variable are worth noting. The assumption was made that the date that a genetic diagnosis was confirmed was the date of diagnosis. Indeed, patients might have entered a date from a hospital letter relating to their diagnosis, rather than the true genetic report date. It may also be a missing variable for some records. We do not know how many at present. As a side note, The TREAT-NMD GRP allows patients to provide multiple records for genetic diagnosis reports. In the case where multiple genetic report dates are given for a patient, the earliest genetic report date was used. This may result in an information bias where duration of diagnosis is underestimated.

In addition, historical data was reported at baseline registration. This data corresponded to events or measures occurring or collected in the patient file before entry to the registry. In this situation, the actual date of occurrence or examination was set prior to the date of registry entry. Historical longitudinal data such as growth or historical events were used when available. Please note that the registry entry date was derived for each patient based on reported event and date stamps. Therefore, it is difficult to estimate the extent to which historical data was used in these analyses.

9.7. Study Size

The study being descriptive by nature, all genetically confirmed SMA patients and available follow-up were used, without any formal sample size calculation. The overall number of patients across all SMA types eligible for inclusion was 2188, with 256 (11.7%) in Belgium, 348 (15.9%) in Czech Republic and

Slovakia, 697 (31.9%) in Germany and Austria, 319 (14.6%) in Spain, 393 (18.0%) in UK & Ireland and 175 (8.0%) in Sweden.

For the exploratory ITS analyses, the power to detect change in outcome trends is especially linked to the number of time points, as the power increases when the number of time points increases. At least 24 time points were recommended to have more than 80% power to detect intervention effects of 1.0 or greater (defined as the expected intervention effect over its standard deviation). All registries provided at least 48 months of data, however, available follow-up after DMT intake was limited. Thus, only Spinraza and Zolgensma were considered. Evrysdi was not considered, as it was not available until 2021-03-26; that did not give us the required number of quarters (8) to estimate post-DMT regression coefficients.

9.8. Data Transformation

Please refer to Part 9.5 of the report for a detailed view of the data transformation part.

9.9. Statistical Methods

Data analysis was based on the approved protocol, and a detailed statistical analysis plan (Appendix E1 - stand-alone document) and was conducted using R software by TREAT-NMD. Data of the registries from Belgium, Sweden, Czech Republic & Slovakia, Spain, and United Kingdom & Ireland were locally extracted with site-specific programs and shared with TREAT-NMD for central analysis. Data from Germany & Austria were extracted and analysed locally, and aggregated data was shared with TREAT-NMD. Data was formatted to a common structure to facilitate the analysis. Pooled analysis using patient-level data or aggregate data were performed when appropriate. Detailed methodology and analyses were described in the SAP. In absence of data access during protocol development, some analyses and definitions in the SAP were refined as required during the statistical analysis process. An SAP addendum has been provided in 9.9.7 and as part of the Appendix E (E2 - stand-alone document).

For descriptive analysis, mean, standard deviations, median and quartiles, minimum and maximum values were presented for continuous variables, and raw number and percentage of patients for categorical variables. Missing data for each variable was counted, overall, by registry, by SMA type as well as in patients with / without DMT. No imputation of missing data was performed as per the SAP. Loss to follow-up was also studied in the same groups of patients and numbers are presented in Table 8 for overall, treated, and never treated groups. To preserve patient confidentiality, cells with a number of patients or events below 5 were marked with asterisk (*).

Stratified and cross-analyses according to SMA types and other pre-specified subpopulations were performed overall and by registry: age at symptom onset, best functional status in never treated or before treatment, *SMN2* copy number, and best achieved milestone.

For each variable, analyses by registry were implemented in all registries where the variable was available, while overall analyses were implemented where the variable was available and considered of good quality. Please refer to the detailed feasibility assessment (Appendix D - stand-alone document) for more information on these variables.

Periods of analysis

Preliminary analyses aiming at assessing the heterogeneity of care management or reporting overtime within each registry and between participating registries were implemented in the ALL cohort, and over the whole period from start to end of data collection by calendar time.

SMA natural history and disease progression (including post-diagnosis outcomes of interest) were studied over the whole study period, according to the patients' current age (age of the patients when they

experienced the outcomes), in the NEVER TREATED cohort and the TREATED cohort, overall and stratified by DMTs.

To assess the SMA clinical management evolution by SMA type in the ALL cohort, calendar time was used. The use of DMT in the TREATED cohort was studied overall during the time when patients were exposed to the DMTs of interest.

On the contrary, ITS was assessed over periods before / after DMT availability according to the information provided by the registry regarding DMT availability. The date of issue of marketing authorization for Spinraza was 30/05/2017, for Zolgensma: 18/05/2020, and for Evrysdi: 26/03/202. The first day of the quarters following the Marketing Authorisation for each DMT was considered as the interruption point.
Incidence rates in patient-years of disease-related outcomes of interest / post-diagnosis outcomes and of SAESI were calculated according to the (whole) period at risk in the NEVER TREATED / TREATED cohorts. These incidence rates were further stratified by SMA type.

9.9.1. Main Summary Measures

9.9.1.1. Preliminary analyses: description of registry specificities in terms of SMA population capture

These descriptive analyses were done in the ALL cohort, overall, by registry, and by type of registries and displayed per SMA type. Please refer to Section 9.4.1 for a Table containing the final list of variables for this objective.

9.9.1.2. Description of SMA natural history and disease progression

SMA natural history, the disease, and its progression, were described in the NEVER TREATED and TREATED overall cohorts and displayed per SMA type. Please refer to Section 9.4.2 for a Table containing the final list of variables for this objective.

9.9.1.3 Description of SMA health care management

Health care management was described in the ALL cohort and DMTs pattern was described in the TREATED cohort and displayed per SMA type. Please refer to Section 9.4.3 for a Table containing the final list of variables for this objective.

9.9.1.4. Safety Analyses

Safety of selected individual DMTs was described in the TREATED cohort per DMTs (e.g., Spinraza/Zolgensma/Risdiplam or combination) presented as 1) crude incidence of patients with at least one adverse event (AE) / serious adverse event (SAE) reported in the registry in relation with Spinraza/Zolgensma/Risdiplam or a combination of these as well as 2) incidence rate of listed SAESI. The list of SAESI included the following:

- Thrombocytopenia and coagulation abnormalities
- Renal toxicity
- Hydrocephalus
- Meningitis
- Hypersensitivity reactions
- Cutaneous vasculitis

- Hepatotoxicity
- Cardiac adverse event

Other relevant comorbidities considered as event of interest were:

- Osteoporosis
- Fractures
- Pulmonary infections
- Sleep apnea
- Pneumothorax
- Atrial or ventricular defect
- Diabetes
- Vertebral fracture
- Non-vertebral fractures
- Bronchopulmonary infections
- Gastrostomy

ICD-10 codes used to identify these comorbidities and adverse events were detailed in the statistical analyses plan in Appendix E1.

9.9.1.5. Analysis of Effectiveness/Clinical Response

Due to the descriptive nature of the study, no formal comparative effectiveness analyses (e.g., no hypothesis testing) were performed. Nevertheless, in addition to the descriptive analysis, we further investigated trends in specific post-SMA diagnosis outcomes (e.g., ventilation, death, composite) with respect to the availability of DMTs using exploratory interrupted time series (ITS) analysis. ITS analysis is useful for investigating the effect of an intervention (here the introduction of DMTs) where randomisation is not suitable or possible. Statistical methods applicable for this objective are described in Section 9.9.2.4

9.9.1.6. Medical Resource Utilisation and Health Economics Analyses

Assessing medical resource utilisation and health economics analyses was beyond the scope of the objectives of this report.

9.9.2. Main Statistical Methods

9.9.2.1. Preliminary analyses: description of registry specificities in terms of SMA population capture

The preliminary analyses aimed to assess the heterogeneity of management of care or reporting over time within each registry and between registries. All indicators (as listed below) were stratified by registry and displayed by SMA type. Descriptive statistics were used to summarise the variables such as counts, means and medians as indicated for each indicator in the table. The study population were all patients (ALL cohort), across the entire study period. The indicators and their related variables are given in the table below.

Table 3. Indicators for Preliminary Analysis

ID	Description	Relevant columns in dataset	Time axis
1.01	Calendar year of registry entry (n, %)	Derived	No
1.02	Calendar year of death (n, %)	Date of death	No
1.03	Sex (n, %)	Sex	No
1.04	Class of age at symptom onset (n, %)	Derived from Symptom onset date	No
1.05	Best functional SMA status (n, %)	Derived from Motor ability	No
1.06	Best achieved motor milestone (n, %)	Motor ability	No
1.07	SMN1 gene mutation type (n, %)	SMN1 variant	No
1.08	Number of SMN2 copies (n, %)	SMN2 copy number	No
1.09	Methods used for genetic testing (n, %)	SMN1 testing method	No
1.10	Duration of follow up (from registry entry to death, end of data or loss to follow-up, in months) (mean, sd, median, IQR)	Derived	No
1.11	Duration of SMA (from onset of symptoms to death, end of data or loss to follow-up, in months) (mean, sd, median, IQR)	Derived	No
1.12	Duration between two consecutive visits collected in the registry (mean, sd, median, IQR)	Derived	No
1.13	Duration between genetic report date and registry entry (mean, sd, median, IQR)	Derived	No
1.14	Reason for genetic testing (n, %)	Screening	Calendar period
1.15	Age at onset of SMA symptoms (mean, sd, median, IQR)	Symptom onset date	Calendar period
1.16	Age at genetic report date (mean, sd, median, IQR)	Genetic report date	Calendar period
1.17	Age at registry entry (mean, sd, median, IQR)	Derived	Calendar period
1.18	Age at death (mean, sd, median, IQR)	Date of death	Calendar period
1.19	Lost to follow-up (n, %)	Derived	Calendar period
1.20	Treated with at least one DMT (n, %)	DMT	Calendar period
1.21	Treated with more than one DMT (n, %)	DMT	Calendar period
1.22	Treated with nusinersen (Spinraza®) (n, %)	DMT	Calendar period
1.23	Treated with Zolgensma (Zolgensma®) (n, %)	DMT	Calendar period
1.24	Treated with risdiplam (Evrysdi®) (n, %)	DMT	Calendar period

ID	Description	Relevant columns in dataset	Time axis
1.25	Invasive ventilation (n, %)	Invasive ventilation episode	Calendar period
1.26	Non-invasive ventilation (n, %)	Non-invasive ventilation episode	Calendar period
1.27	Feeding tube usage (n, %)	Feeding tube usage episode	Calendar period
1.28	Wheelchair usage (n, %)	Wheelchair usage episode	Calendar period
1.29	At least one reported measure by available motor function scale or test, and by at least one PRO (n, %)	Motor ability & PRO	Calendar period
1.30	At least three reported measure by available motor function scale or test, and by at least one PRO (n, %)	Motor ability & PRO	Calendar period
1.31	Available number of records of each motor function scale by patient (mean, sd, median, IQR)	Motor ability & PRO	Calendar period
1.32	Available number of records of each PRO by patients (mean, sd, median, IQR)	Motor ability & PRO	Calendar period

9.9.2.2. Description of SMA natural history and disease progression

SMA natural history, the disease and its progression, was described in the NEVER TREATED and TREATED overall cohorts and displayed per SMA. Statistics were summarised over the entire study period and displayed per SMA type. The results were also stratified in the following manner:

- DMT
- Class of age at symptom onset
- SMN2 copy number
- Functional status at age of symptom onset
- Achieved motor milestone at age of symptom onset

The indicators and their related variables are given in Table 4.

Table 4. Indicators for the SMA natural history and disease progression analysis

ID	Description	Relevant columns in dataset	Time axis
2.01	Sex (n, %)	Sex	None
2.02	Registry (n, %)	Metadata	None
2.03	Age at symptom onset (mean, sd)	Derived from Symptom onset date	None
2.04	Reason for genetic testing (n, %)	Screening	None
2.05	Method used for genetic testing (n, %)	SMN1 testing method	None
2.06	SMN1 variant (n, %)	SMN1 variant	None

ID	Description	Relevant columns in dataset	Time axis
2.07	Functional status at genetic report date (n, %)	Derived from Motor ability episode	None
2.08	Achieved motor milestone at genetic report date (n, %)	Motor ability episode	None
2.09	Best functional status (n, %)	Derived from Motor ability episode	None
2.10	Best achieved motor milestone (n, %)	Motor ability episode	None
2.11	Best functional status before treatment (n, %)	Derived from Motor ability episode	None
2.12	Best functional status after treatment (n, %)	Derived from Motor ability episode	None
2.13	Best achieved motor milestone before treatment (n, %)	Motor ability episode	None
2.14	Best achieved motor milestone after treatment (n, %)	Motor ability episode	None
2.15	Height (mean, sd)	Height	Current Age
2.16	Weight (mean, sd)	Weight	Current Age
2.17	Age at first acquisition of -the best any of the motor ability episodes (mean, sd)	Motor ability episode (early age record if multiple)	None
2.18	Age at first loss of the best any of the motor ability episodes (mean, sd)	Motor ability episode (early age record if multiple)	None
2.19	Full-time or part time wheelchair use (n, %)	Wheelchair usage frequency	Current Age
2.20	Age at first full-time or part-time wheelchair usage (mean, sd)	Wheelchair usage frequency	None
2.21	No contracture, one contracture, more than one contractures (n, %)	Combination of 8 contracture variables	Current Age
2.22	Score for CHOP-INTEND at genetic report date (mean, sd)	Motor Measures	None
2.23	Best score for CHOP-INTEND (mean, sd)	Motor Measures	None
2.24	Most recent score for CHOP-INTEND (mean, sd)	Motor Measures	Current Age
2.25	Score for HFMS(-E) at genetic report date (mean, sd)	Motor Measures	None
2.26	Best score for HFMS(-E) (mean, sd)	Motor Measures	None
2.27	Most recent score for HFMS(-E) (mean, sd)	Motor Measures	Current Age
2.28	Score for RULM at genetic report date (mean, sd)	Motor Measures	None
2.29	Best score for RULM (mean, sd)	Motor Measures	None
2.30	Most recent score for RULM (mean, sd)	Motor Measures	Current Age
2.31	Score for HINE-2 at genetic report date (mean, sd)	Motor Measures	None
2.32	Best score for HINE-2 (mean, sd)	Motor Measures	None
2.33	Most recent score for HINE-2 (mean, sd)	Motor Measures	Current Age
2.34	Score for MFM32 at genetic report date (mean, sd)	Motor Measures	None
2.35	Best score for MFM32 (mean, sd)	Motor Measures	None
2.36	Most recent score for MFM32 (mean, sd)	Motor Measures	Current Age
2.37	Score for 6MWT at genetic report date (mean, sd)	Motor Measures	None

ID	Description	Relevant columns in dataset	Time axis
2.38	Best score for 6MWT (mean, sd)	Motor Measures	None
2.39	Most recent score for 6MWT (mean, sd)	Motor Measures	Current Age
2.40	Change between scores in HFSM-E in consecutive age classes (mean, sd)	Transformation of Motor Measures	Current Age
2.41	Change between scores in RULM in consecutive age classes (mean, sd)	Transformation of Motor Measures	Current Age
2.42	Change between scores in 6MWT in consecutive age classes (mean, sd)	Transformation of Motor Measures	Current Age
2.43	Age at report of (first) best CHOP-INTEND score (mean, sd)	Motor Measures	None
2.44	Age at report of (first) best HFMS(-E) score (mean, sd)	Motor Measures	None
2.45	Age at report of (first) best RULM right side score (mean, sd)	Motor Measures	None
2.46	Age at report of (first) best HINE-2 score (mean, sd)	Motor Measures	None
2.47	Age at report of (first) best MFM32 score (mean, sd)	Motor Measures	None
2.48	Age at report of (first) 6MWT best score (mean, sd)	Motor Measures	None
2.49	Ever diagnosed with scoliosis (n, %)	Scoliosis Diagnosis	Current Age
2.50	Cobb angle value <30°, 30-45°, >45° (n, %)	Convert numeric cobb angle into categories	Current Age
2.51	At least one use of spinal brace ever (n, %)	Rehabilitative Interventions	None
2.52	Surgery for scoliosis (n, %)	Scoliosis surgery performed	Current Age
2.53	Age at surgery for scoliosis (mean, sd)	Transformation of Scoliosis Surgery Date	None
2.54	Annual number of vertebral fracture by patient reported in cause of hospitalisation or as a comorbidity (mean, sd)	Hospitalisation acute reason code	None
2.55	Annual number of non-vertebral fractures by patient reported in cause of hospitalisation or as a comorbidity (mean, sd)	Hospitalisation acute reason code	None
2.56	Age at first reported vertebral fracture (mean, sd)	Hospitalisation acute reason code	None
2.57	Forced vital capacity percent (mean, sd)	Forced vital capacity percentage	Current Age
2.58	Forced vital capacity volume (n, %)	Forced vital capacity volume	Current Age
2.59	At least one episode of airway clearance assistance (n, %)	Airway Clearance Assistance	Current Age
2.60	At least one episode of any non-invasive ventilation (n, %)	Non-invasive ventilation episode	Current Age
2.61	At least one episode of full-time non-invasive ventilation (n, %)	Non-invasive ventilation episode	Current Age
2.62	At least one episode of part-time awake and sleeping non-invasive ventilation (n, %)	Non-invasive ventilation episode	Current Age
2.63	At least one episode of part-time sleeping non-invasive ventilation (n, %)	Non-invasive ventilation episode	Current Age
2.64	Age at start of first full-time non-invasive ventilation episode (mean, sd)	Non-invasive ventilation episode	None
2.65	At least one episode of any invasive ventilation (n, %)	Invasive ventilation episode	Current Age
2.66	At least one episode of full-time invasive ventilation (n, %)	Invasive ventilation episode	Current Age

ID	Description	Relevant columns in dataset	Time axis
2.67	At least one episode of part-time awake and sleeping invasive ventilation (n, %)	Invasive ventilation episode	Current Age
2.68	At least one episode of part-time sleeping invasive ventilation (n, %)	Invasive ventilation episode	Current Age
2.69	Age at start of first full-time invasive ventilation episode (mean, sd)	Invasive ventilation episode	None
2.70	PBronchopulmonary infections reported in cause of hospitalisation or as a comorbidity (n, %)	Hospitalisation acute reason code	Current Age
2.71	At least one episode of respiratory physiotherapy (n, %)	Rehabilitative Interventions	None
2.72	At least one episode of feeding tube usage (n, %)	Feeding tube usage episode	Current Age
2.73	At least one episode of exclusive feeding tube usage (n, %)	Feeding tube usage episode	Current Age
2.74	At least one episode of supplementary feeding tube usage (n, %)	Feeding tube usage episode	Current Age
2.75	At least one gastrostomy reported in cause of hospitalisation or as a comorbidity (n, %)	Hospitalisation acute reason code	Current Age
2.76	Age at first gastrostomy (mean, sd)	Hospitalisation admission date	None
2.77	At least one hospitalisation (n, %)	Hospitalisation admission date	Current Age
2.78	Annual number of hospitalisations (mean, sd)	Hospitalisation admission date	None
2.79	Event-free survival (death or permanent ventilation) (mean, sd)	Date of death or first full-time invasive ventilation or full-time non-invasive ventilation	None
2.80	Causes of death (n, %)	Cause of death code	None
2.81	Causes of hospitalisation (n, %)	Hospitalisation acute reason code	None
2.82	Incidence rate of each listed comorbidity	Comorbidity code	None
2.83	Score for Spain PROFuture Mobility and Independence PRO at genetic report date (mean, sd)	Patient-reported outcome measures	None
2.84	Best score for Spain PROFuture Mobility and Independence PRO (mean, sd)	Patient-reported outcome measures	None
2.85	Most recent score for Spain PROFuture Mobility and Independence PRO (mean, sd)	Patient-reported outcome measures	Current Age
2.86	Score for Belgium ACTIVLIM PRO at genetic report date (mean, sd)	Patient-reported outcome measures	None
2.87	Best score for Belgium ACTIVLIM PRO (mean, sd)	Patient-reported outcome measures	None
2.88	Most recent score for Belgium ACTIVLIM PRO (mean, sd)	Patient-reported outcome measures	Current Age

9.9.2.3. Description of healthcare management

Descriptive statistics of SMA diagnosis, healthcare management and its evolution over time were studied in the ALL cohort and displayed per SMA. The DMTs pattern was described in the TREATED cohort, and displayed per SMA type, across the entire period and in the Calendar Period. The analysis in this section was also stratified in the following manner.

- Registry
- SMN2 copy number
- Functional status at age of symptom onset

The indicators and their related variables are given in Table 5. Note that the population for this analysis varied between indicators.

Table 5. Indicators for SMA healthcare management over time analysis

ID	Population	Description	Relevant columns in dataset	Time axis
3.01	All	SMN1 testing method (n, %)	SMN1 testing method	Calendar period
3.02	All	SMN2 testing method (n, %)	SMN2 copy number testing method	Calendar period
3.03	All	At least one DMT (n, %)	DMT	Calendar period
3.04	All	Taken the drugs listed as comedications at least once from registry entry (n, %)	Allopathic drug	Calendar period
3.05	All	Annual influenza vaccination (n, %)	Allopathic drug	Calendar period
3.06	All	At least one pneumococcal vaccination (n, %)	Allopathic drug	Calendar period
3.07	All	Pneumococcal vaccination at least once every 5 years (n, %)	Allopathic drug	None
3.08	All	At least one episode of any ventilation (n, %)	Invasive ventilation episode or Non-invasive ventilation episode	Calendar period
3.09	All	At least one episode of feeding tube usage (n, %)	Feeding tube usage episode	Calendar period
3.10	All	At least one episode of wheelchair use (n, %)	Wheelchair usage episode	Calendar period
3.11	All	Age at first episode of any ventilation (invasive or non-invasive) (mean, sd, median, IQR)	Invasive ventilation episode or Non-invasive ventilation episode	Calendar period
3.12	All	Age at first episode of invasive ventilation (mean, sd, median, IQR)	Invasive ventilation episode	Calendar period
3.13	All	Age at first episode of feeding tube usage (mean, sd, median, IQR)	Feeding tube usage episode	Calendar period
3.14	All	Age at first episode of gastrostomy(mean, sd, median, IQR)	Hospitalisation acute reason code	None
3.15	All	At least one episode of muscular physiotherapy ever (n, %)	Rehabilitative Interventions	None
3.16	All	At least one episode of respiratory physiotherapy ever (n, %)	Rehabilitative Interventions	None

ID	Population	Description	Relevant columns in dataset	Time axis
3.17	All	At least one episode of contracture management using orthotics ever (n, %)	Rehabilitative Interventions	None
3.18	All	At least one episode of spinal brace ever (n, %)	Rehabilitative Interventions	None
3.19	All	At least one episode of speech therapy ever (n, %)	Rehabilitative Interventions	None
3.20	Treated	Age at first DMT (mean, sd)	DMT	Calendar period
3.21	Treated	Patients who received more than one DMT (n,%)	DMT	Calendar period
3.22	Treated	Treated with nusinersen (Spinraza®) (n, %)	DMT	Calendar period
3.23	Treated	Treated with Zolgensma (Zolgensma®) (n, %)	DMT	Calendar period
3.24	Treated	Treated with risdiplam (Evrysdi®) (n, %)	DMT	Calendar period
3.25	Treated	Treated with nusinersen (Spinraza®) & Zolgensma (Zolgensma®) (n, %)	DMT	Calendar period
3.26	Treated	Treated with nusinersen (Spinraza®) & risdiplam (Evrysdi®) (n, %)	DMT	Calendar period
3.27	Treated	Treated with Zolgensma (Zolgensma®) & risdiplam (Evrysdi®) (n, %)	DMT	Calendar period
3.28	Treated	Treated with nusinersen (Spinraza®) & Zolgensma (Zolgensma®) & risdiplam (Evrysdi®) (n, %)	DMT	Calendar period
3.29	Treated	Age at initiation of nusinersen (Spinraza®) (mean, sd, median, IQR)	DMT	Calendar period
3.30	Treated	Age at initiation of Zolgensma (Zolgensma®) (mean, sd, median, IQR)	DMT	Calendar period
3.31	Treated	Age at initiation of risdiplam (Evrysdi®) (mean, sd)	DMT	Calendar period
3.32	Zolgensma (Zolgensma®)	Adequate dose regarding weight at administration (n, %)	DMT dosage value	Calendar period
3.33	Zolgensma (Zolgensma®)	Co-administration of corticosteroids (n, %)	DMT corticosteroid administration duration > 0	Calendar period
3.34	Zolgensma (Zolgensma®)	Anti-AAV9 antibody test before Zolgensam administration (n, %)	Anti-AAV9 antibody test date & DMT single administration date	Calendar period
3.35	Zolgensma (Zolgensma®)	Positive (>1:50) anti-AAV9 antibody test (n, %)	Anti AAV9 antibody test result	Calendar period
3.36	nusinersen (Spinraza®)	At least one adequate dose (12mg) (n, %)	DMT dosage value	Calendar period
3.37	nusinersen (Spinraza®)	Time between genetic report date and first administration (D0) (mean, sd)	DMT administration schedule deviation	None

ID	Population	Description	Relevant columns in dataset	Time axis
3.38	nusinersen (Spinraza®)	Treatment duration defined as the time from initiation to last available administration date (discontinuation date, death, loss to follow-up, date of data-extraction if the last information indicates that nusinersen (Spinraza®) is ongoing) (mean, sd, median, IQR)	DMT episode	Calendar period
3.39	nusinersen (Spinraza®)	Ongoing nusinersen (Spinraza®) at their last reported dose (n, %)	DMT episode	Calendar period
3.40	nusinersen (Spinraza®)	Treatment discontinuation (n, %)	DMT episode	Calendar period
3.41	nusinersen (Spinraza®)	Reason for treatment discontinuation (n, %)	DMT stopping reason	Calendar period
3.42	nusinersen (Spinraza®)	Treatment duration in patients with treatment discontinuation (mean, sd)	DMT episode	Calendar period
3.43	risdiplam (Evrysdi®)	At least one adequate dose regarding age and weight (n, %)	DMT dosage value	Calendar period
3.44	risdiplam (Evrysdi®)	Treatment duration defined as the time from initiation to last available administration date (discontinuation date, death, loss to follow-up, date of data-extraction if the last information indicates that risdiplam (Evrysdi®) is ongoing) (mean, sd, median, IQR)	DMT episode	Calendar period
3.45	risdiplam (Evrysdi®)	Ongoing risdiplam (Evrysdi®) at their last reported dose (n, %)	DMT episode	Calendar period
3.46	risdiplam (Evrysdi®)	Treatment discontinuation (n, %)	DMT episode	Calendar period
3.47	risdiplam (Evrysdi®)	Reason for treatment discontinuation (n, %)	DMT stopping reason	Calendar period
3.48	risdiplam (Evrysdi®)	Treatment duration in patients with treatment discontinuation (mean, sd)	DMT episode	Calendar period
3.49	Treated	At least one SAE reported in the registry related to any DMT (n, %)	Hospitalisation SAE or Comorbidity SAE	Calendar period
3.50	nusinersen (Spinraza®)	At least one SAE reported in the registry related to nusinersen (Spinraza®) (n, %)	Hospitalisation SAE or Comorbidity SAE	Calendar period
3.51	Zolgensma (Zolgensma®)	At least one SAE reported in the registry related to Zolgensma (Zolgensma®) (n, %)	Hospitalisation SAE or Comorbidity SAE	Calendar period
3.52	risdiplam (Evrysdi®)	At least one SAE reported in the registry related to risdiplam (Evrysdi®) (n, %)	Hospitalisation SAE or Comorbidity SAE	Calendar period
3.53	Treated	Incidence rate of listed SAESI	Hospitalisation acute reason code matches defined ICD-10 list	Calendar period

9.9.2.4. Exploratory analyses: Interrupted time series analysis

In addition to the descriptive analysis, we further investigated trends in post-SMA diagnosis outcomes (death, full-time ventilation, and the composite outcome of the two) with respect to the availability of DMTs using exploratory interrupted time series (ITS) analysis. The main goal was to see if the underlying patterns in the number of events per quarter changed after the introduction of DMT.

The three outcomes (death, having used full-time ventilation or a composite outcome) were analysed separately - no efforts to model dependence between the three outcomes was made.

Although the data was available by months, the outcomes were aggregated and analysed by quarter. Quarterly analysis was chosen as it provided a good trade-off between maximising sample size per observation, whilst providing enough unique time points post-interruption to fit the model correctly. The calendar quarters run with Q1 starting in January and Q4 ending in December. ITS required a minimum of 8 observations (7) before and after the intervention to have sufficient power to estimate the regression coefficients.

Population of interest: For each analysis, the population included all patients (regardless of treatment), who have SMA type 1 or 2. By restricting the population to patients with the most severe type of SMA, we ensured that the underlying populations being compared shared similar characteristics. Moreover, given the severity of these two types of SMA, we also assumed that uptake of newly available therapy options would be rapid post-market approval.

Interruption points definition: For each outcome, two interruption points were considered, relating to the EU marketing authorisation dates for Spinraza® and Zolgensma®. On the other hand, since Evrysdi® was only recently authorised (March 2021), there were not enough observation points post-intervention to consider this interruption point. For Spinraza and Zolgensma, the interruption points were chosen at the start of the next quarter following the market authorisation. For example, Spinraza® was authorised at the end of May 2017, and the considered interruption point was 01/07/2017 (the start of the next quarter.) The market authorisation dates, and related interruption points are detailed in Table 6 below. The use of a single intervention point of the EU market authorisation, rather than considering the availability of DMTs per country of registry separately was necessary. A multiple baseline ITS approach was initially considered, allowing the interruption to vary across registries. However, due to the possible different rollout lag times across registries and the potential complications of COVID-19, it was decided to not allow different interruption points for different registries. Instead, the same, real, calendar time point for all registries was applied.

Table 6. Market authorisation dates for DMTs and interruption time point considered

DMT	Date of issue of marketing authorisation valid throughout the European Union	Interruption point
Spinraza®	30/05/2017	01/07/2017
Zolgensma®	18/05/2020	01/07/2020
Evrysdsi®	26/03/2021	NA

Statistical models: A Poisson GLM with log link function was used to model the rates of the occurrence of each of the specified outcomes. Poisson model was used as this is the classic choice for count data with the base R function glm() to fit the models. For each of the three outcomes, the linear predictor was of the form:

$$\log(\mu(t)) = \eta(t) = \beta_0 + \beta_1 t + (\beta_3 + \beta_4 t) \times I(t > t')$$

In this function, the $\mu(t)$ represented the expected number of events at time t, β terms were unknown coefficients, t' was the interruption point and $I(t > t')$ was an indicator function returning 1 whenever $t > t'$ and 0 otherwise; $\mu(t)$ could be interpreted as the expected number of patients who died/ventilated/both in each quarter.

To ensure model adequacy, various checks and more advanced models (Negative Binomial GLM, Poisson GLM with zero inflation and INGARCH(1, 1) with quarter, DMT intervention and a corresponding interaction term as covariates) were performed to assess the appropriateness of the Poisson ITS model. The checks were also performed to ensure that the choice of the linear predictor was appropriate.

9.9.5. Missing Values

Missing data, being informative on registry completeness, were reported as counts and proportions in descriptive analyses for each relevant variable. Missing data for each variable was counted, overall, by registry, by SMA type as well as in patients with / without DMT. No imputation of missing data was done, as planned.

9.9.6. Sensitivity Analyses

No sensitivity analyses were performed for this descriptive study.

9.9.7. Amendments to the Statistical Analysis Plan

In absence of data access during protocol development, some analyses and definitions in the SAP were refined as required during the statistical analysis process. An SAP addendum has been provided as part of the Appendix E-2.

9.10. Quality control

Quality control was applied throughout the whole process: at registry level, centrally by TREAT-NMD, and at the analytical level. At the registry level, all participating registries applied specific processes and quality standards to assess, control and check the origin and quality of their data. Before data was transferred to TREAT-NMD, the curator of the registry had the responsibility to check all safety reporting instances for accuracy, any validation flags raised by the system. At the central level, all data was collected via the TREAT-NMD Global Registry Platform (GRP). TREAT-NMD applied processes to ensure quality of data stored in their central data warehouse (CDW) ready for analysis. The system had automated validation built into its functionality to ensure that any fields that have missing data, open query were checked, and additional checks were performed by the data-analyst.

All data analyses were performed by Jumping River, on behalf of TREAT-NMD, using the R programming language, version 4.2. All scripts were stored on gitlab.com under the Jumping Rivers account and mirrored to the TreatNMD Git server. No user was able to push to the main branch directly. All code merged into the main branch required two approvals from other developers. All developer roles were detailed in the CODEOWNERS file.

The {renv} framework was used to fully specify the R packages (with associated version numbers) to ensure future reproducibility. A continuous integration process was launched when the code was committed to the Git repository. This used the packages specified via {renv}, a docker image and a dummy but representative data set to test the code. Code that was merged into the main branch passed this continuous integration step.

In addition to code reproducibility, we enforced code style and documentation via the {lintr} package.

Key git commits were tagged to allow for code versioning.

10. RESULTS

Overall, four main analyses (Table 7) were planned and conducted: three descriptive summaries and one exploratory analysis. Three main cohorts were studied:

- Overall cohort of all patients (ALL): to study the SMA care management overtime and differences across European countries/registries
- Never treated patients (NEVER TREATED): to study the natural history of SMA
- All treated patients (TREATED): to study the natural history of SMA and to describe the pattern of DMTs use since their availability on the market.

For each main cohort, results in the tables have been displayed per SMA type.

The results have also been provided by a number of sub-groups. It is to be noted that the results from such sub-groups encountered issues due to the low/ very low number of patients in strata, making it difficult to interpret and draw conclusions. Nevertheless, sub-groups results have been presented in Appendix G (stand-alone document)

Table 7. Main cohorts and sub-groups according to the objectives, at a glance

Analysis	Main cohorts and sub-groups
Preliminary analysis	● Main cohort: ALL, displayed per SMA type ● Sub-groups from ALL: ○ Per registry, displayed per SMA type
SMA natural history and disease progression (Objective 1)	● Main cohorts: ○ NEVER TREATED, displayed per SMA type ○ TREATED, displayed per SMA type ● Sub-groups from TREATED and NEVER TREATED: ○ per DMT, displayed per SMA type ○ per Class of age at symptom onset ○ per SMN2 copy number ○ per Functional status at age of symptom onset ○ per Achieved motor milestone at age of symptom onset
Description of SMA healthcare management over time (Objective 2)	● Main cohort: ALL, displayed per SMA type ● Sub-groups from ALL: ○ per SMN2 copy number

Analysis	Main cohorts and sub-groups
	○ per Functional status at age of symptom onset
Exploratory Analysis	NA (ITS model based on before/after DMT start date)

10.1. Participants

Table 8. Distribution of ALL patients, the TREATED and NEVER TREATED patients

	ALL (N = 2188)	TREATED (N = 1321) *	NEVER TREATED (N = 847)
Registry n (%)			
Belgium	256 (11.7)	202 (15.3)	54 (6.4)
Czech Republic & Slovakia	348 (15.9)	269 (20.4)	79 (9.3)
Germany & Austria	697 (31.9)	302 (22.9)	380 (44.9)
Spain	319 (14.6)	262 (19.8)	57 (6.7)
UK & Ireland	393 (20.0)	170 (12.9)	218 (25.7)
Sweden	175 (8.0)	116 (8.8)	59 (7.0)
Sex			
female / male (%)	48.4 / 51.6	48.3 / 51.7	48.6 / 51.4
SMA type n (%)			
SMA Type 1	432 (19.7)	276 (20.9)	154 (18.2)
SMA Type 2	914 (41.8)	540 (40.9)	361 (42.6)
SMA Type 3	779 (35.6)	476 (36.0)	299 (35.3)
SMA Type 4	22 (1.0)	9 (0.7)	13 (1.5)
SMA Type missing	26 (1.2)	9 (0.7)	16 (1.8)
SMA type other	7 (0.3)	4 (0.3)	3 (0.4)
SMA Type presymptomatic	8 (0.4)	7 (0.5)	1 (0.1)
DMTs**			
Patients treated with at least one	1321 (60.4)*	1321* (100)	NA

DMT (n, %)			
Patients treated at least once with Spinraza (n, %)	1003 (45.8)	1003 (75.9)	NA
Patients treated at least once with Zolgensma (n, %)	101 (4.6)	101 (7.6)	NA
Patients treated at least once with Evrysdi (n, %)	403 (18.5)	403 (30.5)	NA
Patients treated with more than one DMTs (n, %)	186 (8.5)	186 (14.1)	NA
Patients who discontinued treatment (n, %)	NA	(226, 16.9)	NA
Patients who died (n, %)	(37, 1.7)	(11, 0.8)	(26, 3.1)
Patients lost to follow-up (n, %)	(535, 24.5)	(66, 5.0)	(469, 55.4)

*1321 patients have been considered as **TREATED with at least one DMT** and with no missing DMT intake start date (of note, 20 patients have been excluded as DMT intake start date was not available).

**As exposure was assigned based on a time-varying exposure approach, the patients could contribute to more than one exposure category

The three clinician-based registries (Belgium, Czech Republic & Slovakia and Sweden,) contained 779 patients and the 3 patient-based registries (Germany & Austria, Spain, UK & Ireland) 1409 patients. Patients with SMA 1 (19.7%), SMA 2 (41.8%) and SMA 3 (35.6%) were the most observed and 61.3% of patients have been treated with at least one DMT out of which over half were treated with Spinraza (45.8%).

Of note, 24.5% of patients have been lost to follow-up with 55.4% of never treated patients and 5.0% among treated patients.

10.2. Descriptive data

Please refer to the “10.4 main descriptive results” section for the overall summary of results for each objective.

10.3. Outcome data

Please refer to the “10.4 main descriptive results” section for the overall summary of results for each objective.

10.4. Main descriptive results

10.4.1. Preliminary analyses: description of registry specificities in terms of SMA population capture

Please note that all results are available in a stand-alone document - Appendix G (“Objective 0 (Preliminary) Results 2024_03_13”), submitted along with this report.

All Cohort (N=2188)

Cohort ALL was used to assess the ability of registries to capture and report SMA management (Table 10).

A total of 2188 patients met the study eligibility criteria. Out of these, 432 patients were classified as SMA type 1 (19.7%), 914 patients were classified as SMA type 2 (41.8%), 779 as SMA type 3 (35.6%), 22 as SMA type 4 (1.0%), 7 (0.3%) as SMA type Other, 8 (0.4%) as SMA type Presymptomatic, and 26 (1.2%) had an SMA type missing.

Table 9: Description of ALL cohort per SMA 1, SMA 2 and SMA 3

	ALL (N=2188)	SMA Type 1 (N=432)	SMA Type 2 (N=914)	SMA Type 3 (N=779)
Calendar year of registry entry; n (%)				
2008	27 (1.2%)	6 (1.4%)	14 (1.5%)	5 (0.6%)
2009	23 (1.1%)	5 (1.2%)	9 (1.0%)	8 (1.0%)
2010	41 (1.9%)	*	25 (2.7%)	10 (1.3%)
2011	59 (2.7%)	14 (3.2%)	20 (2.2%)	24 (3.1%)
2012	147 (6.7%)	21 (4.9%)	64 (7.0%)	62 (8.0%)
2013	101 (4.6%)	15 (3.5%)	49 (5.4%)	37 (4.7%)
2014	203 (9.3%)	32 (7.4%)	88 (9.6%)	83 (10.7%)
2015	187 (8.5%)	29 (6.7%)	89 (9.7%)	67 (8.6%)
2016	136 (6.2%)	43 (10.0%)	55 (6.0%)	37 (4.7%)
2017	199 (9.1%)	36 (8.3%)	90 (9.8%)	72 (9.2%)
2018	428 (19.6%)	75 (17.4%)	188 (20.6%)	157 (20.2%)
2019	193 (8.8%)	48 (11.1%)	66 (7.2%)	70 (9.0%)
2020	150 (6.9%)	32 (7.4%)	69 (7.5%)	46 (5.9%)
2021	114 (5.2%)	25 (5.8%)	33 (3.6%)	48 (6.2%)
2022	121 (5.5%)	33 (7.6%)	37 (4.0%)	36 (4.6%)
2023	43 (2.0%)	7 (1.6%)	15 (1.6%)	15 (1.9%)
Missing	16 (0.7%)	7 (1.6%)	*	*
Sex; n (%)				
Female	1059 (48.4%)	206 (47.7%)	457 (50.0%)	367 (47.1%)
Male	1129 (51.6%)	226 (52.3%)	457 (50.0%)	412 (52.9%)
Class of age at symptom onset; n (%)				
Presymptomatic	8 (0.4%)	-	-	-
Prenatal	6 (0.3%)	*	*	-
< 1 month	32 (1.5%)	22 (5.1%)	*	5 (0.6%)
[1 - 3 months)	111 (5.1%)	102 (23.6%)	7 (0.8%)	*
[3 - 6 months)	146 (6.7%)	108 (25.0%)	36 (3.9%)	*
[6 - 18 months)	645 (29.5%)	47 (10.9%)	500 (54.7%)	95 (12.2%)
[1.5 - 2 years)	116 (5.3%)	*	47 (5.1%)	68 (8.7%)
[2 - 6 years)	254 (11.6%)	-	18 (2.0%)	236 (30.3%)
[6 - 11 years)	59 (2.7%)	-	*	54 (6.9%)
[11 - 18 years)	102 (4.7%)	*	*	94 (12.1%)
18 years +	30 (1.4%)	-	-	16 (2.1%)
Missing	679 (31.0%)	148 (34.3%)	296 (32.4%)	208 (26.7%)
Duration of follow up (months)				
Mean (SD)	70.9 (38.4)	59.2 (33.2)	76.4 (38.4)	73.1 (38.6)
Missing; n (%)	16 (0.7%)	7 (1.6%)	*	*

Duration of SMA (months)				
Mean (SD)	252.1 (195.8)	90.1 (78)	240 (166.6)	343.1 (210.2)
Missing; n (%)	699 (31.9%)	153 (35.4%)	299 (32.7%)	210 (27.0%)
Number of SMN2 copies; n (%)				
0	15 (0.7%)	*	7 (0.8%)	6 (0.8%)
1	10 (0.5%)	*	*	*
2	321 (14.7%)	235 (54.4%)	52 (5.7%)	29 (3.7%)
3	800 (36.6%)	85 (19.7%)	479 (52.4%)	223 (28.6%)
4	251 (11.5%)	-	30 (3.3%)	208 (26.7%)
>4	10 (0.5%)	*	*	7 (0.9%)
Other	52 (2.4%)	*	*	39 (5.0%)
Missing	729 (33.3%)	105 (24.3%)	337 (36.9%)	263 (33.8%)
Methods used for genetic testing; n (%)				
DNA Sequencing	-	-	*	-
HRM	-	-	-	*
MLPA	527 (24.1%)	88 (20.4%)	195 (21.3%)	215 (27.6%)
RFLP	5 (0.2%)	-	5 (0.5%)	-
ddPCR	*	-	*	*
qRT-PCR	25 (1.1%)	*	7 (0.8%)	13 (1.7%)
Missing	1625 (74.3%)	340 (78.7%)	705 (77.1%)	547 (70.2%)

With respect to the **calendar year of registry entry**, the highest percentage of patients entered in 2018, 19.6% of the overall population (of note: 2018 corresponded to the start of data collection in Belgium - 190 Belgium patients (74%) entered in the Belgium registry in 2018 - and it is also the year when TREAT-NMD expanded the SMA V1 core dataset in September 2018, and Spinraza was approved in 2017). Between 2008-2011, only a few patients entered the registry data collection with <3% for each year across SMA types. For the other years, entry into the registries were similar with % ranging from 4.6 to 9.3% for the overall population of patients.

Overall, there was an equal split across **male** (51.6%) and **female** (48.4%), with the distribution being consistent across SMA types.

The most frequent **age at symptom onset** was 6-18 months across all SMA types, driven by SMA type 2 which mostly manifest symptoms at this age (54.7%). SMA type 1 was symptomatic earlier between 1-3 months and 3-6 months (23.6% and 25.0%) while SMA type 3 was symptomatic later, between 2-6 years 30.3%. Overall, close to one third of patients had missing values recorded for this variable, with the % being consistent across SMA types.

The longest **duration of follow-up** was for SMA type 2 and 3 with a mean of 76.4 months (SD=38.4) and 73.1 (SD=38.6); SMA type 4 had a duration of only 41.8 (SD=18.7) months; the variable was well recorded with only 0.7% missing.

Mean duration of SMA by type: SMA type 1 and 2 had mean durations of 90.1 and 240 months, respectively. SMA type 3 and 4 had the longest durations, with 343.1 and 319.9 months, respectively; with an overall % of missingness around 31.9% across all SMA types.

The overall mean **duration between genetic report dates and registry entry** was 72.8 months (SD=94), with SMA type 1 having a shorter duration: mean of 22.6 (SD=50.7). Again, there was 26% missingness for this variable.

Best functional SMA status is reported with 34.5% of missing value, from 25.9% in SMA type 3 to 51.6% in SMA type 1. In SMA type 1, 15.7% were non-sitters, 25% were sitters, and 7.6% were walkers. Among SMA type 2: the majority were sitters (44.7%) with 17.6% being able to walk. SMA type 3, more than half were able to walk (68.7%), with that percentage increasing for SMA type 4. For the **best achieved motor milestone**: overall, 34.5% had missing data with the highest percentage of missingness across SMA type 1. SMA type 3 and SMA type 4 had high numbers of patients who were able to climb stairs (49.4% and 63.6% respectively). For SMA type 1, 18.8% were able to sit without support, with this number being higher for SMA type 2 (27.9%).

Regarding the **number of SMN2 copies**, SMA type 1: 54.4% had 2 copies, SMA type 2: 52.4% had 3 copies, SMA type 3: 28.6% had 3 copies and 26.7% had 4 copies. The **method used for genetic testing** was mostly not reported/missing with 74.3% missingness across all SMA types. When reported, the primary method was MLPA: 24.1% overall and 20.4% -45.5% across SMA subtypes.

DMT usage started in 2017 with 12.2% of patients treated with at least one DMT and steadily increased over the years to peak at 68.4% in 2021. Of note, very few patients, 2.2.%, received some treatments in 2014-2016, before approval, only as part of clinical trials.

Treatment with **Spinraza** started in 2017 (11.7%) and steadily increased across calendar periods, with the highest proportion of patients treated with Spinraza in 2021 (51.1%). Patients with SMA type 1 had the highest percentages of patients treated with Spinraza. Overall, treatment with **Zolgensma** was less common across calendar periods, with the highest % observed in 2022 (5.9%). Patients with SMA type 1 had the highest proportion treated with Zolgensma than patients with SMA type 2 and 3. Treatment with **Evrysdi** was observed beginning in 2017 (i.e., clinical trials) and the overall usage was less common, with the highest percentage observed in 2022 (23.0%). Evrysdi was relatively more common among SMA type 2 patients, with the highest percentage observed in 2022 (28.1%).

Overall, approximately 9% of patients reported using **feeding tubes** and proportion of patients receiving feeding tube usage in the SMA type 1 was highest, i.e., approximately 40% and was fairly consistent across the calendar periods. More than 50% of overall patients had at least one episode of **wheelchair use**, with this trend being consistent across SMA types.

Quality of life (QoL) using patient-reported outcomes (PROs) were available in Spain (i.e., PROFuture Mobility and Independence PRO) and in Belgium (i.e., ACTIVLIM PRO). On average, patients across SMA types had approximately one available record of PRO for each patient.

ALL cohort per registry

Table 10: Description of ALL cohort per registry

	ALL (N=2188)	Belgium (N=256)	Czech republic & Slovakia (N=348)	Germany & Austria (N=697)	Spain (N=319)	UK & Ireland (N=393)	Sweden (N=175)
Calendar year of registry entry; n (%)							
2008	27 (1.2%)	-	-	*	-	23 (5.9%)	-
2009	23 (1.1%)	-	-	13 (1.9%)	-	10 (2.5%)	-
2010	41 (1.9%)	-	-	8 (1.1%)	-	*	29 (16.6%)
2011	59 (2.7%)	-	12 (3.4%)	11 (1.6%)	-	7 (1.8%)	29 (16.6%)
2012	147 (6.7%)	-	22 (6.3%)	117 (16.8%)	-	*	6 (3.4%)
2013	101 (4.6%)	-	10 (2.9%)	83 (11.9%)	-	*	7 (4.0%)

2014	203 (9.3%)	-	16 (4.6%)	123 (17.6%)	-	48 (12.2%)	16 (9.1%)
2015	187 (8.5%)	-	16 (4.6%)	75 (10.8%)	7 (2.2%)	85 (21.6%)	*
2016	136 (6.2%)	-	16 (4.6%)	51 (7.3%)	25 (7.8%)	36 (9.2%)	8 (4.6%)
2017	199 (9.1%)	-	23 (6.6%)	68 (9.8%)	80 (25.1%)	21 (5.3%)	7 (4.0%)
2018	428 (19.6%)	190 (74.2%)	47 (13.5%)	55 (7.9%)	85 (26.6%)	33 (8.4%)	18 (10.3%)
2019	193 (8.8%)	38 (14.8%)	31 (8.9%)	36 (5.2%)	44 (13.8%)	24 (6.1%)	20 (11.4%)
2020	150 (6.9%)	15 (5.9%)	60 (17.2%)	24 (3.4%)	33 (10.3%)	9 (2.3%)	9 (5.1%)
2021	114 (5.2%)	11 (4.3%)	47 (13.5%)	13 (1.9%)	20 (6.3%)	11 (2.8%)	12 (6.9%)
2022	121 (5.5%)	-	34 (9.8%)	12 (1.7%)	21 (6.6%)	46 (11.7%)	8 (4.6%)
2023	43 (2.0%)	-	*	*	*	31 (7.9%)	*
Missing	16 (0.7%)	*	10 (2.9%)	*	-	*	*
Sex; n (%)							
Female	1059 (48.4%)	129 (50.4%)	176 (50.6%)	341 (48.9%)	145 (45.5%)	179 (45.5%)	89 (50.9%)
Male	1129 (51.6%)	127 (49.6%)	172 (49.4%)	356 (51.1%)	174 (54.5%)	214 (54.5%)	86 (49.1%)
Class of age at symptom onset; n (%)							
Presymptomatic	8 (0.4%)	-	6 (1.7%)	*	-	*	-
Prenatal	6 (0.3%)	*	-	*	-	*	-
< 1 month	32 (1.5%)	*	6 (1.7%)	10 (1.4%)	7 (2.2%)	5 (1.3%)	*
[1 - 3 months)	111 (5.1%)	13 (5.1%)	34 (9.8%)	14 (2.0%)	30 (9.4%)	7 (1.8%)	13 (7.4%)
[3 - 6 months)	146 (6.7%)	20 (7.8%)	38 (10.9%)	24 (3.4%)	31 (9.7%)	18 (4.6%)	15 (8.6%)
[6 - 18 months)	645 (29.5%)	88 (34.4%)	110 (31.6%)	153 (22.0%)	154 (48.3%)	88 (22.4%)	52 (29.7%)
[1.5 - 2 years)	116 (5.3%)	18 (7.0%)	20 (5.7%)	18 (2.6%)	26 (8.2%)	14 (3.6%)	20 (11.4%)
[2 - 6 years)	254 (11.6%)	35 (13.7%)	56 (16.1%)	71 (10.2%)	34 (10.7%)	35 (8.9%)	23 (13.1%)
[6 - 11 years)	59 (2.7%)	10 (3.9%)	18 (5.2%)	11 (1.6%)	6 (1.9%)	7 (1.8%)	7 (4.0%)
[11 - 18 years)	102 (4.7%)	15 (5.9%)	15 (4.3%)	40 (5.7%)	13 (4.1%)	11 (2.8%)	8 (4.6%)
18 years +	30 (1.4%)	*	12 (3.4%)	7 (1.0%)	*	*	*
Missing	679 (31.0%)	48 (18.8%)	33 (9.5%)	347 (49.8%)	16 (5.0%)	202 (51.4%)	33 (18.9%)
Duration of follow up (months)							
Mean (SD)	70.9 (38.4)	55.5 (13.7)	51.6 (34.3)	86.9 (35.4)	58.3 (22.2)	67.8 (43.9)	96.9 (49.9)
Missing; n (%)	16 (0.7%)	*	10 (2.9%)	*	-	*	*
Duration of SMA (months)							
Mean (SD)	252.1 (195.8)	235.8 (163.3)	209.8 (170.3)	300.7 (215.2)	232 (186)	311.1 (225.9)	211.5 (171.6)
Missing; n (%)	699 (31.9%)	52 (20.3%)	45 (12.9%)	348 (49.9%)	16 (5.0%)	205 (52.2%)	33 (18.9%)
Number of SMN2 copies; n (%)							
0	15 (0.7%)	-	*	13 (1.9%)	-	*	-

1	10 (0.5%)	*	6 (1.7%)	*	-	-	-
2	321 (14.7%)	37 (14.5%)	72 (20.7%)	94 (13.5%)	73 (22.9%)	18 (4.6%)	27 (15.4%)
3	800 (36.6%)	126 (49.2%)	156 (44.8%)	214 (30.7%)	183 (57.4%)	61 (15.5%)	60 (34.3%)
4	251 (11.5%)	-	77 (22.1%)	99 (14.2%)	32 (10.0%)	12 (3.1%)	31 (17.7%)
>4	10 (0.5%)	-	-	10 (1.4%)	-	-	-
Other	52 (2.4%)	50 (19.5%)	*	*	-	-	-
Missing	729 (33.3%)	42 (16.4%)	35 (10.1%)	263 (37.7%)	31 (9.7%)	301 (76.6%)	57 (32.6%)
Methods used for genetic testing; n (%)							
DNA Sequencing	-	*	-	-	-	-	-
HRM	-	*	-	-	-	-	-
MLPA	527 (24.1%)	201 (78.5%)	93 (26.7%)	82 (11.8%)	-	27 (6.9%)	124 (70.9%)
RFLP	5 (0.2%)	*	-	-	-	*	-
ddPCR	*	*	-	-	-	-	-
qRT-PCR	25 (1.1%)	15 (5.9%)	*	6 (0.9%)	-	*	-
Missing	1625 (74.3%)	30 (11.7%)	254 (73.0%)	609 (87.4%)	319 (100.0%)	362 (92.1%)	51 (29.1%)
Patients in treated group (n, %)	1321 (60.4%)	202 (78.9%)	269 (77.3%)	302 (43.3%)	262 (82.1%)	170 (43.3%)	116 (66.3%)
Patients in never treated group (n, %)	847 (38.7%)	54 (21.1%)	79 (22.7%)	380 (54.5%)	57 (17.9%)	218 (55.5%)	59 (33.7%)

Belgium

Overall, 256 patients in the Belgium registry met study eligibility criteria. Select characteristics for the overall population in the Belgium registry are presented in Table 10. Among these patients, 34 (13.3%) patients were classified as SMA type 1, 101 (39.5%) patients were classified as SMA type 2, 103 (40.2%) as SMA type 3, 8 (3.1%) as SMA type 4, 3 (1.2%) as SMA type Other, 7 (2.7%) had SMA type missing, and 0 patients had SMA type Presymptomatic.

In Belgium, the **study period** covered January 2018 to December 2021. With respect to the calendar **year of registry entry**, the highest proportion of patients entered in 2018 (74.2%) at registry initiation. The proportion of patients entering the registry in subsequent years was between 4.3% -14.8%.

Overall, the proportions of **male** (49.6%) and **female** (50.4%) were similar, and the distribution was similar across the SMA types with reported values.

With respect to the class of **age at symptom onset**, the most commonly observed age in the overall group was 6-18 months (34.4%). Data on class of age at symptom onset was missing for 18.8% of patients overall. For SMA type 1, the most common age of symptom onset was 3-6 months, 6-18 months for SMA type 2 and 2-6 years for SMA type 3.

The mean **duration of follow-up**, overall, was 55.5 months (SD=13.7). This estimate was fairly consistent across all the SMA types. A limited number of patients were **lost to follow-up** until 2021 with fewer than 15 SMA patients (less than 5.9% of patients overall) being lost to follow-up between 2018-2021 (of note, Belgium registry covers 2018-2021 and is updated once a year. Belgium data have not been updated after 2021). The majority of the patients lost to follow-up were with SMA type 3.

Regarding the **mean duration of SMA**, SMA type 1 had a duration of 83.3 months and SMA type 2 had a duration of 221.7 months. SMA types 3 and 4 had the longest durations, with 301.4 months and 310.7

months, respectively. Data were missing for 20.3% of patients across all SMA types. The overall mean **duration between genetic report dates and registry entry** was 99.2 months (SD=96.7), with SMA type 1 having the shortest durations of 8.5 [1, 22.8] months. The highest mean duration of 124.7 months (SD=103.8) was noted for SMA type 3.

Data on **best functional SMA status**, and best achieved motor milestone was missing for 2.7% of patients overall. “Walker" was the most common best functional status among the overall patients (51.2%), of which, the majority had SMA type 3. “Sitter” was the most common best functional SMA status among patients with SMA type 1 (55.9%) and type 2 (82.2%). The most common **best achieved motor milestone** was “sit without support” among patients with SMA type 1 (47.1%) and SMA type 2 (58.4%). For the SMA type 3 (85.4%) and type 4 (100.0%), the most common motor milestone was “climb stairs”. Limited data was available for other SMA type stratifications.

Data on the **number of SMN2 copies** was missing for 16.4% of patients overall. For patients with SMA type 1, 70.6% had 2 copies and 14.7% had 3 copies. For patients with SMA type 2, 68.3% had 3 copies and 7.9% had 2 copies. For the SMA type 3 group, 44.7% had 3 copies. MLPA was the most common **method used for genetic testing** across all SMA types (78.5%). Missingness associated with this variable was 11.7% across all SMA types.

DMT use was observed from 2018, corresponding to the start of data collection in this registry. In 2018, 49.5% of patients were treated with a DMT. The percentage of DMT usage increased in the subsequent years up to 85.3% in 2021. The majority of the patients in our study cohort, across SMA types, first started receiving treatment with a DMT in 2021. Patients across all SMA types were not treated with more than one DMT until 2019; SMA type 1 patients in 2020 had the highest proportion (25.9%) of patients receiving treatment with more than one DMT. The data was limited for this variable.

Treatment with **Spinraza** was common across calendar periods, 2018-2021, with the highest proportion of patients treated with Spinraza in 2020 (60.1%). Patients with SMA type 1 had the highest percentage of patients treated with Spinraza during 2020 (70.4%). Treatment with **Evrysdi** did not begin until 2018 and the overall usage was less common, with the highest percentage observed in 2021 (28.4%). Evrysdi usage was common among patients with SMA type 2. Treatment with **Zolgensma** did not begin until 2019, with the overall usage being rare across all SMA types. In the overall group, the highest percentage of usage was observed in 2021 (3.1%).

Overall, approximately 14% of patients reported using **feeding tubes** and the proportion of patients receiving feeding tube usage in the SMA type 1 group was highest. More than 50% of overall patients had at least one episode of **wheelchair use** since 2018 and the highest proportion of patients reporting at least one episode of wheelchair usage was in 2018 (78.9%). Patients with SMA type 2 had the highest proportion of patients reporting at least one episode of wheelchair usage followed by SMA type 3 across the calendar periods.

On average, patients across SMA types had approximately one **available record of PRO** for each patient from calendar periods 2017 to 2021.

Czech Republic and Slovakia

Among patients in the Czech Republic and Slovakia registries, a total of 348 patients met the study eligibility criteria. Select characteristics for the overall population in this registry are presented in Table 10. Overall, 96 patients were classified as SMA type 1 (27.6%), 117 patients were classified as SMA type 2 (33.6%), 120 as SMA type 3 (34.5%), 8 as SMA type 4 (2.3%), 1 (0.3%) as SMA type Other, 6 (1.7%) as SMA type Presymptomatic, and 0 patients had an SMA type missing.

In the Czech Republic and Slovakia, the **data collection period** covered May 2011 to May 2023. With respect to the **calendar year of registry entry**, more patients entered in 2020 than any other year (17.2% of the overall population). Between registry initiation in 2011 and 2017, <7% of patients entered the registry data collection each year across SMA types. From 2018 to 2022, percentages for entry into the

registry ranged from 8.9% to 17.2% of patients. There was limited missing information for this indicator (overall 2.9%).

Overall, there was an almost equal split across **males** (49.4%) and **females** (50.6%).

With respect to the **class of age at symptom onset**, 30.2% of SMA type 1 patients from the Czech Republic and Slovakia registries had their symptom onset between 1-3 months, 29.2% between 3-6 months and 16.7% between 6-18 months. The majority (64.1%) of SMA type 2 had their symptom onset between 6-18 months, and 44.2% of SMA type 3 had their symptom onset between 2-6 years of age. Overall, close to 10% of patients had missing values recorded for this variable, with the percentage being consistent among SMA type 2 patients but increasing to 19.8% among SMA type 1 patients.

The overall mean **duration of follow-up** was 51.6 (SD=34.3) months. The longest duration of follow-up was for SMA type 2 with a mean of 61.5 months (SD=36.2). SMA type 4 had a duration of only 30 (SD=12.3) months. Patients **lost to follow-up** represented a low percentage of the registry population across calendar periods i.e., less than or equal to 10% across the calendar periods.

Regarding the **mean duration of SMA**, SMA type 1 had a duration of 89.9 months and SMA type 2 had a duration of 221.6 months. SMA types 3 and 4 had the longest durations, with 276 and 294 months, respectively. Data were missing for 12.9% of patients across all SMA types. The overall **mean duration between two consecutive visits** was 7.1 (SD=9.3) months and was consistent across all SMA types, with 15.2% missingness for this variable. The overall **mean duration between genetic report dates and registry entry** was 88.1 (SD=132.8) months, with SMA type 1 and type 4 having the shortest durations of 27.8 (SD=65.3) and 27.7 (SD=33) months, respectively. There was low missingness (2.9%) for this variable.

Data on **best functional SMA status** were missing for 24.7% of all patients in the registry, 57.3% of SMA type 1 patients, 16.2% of SMA type 2 patients, 5.8% of SMA type 3 patients, and fewer than five SMA type 4 patients. Among SMA type 1 patients, 28.1% of patients were sitters, 12.5% were non-sitters, and fewer than five patients were walkers. Among SMA type 2 patients, 58.1% were sitters, 18.8% were non-sitters, and 6.8% were walkers. Among SMA type 3 patients 66.7% of patients were walkers, 20.8% were sitters, and 6.7% were non-sitters. Three quarters of SMA type 4 patients were walkers. For the **best achieved motor milestone**, data were missing for the same proportions of patients. Among SMA types 1 and 2 patients, the highest proportion of patients were able to sit without support (22.9% and 33.3%, respectively). For SMA type 3 patients, the majority (54.2%) were able to climb stairs.

Data on the **number of SMN2 copies** was missing for 10.1% of patients overall. For patients with SMA type 1, 59.4% had 2 copies and 28.1% had 3 copies. For patients with SMA type 2, 78.6% had 3 copies, 7.7% had 2 copies and 4.3% had 4 copies. For the SMA type 3 group, 54.2% had 4 copies and 27.5% had 3 copies. The majority of **methods used for genetic testing** were MLPA: 26.7% across all SMA types, with similar numbers across SMA type 1, 2, 3 and 4. This variable had a high extent of missingness with 73% across all SMA types.

DMT use: Patients across SMA types began receiving treatment with a DMT as of 2017 (13.4% of patients overall). This percentage increased in 2018, with most SMA types 1 and 2 receiving treatment with a DMT from 2018 onward. A majority of SMA type 3 patients began receiving treatment with a DMT from 2019 onward. SMA type 1 patients in 2021 had the highest proportion (13.3%) of patients receiving treatment with more than one DMT. Overall, treatment with more than 1 DMT was less common.

Treatment with **Spinraza** was common across calendar periods (2017-2023), with the highest proportion of patients treated with Spinraza in 2020 (79.2%). Patients with SMA type 1 had the highest percentage of patients treated with Spinraza across the calendar periods compared to patients with other SMA types. Treatment with **Evrysdi** was less common, with the highest percentage observed in 2022 (29.2%). SMA

type 2 patients had the highest percentage treated with Evrysdi. Overall, treatment with **Zolgensma** was the least common across calendar periods, with the highest percentage observed in 2023 (16.7%). Patients with SMA type 1 had the highest proportion treated with Zolgensma.

Overall, 8.6-16.4% of patients reported using **feeding tubes** of which the majority of the patients were SMA type 1. More than 50% of patients across SMA types had at least one episode of **wheelchair use**. SMA type 2 patients had the highest percentages of patients with wheelchair use across calendar periods, with the highest percentage reported for 2014 to 2016 (100%). SMA type 3 had the lowest percentages of patients with wheelchair use, with the highest percentage reported for 2020 (41.5%).

Germany and Austria

A total of 697 patients in the Germany and Austria registry met study eligibility criteria. Selected characteristics for the overall population in this registry are presented in Table 10. 134 patients were classified as SMA type 1 (19.2%), 291 as SMA type 2 (41.8%), 269 as SMA type 3 (38.6%), 2 as SMA type 4 (0.3%), 0 as SMA type other, 1 as presymptomatic SMA (0.1%), and 0 were missing SMA type information.

In Germany and Austria, the **data collection period** covered April 2008 to May 2023. With respect to the **calendar year of registry entry**, the highest percentage of patients entered in 2014 (17.6%). Few patients had a registry entry date from 2008 through 2011, or from 2021 through 2023 (<2% in each year). The percentage of patients with a registry entry date in other calendar years ranged from 3.4% to 16.8%.

Overall, around half of patients were **female** (48.9%), and this distribution was similar across SMA types.

Data on **class of age at symptom** onset was missing for 49.8% of patients overall, with the highest missingness in the SMA type 1 group 60.4%. Patients with SMA type 1 had the earliest symptom onset on average, with most patients having onset at 18 months or earlier. For the SMA type 2 group, the most common age of symptom onset was 6-18 months (40.9%). For patients with SMA type 3, symptom onset before 6 months was rare, and the most common age was 2-6 years (23.8%). Limited data was available for SMA types of stratifications.

Overall, patients had a mean of 86.9 (SD=35.4) months of follow-up. Patients in the SMA type 3 group had the longest mean **duration of follow-up** (91.8 months, SD=33.8), followed by patients with SMA type 2 (90.3 months, SD =35.0), and SMA type 1 (71 months, SD=33.9). Patients **lost to follow-up** ranging from 0.9% in 2019 to 41.9% in 2022.

Mean **duration of SMA** was 300.7 months overall. Patients with SMA type 3 had the longest duration (409.6 months), followed by patients with SMA type 2 (251.3 months), and patients with SMA type 1 (112.7 months). Missingness for this variable was 49.9% overall. The overall mean **duration between two consecutive visits** was 25.2 months and was consistent across all SMA types, with 5.3% missingness for this variable. The overall mean **time between genetic report date and registry entry** was 55.1 months. This duration was shorter in patients with SMA type 1 (18.7 months). Missingness for this variable was 23.0% overall.

Data on **best functional SMA status**, and best achieved motor milestone was missing for 49.6% of patients overall, and 65.7% of patients in the SMA type 1 group. “Non-sitter” was the most common best functional status for the SMA type 1 group (15.7%), whereas in the SMA type 2 group “sitter” was most common, (58.1%). “Walker” was the most common best functional SMA status among patients with SMA type 3 (58.7%) The most common **best achieved motor milestone** was “roll onto side” among patients with SMA type 1 (10.4%) and “sit without support” for patients with SMA type 2 (14.8%). For the SMA type 3 group, the most common motor milestone was “climb stairs” (51.7%). Limited data was available for other SMA type stratifications.

Data on the **number of SMN2 copies** was missing for 37.7% of patients overall. For patients with SMA type 1, 48.5% had 2 copies. For patients with SMA type 2, 42.6% had 3 copies. For the SMA type 3 group, 21.2% had 3 copies and 28.6% had 4 copies. Data on the **methods used for genetic testing** had high missingness (87.4% overall). Of patients with this information, almost all had MLPA as the method used (11.8% overall).

DMT use: Prior to 2017, very few patients were treated, only as part of clinical trials, with at least one DMT (3.1% or less across calendar periods). DMT use increased in 2017, with 14.7% of patients overall treated with at least one DMT, a 30.1% of SMA type 1 patients. Overall, the highest proportion of patients with DMT use was in 2023 (63.6%). Treatment with more than one DMT was rare.

Treatment with **Spinraza** was common from 2017 onward (ranging from 14.3% of patients in 2017 to 43.9% in 2021). Patients with SMA type 1 were more likely to receive Spinraza vs other SMA types. Treatment with **Evrysdi** was observed in very few patients from 2017 through 2019 (n<5 in each calendar period) then was more common from 2021 onward, with the highest proportion of patients receiving the treatment in 2022 and 2023 (26.0% overall in both years). Use of Evrysdi was more common in the SMA type 2 group. Treatment with **Zolgensma** was less common across calendar periods, but was observed from 2022 onward, with the highest proportion observed in 2023 (6.5% overall). Patients in the SMA type 1 group were more likely to receive Zolgensma.

Overall, less than 10% of patients reported using **feeding tubes** of which the majority of the patients were SMA type 1. Across calendar periods, roughly 50% or more of patients overall had at least one episode of **wheelchair usage**. Wheelchair usage was most common among patients with SMA type 2, with the highest percentage observed in the Before 2011 calendar period where 90% of SMA type 2 patients had wheelchair usage.

Spain

Among patients in the Spain registry, a total of 319 patients met the study eligibility criteria. Select characteristics for the overall population in this registry are presented in Table 10. Overall, 71 patients were classified as SMA type 1 (22.3%), 153 patients were classified as SMA type 2 (48.0%), 93 as SMA type 3 (29.2%), 2 as SMA type 4 (0.6%), and 0 patients had SMA type Other, SMA type Presymptomatic, or had an SMA type missing.

In Spain, the **data collection period** covered February 2015 to April 2023. With respect to the **calendar year of registry entry**, more patients entered in 2018 than any other year (26.6% of the overall population), followed by 2017 (25.1%).

Overall, there were slightly more **male** (54.5%) than **female** (45.5%) patients, with this distribution remaining consistent across SMA types 1 and 2 and levelling out among SMA type 3 patients (49.5% female).

With respect to the **class of age at symptom onset**, 9.9% of SMA type 1 patients from the Spain registry had their symptom onset at less than 1 month, 42.3% between 1-3 months, 40.8% between 3-6 months and 7% between 6-18 months. A majority (90.2%) of SMA type 2 had their symptom onset between 6-18 months, and 36.6% of SMA type 3 had their symptom onset between 2-6 years of age. Overall, 5% of patients had missing values recorded for this variable, with the highest percentage of missingness among SMA type 3 patients (12.9%).

The longest **duration of follow-up** was for SMA type 2 patients with a mean of 61.5 months (SD=20.8), followed by SMA type 3 with a mean of 58.4 (SD=22.1), and SMA type 1 with a mean of 51.6 (23.1). This variable was recorded for all patients. There were no, or very few, patients **lost to follow-up** across calendar periods.

Regarding the **mean duration of SMA**, SMA type 1 had a duration of 83.4 months, SMA type 2 had a duration of 234.9 months, and SMA type 3 had the longest duration of 349.9 months. Data were missing

for 5% of patients across all SMA types. The overall mean **duration between two consecutive visits** was 9.5 months, with 2.5% missingness for this variable. The overall mean **duration between genetic report dates and registry entry** was 80 months, with SMA type 1 having the shortest duration of 26.4 months. There was low missingness (3.1%) for this variable.

Data on **best functional SMA status** were missing for 9.1% of all patients in the registry, 25.4% of SMA type 1 patients, 3.9% of SMA type 2 patients, and 5.4% of SMA type 3 patients. Among SMA type 1 patients, 32.4% of patients were sitters, 26.8% were walkers, and 15.5% were non-sitters. Among SMA type 2 patients, 60.1% of patients were sitters and 35.9% were walkers. Among SMA type 3 patients, 93.5% of patients were walkers. For the **best achieved motor milestone**, data were missing for the same proportions of patients. Among SMA types 1 and 2 patients, the highest proportion of patients were able to sit without support (28.2% and 56.9%, respectively). For SMA type 3 patients, 72% of patients were able to walk 10 metres without assistance and 21.5% were able to climb stairs.

Data on the **number of SMN2 copies** was missing for 9.7% of patients overall. For patients with SMA type 1, 78.9% had 2 copies and 19.7% had 3 copies. For patients with SMA type 2, 73.2% had 3 copies, 8.5% had 2 copies, and 3.69% had 4 copies. For the SMA type 3 group, 61.3% had 3 copies and 26.9% had 4 copies. Data were missing or limited for other SMA types. Data on the **methods used for genetic testing** was missing for all patients.

DMT use: Patients across SMA types began receiving treatment with a DMT as of 2017 (18.9% of patients overall). This percentage increased in 2018, with a majority of patients across SMA types 1 and 2 receiving treatment with a DMT from 2018 onward. A majority of SMA type 3 patients began receiving treatment with a DMT from 2020 onward. SMA type 1 patients in 2022 had the highest proportion (8.8%) of patients receiving treatment with more than one DMT.

Treatment with **Spinraza** was common across calendar periods (2017-2023), with the highest proportion of patients treated with Spinraza in 2021 (66.3%). Patients with SMA type 1 had the highest percentage of patients treated with Spinraza and the highest percentage overall in 2018 (90.6%). Treatment with Evrysdi was less common, with the highest percentage observed in 2021 (12.8%). SMA type 2 patients had the highest percentage treated with **Evrysdi**. Overall, treatment with **Zolgensma** was the least common across calendar periods, with the highest percentage observed in 2022 (3.6%). Patients with SMA type 1 had the highest proportion treated with Zolgensma (of note: In Spain, Zolgensma is only reimbursed for type 1 or patients younger than 6 weeks of age, but there is no newborn screening done nationally so, logically, the treated are type 1).

Overall, approximately 10% of patients reported using **feeding tubes** of which the majority of the patients were SMA type 1. More than 50% of overall patients had at least one episode of **wheelchair use**, with this trend being consistent across SMA types for all calendar periods except for 2018, during which SMA type 1 patients had 46.9% and SMA type 3 patients had 43.1% with at least one episode of wheelchair use. SMA type 2 had the highest percentages of patients with wheelchair usage, with the highest observed in 2023 (94.6%).

On average, patients across SMA types had approximately one **available record of each PRO** from calendar periods 2020 to 2023.

UK and Ireland

Among patients in the UK and Ireland, a total of 393 patients met the study eligibility criteria. Select characteristics for the overall population in this registry are presented in Table 10. Overall, 69 patients were classified as SMA type 1 (17.5%), 183 patients were classified as SMA type 2 (46.6%), 123 as SMA type 3 (31.3%), 0 as SMA type 4 or SMA type Other, 1 as SMA type Presymptomatic, and 17 (4.3%) had an SMA type missing.

In the UK and Ireland, the **data collection period** covered December 2008 to May 2023. With respect to the **calendar year of registry entry,** most patients entered in 2015 (21.6% of the overall population),

with a steady flow of data participants entering throughout the study period. There was very little missing data for this indicator (overall <5 patients). This trend was similar across SMA types.

Overall, there was an almost equal split between **male** (54.5%) than **female** (45.5%) patients, with this distribution remaining consistent across SMA types 1, 2 and 3.

With respect to the **class of age at symptom onset**, 10.1% of SMA type 1 patients from UK & Ireland had their symptom onset between 1-3 months, 17.4% between 3 and 6, and 8.7% between 6-18 months. Overall, there was a high degree of missingness (51.4%) for this indicator.

Duration of follow-up was highest among the SMA type 2 patients [74.1 months, (SD=45.4)] with the overall mean duration of follow-up for the overall population in this registry being 67.8 months (SD=43.9). This variable was well recorded with less than 5 patients having missing information across all SMA types. The percentage of patients **lost to follow-up** ranged from 2.2% in 2016 to 16.2% before 2011.

Regarding the **mean duration of SMA**, SMA type 1 had a duration of 90 months, SMA type 2 had a duration of 296.2 months, and SMA type 3 had the longest duration of 419.4 months. Data were missing for 52.2% of patients across all SMA types. The overall mean **duration between two consecutive visits** was 33.2 months, with 19.1% missingness for this variable. The overall mean **duration between genetic report dates and registry entry** was 83.6 months, with SMA type 1 having the shortest duration (13.6 months). There was a high degree of missingness (85.5%) for this variable.

Data on **best functional SMA status** were missing for 53.7% of all patients in the registry, with an even higher percentage observed for SMA type 1 patients: 68.1%. Overall, 18.8% were sitters: among SMA type 1 patients, and 25.1% of patients among SMA type 2; 18.6% were walkers among SMA type 3 and 54.5% among SMA type 4. For the **best achieved motor milestone**, data were missing for 53.7%% of all patients in the registry. There was a high percentage of patients who had at some point during the follow-up a best achieved motor milestone as “climbs stairs”: 43.9% for SMA type 3. Among SMA types 1 and 2 patients, the highest proportion of patients were able to stand with assistance and roll onto one side.

Data on the **number of SMN2 copies** was missing for 76.6% of patients overall. For patients with SMA type 1, 18.8% had 2 copies. For patients with SMA type 2, 21.9% had 3 copies. For the SMA type 3 group, 13.0% had 3 copies and 9.8% had 4 copies. The most commonly used **methods used for genetic testing** were MLPA: 6.9% overall, with similar numbers across SMA type 1, 2, 3 and 4. This variable had a very high extent of missingness with 92.3% across all SMA types.

DMT use: Patients across SMA types began receiving treatment with a DMT as of 2017. This percentage started to increase over the years. Overall, patients in 2022 had the highest proportion (43.2%) of patients receiving treatment with at least one DMT. Treatment with more than 1 DMT was rare across all the SMA types.

Treatment with **Spinraza** was common across calendar periods (2018-2023), with the highest proportion of patients treated with Spinraza in 2021 (16.3%). Overall, Spinraza treatment was more common among patients with SMA type 3. Treatment with **Evrysdi** was less common, with the highest being 22.7% in 2022. Overall, treatment with Evrysdi was more common among patients with SMA type 2. Treatment with **Zolgensma** was least common across all SMA types with the highest proportion (5%) being treated in 2022.

The highest percentage of **feeding tube usage** was observed between 2014-2016, with 14.7% of patients having at least one episode, with SMA type 1 patients having the highest proportion of feeding tube usage, followed by SMA type 2. **Wheelchair usage** was fairly common across all calendar periods, approximately 40% of overall patients. Proportion of patients using wheelchairs was higher among patients with SMA type 2 compared to all other types.

Sweden

Overall, 175 patients in the Swedish registry met study eligibility criteria. Select characteristics for the overall population in this registry are presented in Table 10. Overall, 28 (16.0%) patients were classified as SMA type 1, 69 (39.4%) patients were classified as SMA type 2, 71 (40.6%) as SMA type 3, 2 (1.1%) as SMA type 4, 3 (1.7%) as SMA type Other, 2 (1.1%) had SMA type missing, and 0 patients had SMA type Presymptomatic.

In Sweden, the **data collection period** covered October 2010 to May 2023. The highest proportions of patients entered the registry in 2010 (16.6%) and 2011 (16.6%), then registry entry slowed down until peaking again in 2019 (11.4%).

Overall, 50.9% of patients were **female** and the distribution of sex was similar across the SMA types with reported values, except for SMA type 1, 60.7% were **male**.

With respect to the **class of age at symptom onset**, 29.7% of the overall patients had their symptom onset between 6-18 months. Data on class of age at symptom onset was missing for 18.9% of patients overall. For SMA type 1, the most common age of symptom onset was 1-3 months, 6-18 months for SMA type 2 and 2-6 years for SMA type 3.

The mean **duration of follow-up**, overall, was 96.9 (SD=49.9) months. The longest mean duration of follow-up was noted for SMA type 2 (107.9, SD=49.7) and type 3 (104.9, SD=45), whereas SMA type 1 group had the shortest mean duration of follow-up (55.9, SD=35.9). This variable was well recorded with minimal missing values across all SMA types. There were no patients **lost to follow-up**.

The **mean duration of SMA** varied by SMA type, with SMA type 1 having a duration of 67.2 months, SMA type 2 having a duration of 204.7 months, and SMA type 3 having a duration of 252.2 months. The overall median **duration between two consecutive visits** was 8.3 [5.1, 12] months, with minimal missingness for this variable. Patients with SMA type 3 had the longest duration between two consecutive visits, i.e., 9.4 [6.5, 15.6] months. The overall median duration between genetic report dates and registry entry was 8 [1, 56.2] months, with SMA type 2 having the longest duration of 19 [1, 75] months.

Data on **best functional SMA status,** and **best achieved motor milestone** was missing for 42.9% of patients overall. “Walker" was the most common best functional status among the overall patients (30.9%), of which, the majority had SMA type 3 (59.2%). “Sitter” was the most common best functional status among patients with SMA type 1 (35.7%) and type 2 (39.1%). The most common best achieved motor milestone was “sit without support” among patients with SMA type 1 (32.1%) and SMA type 2 (20.3%). For the SMA type 3 (26.8%), the most common motor milestone was “climb stairs”. Limited data was available for other SMA type stratifications.

Data on the **number of SMN2 copies** was missing for 32.6% of patients overall. For patients with SMA type 1, 71.4% had 2 copies. For patients with SMA type 2, 60.9% had 3 copies, and 7.2% had 2 copies. For the SMA type 3 group, 40.8% had 4 copies and 19.7% had 3 copies. MLPA was the most common **method used for genetic testing** across all SMA types (70.9%). Missingness associated with this variable was 29.1% across all SMA types.

DMT use: Patients across SMA types began receiving treatment with a DMT between 2014 and 2016. Approximately 60% patients received treatment with at least one DMT in 2019 and this proportion fairly remained consistent until 2023. Treatment with at least one DMT was most common in SMA type 1, with at least 82.1% of patients in this group receiving treatment with a DMT in each year from 2017 onward. Patients across all SMA types were not treated with more than one DMT until 2021; SMA type 1 patients in 2022 had the highest proportion (42.9%) of patients receiving treatment with more than one DMT. The data was limited for this variable.

Treatment with **Spinraza** was common across calendar periods, 2017-2023, with the highest proportion of patients treated with Spinraza in 2020 (64.5%). Patients with SMA type 1 had the highest percentage of patients treated with Spinraza during 2021 (91.3). Treatment with **Zolgensma** did not begin until 2021 and the overall usage was less common, with 2.9% of patients receiving treatment with Zolgensma in 2022 and 2023. Treatment with **Evrysdi** did not begin until 2021, with the highest percentage of usage observed in 2022 (30.8%). Patients with SMA type 1 had the highest proportion of patients treated with Zolgensma followed by SMA type 3.

Overall, less than 5% of overall patients **reported using feeding tubes** and the usage was common among patients with SMA type 1 compared to other SMA types. Close to 50% or higher percentage of overall patients had at **least one episode of wheelchair use** across the calendar periods. The highest proportion of patients reporting at least one episode of wheelchair usage was in 2021 (65.2%). Patients with SMA type 2 had the highest proportion of patients reporting at least one episode of wheelchair usage followed by SMA type 3 across the calendar periods.

10.4.2. Description of the SMA natural history and disease progression

Please note that all results are available in a stand-alone document - Appendix G ("Objective 1 (Natural History) Results 2024_1_26"), submitted along with this report. Additional sub-group analyses are also available in Appendix G ("Supplementary Results Objective 1 (Natural History) 2024_1_26").

10.4.2.1 Never treated SMA Patients

Overall (Table 11), 847 patients were never treated. Among these patients 154 (18.2%) had SMA Type 1, 361 (42.6%) had SMA type 2, 299 (35.3%) had SMA type 3, 13 (1.5%) had SMA type 4, 3 (0.4%) had SMA type other, 1 (0.1%) had presymptomatic SMA, and SMA type information was missing for 16 (1.9%) patients.

Among never treated patients, the largest proportion came from the Germany/Austria registry (44.9%), followed by the United Kingdom and Ireland (25.7%), Czech Republic and Slovakia (9.3%), Sweden (7.0%), Spain (6.7%), and Belgium (6.4%).

Males represented 51.4% of all never treated patients and were more present in SMA type 2 than **females**.

Median **age at symptom onset** was 0.3 months in SMA type 1, 1 year in SMA type 2 and 3 years in SMA type 3.

Regarding the reason for **genetic testing**, most patients did not have this information recorded (75.0%), while 23.1% had "no screening." The majority of patients (86.0%) were missing data on the method used for genetic testing. The most common recorded method was MLPA (12.9%).

Table 11: Sex, registry, age at symptom onset and method used for genetic testing in SMA 1, SMA 2 and SMA 3 never treated patients

	Overall (N =847)	SMA Type 1 (N =154)	SMA Type 2 (N =361)	SMA Type 3 (N =299)
Sex: female / male (%)	48.6% / 51.4%	56.5% / 43.5%	45.7% / 54.3%	49.2% / 50.8%
Registry n, %				
Belgium	54 (6.4%)	5 (3.2%)	18 (5.0%)	26 (8.7%)
Czech R & Slovakia	79 (9.3%)	25 (16.2%)	17 (4.7%)	30 (10.0%)
Germany & Austria	380 (44.9%)	80 (51.9%)	165 (45.7%)	134 (44.8%)

Spain	57 (6.7%)	*	34 (9.4%)	20 (6.7%)
UK & Ireland	218 (25.7%)	41 (26.6%)	103 (28.5%)	60 (20.1%)
Sweden	59 (7.0%)	*	24 (6.6%)	29 (9.7%)
Age at symptom onset (years) - Median [IQR]	1.5 [0.8, 4]	0.3 [0.1, 0.5]	1 [0.6, 1]	3 [1.8, 10]
Method used for genetic testing; n (%)				
MLPA	109 (12.9%)	6 (3.9%)	40 (11.1%)	57 (19.1%)
missing	728 (86.0%)	148 (96.1%)	318 (88.1%)	235 (78.6%)
Reason for genetic testing; n (%)				
Family screening	14 (1.7%)	*	*	8 (2.7%)
Newborn screening	*	*	-	-
No screening	196 (23.1%)	5 (3.2%)	88 (24.4%)	94 (31.4%)
Missing	635 (75.0%)	146 (94.8%)	272 (75.3%)	197 (65.9%)

Motor function assessment (Table 12)

Functional status at genetic report date was missing to a large extent (94.5%), with "non-sitter" being the most common recorded functional status (2.1%) and a higher proportion of SMA type 3 patients with "walker" status (4.0%). **The best functional status** is highly missing overall (99.1%) and when reported it was for "non-sitter" status (0.9%)

Achieved motor milestones at the genetic report date was missing for 94.5% of patients. Of patients with data on this indicator, "hold head without support" was the most common milestone recorded (1.4%), followed by "sit without support" (1.3%).

The **best achieved motor milestones** were missing to a large extent (99.1%). Only 7 (1.9%) SMA 2 patients reported "Roll onto side" (0.8%) and less than 5 reported "Hold head without support". Median **age at first acquisition of the best motor ability episodes** ranged from 3.5 years in SMA type 1 to 24.2 years in SMA type 2 to 39.2 years in SMA type 3. And median **age at first loss of the best motor ability episodes** was 25.8 and 46.5 years in SMA Types 2 and 3, respectively; and non-estimable (<5 cases) for SMA type 1.

Best CHOP-INTEND score was missing for 98.9% of patients overall. The median scores by SMA type were non-estimable (< 5 cases).

Best HFMS(-E) score was missing for 97.8% of patients overall. The median score for SMA type 3 was 51 [14.5, 60]. This indicator was non-estimable for SMA types 1 and 2.

Best RULM score was missing for 98.5% of patients overall. The median score for SMA type 3 was 33 [23.2, 37]. This indicator was non-estimable for SMA types 1 and 2.

Best MFM32 score was missing for 99.3% of patients overall. The median score was non-estimable for SMA types 1, 2, and 3.

Best 6MWT score was missing for 98.5% of patients overall. The median score for SMA type 3 was 435.5 [251, 599.8]. This indicator was non-estimable for SMA types 1 and 2.

Table 12: Motor function assessment in SMA 1, SMA 2 and SMA 3 never treated patients

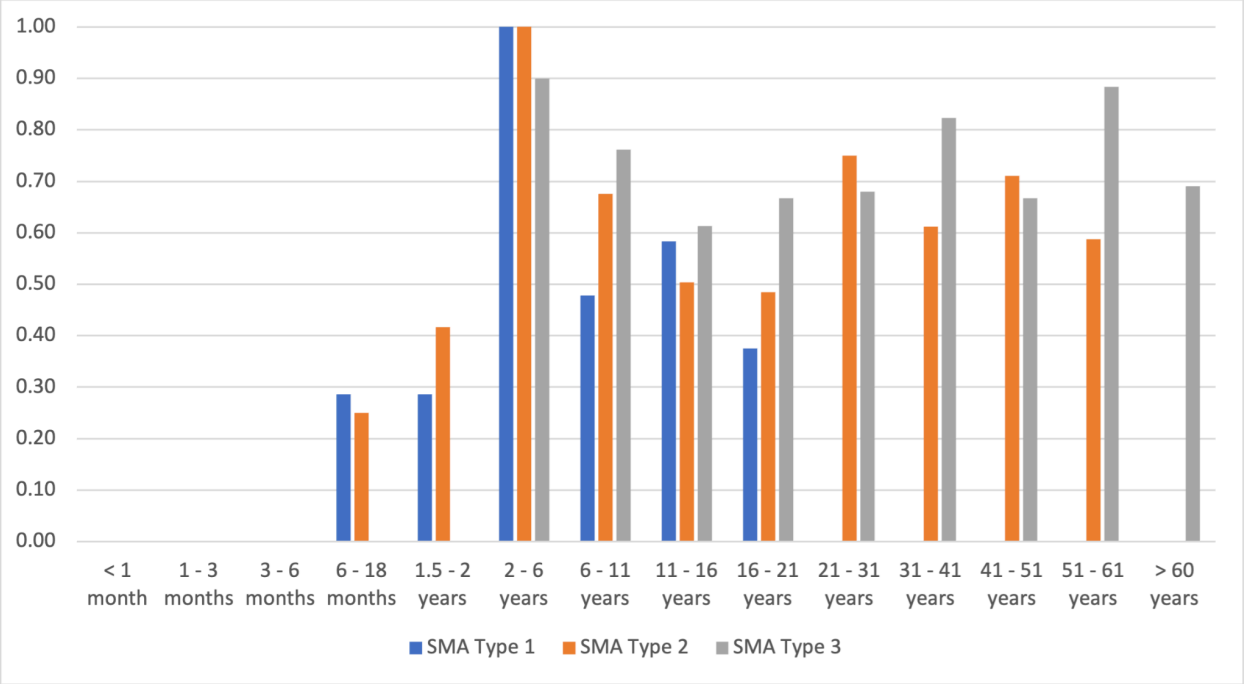
	Overall (N = 847)	SMA Type 1 (N = 154)	SMA Type 2 (N = 361)	SMA Type 3 (N = 299)
Functional status at genetic report; n (%)				
Non-sitter	18 (2.1%)	-	9 (2.5%)	8 (2.7%)
Sitter	15 (1.8%)	-	11 (3.0%)	*
Walker	14 (1.7%)	-	*	12 (4.0%)
Missing	800 (94.5%)	154 (100.0%)	340 (94.2%)	275 (92.0%)
Best functional status ; n (%)				
Non-sitter	8 (0.9%)	-	8 (2.2%)	-
Missing	839 (99.1%)	154 (100.0%)	353 (97.8%)	299 (100.0%)
Achieved motor milestone at genetic report; n (%)				
Climb stairs	-	-	-	-
Crawl	*	-	-	*
Hold head without support	12 (1.4%)	-	*	8 (2.7%)
Roll onto side	6 (0.7%)	-	6 (1.7%)	-
Sit without support	11 (1.3%)	-	10 (2.8%)	*
Stand with assistance	*	-	*	*
Stand without assistance	-	-	-	-
Unknown	-	-	-	-
Walk 10 metres without assistance	9 (1.1%)	-	*	8 (2.7%)
Walk with assistance	-	-	-	-
Walk without assistance	5 (0.6%)	-	-	*
Missing	800 (94.5%)	154 (100.0%)	340 (94.2%)	275 (92.0%)
Best achieved motor milestone; n (%)				
Climb stairs	-	-	-	-
Crawl	-	-	-	-
Hold head without support	*	-	*	-
Roll onto side	7 (0.8%)	-	7 (1.9%)	-
Sit without support	-	-	-	-
Stand with assistance	-	-	-	-
Stand without assistance	-	-	-	-
Unknown	-	-	-	-
Walk 10 metres without assistance	-	-	-	-
Walk with assistance	-	-	-	-
Walk without assistance	-	-	-	-
Missing	839 (99.1%)	154 (100.0%)	353 (97.8%)	299 (100.0%)
Age at first acquisition of the best motor ability episodes				
Median [IQR]	33.2 [18.8, 47.6]	3.5 [2.1, 3.7]	24.2 [15.6, 33.4]	39.2 [23.7, 52.2]
Missing	650 (76.7%)	149 (96.8%)	297 (82.3%)	183 (61.2%)
Age at first loss of the best motor ability				

episodes				
Median [IQR]	34.9 [22.1, 50.8]	*	25.8 [20.7, 38.3]	46.5 [33.6, 57.3]
Missing	686 (81.0%)	150 (97.4%)	283 (78.4%)	221 (73.9%)
Best score for CHOP-INTEND				
Median [IQR]	27 [13, 42]	*	*	*
Missing	838 (98.9%)	150 (97.4%)	358 (99.2%)	298 (99.7%)
Best score for HFMS(-E)				
Median [IQR]	36 [5, 60]	*	*	51 [14.5, 60]
Missing	828 (97.8%)	153 (99.4%)	359 (99.4%)	284 (95.0%)
Best score for RULM				
Median [IQR]	31 [18, 37]	-	*	33 [23.2, 37]
Missing	834 (98.5%)	154 (100.0%)	360 (99.7%)	287 (96.0%)
Best score for MFM32				
Median [IQR]	83 [61, 93]	-	*	*
Missing	841 (99.3%)	154 (100.0%)	360 (99.7%)	295 (98.7%)
Best score for 6MWT				
Median [IQR]	456 [276, 598]	-	-	435.5 [251, 599.8]
Missing	834 (98.5%)	154 (100.0%)	361 (100.0%)	287 (96.0%)

Note: * indicates n < 5 patients

A majority of overall never treated patients aged 2 years or older had **full-time or part-time wheelchair** use (Figure 1), with the highest use reported for patients aged 2-6 years (n=202; 99%). The median **age at first full-time or part-time wheelchair usage** for overall never treated patients was 3.6 years and ranged from 2 years in SMA type 1 patients to 13.3 years in SMA type 3 patients.

Figure 1. Proportion of patients with full-time or part-time wheelchair use per class of age in SMA 1, SMA 2 and SMA 3 never treated patients.



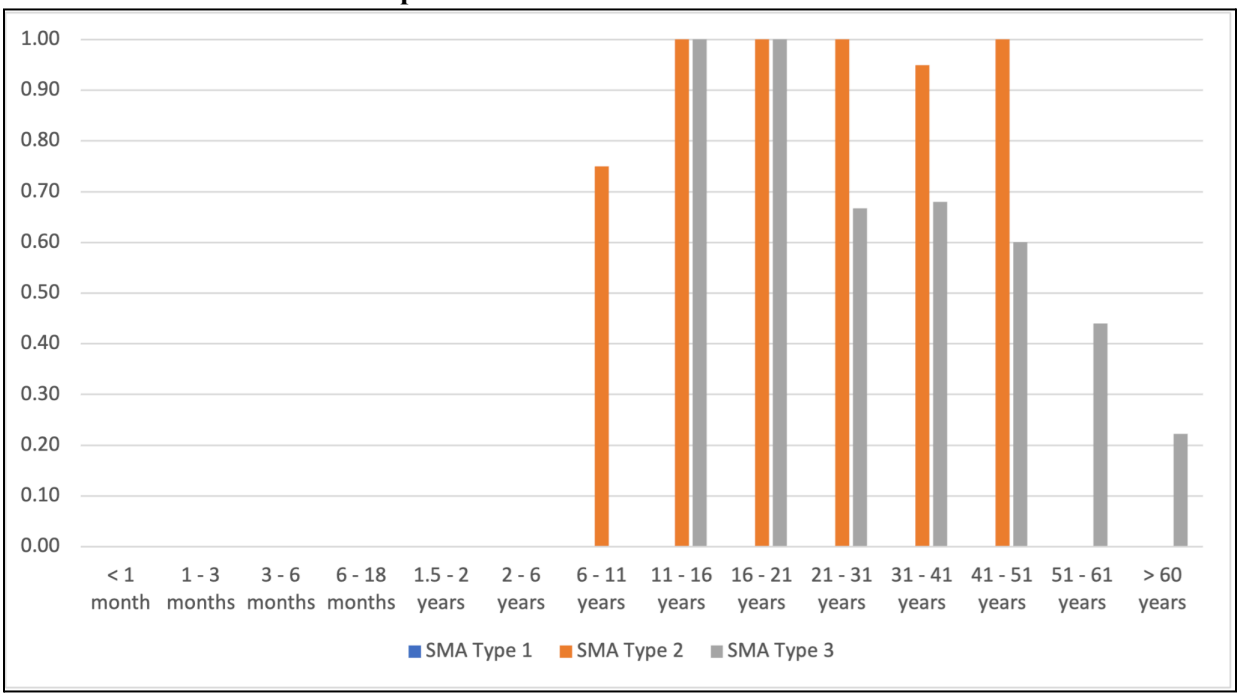
*Data are only displayed for age categories with sufficient sample size (i.e. > 5 cases) to report proportions. For SMA type 1, the age category 21-31 years was excluded from the figure. For SMA type 2, the age category >60 years was excluded from the figure.

Skeletal deformities (Figure 2)

The proportion of patients ever diagnosed with **scoliosis** varied by age group. The highest proportion of patients diagnosed with scoliosis was observed in the 11-16 year age group (100%), followed by the 16-21 year age group (95.8%).

Surgery for scoliosis was less common for patients aged 1 month to 11 years and aged 31 years or older, with a majority of these patients never having undergone surgery, whereas a majority of patients 11 to 31 years did have surgery. This trend varied by SMA type: 96.7% of patients with SMA type 2 aged 16-21 years had surgery for scoliosis and a majority of SMA type 3 in all age groups had never had surgery for scoliosis. For patients with SMA type 1, most patients younger than 11 had not had surgery and there was limited information for older age groups. The **median age at surgery for scoliosis** among all never treated patients was 17.2 years and ranged from 2.2 years in SMA type 1 patients to 35.9 years in SMA type 3 patients.

Figure 2. Proportion of patients ever diagnosed with scoliosis per class of age in SMA 1, SMA 2 and SMA 3 never treated patients

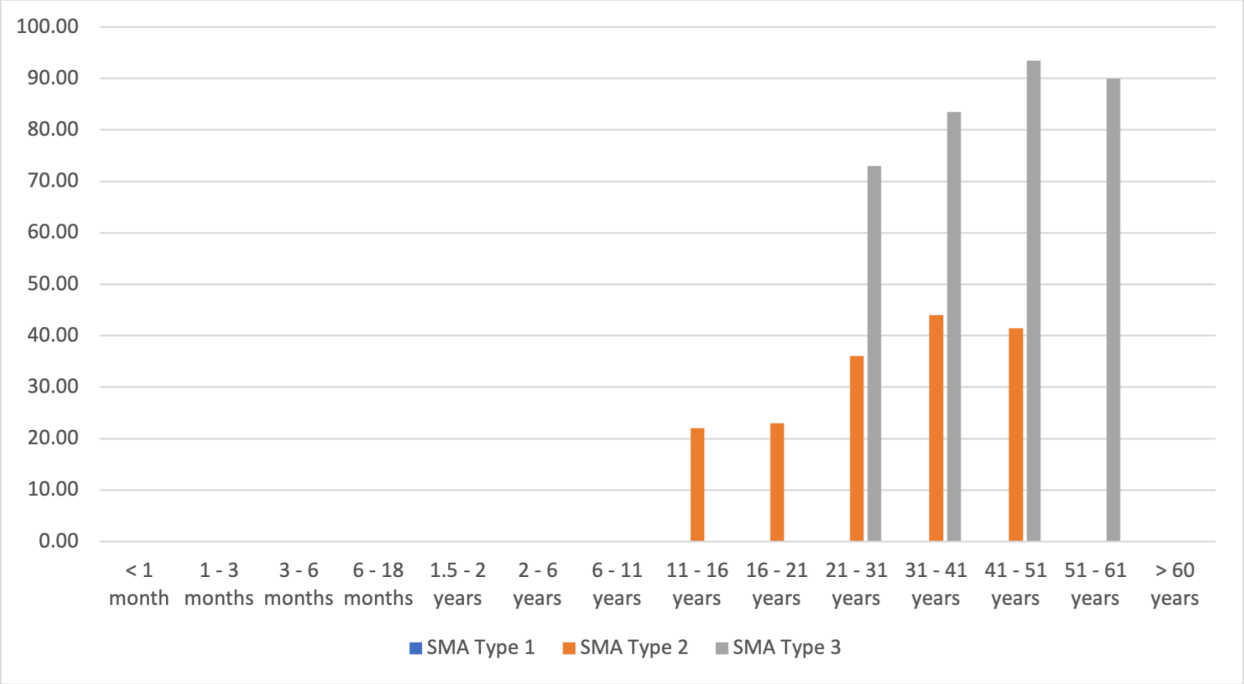


*Data are only displayed for age categories with sufficient sample size (i.e. > 5 cases) to report proportions. For SMA type 1, age categories 2-6 years, 6-11 years, 11-16 years, 16-21 years, and 21-31 years were excluded from the figure. For SMA type 2, age categories 51-61 years and >60 years were excluded from the figure. For SMA type 3, the age category 6-11 years was excluded from the figure.

Respiratory function (Figures 3-5)

Forced vital capacity percentage (fig. 3) was estimable for SMA type 2 patients aged 11-16 years to 41-51 years and SMA type 3 patients aged 21-31 years to 51-61 years. The lowest value was observed among SMA type 2 patients aged 11-16 years (22% [18%, 50%]) and the highest value was observed among SMA type 3 patients aged 41-51 years (93.5% [66%, 99.5%]).

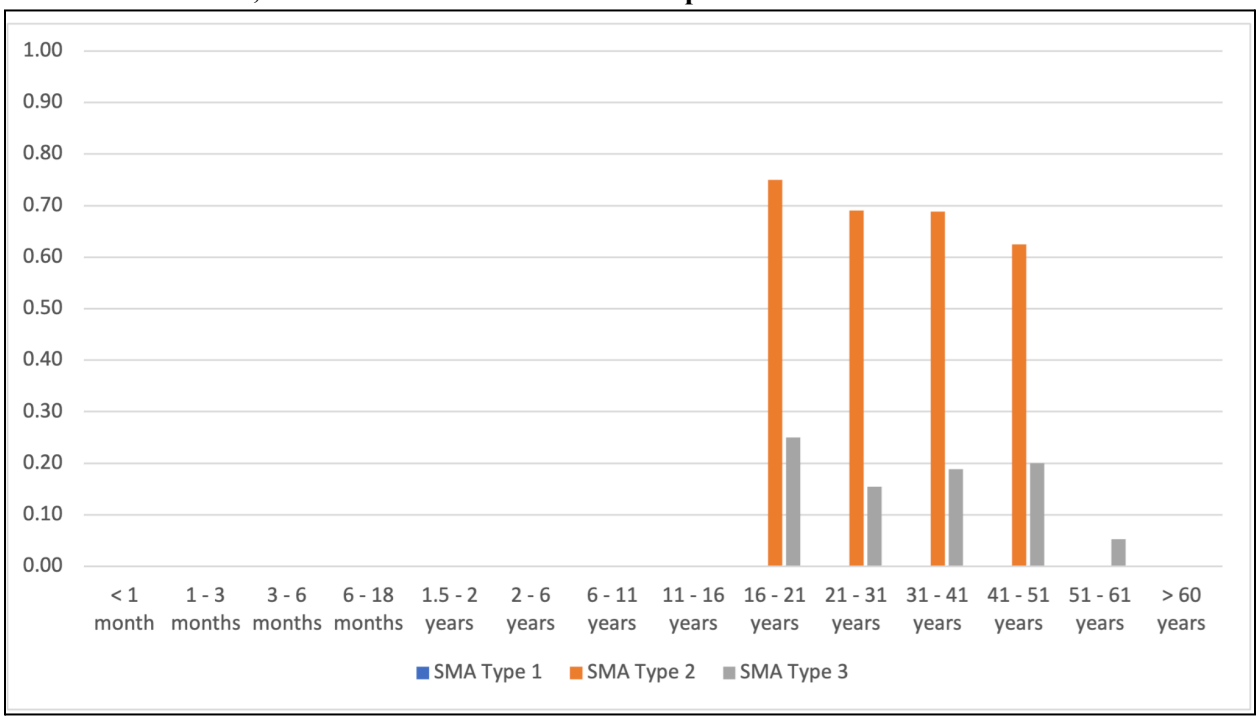
Figure 3. Median forced vital capacity percentage per class of age in SMA 1, SMA 2 and SMA 3 never treated patients



*Data are only displayed for age categories with sufficient sample size (i.e. > 5 cases) to report proportions. For SMA type 1, age categories 1.5-2 years, 2-6 years, and 11-16 years were excluded from the figure. For SMA type 2, age categories 6-11 years and 51-61 years were excluded from the figure. For SMA type 3, age categories 6-11 years, 11-16 years, 16-21 years, and >60 years were excluded from the figure.

The proportion of patients who had ever received **airway clearance assistance** (fig. 4) varied by age group, with the highest proportion observed in the 16-21 year category (59.3%). Airway clearance assistance was not reported for SMA type, 1 was more common in SMA type 2 patients than SMA type 3 patients.

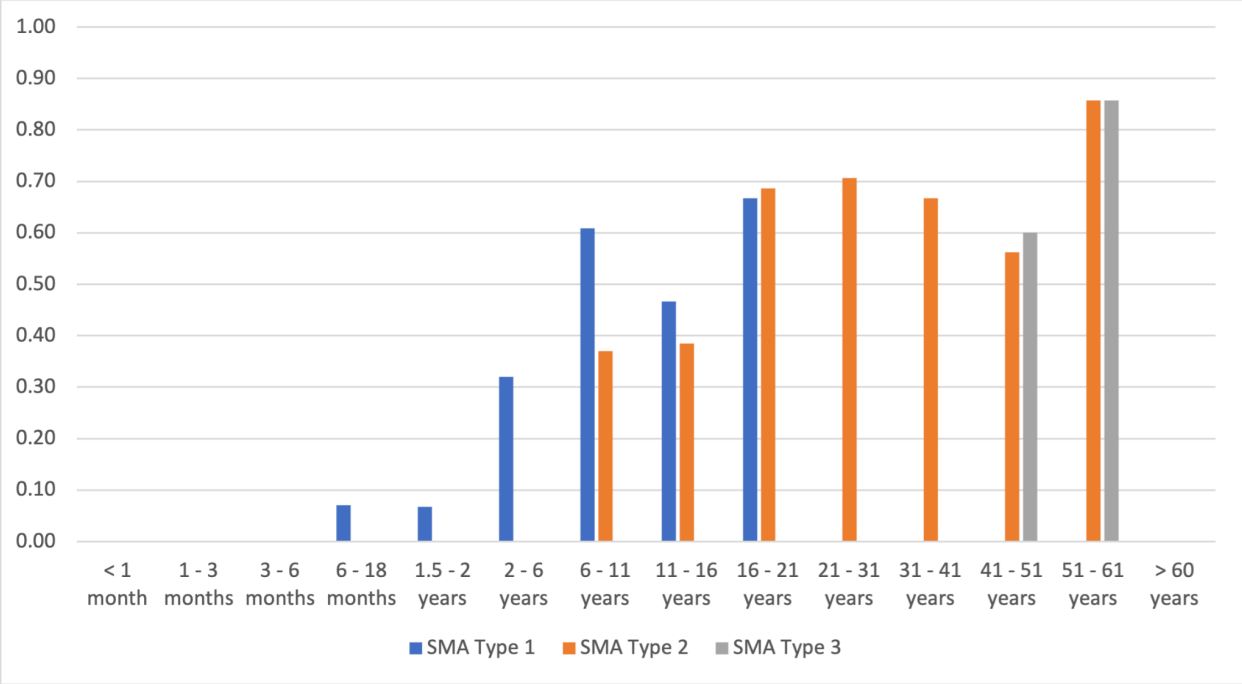
Figure 4. Proportion of patients with at least one episode of air clearance assistance per class of age in SMA 1, SMA 2 and SMA 3 never treated patients



*Data are only displayed for age categories with sufficient sample size (i.e. > 5 cases) to report proportions. For SMA type 1, age categories 6-18 months, 2-6 years, 6-11 years, 16-21 years, and 21-31 years were excluded from the figure. For SMA type 2, age categories 2-6 years, 6-11 years, and 51-61 years were excluded from the figure.

A majority of never treated patients aged 16 to 61 years had at least one episode of **non-invasive ventilation (fig.5)**, with the highest proportions observed among SMA type 2 patients aged 51-61 years (n=6; 85.7%) and SMA type 3 patients aged 51-61 years (n=6; 85.7%).

Figure 5. Proportion of patients with at least one episode of non-invasive ventilation per class of age in SMA 1, SMA 2 and SMA 3 never treated patients.



*Data are only displayed for age categories with sufficient sample size (i.e. > 5 cases) to report proportions. For SMA type 1, the age category 21-31 years was excluded from the figure. For SMA type 2, the age category >60 years was excluded from the figure. For SMA type 3, age categories 11-16 years, 21-31 years, 31-41 years, and >60 years were excluded from the figure

Data on **invasive ventilation** were available only for SMA type 1 patients. Invasive ventilation was observed in 100% (n=9) of SMA 1 patients aged 6-11 years and full time invasive ventilation was observed in the majority of the 6-11 year age group (n=8; 88.9%).

Pulmonary infections reported as a cause of hospitalisation or as a comorbidity was rare across all age groups (fewer than five patients in age groups 16-21 years and 21-31 years). Data on **respiratory physiotherapy** were missing for 814 patients overall; among SMA type 2 patients, 75% (n=12) of patients aged 21-31 years and 75% (n=6) of patients aged 31-41 years had at least one episode of respiratory therapy.

Nutritional function

Exclusive feeding tube usage was reported in few patients aged 16-21 years (n=5, 26.3%) and 21-31 years (n=5; 29.4%). The majority of SMA types 1 and 2 patients in age groups for which data were estimable did not have an episode of exclusive feeding tube usage. **Gastrostomy** was observed in very few patients overall (n<5 in each age category).

Hospitalisations and deaths

Data on the annual number of **hospitalisations** was missing for 94.3% of patients. The median number of annual hospitalizations was 1 [1, 1.4] and was similar across SMA type 1, 2 and 3 groups.

Cause of death data was missing for 99.2% of patients, with n<5 patients in each reported category.

The median event-free survival (death or permanent ventilation) was 11.5 months in SMA type 1, 219 months in SMA type 2, and 532 months in SMA type 3.

Quality of life (QoL) using patient-reported outcomes (PROs) (Table 13)

Spain PROFuture Mobility and Independence PRO at genetic report date was available for 25 (43.9%) patients and the median [IQR] score for the entire never treated population was 50 [42, 60.6]. The **best score** for Spain PROFuture Mobility and Independence PRO was also available for 25 (43.9%) never treated patients. Among the never treated patients for whom the best score for Spain PROFuture Mobility and Independence PRO was reported, the median score was 50 [40.2, 59] for overall never treated patients and was highest for SMA type 2 (56.9, [51, 64.9]) and least for SMA type 3 (42, [27.4, 50]).

Belgium ACTIVLIM PRO at genetic report date was available for 47 (87.0%) never treated patients and the median [IQR] score for the entire never treated population was -8.1 [-8.1, -2.9]. The **best score** for Belgium ACTIVLIM PRO was available for 46 (85.2%) never treated patients and the median score was -6.6 [-8.1, -2.7] for overall never treated patients and was lowest for SMA type 2 (-8.1, [-8.1, -8.1]) and highest for SMA type 3 (-3.5, [-8.1, -2.6]).

Table 13 - In Spain and Belgium, Quality of life (QoL) using patient-reported outcomes (PROs) in SMA 1, SMA 2 and SMA 3 never treated patients

Spain	Overall (N = 57)	SMA Type 1 (N < 5)	SMA Type 2 (N = 34)	SMA Type 3 (N = 20)
Score for Spain PROFuture Mobility and Independence PRO at genetic report date				
Median [IQR]	50 [42, 60.6]	-	59.3 [51.5, 67.5]	43.3 [36.5, 50]
PRO available; n (%)	25 (43.9%)	0 (0.0%)	12 (35.3%)	13 (65.0%)
Best score for Spain PROFuture Mobility and Independence PRO				
Median [IQR]	50 [40.2, 59]	-	56.9 [51, 64.9]	42 [27.4, 50]
PRO available; n (%)	25 (43.9%)	0 (0.0%)	12 (35.3%)	13 (65.0%)
Belgium	**Overall (N = 54)**	**SMA Type 1 (N = 5)**	**SMA Type 2 (N = 18)**	**SMA Type 3 (N = 26)**
Score for Belgium ACTIVLIM PRO at genetic report date				
Median [IQR]	-8.1 [-8.1, -2.9]	*	-8.1 [-8.1, -8.1]	-5.2 [-8.1, -2.7]
PRO available; n (%)	47 (87.0%)	1 (20.0%)	17 (94.4%)	24 (92.3%)
Best score for Belgium ACTIVLIM PRO				
Median [IQR]	-6.6 [-8.1, -2.7]	*	-8.1 [-8.1, -8.1]	-3.5 [-8.1, -2.6]
PRO available; n (%)	46 (85.2%)	1 (20.0%)	17 (94.4%)	23 (88.5%)

10.4.2.2 SMA Patients Treated with DMTs

Overall (Table 14), 1,321 patients were ever treated across all registries, 276 (20.9%) patients having SMA type 1, SMA type 2 having 540 (40.9%) patients, SMA type 3 having 476 (36.0%) patients, SMA type 4 having 9 (0.7%) patients, SMA type other having 4 (0.3%) patients, SMA type presymptomatic having 7 (0.5%) patients, and 9 (0.7%) patients with a missing SMA type.

Out of all patients that were treated, the largest proportion of patients were included in **registries** from the Germany and Austria (22.9%), followed by Czech Republic and Slovakia (20.4%), Spain (19.8%), Belgium (15.3%), United Kingdom and Ireland (12.9%), and Sweden (8.8%).

Males represented 51.7% of all patients and were more present in SMA type 1 and 3 while **females** were 52.8% in SMA type 2.

Methods used for genetic testing were missing for the majority of treated patients. However, among 437 treated patients with non-missing data (33.1% of total treated population), the majority (n=412) had MLPA as their method used for genetic testing, with similar trends observed across all SMA types. The majority (88.9%) of all treated patients had a homozygous deletion of exon 7 as their SMN1 variant and similar trends were observed across all SMA types.

Table 14: Sex, registry, age at symptom onset and method used for genetic testing in SMA 1, SMA 2 and SMA 3 treated patients

	Overall (N = 1321)	SMA Type 1 (N = 276)	SMA Type 2 (N = 540)	SMA Type 3 (N = 476)
Sex: female / male (%)	48.3% / 51.7%	42.8% / 57.2%	52.8% / 47.2%	46.2% / 53.8%
Registry n, %				
Belgium	202 (15.3%)	29 (10.5%)	83 (15.4%)	77 (16.2%)
Czech R & Slovakia	269 (20.4%)	71 (25.7%)	100 (18.5%)	90 (18.9%)
Germany & Austria	302 (22.9%)	53 (19.2%)	116 (21.5%)	131 (27.5%)
Spain	262 (19.8%)	70 (25.4%)	119 (22.0%)	73 (15.3%)
UK & Ireland	170 (12.9%)	27 (9.8%)	77 (14.3%)	63 (13.2%)
Sweden	116 (8.8%)	26 (9.4%)	45 (8.3%)	42 (8.8%)
Age at symptom onset (years) - Median [IQR]	1 [0.5, 2]	0.2 [0.1, 0.3]	0.8 [0.6, 1.1]	2.5 [1.5, 6]
Method used for genetic testing; n (%)				
MLPA	412 (31.2%)	80 (29.0%)	153 (28.3%)	156 (32.8%)
missing	884 (66.9%)	192 (69.6%)	377 (69.8%)	310 (65.1%)

Motor function assessment (table 15)

With respect to **functional status at genetic report**, data were missing for a majority (75.9%) of all treated patients. However, among 319 treated patients with non-missing data, a majority (n=197 - 14.9%) had non-sitter as their functional status, which held true across all SMA types 1, 2, and 3. Patients with SMA type 3 had a higher proportion of walkers (10.7%) than the overall population (4.3%).

With respect to **best functional status after treatment with a DMT**, data were missing for 11.7% of all treated patients. Among SMA type 1 patients, 36.6% of patients achieved “sitter” status, followed by 23.6% who achieved “non-sitter” status, and 12% who achieved “walker” status. These trends differed among other SMA type subgroups, with 60.9%, 24.6%, and 5.9% of SMA type 2 patients achieving “sitter,” “walker,” and “non-sitter,” status, respectively. Among SMA type 3 patients, 87.8% of patients

achieved “walker” status, followed by 5.3% of patients who achieved “sitter” status and 1.5% of patients who achieved “non-sitter” status.

Among all treated patients, 11.7% also had missing data for their **best achieved motor milestone after treatment with a DMT**. The largest proportion of patients had achieved climbing stairs after treatment (n=330; 25%). This trend was largely driven by SMA type 3 patients, among whom 63.4% had achieved this motor milestone. However, among SMA types 1 and 2, the motor milestone with the highest observed proportion of patients was sitting without support, with 75 (27.2% of all SMA type 1 patients) and 205 (38% of all SMA type 2 patients) achieving this milestone, respectively. Among SMA type 3 patients, 92 (19.3% of all SMA type 3 patients) had achieved walking 10 metres without assistance. A majority (88.9%) of SMA type 4 patients had achieved climbing stairs.

For the best score for **CHOP-INTEND**, data were missing for 83.6% of patients. The median [IQR] best score for all treated patients was 46 [33.8, 56.2], with SMA types 1 and 2 having median best scores of 44 [33, 54] and 46 [35, 57.5], respectively. SMA type 3 patients had a median best score of 51 [28.5, 64] and SMA type presymptomatic patients had a median best score of 53 [38, 62]. At the report of the first best CHOP-INTEND score, the mean ages for SMA types 1 and 2 were 3.4 (SD=3.3) years and 8.7 (SD=8.6) years, respectively, while the mean ages for SMA types 3 and presymptomatic were 21.4 (SD=16) years and 0.2 (SD=0.2) years, respectively.

For the best score for **HFSM(-E),** data were missing for 68.7% of patients. SMA types 1 and 2 had lower median values of 15 [3, 27] and 12.5 [4, 31.2], respectively, while SMA types 3 and 4 had median values of 50 [29.8, 58] and 44 [39, 62], respectively. At the report of the first best HFSM(-E) score, the mean age increased across SMA types 1, 2, 3, and 4, with mean ages of 5.9 (SD=6.6) years, 11.8 (SD=9.5) years, 21.4 (SD=15.5) years, and 42.3 (SD=10.8) years, respectively.

For the best score for **RULM**, data were missing for 73.2% of patients. The median best recorded score increased across SMA types 1, 2, and 3, with values of 11.5 [8.2, 19.5], 17 [10, 24], and 35.5 [26.8, 37], respectively. At the report of the first best RULM right side score, the mean ages of SMA types 1, 2, and 3 patients were 5.4 (SD=3.7) years, 12.7 (SD=9.1) years, and 12 (SD=4.3) years, respectively.

For the best score for **MFM32,** data were missing for a majority (94.3%) of all treated patients. The median best recorded score for SMA type 2 patients was 37 [26, 48], while the median best recorded score for SMA type 3 patients was 80 [53.5, 90].

Data on the best recorded score for **HINE-2** were not reported/missing for 100% of patients. Regarding the best recorded **6MWT** score, data were missing for 100% of SMA type 1 patients and 99.8% of SMA type 2 patients. The median best scores for SMA type 3 and type 4 patients were 376 [275, 458] and 450 [190, 525], respectively. The mean ages at the report of the first best 6MWT score for SMA type 3 and type 4 patients were 21.5 (SD=15) years and 42.5 (SD=9.9) years, respectively.

Table 15: Motor function assessment in SMA 1, SMA 2 and SMA 3 treated patients

	Overall (N = 1321)	SMA Type 1 (N = 276)	SMA Type 2 (N = 540)	SMA Type 3 (N = 476)
Functional status at genetic report; n (%)				
Non-sitter	197 (14.9%)	25 (9.1%)	111 (20.6%)	59 (12.4%)
Sitter	65 (4.9%)	*	53 (9.8%)	10 (2.1%)
Walker	57 (4.3%)	-	6 (1.1%)	51 (10.7%)
Missing	1002 (75.9%)	249 (90.2%)	370 (68.5%)	356 (74.8%)
Best functional status before treatment; n				

(%)				
Non-sitter	*	*	*	-
Sitter	15 (1.1%)	-	15 (2.8%)	-
Walker	18 (1.4%)	-	*	14 (2.9%)
Missing	1286 (97.4%)	275 (99.6%)	521 (96.5%)	462 (97.1%)
Best functional status after treatment; n (%)				
Non-sitter	106 (8.0%)	65 (23.6%)	32 (5.9%)	7 (1.5%)
Sitter	460 (34.8%)	101 (36.6%)	329 (60.9%)	25 (5.3%)
Walker	600 (45.4%)	33 (12.0%)	133 (24.6%)	418 (87.8%)
Missing	155 (11.7%)	77 (27.9%)	46 (8.5%)	26 (5.5%)
Best achieved motor milestone after treatment; n (%)				
Climb stairs	330 (25.0%)	*	15 (2.8%)	302 (63.4%)
Crawl	92 (7.0%)	6 (2.2%)	75 (13.9%)	9 (1.9%)
Hold head without support	41 (3.1%)	14 (5.1%)	21 (3.9%)	5 (1.1%)
Roll onto side	65 (4.9%)	51 (18.5%)	11 (2.0%)	*
Sit without support	296 (22.4%)	75 (27.2%)	205 (38.0%)	13 (2.7%)
Stand with assistance	62 (4.7%)	20 (7.2%)	42 (7.8%)	-
Stand without assistance	10 (0.8%)	-	7 (1.3%)	*
Unknown	-	-	-	-
Walk 10 metres without assistance	115 (8.7%)	5 (1.8%)	16 (3.0%)	92 (19.3%)
Walk with assistance	107 (8.1%)	18 (6.5%)	86 (15.9%)	*
Walk without assistance	48 (3.6%)	8 (2.9%)	16 (3.0%)	22 (4.6%)
Missing	155 (11.7%)	77 (27.9%)	46 (8.5%)	26 (5.5%)
Best score for CHOP-INTEND				
Median [IQR]	46 [33.8, 56.2]	44 [33, 54]	46 [35, 57.5]	51 [28.5, 64]
Missing	1105 (83.6%)	170 (61.6%)	453 (83.9%)	466 (97.9%)
Best score for HFMS(-E)				
Median [IQR]	29 [8.2, 50]	15 [3, 27]	12.5 [4, 31.2]	50 [29.8, 58]
Missing	907 (68.7%)	221 (80.1%)	372 (68.9%)	296 (62.2%)
Best score for RULM				
Median [IQR]	24 [14, 36]	11.5 [8.2, 19.5]	17 [10, 24]	35.5 [26.8, 37]
Missing	967 (73.2%)	242 (87.7%)	377 (69.8%)	328 (68.9%)

Note: * indicates n < 5 patients

Skeletal deformities

A majority of SMA type 1 patients had been diagnosed with **scoliosis** from ages 2 (n=72; 63.7%) to 31 years (n=9; 90%), peaking within the age groups of 11 to 16 years (n=13; 100%) and 16 to 21 years (n=6; 100%). Among SMA type 1 patients younger than 2 years, 40% (n=12) of patients aged 6 to 18 months and 35.7% (n=5) of patients aged 1.5 to 2 years had been diagnosed with scoliosis. Among SMA type 2 patients, a majority of patients in the age ranges 6-11 years (n=81; 76.4%) through 51-61 years (n=15; 93.8%) had been diagnosed with scoliosis, with the lowest proportion observed among patients aged 2 to

6 years (n=34; 45.3%). A smaller proportion of SMA type 3 patients had been diagnosed with scoliosis, with the majority of patients in the age groups 11-16 (n=38; 70.4%) through 31-41 years (n=25; 55.6%) being diagnosed while 12.5% (n < 5) of patients aged 2 to 6 years and 27.6% (n=8) of patients aged older than 60 years had been diagnosed.

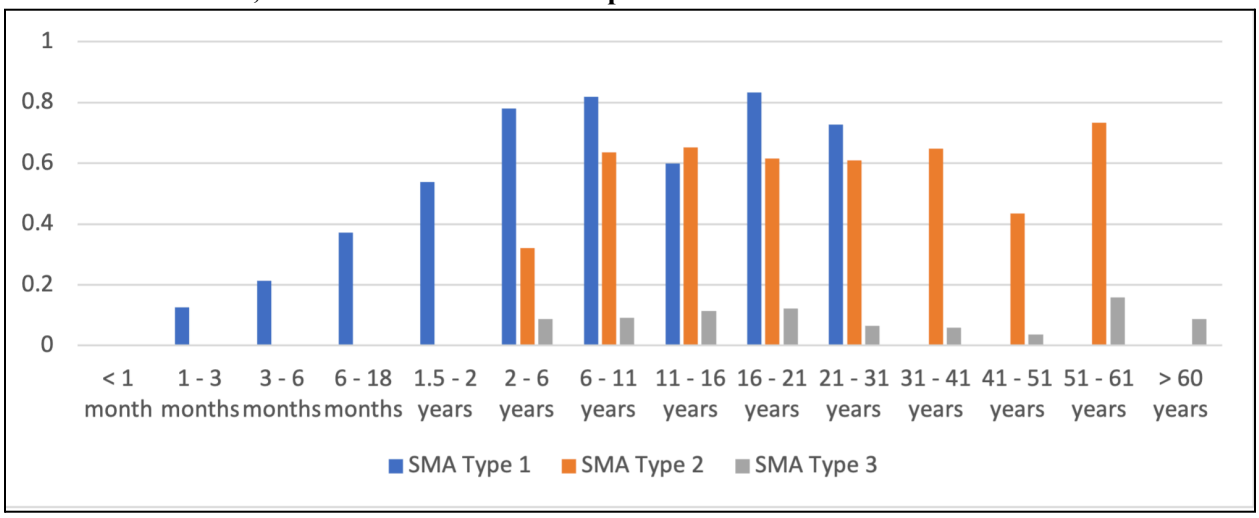
Almost one third (32.2%) of SMA type 1 patients had reported at least one use of a **spinal brace ever**, while 15% of SMA type 2 patients and 4% of SMA type 3 patients had reported at least one use.

Among SMA type 1 patients, **surgery for scoliosis** was observed among patients aged 2 to 31 years, with the highest proportion observed among patients aged 11 to 16 years (n=8; 61.5%); the mean age at surgery was 7 (SD=7.2) years. Among SMA type 2 patients, surgery for scoliosis was observed among patients aged 2 to 61 years, with the majority of patients in the age groups 11-16 (n=75; 81.5%) through 31-41 years (n=24; 53.3%) having had surgery. The highest proportion of patients with surgery was observed in the age class 16 to 21 years (n=71; 93.4%); the mean age at surgery was 18.7 (SD=13.3) years. A smaller proportion of SMA type 3 patients had reported having surgery for scoliosis; with surgery beginning at 6-11 years (n < 5; 7.7%), peaking in the 11 to 16 year age group (n=15; 33.3%), and extending to the 51 to 61 year age group (n=5; 10%). The mean age at surgery for SMA type 3 patients was 32.9 (SD=18.7) years.

Respiratory function (figures 6, 7, 8)

With respect to **airway clearance assistance,** a growing majority of SMA type 1 treated patients in the age groups 0.5-1.5 years (n=16; 37.2%) through 21-31 years (n=8; 72.7%) had at least one episode of assistance. Among SMA type 2 treated patients, a majority of patients in the age groups 6-11 years (n=68; 63.6%) through 51-61 years (n=11; 73.3%) had at least one episode of airway clearance assistance while a majority of SMA type 3 treated patients did not require airway clearance assistance. Data were limited for other SMA types.

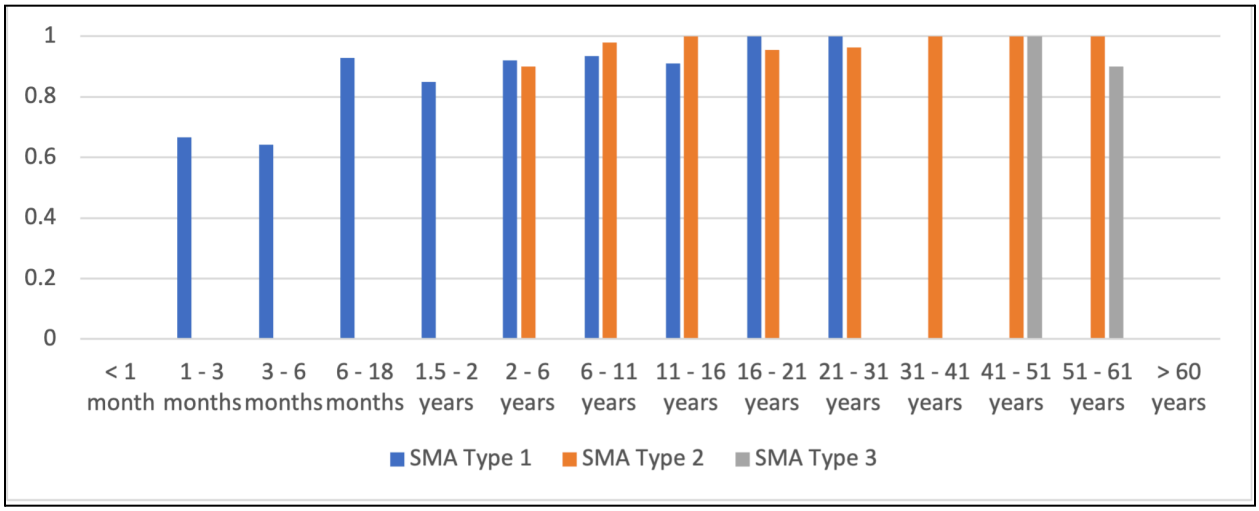
Figure 6: Proportion of patients with at least one episode of air clearance assistance per class of age in SMA 1, SMA 2 and SMA 3 treated patients



With respect to **non-invasive ventilation,** a majority of SMA type 1 treated patients in the age groups 1-3 months (n=12; 66.7%) through 21-31 years (n=9; 100%) had at least one episode. Among SMA type 2 treated patients, a majority of patients in the age groups 2-6 years (n=18; 90%) through 51-61 years (n=8;

100%) had at least one episode of non-invasive ventilation, while a majority of SMA type 3 treated patients in the age groups 41-51 (n=7; 100%) through 51-61 years (n= 9; 90%) had at least one episode. Data were limited for other SMA types.

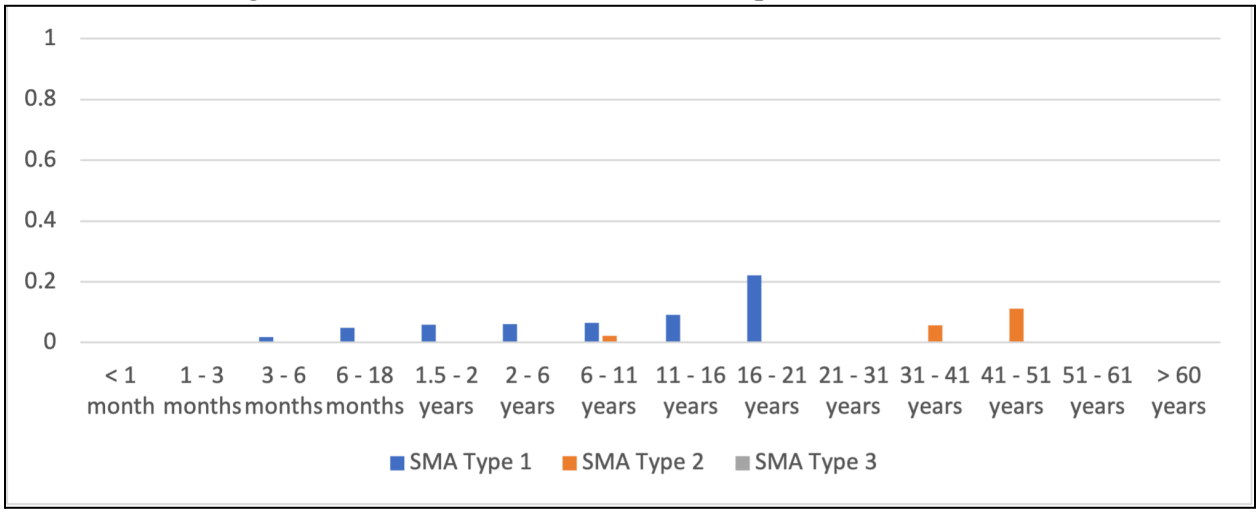
Figure 7: Proportion of patients with at least one episode of any non-invasive ventilation per class of age in SMA 1, SMA 2 and SMA 3 treated patients



*Data are only displayed for age categories with sufficient sample size (i.e. > 5 cases) to report proportions. For SMA type 3, age categories 6-11 years, 11-16 years, 21-31 years, 31-41 years, and >60 years were excluded from the figure.

With respect to **full-time non-invasive ventilation**, a majority of SMA type 1 patients did not have an episode; a growing proportion of patients in the age groups 3-6 months (n < 5; 1.9%) through 11-16 years (n < 5; 9.1%) had at least one episode of full-time non-invasive ventilation. Similarly, a majority of SMA type 2 patients did not have an episode, with the highest proportion reported among patients aged 51 to 61 years (n < 5; 11.1%). There were no SMA type 3 patients with an episode of full-time non-invasive ventilation.

Figure 8: Proportion of patients with at least one episode of full-time non-invasive ventilation per class of age in SMA 1, SMA 2 and SMA 3 treated patients



Invasive ventilation has been observed primarily in SMA type 1. A majority of treated SMA type 1 patients from age categories 6 to 18 months (n=13; 81.2%) to 16 to 21 years (n < 5; 100%) had

experienced at least one episode of any invasive ventilation. Few SMA type 2 patients, and SMA type 3 patients, (<5 patients per age category) reported invasive ventilation from 6 years and older, and from 41 years and older, respectively. Regarding **full-time invasive ventilation**, 60% (n=12) of SMA type 1 patients aged 6 to 11 years and 66.7% (n=6) of patients aged 11 to 16 years had experienced at least one episode of full-time invasive ventilation. This information was limited to SMA type 1 patients.

Pulmonary infections reported as a cause of hospitalisation or as a comorbidity were rare across all age groups and SMA type, with less than 5 cases when occurred. **Respiratory physiotherapy** episodes were observed in the majority of SMA type 1 patients, starting from 1 month with increasing percentages. A similar trend was observed in patients with SMA type 2, and very few cases (fewer than 5) in SMA 3.

Nutritional function

Exclusive feeding tube usage was most common in SMA type 1 patients with a majority of patients in the age groups 3-6 months (n=14; 31.8%) through 6-11 years (n=14; 73.7%) experiencing at least one episode of exclusive feeding tube usage. SMA type 2 patients experienced exclusive feeding tube usage to a lesser extent and for older age categories in the age groups 6-11 years (n=6; 100%) through 11-16 years (n=7; 58.3%) with some cases reported until 51-61 years. No **gastrostomy** was observed.

Hospitalisations and deaths (table 16)

Data on the annual number of hospitalisations were missing for the majority of all treated patients (n=802; 60.7%). Among all treated patients, the median [IQR] annual number of hospitalisations was 1 [1, 2], with identical values across SMA types 1, 2, and 3. There were insufficient data to report this variable across other SMA types.

Causes of death were poorly reported (these data were missing for 99.8%) and the most commonly reported ones were for “Pneumonia, organism unspecified,” “Hypovolaemic shock,” or “Instantaneous death,” with fewer than five patients in each category.

The median event-free survival (death or permanent ventilation) was 10 months in SMA type 1 and 143 months in SMA type 2 and no event (death/permanent ventilation) has been reported in SMA 3 patients.

Table 16: Hospitalisation and event-free survival in SMA 1, SMA 2 and SMA 3 treated patients

	Overall (N = 1321)	SMA Type 1 (N = 276)	SMA Type 2 (N = 540)	SMA Type 3 (N = 476)
Annual number of hospitalisations				
Median [IQR]	1 [1, 2]	1 [1, 2]	1 [1, 2]	1 [1, 2]
Missing	802 (60.7%)	134 (48.6%)	318 (58.9%)	328 (68.9%)
Event-free survival, death or permanent ventilation (months)				
Median [IQR]	13 [6, 35]	10 [6, 24]	143 [83, 246]	-
Number (%) of censored patients	1271 (96.2%)	235 (85.1%)	531 (98.3%)	476 (100%)

Quality of life (QoL) using patient-reported outcomes (PROs) (Table 17)

Spain PROFuture Mobility and Independence PRO at genetic report date was available for 123 (46.9%) treated patients and the median [IQR] score for the entire treated population was 44 [22.3, 66.1]. The **Best score** for Spain PROFuture Mobility and Independence PRO was available for 114 (43.5%) treated patients. Among the treated patients for whom this score was reported, the median score was 39.5

[17.8, 64.8] for overall treated patients and was the highest for SMA type 1 and the lowest for SMA type 3.

Belgium ACTIVLIM PRO at genetic report date was available for 148 (73.3%) treated patients and the median [IQR] score for the entire treated population was -3.7 [-8.1, 0.1]. The **Best score** for Belgium ACTIVLIM PRO was available for 139 (68.8%) treated patients and the median score was -3 [-8.1, 0.4] for overall treated patients.

Table 17 - In Spain and Belgium, Quality of life (QoL) using patient-reported outcomes (PROs) in SMA 1, SMA 2 and SMA 3 treated patients

Spain	Overall (N = 262)	SMA Type 1 (N = 70)	SMA Type 2 (N = 119)	SMA Type 3 (N = 73)
Score for Spain PROFuture Mobility and Independence PRO at genetic report date				
Median [IQR]	44 [22.3, 66.1]	65.9 [46.5, 80.6]	51.5 [38.6, 67.8]	13.1 [6, 29.7]
PRO available; n (%)	123 (46.9%)	23 (32.9%)	62 (52.1%)	38 (52.1%)
Best score for Spain PROFuture Mobility and Independence PRO				
Median [IQR]	39.5 [17.8, 64.8]	64.5 [48.8, 80.1]	50 [28.2, 66.3]	10.9 [4.8, 27.7]
PRO available; n (%)	114 (43.5%)	22 (31.4%)	56 (47.1%)	36 (49.3%)
Belgium	**Overall (N = 202)**	**SMA Type 1 (N = 29)**	**SMA Type 2 (N = 83)**	**SMA Type 3 (N = 77)**
Score for Belgium ACTIVLIM PRO at genetic report date				
Median [IQR]	-3.7 [-8.1, 0.1]	*	-8.1 [-8.1, -3.9]	-0.1 [-3.5, 2.5]
PRO available; n (%)	148 (73.3%)	*	70 (84.3%)	69 (89.6%)
Best score for Belgium ACTIVLIM PRO				
Median [IQR]	-3 [-8.1, 0.4]	*	-6.6 [-8.1, -3.7]	0.1 [-2.4, 2.8]
PRO available; n (%)	139 (68.8%)	*	65 (78.3%)	65 (84.4%)

SMA Patients Treated with Evrysdi

Overall (Table 18), 403 patients were treated with Evrysdi across all registries. Of these patients, 64 (15.9%) had SMA Type 1, 226 (56.0%) had SMA type 2, 101 (25.1%) had SMA type 3, 1 (0.2%) had SMA type 4, 3 (0.7%) had SMA type other, 1 (0.2%) had presymptomatic SMA, and SMA type information was missing for 7 (1.7%) patients. The largest proportion of patients was from the Germany/Austria registry (21.8%), followed by the United Kingdom and Ireland (20.3%), Czech Republic and Slovakia (18.1%), Belgium (15.9%), Sweden (13.9%), and Spain (9.9%).

Males represented 46.4% of all patients. More than 50% of patients with SMA type 1 and type 3 were males, while 57.5% of patients with SMA type 2 were **females**.

Methods used for genetic testing were missing for 59.1% of treated patients. Among treated patients with non-missing data, the majority had MLPA as their method used for genetic testing (38.5%), with similar trends observed across all SMA types. The majority (86.1%) of all treated patients had a

homozygous deletion of exon 7 as their SMN1 variant and similar trends were observed across all SMA types.

Table 18: Sex, registry, age at symptom onset and method used for genetic testing among patients with SMA type 1, SMA type 2 and SMA type 3 treated with Evrysdi

	Overall (N = 403)	SMA Type 1 (N = 64)	SMA Type 2 (N =226)	SMA Type 3 (N = 101)
Sex: female / male (%)	53.6%/46.4%	46.9%/53.1%	57.5%/42.5%	47.5%/52.5%
Registry n, %				
Belgium	64 (15.9%)	11 (17.2%)	38 (16.8%)	9 (8.9%)
Czech R & Slovakia	73 (18.1%)	17 (26.6%)	38 (16.8%)	16 (15.8%)
Germany & Austria	88 (21.8%)	12 (18.8%)	46 (20.4%)	30 (29.7%)
Spain	40 (9.9%)	7 (10.9%)	30 (13.3%)	*
UK & Ireland	82 (20.3%)	*	56 (24.8%)	20 (19.8%)
Sweden	56 (13.9%)	13 (20.3%)	18 (8.0%)	23 (22.8%)
Age at symptom onset (years) - Median [IQR]	1 [0.5, 1.5]	0.2 [0.2, 0.4]	0.9 [0.6, 1.2]	2 [1.5, 3]
Method used for genetic testing; n (%)				
MLPA	155 (38.5%)	29 (45.3%)	74 (32.7%)	42 (41.6%)
missing	238 (59.1%)	33 (51.6%)	145 (64.2%)	58 (57.4%)

Motor function assessment (Table 19)

Data on **functional status at genetic report** date was missing for the majority of patients (75.4%), with "non-sitter" being the most common recorded functional status overall (17.4%), and across all SMA type stratifications with available data. Data on **achieved motor milestones at genetic report date** was also missing for 75.4% of patients. Of patients with data on this indicator, "hold head without support" was the most common milestone recorded (15.1%), followed by "sit without support" (5.0%).

Data on the **best functional status after treatment**, as well as the best achieved motor milestone after treatment was missing for 16.4% of patients overall. "Sitter" was the most common status recorded overall (40.4%) and for SMA type 2 patients (58.5%). Among SMA type 1 patients, 29.7% had achieved "non-sitter" and 29.7% had achieved "sitter." Among SMA type 3 patients, 83.2% of patients had achieved "walker" and 7.9% had achieved "sitter." For the **best achieved motor milestone after treatment with a DMT**, the most common milestones overall were "sit without support" (26.1%) and "climb stairs" (15.4%). A majority (54.5%) of SMA type 3 patients achieved climbing stairs, while no SMA type 1 patients and fewer than 5 SMA type 2 patients achieved this milestone. Among SMA type 1 patients, 23.4% achieved sitting without support and 20.3% achieved rolling onto their side. Among SMA type 2 patients, 36.3% achieved sitting without support, while 2.2% achieved walking 10 metres without assistance.

The best score for **CHOP-INTEND** was 36 [28.8, 50.2]. The median scores for patients with SMA type 1 and 2 were fairly consistent with the overall estimate. Data relating to CHOP-INTEND for other SMA types was either limited or missing. At the report of the first best CHOP-INTEND score, the overall median age was 2.8 [1.7, 12.6] years. The best score for **HFMS(-E)** was 15 [3, 34] overall, with lower scores observed for patients with SMA type 1 (5 [0.5, 20.5]) and SMA type 2 (6 [2.8, 21.2]), and a higher score for patients with SMA type 3 (39 [24.8, 60]). At the report of the first best HFSM(-E) score, the overall median age was 11.2 [6.7, 15.5] years and patients with SMA type 1 were youngest with median age being 5.2 [3.6, 11.3] years. Regarding the best score for **RULM**, data were missing for 72.5% of patients. The median best recorded score increased across SMA types 1, 2, and 3, with values of 10.5 [-, 14.2], 15 [9, 22], and 36 [22, 37], respectively. At the report of the first best RULM right side score, the median age of SMA types 1, 2, and 3 patients were 3.3 [2.8, 5] years, 10.1 [4.4, 19.2] years, and 12.8 [10.6, 14.7] years, respectively. The best score for **MFM32** were missing for a majority (91.1%) of all treated patients. The median best recorded score for SMA type 2 patients was 34.5 [26, 45.2], while the median best recorded score for SMA type 3 patients was 46 [35.8, 69.5]. Data on the best recorded score for **HINE-2** were missing for 100% of patients. Regarding the best recorded **6MWT** score, data were missing for 93.6% of the patients. The median best scores for SMA type 3 were 485 [353, 539.8]. The median age at the report of the first best 6MWT score for SMA type 3 was 11.2 [8.8, 12.2] years.

Table 19: Motor function assessment in patients with SMA type 1, SMA type 2 and SMA type 3 treated with Evrysdi

	Overall (N = 403)	SMA Type 1 (N = 64)	SMA Type 2 (N =226)	SMA Type 3 (N = 101)
Functional status at genetic report; n (%)				
Non-sitter	70 (17.4%)	9 (14.1%)	38 (16.8%)	22 (21.8%)
Sitter	24 (6.0%)	-	22 (9.7%)	*
Walker	5 (1.2%)	-	*	*
Missing	304 (75.4%)	55 (85.9%)	164 (72.6%)	74 (73.3%)
Best functional status before treatment; n				

(%)				
Non-sitter	*	*	*	-
Sitter	7 (1.7%)	-	7 (3.1%)	-
Walker	*	-	*	*
Missing	391 (97.0%)	63 (98.4%)	217 (96.0%)	99 (98.0%)
Best functional status after treatment; n (%)				
Non-sitter	39 (9.7%)	19 (29.7%)	17 (7.5%)	*
Sitter	163 (40.4%)	19 (29.7%)	133 (58.8%)	8 (7.9%)
Walker	135 (33.5%)	*	45 (19.9%)	84 (83.2%)
Missing	66 (16.4%)	25 (39.1%)	31 (13.7%)	7 (6.9%)
Best achieved motor milestone after treatment; n (%)				
Climb stairs	62 (15.4%)	-	*	55 (54.5%)
Crawl	35 (8.7%)	*	32 (14.2%)	*
Hold head without support	18 (4.5%)	6 (9.4%)	10 (4.4%)	*
Roll onto side	21 (5.2%)	13 (20.3%)	7 (3.1%)	-
Sit without support	105 (26.1%)	15 (23.4%)	82 (36.3%)	5 (5.0%)
Stand with assistance	20 (5.0%)	*	17 (7.5%)	-
Stand without assistance	*	-	*	*
Unknown	-	-	-	-
Walk 10 metres without assistance	27 (6.7%)	-	5 (2.2%)	21 (20.8%)
Walk with assistance	31 (7.7%)	-	30 (13.3%)	*
Walk without assistance	15 (3.7%)	*	6 (2.7%)	7 (6.9%)
Missing	66 (16.4%)	25 (39.1%)	31 (13.7%)	7 (6.9%)
Best score for CHOP-INTEND				
Median [IQR]	36 [28.8, 50.2]	38 [24, 46]	34 [30, 40]	*
Missing	367 (91.1%)	47 (73.4%)	213 (94.2%)	99 (98.0%)
Best score for HFMS(-E)				
Median [IQR]	15 [3, 34]	5 [0.5, 20.5]	6 [2.8, 21.2]	39 [24.8, 60]
Missing	296 (73.4%)	45 (70.3%)	170 (75.2%)	73 (72.3%)
Best score for RULM				
Median [IQR]	19 [10, 26]	10.5 [-, 14.2]	15 [9, 22]	36 [22, 37]
Missing	292 (72.5%)	52 (81.2%)	156 (69.0%)	74 (73.3%)

Note: * indicates n < 5 patients

Skeletal deformities

For overall patients, **scoliosis diagnosis** was seen in patients as young as 6-18 months. The highest proportion of patients with a scoliosis diagnosis was in the 16-21 year age group (n=48; 100.0%). SMA type 2 had the highest proportion of patients with scoliosis diagnosis. Overall, 20.3% of SMA type 1 patients had reported at least one use of a **spinal brace ever**, while 10.6% of SMA type 2 patients and 5.9% of SMA type 3 patients had reported at least one use. **Surgery for scoliosis** was less common for all treated patients aged less than 6 years, whereas 50% or more of patients 11 to 40 years did have surgery (n=17; 50% of patients aged 31-41 years to n=58; 84.1% of patients aged 11-16 years). Trends observed for individual SMA type subgroups differed, though this may be influenced by small sample size and

limited data within stratifications. Patients with SMA type 2 were more likely to have had surgery vs patients overall.

Respiratory function

The proportion of patients who had ever received **airway clearance assistance** varied by age group, with the highest proportion observed in the 6-11 year category (n=23; 71.9%). Airway clearance assistance was more common in the SMA type 2 group, for age categories with available data. In general, data availability by stratification was limited for this indicator. With respect to **any non-invasive ventilation,** SMA type 1 treated patients aged 1 month to 31 years had at least one episode. Among SMA type 2 treated patients, a majority of patients aged 2 to 61 years had at least one episode of non-invasive ventilation. Data were limited for other SMA types. Data availability was either limited or missing for any **invasive ventilation and full-time invasive ventilation**, hence no interpretations were made for this variable.

Pulmonary infections reported in cause of hospitalisation or as a comorbidity were rare (n<5 in each age category) across all age groups. Respiratory physiotherapy was observed in patients as young as 3-6 months old, with the highest proportions observed in the 16-21 years age group (n=12; 100%) and 21-31 years age group (n=7; 100.0%). Data for SMA type stratifications was limited.

Nutritional function

Exclusive feeding tube usage was observed in patients as young as 3-6 months old, with the highest proportions observed in the 2-6 years age group (n=11; 100%) and 6-11 years age group (n=6; 100.0%). Data for SMA type stratifications was limited. No case of **gastrostomy** was noted across the different age categories.

Hospitalisations and death

Data on annual number of hospitalisations was missing for 75.7% of patients overall. Of overall patients with data available, the median number of annual hospitalizations was 1 [1, 1]. The highest median number of hospitalisations was observed for SMA type 2 patients (1 [1, 1.3]). Cause of death data was missing for 99.5% of patients overall. The event-free survival was 8 months in SMA type 1 and 120 months in SMA type 2 and no event (i.e., death or permanent ventilation) in SMA type 3. For the incidence rate of comorbidities per patient-year, zero comorbidities were noted in the overall group.

Quality of life (QoL) using patient-reported outcomes (PROs)

Spain PROFuture Mobility and Independence PRO at genetic report date was missing for 94.5% of the overall population, and the median score for the remaining patients with data was 57 [47.2, 74.8]. The **Best score for Spain PROFuture Mobility and Independence PRO at genetic report** was missing for 95.0% of treated patients. Among the treated patients, the Best score for Spain PROFuture Mobility and Independence PRO was only reported for SMA type 2 (54.5 [40.9, 67.3]).

Belgium ACTIVLIM PRO at genetic report date was missing for 88.6% of the overall population, and median score for overall patients with data was -5.6 [-8.1, -3.1]. The **Best score for Belgium ACTIVLIM PRO** was missing for 91.6% of treated patients and the median score was -5.3 [-8.1, -2.5] for overall treated patients.

SMA Patients Treated with Spinraza

Overall (Table 20), there were 1,003 patients treated with Spinraza across all registries. Of these patients, 215 (21.4%) had SMA Type 1, 363 (36.2%) had SMA type 2, 411 (41.0%) had SMA type 3, 8 (0.8%) had SMA type 4, 1 (0.1%) had SMA type other, 2 (0.2%) had presymptomatic SMA, and SMA type information was missing for 3 (0.3%) patients.

The largest proportion of patients was from the Germany/Austria registry (22.5%), followed by Spain (22.2%), Czech Republic and Slovakia (21.1%), Belgium (15.7%), Sweden (10.7%), and United Kingdom and Ireland (7.8%),

Males represented 52.9% of all patients and a similar trend was observed across the SMA types.

Methods used for genetic testing were missing for 69.2% of treated patients. Among treated patients with non-missing data, the majority had MLPA as their method used for genetic testing (29.3%), with similar trends observed across all SMA types. The majority (90.0%) of all treated patients had a homozygous deletion of exon 7 as their SMN1 variant and similar trends were observed across all SMA types.

Table 20: Sex, registry, age at symptom onset and method used for genetic testing among patients with SMA type 1, SMA type 2 and SMA type 3 treated with Spinraza

	Overall (N =1003)	SMA Type 1 (N =215)	SMA Type 2 (N =363)	SMA Type 3 (N = 411)
Sex: female / male (%)	47.1%/52.9%	42.3%/57.7%	49.6%/50.4%	47.0%/53.0%
Registry n, %				
Belgium	157 (15.7%)	23 (10.7%)	57 (15.7%)	70 (17.0%)
Czech R & Slovakia	212 (21.1%)	58 (27.0%)	71 (19.6%)	80 (19.5%)
Germany & Austria	226 (22.5%)	41 (19.1%)	77 (21.2%)	106 (25.8%)
Spain	223 (22.2%)	56 (26.0%)	97 (26.7%)	70 (17.0%)
UK & Ireland	78 (7.8%)	15 (7.0%)	20 (5.5%)	43 (10.5%)
Sweden	107 (10.7%)	22 (10.2%)	41 (11.3%)	42 (10.2%)
Age at symptom onset (years) - Median [IQR]	1 [0.5, 2]	0.2 [0.1, 0.3]	0.8 [0.6, 1.1]	3 [1.5, 6]
Method used for genetic testing; n (%)				
MLPA	294 (29.3%)	54 (25.1%)	96 (26.4%)	133 (32.4%)
missing	694 (69.2%)	159 (74.0%)	264 (72.7%)	269 (65.5%)

Motor function assessment (table 21)

Data on **functional status at genetic report date** was missing for the majority of overall patients (74.2%), with remaining patients as “non-sitter” (16.0%), “walker” (5.3%) and “sitter” (4.6%). Data on **achieved motor milestones at genetic report date** was also missing for 74.2% of patients. Of the remaining patients with data on this indicator, “hold head without support” (13.2%) was the most common milestone recorded followed by “sit without support” (3.9%).

Data on the best functional status after treatment, as well as **best achieved motor milestones after treatment** was missing for 9.6% of patients overall. “Walker” was the most common status recorded overall (49.1%), followed by “sitter” (34.1%). A higher proportion of patients achieved “walker” status in the SMA type 3 group (87.1%). For best achieved motor milestones after treatment, the most common milestone overall was “climb stairs” (28.0%), followed by “sit without support” (22.6%). A majority (63.5%) of SMA type 3 patients achieved climbing stairs, while fewer than 5 SMA type 1 patients achieved this milestone. Among patients with SMA type 2, 40.5% and 32.1% of patients with SMA type 1 achieved “sit without support”.

The best score for **CHOP-INTEND** was 44 [32.8, 55.2]. The median scores for patients with SMA type 1 and 2 were fairly consistent with the overall estimate, while the score was higher for SMA type 3 (61 [39, 64]). Data relating to CHOP-INTEND for other SMA types was either limited or missing. At the report of the first best CHOP-INTEND score, the overall median age was 3.3 [1.9, 7.3] years. The median best

score for **HFMS(-E) score** was 31 [11, 51] overall, with a highest score for patients with SMA type 3 (50 [29, 58]). At the report of the first best HFSM(-E) score, the overall median age was 10.2 [5.4, 20.8] years and patients with SMA type 1 were youngest with median age being 3.8 [2.5, 5.2] years. Regarding the best recorded score for **RULM**, data were missing for 72.3% of patients. The median best recorded score increased across SMA types 1, 2, and 3, with values of 12 [9, 21.8], 18 [11.2, 25], and 35 [27, 37], respectively. At the report of the first best RULM right side score, the median age of SMA types 1, 2, and 3 patients were 4.1 [3.3, 6.2], 9.5 [5.2, 16.8], and 12.5 [8.8, 14.6] years, respectively. Data surrounding the best recorded score for **MFM32** were missing for a majority (95.3%) of all treated patients. The median best recorded score for SMA type 2 patients was 39 [33, 48], while the median best recorded score for SMA type 3 patients was 84 [69, 91]. Data on the best recorded score for **HINE-2** were missing for 99.9% of patients. Regarding the best recorded **6MWT** score, data were missing for 89.8% of the patients. The median best scores for SMA type 3 was 376 [269, 458]. The median age at the report of the first best 6MWT score for SMA type 3 was 17.6 [10.4, 29.1] years.

Table 21: Motor function assessment in patients with SMA type 1, SMA type 2 and SMA type 3 treated with Spinraza

	Overall (N =1003)	SMA Type 1 (N =215)	SMA Type 2 (N =363)	SMA Type 3 (N = 411)
Functional status at genetic report; n (%)				
Non-sitter	160 (16.0%)	19 (8.8%)	89 (24.5%)	51 (12.4%)
Sitter	46 (4.6%)	*	36 (9.9%)	8 (1.9%)
Walker	53 (5.3%)	-	*	49 (11.9%)
Missing	744 (74.2%)	194 (90.2%)	234 (64.5%)	303 (73.7%)
Best functional status before treatment; n (%)				
Non-sitter	*	*	*	-
Sitter	10 (1.0%)	-	10 (2.8%)	-
Walker	16 (1.6%)	-	*	13 (3.2%)
Missing	975 (97.2%)	214 (99.5%)	350 (96.4%)	398 (96.8%)
Non-sitter	73 (7.3%)	46 (21.4%)	19 (5.2%)	6 (1.5%)
Sitter	342 (34.1%)	90 (41.9%)	230 (63.4%)	22 (5.4%)
Walker	492 (49.1%)	28 (13.0%)	95 (26.2%)	358 (87.1%)
Missing	96 (9.6%)	51 (23.7%)	19 (5.2%)	25 (6.1%)
Best achieved motor milestone after treatment; n (%)				
Climb stairs	281 (28.0%)	*	11 (3.0%)	261 (63.5%)
Crawl	63 (6.3%)	*	51 (14.0%)	8 (1.9%)
Hold head without support	25 (2.5%)	7 (3.3%)	13 (3.6%)	*
Roll onto side	48 (4.8%)	39 (18.1%)	6 (1.7%)	*
Sit without support	227 (22.6%)	69 (32.1%)	147 (40.5%)	11 (2.7%)
Stand with assistance	43 (4.3%)	17 (7.9%)	26 (7.2%)	-
Stand without assistance	9 (0.9%)	-	6 (1.7%)	*
Unknown	-	-	-	-
Walk 10 metres without assistance	94 (9.4%)	*	11 (3.0%)	77 (18.7%)

Walk with assistance	77 (7.7%)	14 (6.5%)	62 (17.1%)	*
Walk without assistance	40 (4.0%)	8 (3.7%)	11 (3.0%)	19 (4.6%)
Missing	96 (9.6%)	51 (23.7%)	19 (5.2%)	25 (6.1%)
Best score for CHOP-INTEND				
Median [IQR]	44 [32.8, 55.2]	42.5 [29, 52]	45 [36, 56]	61 [39, 64]
Missing	831 (82.9%)	127 (59.1%)	290 (79.9%)	403 (98.1%)
Best score for HFMS(-E)				
Median [IQR]	31 [11, 51]	14 [4.2, 25.2]	14 [4, 33]	50 [29, 58]
Missing	669 (66.7%)	185 (86.0%)	232 (63.9%)	243 (59.1%)
Best score for RULM				
Median [IQR]	26.5 [16, 37]	12 [9, 21.8]	18 [11.2, 25]	35 [27, 37]
Missing	725 (72.3%)	189 (87.9%)	253 (69.7%)	276 (67.2%)

Note: * indicates n < 5 patients

Skeletal deformities

Relating to **scoliosis diagnosis**, overall patients aged 6 months to 51 years, the majority in each age group had a scoliosis diagnosis. The same was true across SMA types, where data was available. The highest proportion of patients with a scoliosis diagnosis was in the 16-21 year age group (n=73; 89.0%). Overall, 34.4% of SMA type 1 patients had reported at least one use of a **spinal brace ever**, while 19.3% of SMA type 2 patients and 3.9% of SMA type 3 patients had reported at least one use. **Surgery for scoliosis** was less common for all treated patients across the SMA types aged less than 6 years and aged 51 years and older. Proportions of patients undergoing surgery for scoliosis was highest in the 11-16 years age group [n=62 (59.0%)]. Patients with SMA type 2 were more likely to have had surgery vs patients overall.

Respiratory function

The proportion of patients who had ever received **airway clearance assistance** varied by age group, with the highest count observed in the 6-11 year category (n=80; 54.1%). Airway clearance assistance was more common for patients with SMA type 1 aged less than 16 years and SMA type 2 aged 6 years and older. With respect to **any non-invasive ventilation,** a majority of SMA type 1 treated patients in the age groups 1-3 months (n=10; 62.5%) through 16-21 years (n=5; 100%) had at least one episode. Among SMA type 2 treated patients, a majority of patients in the age groups 2-6 years (n=17; 89.5%) through 31-41 years (n=11; 100%) had at least one episode of non-invasive ventilation. Data were limited for other SMA types. Data availability was limited for **any invasive ventilation and full-time invasive ventilation**. At least one episode of full time invasive ventilation was most commonly observed in patients aged 2-6 years (n=12; 37.5%) and 6-11 years old (n=10; 58.8%) with SMA type 1. Limited data was available for other SMA type stratifications.

Pulmonary infections reported in cause of hospitalisation or as a comorbidity was rare across all age groups, with the highest proportion reported in the 2-6 year age group (n=6; 4.4%). Occurrence of **respiratory physiotherapy** was observed in patients as young as 1-3 months old, with the highest proportion observed in the 11-16 years age group (n=32; 86.5%). Data for SMA type stratifications was limited.

Nutritional function

Exclusive feeding tube usage was observed in overall patients aged from 1 months through 51 years overall and was highest specifically in the 6-11 year age category (n=16; 80.0%). No cases of **gastrostomy** were noted.

Hospitalisations and death

Data on annual number of hospitalisations was missing for 59.6% of patients overall. Of overall patients with data available, the median number of annual hospitalizations was 1 [1, 2]. Cause of death data was missing for 99.8% of patients overall; no summary statistics were calculated. The event-free survival was 10 months among SMA type 1 patients and no events (i.e., death or permanent ventilation) were observed in other SMA types. For the incidence rate of comorbidities per patient-year, rates of 0 were observed for all the conditions.

Quality of life (QoL) using patient-reported outcomes (PROs)

Spain PROFuture Mobility and Independence PRO at genetic report date was missing for 89.4% of the overall population. Of overall patients with data available, the median score for Spain PROFuture Mobility and Independence PRO at genetic report date was 40.1 [18.3, 64.8]. T**he Best score for Spain PROFuture Mobility and Independence PRO at genetic report** was missing for 90.3% of treated patients. The overall median Best score for Spain PROFuture Mobility and Independence PRO was 37.5 [15.5, 60.6].

Belgium ACTIVLIM PRO at genetic report date was missing for 88.4% of the overall population. Of overall patients with data available, the median score for Belgium ACTIVLIM PRO at genetic report was -3.5 [-8.1, 0.8]. **The Best score for Belgium ACTIVLIM PRO** was missing for 89.1% of treated patients and the median score was -2.4 [-8.1, 1.2] for overall treated patients.

SMA Patients Treated with Zolgensma

Overall (Table 22), 101 patients were treated with Zolgensma across all registries, with SMA type 1 having 68 (67.3%) patients, SMA type 2 having 22 (21.8%) patients, SMA type 3 having 4 (4.0%) patients, SMA type 4 having 0 patients, SMA type other having 1 (1%) patients, SMA type presymptomatic having 6 (5.9%) patients, and SMA type missing having 0 patients. Out of all patients that were treated with Zolgensma, the largest proportion of patients were included from the Czech Republic and Slovakia registries (42.6%), followed by the United Kingdom and Ireland (17.8%), Germany and Austria (16.8%), Spain (10.9%), Belgium (6.9%), and Sweden (5.0%).

Males represented 61.4% of all patients. More than 50% of patients with SMA type 1 were males, while 54.5% of patients with SMA type 2 were **females**. Data was missing for other SMA types.

Methods used for genetic testing were missing for 56.4% of treated patients. Among treated patients with non-missing data, the majority had MLPA as their method used for genetic testing (42.6%), with similar trends observed across all SMA types. The majority (86.1%) of all treated patients had a homozygous deletion of exon 7 as their SMN1 variant and similar trends were observed across all SMA types.

Table 22: Sex, registry, age at symptom onset and method used for genetic testing among patients with SMA type 1, SMA type 2 and SMA type 3 treated with Zolgensma

	Overall (N = 101)	SMA Type 1 (N = 68)	SMA Type 2 (N = 22)	SMA Type 3 (N = 4)
Sex: female / male (%)	38.6%/61.4%	36.8%/63.2%	54.5%/45.5%	*
Registry n, %				
Belgium	7 (6.9%)	*	*	-
Czech R & Slovakia	43 (42.6%)	22 (32.4%)	12 (54.5%)	*
Germany & Austria	17 (16.8%)	12 (17.6%)	5 (22.7%)	-
Spain	11 (10.9%)	11 (16.2%)	-	-
UK & Ireland	18 (17.8%)	15 (22.1%)	*	-
Sweden	5 (5.0%)	*	*	-
Age at symptom onset	0.2 [0.1, 0.5]	0.2 [0.1, 0.3]	0.8 [0.5, 0.8]	*

(years) - Median [IQR]				
Method used for genetic testing; n (%)				
MLPA	43 (42.6%)	24 (35.3%)	10 (45.5%)	*
missing	57 (56.4%)	44 (64.7%)	11 (50.0%)	*

Motor function assessment (Table 23)

With respect to **functional status at genetic report**, data were missing for a majority (88.1%) of all Zolgensma-treated patients. However, among 12 treated patients with non-missing data, all had non-sitter as their functional status, which held true across SMA types 1 and 2. There was also a large extent of missingness for best achieved functional status and best achieved motor milestone, with data missing for 100% of all Zolgensma-treated patients. With respect to **best functional status after treatment with Zolgensma,** data were missing for 13.9% of all patients. Among SMA type 1 patients, 42.6% had achieved “sitter” status,” followed by 27.9% of patients who achieved “non-sitter” status and 11.8% of patients who achieved “walker” status. Among SMA type 2 patients, 63.6% had achieved “sitter” status, followed by 31.8% of patients who had achieved “walker” status. **Data on the best achieved motor milestone after treatment with Zolgensma** were missing for 13.9% of patients. Among SMA type 1 patients, 26.5% had achieved sitting without support, 25% had achieved rolling onto their side, and 11.8% had achieved standing with assistance. Among SMA type 2 patients, 27.3% had achieved sitting without support and 27.3% had achieved crawling.

Data on the **best score for CHOP-INTEND** were missing for 59.4% of patients treated with Zolgensma.The median [IQR] best score for CHOP-INTEND for all patients was 53 [39, 60], while SMA types 1, 2, and presymptomatic patients had best scores of 46.5 [34.2, 54], 60 [54, 64], and 62 [36, 62], respectively. At the report of the first best CHOP-INTEND score, the overall median age was 1.7 [0.8, 2.2] years. Data on the **best score for HFMS(-E)** were missing for 75.2% of the Zolgensma-treated population. For the overall population, the median [IQR] best recorded score for HFMS(-E) was 41 [33, 53]. Among SMA type 1 and type 2 patients, the median [IQR] best recorded scores were 38 [12, 59] and 37.5 [34, 42.5], respectively. At the report of the first best HFSM(-E) score, the overall median age was 2.5 [1.8, 3] years. Regarding the **best recorded score for RULM**, data were missing for 95.0% of patients. The overall median best recorded score score for RULM was 28 [14, 31]. Data surrounding the best recorded score for **MFM32** were missing for all treated patients. Data on the best recorded score for **HINE-2** and **6MWT** were limited and missing for the majority of the patients, hence, no interpretations were made.

Table 23: Motor function assessment in patients with SMA type 1, SMA type 2 and SMA type 3 treated with Zolgensma

	Overall (N = 101)	SMA Type 1 (N = 68)	SMA Type 2 (N = 22)	SMA Type 3 (N = 4)
Functional status at genetic report; n (%)				
Non-sitter	12 (11.9%)	6 (8.8%)	6 (27.3%)	-
Sitter	-	-	-	-
Walker	-	-	-	-
Missing	89 (88.1%)	62 (91.2%)	16 (72.7%)	*
Best functional status before treatment; n (%)				

Non-sitter	-	-	-	-
Sitter	-	-	-	-
Walker	-	-	-	-
Missing	101 (100.0%)	68 (100.0%)	22 (100.0%)	*
Best functional status after treatment; n (%)				
Non-sitter	21 (20.8%)	19 (27.9%)	*	-
Sitter	45 (44.6%)	29 (42.6%)	14 (63.6%)	-
Walker	21 (20.8%)	8 (11.8%)	7 (31.8%)	*
Missing	14 (13.9%)	12 (17.6%)	-	-
Best achieved motor milestone after treatment; n (%)				
Climb stairs	5 (5.0%)	-	*	*
Crawl	11 (10.9%)	*	6 (27.3%)	-
Hold head without support	*	*	-	-
Roll onto side	19 (18.8%)	17 (25.0%)	*	-
Sit without support	24 (23.8%)	18 (26.5%)	6 (27.3%)	-
Stand with assistance	10 (9.9%)	8 (11.8%)	*	-
Stand without assistance	-	-	-	-
Unknown	-	-	-	-
Walk 10 metres without assistance	5 (5.0%)	*	*	-
Walk with assistance	7 (6.9%)	*	*	-
Walk without assistance	*	*	*	*
Missing	14 (13.9%)	12 (17.6%)	-	-
Best score for CHOP-INTEND				
Median [IQR]	53 [39, 60]	46.5 [34.2, 54]	60 [54, 64]	-
Missing	60 (59.4%)	42 (61.8%)	13 (59.1%)	*
Best score for HFMS(-E)				
Median [IQR]	41 [33, 53]	38 [12, 59]	37.5 [34, 42.5]	*
Missing	76 (75.2%)	57 (83.8%)	14 (63.6%)	-
Best score for RULM				
Median [IQR]	28 [14, 31]	*	*	-
Missing	96 (95.0%)	66 (97.1%)	19 (86.4%)	*

Note: * indicates n < 5 patients

Skeletal deformities

Data on **scoliosis diagnoses** were available only for Zolgensma-treated patients aged 6 months to 6 years. A majority of overall patients had not been diagnosed with scoliosis, however, a majority (n=14; 53.8%) of SMA type 1 patients aged 2 to 6 years had been diagnosed with scoliosis. Overall, 27.9% of SMA type 1 patients had reported at least one use of a **spinal brace ever**, data relating to other SMA types were missing. Data on **surgery for scoliosis** were also limited to Zolgensma-treated patients aged 6 months to 6 years, with 100% of patients never having had surgery.

Respiratory function

Information regarding **airway clearance assistance** was available only for Zolgensma-treated patients aged 1 month to 6 years. A majority of overall patients did not have at least one episode of airway

clearance assistance. However, among SMA type 1 patients aged 2 to 6 years, 66.7% (n=12) of patients had at least one episode of airway clearance assistance. Among SMA type 2 patients aged 1.5 to 2 years, 100% (n=6) of patients did not have at least one episode of airway clearance assistance. With respect to **any non-invasive ventilation,** a majority of SMA type 1 patients in age categories 3-6 months to 2-6 years had at least one episode, peaking in the 6-18 month age category (n=18; 94.7%). Data were unavailable for other SMA types. Data on any invasive ventilation were not available for any Zolgensma-treated patients.

All treated patients across all available age categories (1 to 3 months to 2 to 6 years) did not have **pulmonary infections** reported in cause of hospitalisation or as a comorbidity, a trend largely driven by SMA type 1 patients. For SMA type 2 patients, this variable was reported only for the age category of 2 to 6 years, among whom 100% (n=7) of patients did not have pulmonary infections reported in cause of hospitalisation or as a comorbidity. Data on **respiratory physiotherapy** were available for SMA type 1 patients from age categories 6 to 18 months to 2 to 6 years. A majority of these patients had experienced at least one episode of respiratory physiotherapy. The 2 to 6 years age category had the highest proportion (n=9; 75%) of patients with at least one episode of respiratory physiotherapy.

Nutritional function

Exclusive feeding tube usage was reported for SMA type 1 patients from age categories 6 to 18 months to 2 to 6 years. Among patients aged 6 to 18 months and 1.5 to 2 years, a majority (n=8; 61.5% and n=9; 64.3%, respectively) did not have at least one episode of exclusive feeding tube usage. Half (n=9) of patients aged 2 to 6 years had at least one episode of exclusive feeding tube usage. All patients treated with Zolgensma aged 1 month to 6 years (age categories for which data were reported) did not have a **gastrostomy**.

Hospitalisations and death

Data surrounding the annual number of hospitalisations were missing for 47.5% of all Zolgensma-treated patients. Among all treated patients, the median [IQR] annual number of hospitalisations was 1 [1, 1.3], while the median [IQR] annual number of hospitalisations for SMA types 1 and 2 were 1 [1, 1] and 1.2 [1, 2], respectively. There were insufficient data to report this variable across other SMA types. With regard to causes of death, these data were missing for 100% of all treated patients. Event-free survival has not been estimated because no event (i.e., death or permanent ventilation) has been reported in the Zolgensma group. For the incidence rate of comorbidities per patient-year, a rate of 0 was observed for each comorbidity.

Quality of life (QoL) using patient-reported outcomes (PROs)

Data on the score for **Spain PROFuture Mobility and Independence PRO at genetic report** date was missing for 99% of the overall population, and data on the **score for Belgium ACTIVLIM PRO at genetic report date** was missing for 100% of the overall population.

10.4.3. Description of SMA healthcare management

Please note that all results are available in a stand-alone document - Appendix G ("Objective 2 (Healthcare) Results 2024_03_13"), submitted along with this report. Additional sub-group analyses are also available in Appendix G ("Supplementary Results Objective 2 (Healthcare) 2024_03_13").

10.4.3.1 Evolution of diagnosis methods and of medicinal and non-medicinal treatment over time.

This objective was described in the ALL cohort (i.e., 2188 patients).

Methods used to diagnose SMA over time
For SMN1 copy and SMN 2 copy, we observed a similar testing method across calendar years from before 2011 until 2023 with the most common methods being MLPA; this trend was consistent across SMA types as well.

Evolution of medicinal treatment over time:

- **Use of DMT** (figure 8 in 10.4.3.2) has started in 2014/16 with few users initially (8.2% in SMA type 1 and very few or no users in other SMA types), followed by a yearly increase until 2021 (81.9% of DMT users in SMA type 1, 67.5% in SMA 2 and 63.6% in SMA 3).
- The use of **listed comedications** (Vit D, Calcium, bisphosphonates, drugs for constipation, for gastroesophageal reflux, …) has started from 2014/16 with around 10% of users until 2019, and then increasing to 18-20% in 2021 similarly across SMA types.
- **Annual influenza vaccination** has been in place since 2014 in around 20-30% of patients per year and similarly between SMA types.
- **Pneumococcal vaccination** has been reported in very few patients (less than 5 per year) irrespective of SMA type.

Evolution of non-medicinal treatment over time:

- With respect to **any ventilation**, before 2011 fewer than 5 patients across all types of SMA reported at least one episode of any ventilation. There were 34 (8.7%) patients across all SMA type from 2011-2013, 97 (11.1%) patients from 2014-2016, 153 (15.3%) patients in 2017, 285 (20.2%) patients in 2018, 320 (20.3%) patients in 2019, 445 (26.3%) patients in 2020, 369 (24.7%) patients in 2021, 295 (22.9%) patients in 2022, and 156 (19.9%) patients in 2023. Ventilation usage in SMA type 1 has evolved from 18.8% in 2011/13 to 57.0% in 2020, in SMA type 2 from 10.3% in 2011/13 to 32.2% in 2020. In other SMA types, usage of ventilation has remained low over time.
- Regarding **wheelchair usage**, before 2011, 51 (56.0%) patients across all types of SMA reported at least one episode of wheelchair usage. There were 207 (53.2%) patients across all SMA type with at least one episode of wheelchair usage from 2011-2013, 558 (64.0%) patients from 2014-2016, 630 (63.1%) patients in 2017, 899 (63.8%) patients in 2018, 957 (60.6%) patients in 2019, 995 (58.7%) patients in 2020, 990 (66.2%) patients in 2021, 810 (62.9%) patients in 2022, and 454 (57.9%) patients in 2023. Wheelchair usage in SMA type 1 increased from 21.9% (n=14) in 2011/13 to 63.6% (n=152) in 2022, in SMA type 2 from 66.7% (n=32) before 2011 to 72.8% (n=409) in 2022, in SMA type 3 approximately 50% of patients consistently reported wheelchair usage across all the calendar years. The data were limited for other SMA types.
- **Feeding tube usage** was reported in patients with SMA type 1 and SMA type 2 starting in 2011/2013. There were 24 (6.2%) patients across all SMA type with at least one episode of feeding tube usage from 2011-2013, 82 (9.4%) patients from 2014-2016, 65 (6.5%) patients in 2017, 137 (9.7%) patients in 2018, 146 (9.2%) patients in 2019, 154 (9.1%) patients in 2020, 144 (9.6%) patients in 2021, 115 (8.9%) patients in 2022, and 54 (6.9%) patients in 2023. Feeding tube usage in SMA type 1 increased from 25.0% in 2011/13 to 40.6% in 2021, in SMA type 2 from 4.6% 2011/2013 to 6.0% in 2021. The data were limited for other SMA types.

At least one rehabilitative intervention (Table 24)

All rehabilitative interventions have been reported in approximately half of patients (i.e., 55% of missing).

36.9% of patients had at least one **muscular physiotherapy**, similarly across all SMA types. Other rehabilitative interventions (i.e., **respiratory physiotherapy, contracture management, spinal brace**

and **speech therapy),** have been more reported in SMA type 1 patients than in SMA type 2 and SMA type 3.

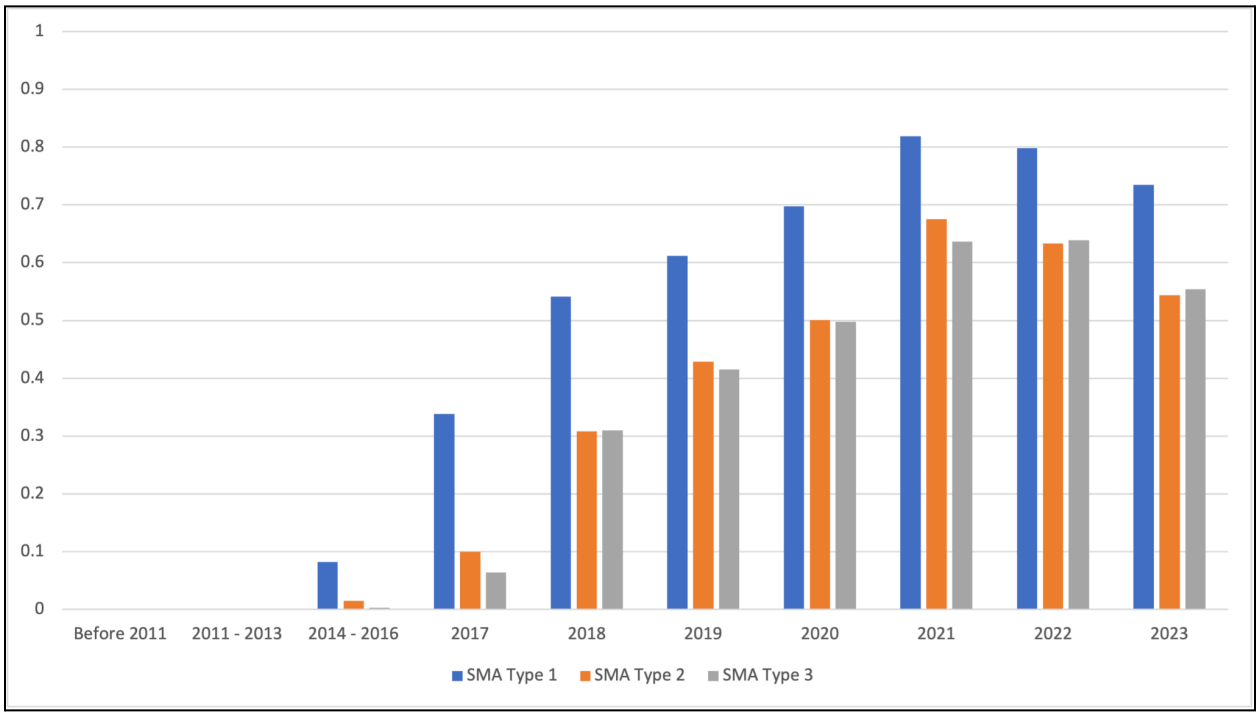
Table 24: Usage of rehabilitative interventions in SMA1, SMA2 and SMA3

	Overall (N=2188)	SMA Type 1 (N=432)	SMA Type 2 (N=914)	SMA Type 3 (N=779)
All - At least one episode of muscular physiotherapy ever (n, %)				
no	171 (7.8%)	14 (3.2%)	76 (8.3%)	78 (10.0%)
yes	808 (36.9%)	173 (40.0%)	355 (38.8%)	270 (34.7%)
missing	1209 (55.3%)	245 (56.7%)	483 (52.8%)	431 (55.3%)
At least one episode of respiratory physiotherapy ever (n, %)				
no	702 (32.1%)	87 (20.1%)	285 (31.2%)	317 (40.7%)
yes	277 (12.7%)	100 (23.1%)	146 (16.0%)	31 (4.0%)
missing	1209 (55.3%)	245 (56.7%)	483 (52.8%)	431 (55.3%)
At least one episode of contracture management using orthotics ever (n, %)				
no	577 (26.4%)	59 (13.7%)	233 (25.5%)	273 (35.0%)
yes	402 (18.4%)	128 (29.6%)	198 (21.7%)	75 (9.6%)
missing	1209 (55.3%)	245 (56.7%)	483 (52.8%)	431 (55.3%)
At least one episode of spinal brace ever (n, %)				
no	768 (35.1%)	97 (22.5%)	334 (36.5%)	325 (41.7%)
yes	211 (9.6%)	90 (20.8%)	97 (10.6%)	23 (3.0%)
missing	1209 (55.3%)	245 (56.7%)	483 (52.8%)	431 (55.3%)
At least one episode of speech therapy ever (n, %)				
no	802 (36.7%)	85 (19.7%)	378 (41.4%)	326 (41.8%)
yes	177 (8.1%)	102 (23.6%)	53 (5.8%)	22 (2.8%)
missing	1209 (55.3%)	245 (56.7%)	483 (52.8%)	431 (55.3%)

10.4.3.2 DMTs use patterns

Overall (see figure 9), 1321 patients received **at least one DMT**, 1003 patients were treated with Spinraza, 403 by Evrysdi and 101 by Zolgensma.
Overall, 19 (2.2%) patients were treated with at least one DMT from 2014 to 2016, 122 (12.2%) in 2017, 488 (34.7%) in 2018, 717 (45.4%) in 2019, 901 (53.2%) in 2020, 1023 (68.4%) in 2021, 851 (66.1%) in 2022 and 454 (58.0%) in 2023. The total number of patients being treated with at least one DMT peaked in the year 2021 (n=1023), with SMA type 1 having 208 (81.9%) treated patients with at least one DMT, SMA type 2 having 447 (67.5%) patients, SMA type 3 having 350 (63.6%) patients, SMA type 4 having 7 (50%) patients, SMA type other and SMA type presymptomatic having less than 5 patients, and SMA type missing having 6 (66.7%) patients.
Of note, some patients started receiving DMT from 2014, before the respective marketing authorization. This exposure to DMT corresponds to patients exposed in clinical trials.

Figure 9: Proportion of patients treated with at least one DMT over time in SMA 1, SMA 2 and SMA 3



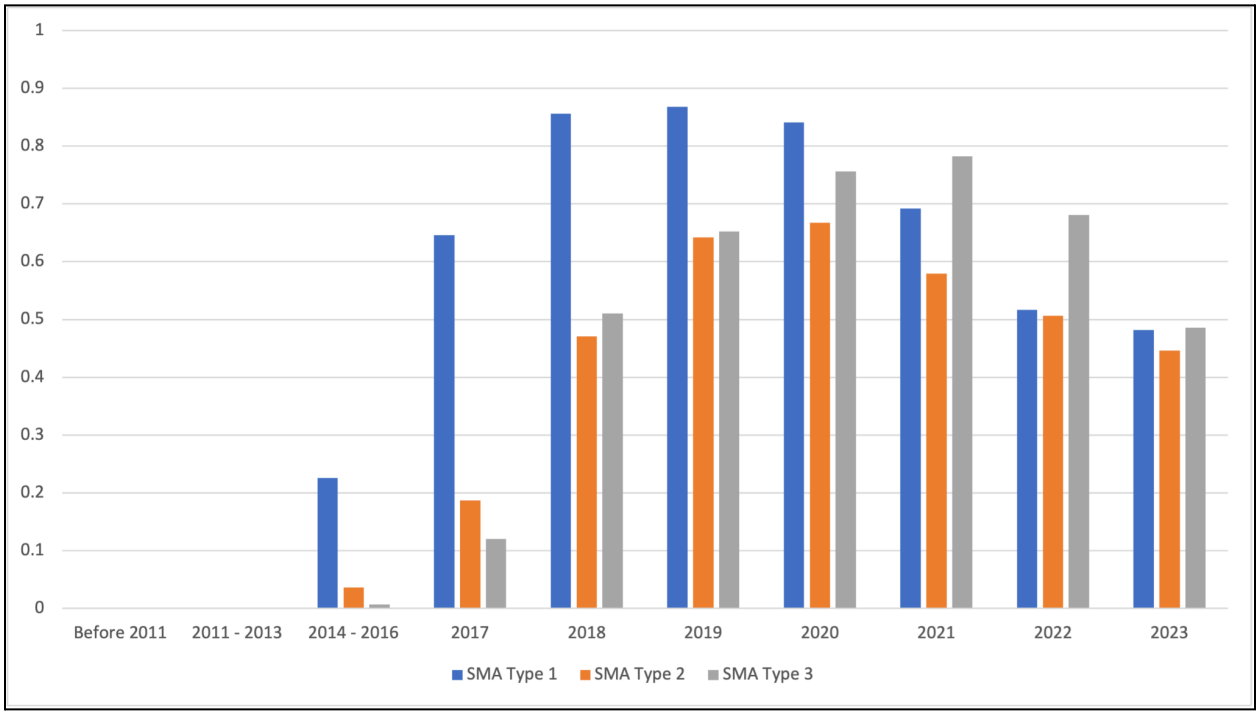
Treated with Spinraza (Figure 10):

1003 patients have been treated at **least once with Spinraza**. Between 2014-2016, 19 (5.3%) patients were treated with Spinraza across all SMA types, 117 (23.4%) patients in 2017, 454 (55.2%) in 2018, 669 (68.7%) in 2019, 799 (73.2%) patients in 2020, 760 (67.5%) patients in 2021, 544 (56.9%) patients in 2022, 261 (46.1%) patients in 2023. A higher proportion of patients with SMA type 1 compared to other types were treated with Spinraza across all calendar periods.

The mean **time between "Genetic report date" and "first Spinraza administration date"** was 71.2 months; ranging from 18.4 months in SMA 1, 77.4 months in SMA 2 and 97 months in SMA 3.

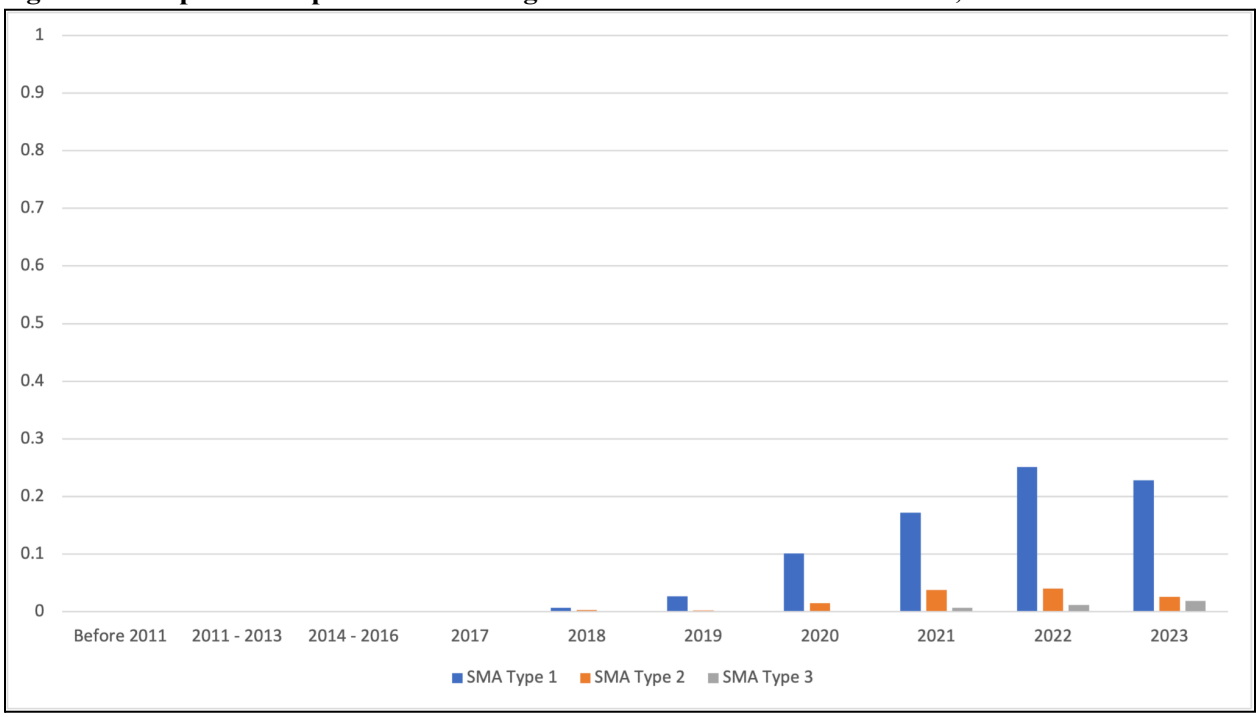
Regarding the **treatment duration for Spinraza**, the overall mean duration once on the market steadily decreased from 2017 to 2022 spanning from 61.6 months to 10.4 months. Conversely, the **treatment discontinuation** for Spinraza increased over time; very few patients in 2017 (<5) to 100% in 2022. **Reasons for discontinuation** were mainly driven by "Elective choice" but other reasons have been reported in less than 10% of cases as Insufficient benefit, "*Insufficient initial improvement, Loss of response, Scoliosis, Side effects from drug, Side effects from procedure*".

Figure 10: Proportion of patients with Spinraza intake over time in SMA 1, SMA 2 and SMA 3



Treated with Zolgensma (Figure 11):
101 patients have been treated **with Zolgensma**. In 2018, less than 5 patients were treated with Zolgensma across all SMA types, 7 (0.7%) in 2019, 29 (2.7%) patients in 2020, 61 (5.4%) patients in 2021, 76 (7.9%) patients in 2022, 42 (7.4%) patients in 2023. A higher proportion of patients with SMA type 1 were treated with Zolgensma across all calendar periods than all other SMA types, whereas none of the patients with SMA type 4 were treated with Zolgensma. Adequate dose regarding weight at administration is poorly reported.

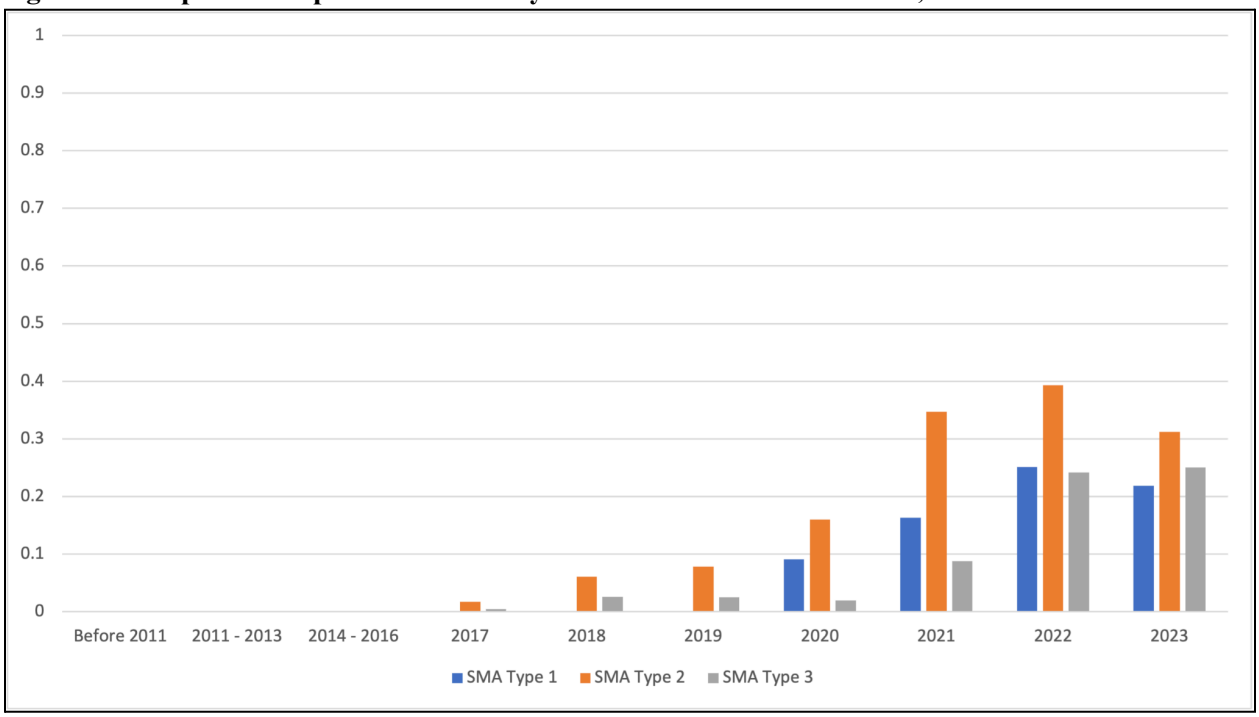
Figure 11: Proportion of patients with Zolgensma intake over time in SMA 1, SMA 2 and SMA 3



Treated with Evrysdi (Figure 12):
403 patients have been treated at **least once with Evrysdi.** In 2017, 5 (1.0%) patients were treated with Evrysdi across all SMA types, 32 (3.9%) patients in 2018, 44 (4.5%) in 2019, 105 (9.6%) patients in 2020, 244 (21.7%) patients in 2021, 296 (31.0%) patients in 2022, 152 (26.9%) patients in 2023. A higher proportion of patients with SMA type 2 were treated with Evrysdi across all calendar periods.
Regarding **treatment duration** for Evrysdi, the overall mean duration in 2017 was 63 months (SD=16.9) across the SMA types. The mean duration of treatment steadily decreased over the years, in 2022 the mean treatment duration for Evrysdi was 11.5 months (SD=3.1). Regarding treatment discontinuation, overall, 5 (100%) patients in 2021 discontinued the treatment and the mean duration of treatment was 4 months (SD=1.9) among patients with discontinuation. In 2022, 9 (81.8%) patients discontinued the treatment and the mean duration of treatment was 11 months (SD=7.3). Data on discontinuation was missing (or present in less than 5 patients) for all other calendar years.

Reasons for discontinuation were mainly driven by "Elective choice" across the SMA types and calendar years. Other reasons have been reported were, "*Availability, Scoliosis, Insufficient Benefit, Side effects from procedure*".

Figure 12: Proportion of patients with Evrysdi intake over time in SMA 1, SMA 2 and SMA 3



The number of patients treated with **more than one DMT** was low, starting from 2020 with 34 patients, (2.1%) to 2022 with 69 patients (7.2%). Relating to treatment in combination with Spinraza and Zolgensma, less than 5 patients across the SMA types were treated with the combination in 2019, 16 (1.5%) patients in 2020, 17 (1.5%) patients in 2021, 8 (0.8%) patients in 2022 and 5 (0.9%) patients in 2023. A higher proportion of the patients with SMA type 1 received treatment with Spinraza and Zolgensma compared to other types. With regard to treatment in combination with Spinraza and Evrysdi, less than 5 patients overall were treated with the combination in 2019, 17 (1.6%) in 2020, 28 (2.5%) in 2021, 56 (5.9%) in 2022, and 0 in 2023. Relating to treatment with a combination of Zolgensma and Evrysdi, very few patients were treated with these combinations across all SMA types and across all calendar periods. Also, the data were limited or missing for SMA type 4, SMA type other, SMA type presymptomatic, and those with missing SMA type.

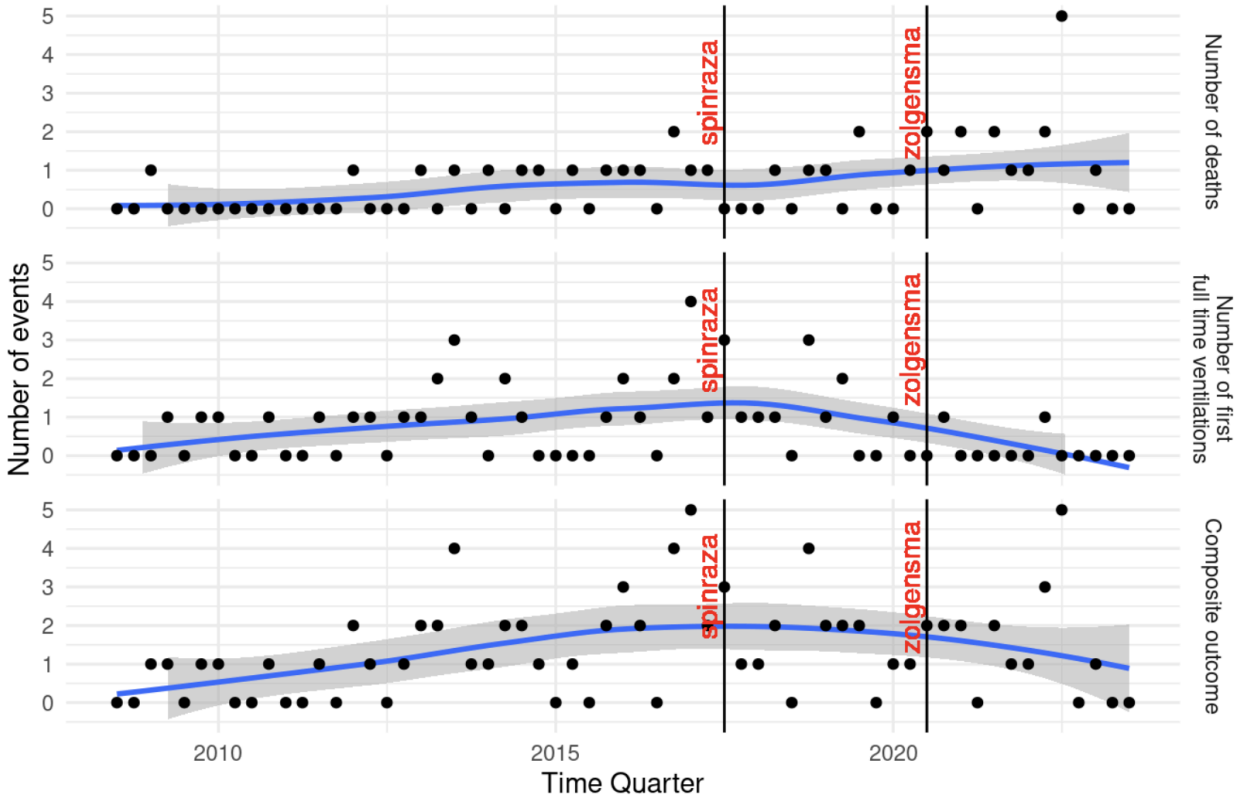
10.5. Exploratory analyses: Interrupted time series analysis

All the ITS implementation, model validation and detailed results have been described in the full ITS report (Provided as stand-alone document).

Number of patients per quarter who have died, started full time ventilation for the first time and the composite outcome was plotted (Figure 13) allowing the following initial observations:

- Prior to 2012-01-01, only one death was recorded across all registries and the number of recorded deaths has steadily increased over time.
- The number of patients receiving full time ventilation for the first time was increasing until about 2017, where the numbers started to decrease.
- For the composite outcome, numbers are quite small pre 2012 and then start to rise until about 2015 where numbers become fairly stable.
- For each quarter, the number of events is typically quite small (less than 5 cases).

Figure 13. Time series of patients who have died, started full time ventilation for the first time and the composite outcome.



Note: Vertical lines are superimposed at the start of the quarter following DMT availability on the market. Solid blue like is a Loess curve, with corresponding grey 95% confidence interval for the mean number of events per quarter.

Based on these initial observations, including limitation to the very few number of quarterly outcomes, various ITS models were applied and based on the most appropriate GLM model the following trends have been observed:

- After the introduction of Spinraza (i.e., after 2017-07-01), a statistically significant (at the 5% level) reduction in the numbers of patients first receiving full time ventilation was observed (Figure 14), and also a statistically significant reduction in the composite outcome (Figure 15). No change has been observed for the number of patients who died per quarter.
- Following Zolgensma introduction (i.e., 2020-07-01), none of the coefficients has been deemed statistically significant; thus no change in quarterly number of patients who died, started full time ventilation or the composite outcome after 2020-07-01 was observed.

Figure 14. Fitted model with 80% and 95% prediction intervals superimposed for the quarterly full time ventilation and Spinraza interruption.

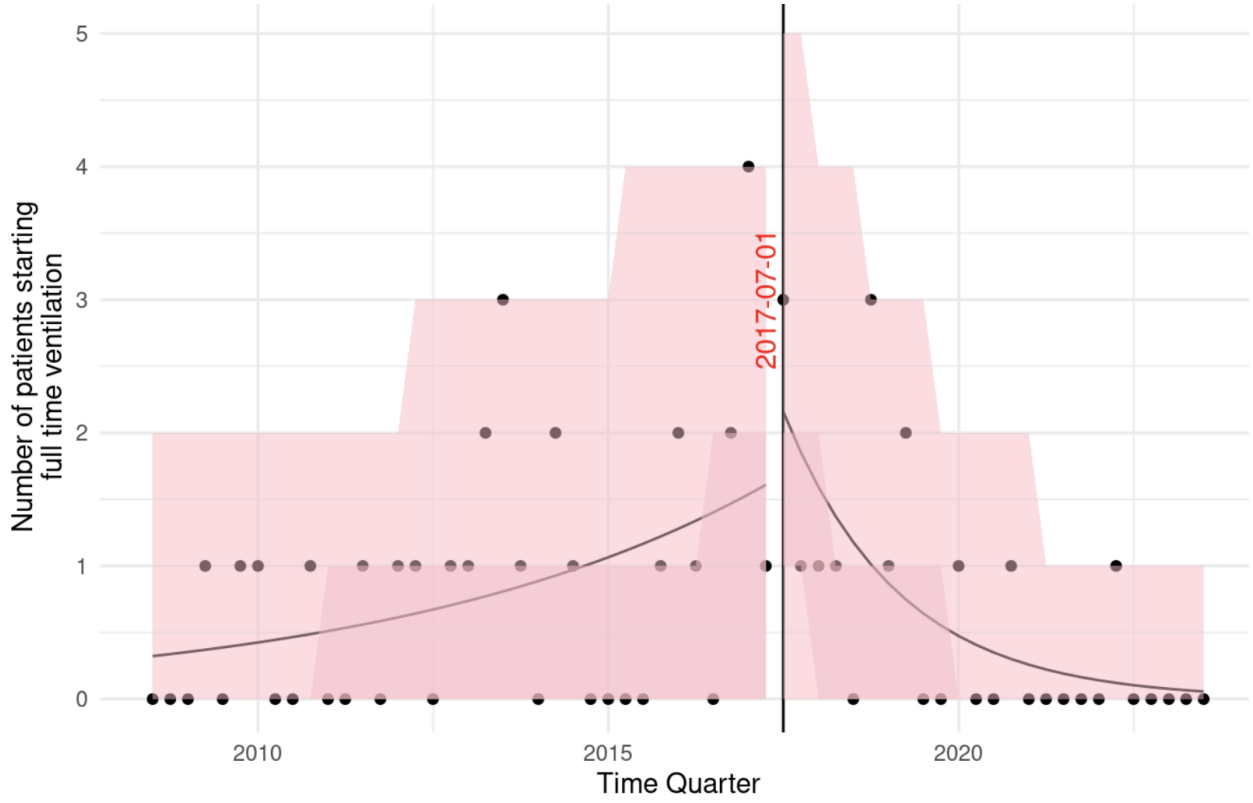
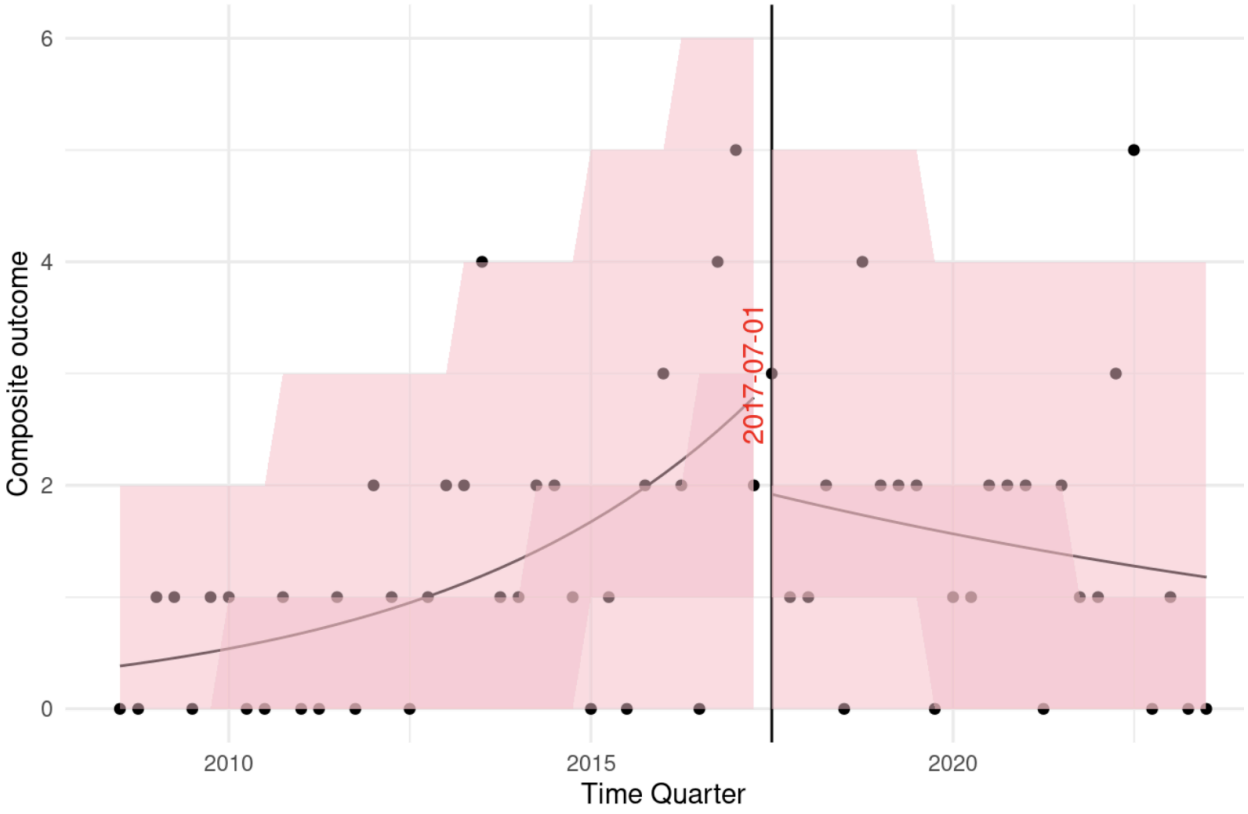


Figure 15. Fitted model with 80% and 95% prediction intervals superimposed for the quarterly composite outcome and Spinraza interruption.



10.6. Serious adverse events occurring in SMA patients

Across all registries, there were very few SAESI events observed, with a total of 5 events observed in the overall cohort (n=2,188). The specific SAESI events observed were renal toxicity, hypersensitivity reactions and hepatotoxicity. Less than 5 patients with SMA type 1 and 3 treated with Spinraza had a record of an SAE in 2018 and 2020, respectively. No SAE were noted in association with Zolgensma treatment. Less than 5 patients with SMA type 2 treated with Evrysdi had a record of an SAE in 2023.

11. DISCUSSION

11.1. Key results

11.1.1 Description of registry specificities in terms of SMA population capture (in "ALL", N=2,188):

Among the 2,188 patients with SMA across all registries overall, the greatest number **of patients** were identified from the Germany and Austria registry (31.8%), and the lowest from Sweden (8.0%); The breakdown for the other registries was 18.0% in the UK and Ireland, 15.9% in Czech Republic, 14.6% in Spain and 11.7% in Belgium. Among the 2,188 patients, 1,321 were classified as treated ("TREATED"), 847 were never treated ("NEVER TREATED")

Per SMA type: Overall, SMA type 1 represented 19.7% of patients, SMA type 2, 41.8% and SMA type 3, 35.6% of patients. Across all registries, SMA type 1 ranged from 13.3% in Belgium to 27.6% in the Czech Republic and Slovakia; SMA type 2 ranged from 33.6% in the Czech Republic and Slovakia to 48.0% in Spain and SMA type 3 ranged from 29.2% in Spain to 40.6% in Sweden.

Registry time coverage varied with Germany, Austria registry, and UK and Ireland registries covering 15 years (2008 to 2023) while Belgium covering only 4 years (2018 to 2021). The observed **duration of follow-up** ranged from 42 months (in Czech Republic and Slovakia) to 104.5 months (Sweden).

There was an almost equal split between **male** (51.6%) and **female** (48.4%) patients in the overall SMA population, with the distribution being similar across all registries, except, there were slightly more male than female patients in the Spain registry, and UK and Ireland registry (54.5% male in both registries).

With respect to the **age group at symptom onset,** the most common age at onset of symptoms was less than 6 months old for patients with SMA type 1, 6-18 months old for patients with SMA type 2, and 2-6 years old for SMA type 3 across all the registries.

With regards to **best functional SMA status**, "Sitter" was the most common status among all patients with SMA type 1 (25.0%) and type 2 (44.7%). "Walker" was the most common status among all SMA type 3 patients (68.7%). These trends were consistent across all the registries.

The **most common best achieved motor milestone** was the ability to "sit without support" among patients with SMA type 1 (18.8%) and SMA type 2 (27.9%) in all registries, except for patients in the UK and Ireland registry where the most common milestones in patients with SMA type 1 were "stand with assistance" (10.1%) and "roll onto side" (10.1%), and Germany where the most common milestone was "roll onto side" (10.4%). For SMA type 3, the most common motor milestone was the ability to "climb stairs" (49.4%), with the only exception being the Spain registry wherein most of the SMA type 3 patients (72.0%) had the ability to walk 10 metres without assistance.

With respect to the **methods of genetic testing and the diagnosis of SMA** across registries, MLPA, which is a gold standard for SMA diagnosis, was the most common method used for genetic testing across all SMA types and registries (24.1%). Overall, missingness associated with this variable was high

(74.3%). When reported in very few cases, **the reason for genetic testing** was only “family screening” until 2017 and “Newborn screening” had also started to be reported from 2018 onwards in Belgium, from 2020 onwards in Germany and Austria, and from 2022 onwards in Czech Republic and Slovakia (of note, systematic newborn genetic screening (NBS) was introduced in Germany in October 2021 and in Belgium in March 2021; a pilot NBS project was introduced in the Czech Republic in January 2022).

Duration of the disease across registries was on average 252.1 months overall. SMA type 3 and SMA type 4 are a milder form of the disease and do not affect a patient's life expectancy. Hence, SMA types 3 and 4 had the longest mean duration of the disease across registries, averaging approximately to 300 months. For patients with SMA type 2, which is an intermediate form of disease that can plausibly affect the life span of patients, the mean duration of the disease was 240 months. SMA type 1 is the most severe form of disease with the shortest duration observed across the registries, averaging to 90 months. Missingness for this variable was 31.9% overall across all SMA types.

Regarding the **duration between genetic report and registry entry**, for SMA type 1, the two events were closer in time (22.6 months) and SMA type 3 had the highest recorded time (90.4 months). This suggests that efforts were made to enrol patients of SMA type 1 shortly after their SMA diagnosis.

Overall, 24.5% of patients were **lost to follow-up** across all the country-specific registries. Of note, no patient loss of follow-up has been observed in Spain and Sweden.

The proportion of patients treated with **at least one DMT** increased over time, from 2.2% in 2014-2016 to a peak of 68.4% in 2021 and 66.1% in 2022 (prior to 2017, this usage included only treatment intakes during clinical trials). Patients with SMA type 1 were most likely to receive a treatment with DMT across all registries. Treatment with Spinraza was common across calendar periods, (2014-2023), and across all registries with the highest distribution of patients treated with Spinraza in 2021 (51.1%). Patients with SMA type 1 had the highest percentage of patients treated with Spinraza. Treatment with Evrysdi did not begin until 2018 and the overall usage was less common, with the highest percentage observed in 2022 (23.0%). Evrysdi was relatively more common among SMA type 2 patients than other SMA types. Treatment with Zolgensma did not begin until 2018 and was rare across all SMA types and across all registries. Treatment with more than 1 DMT was also rare across all SMA types and registries.

Supportive strategies like invasive, non-invasive ventilation and feeding tube usage were most commonly reported in patients with SMA type 1 across all the registries. The proportion of patients receiving feeding tube usage in the SMA type 1 was approximately 40% and was fairly consistent across the calendar periods. Overall, more than 50% of patients had at least one episode of wheelchair across all the calendar periods. Patients with SMA type 2 had the highest proportion (around 75%) of patients reporting at least one episode of wheelchair usage across the registries.

PROs were available in Belgium and Spain registries only, between 2018-2021 and 2020-2023 respectively. On average, patients across SMA types had approximately only one available record of PRO for each patient.

11.1.2 Natural history and impact of DMT treatments on disease progression (in “NEVER TREATED”, N=847 and “TREATED”, N=1,321):

In the SMA type 1 population, an improvement in “Best functional status” and “Best achieved motor milestones” has been observed after patients started treatment, suggesting a positive effect of DMT on disease progression for SMA type 1 patients.

- **In never treated patients (N=154)**
    - **Best Motor function:**

        - Functional status and achieved motor milestones were not reported
        - The CHOP-INTEND best score median was non-estimable (<5 cases).
    - **Median event-free survival** (death or permanent ventilation) was 11.5, [5.2, 39.8] months
    - **PRO** was non-estimable (< 5 cases) in both Spain and Belgium registries.

- **In treated patients** (N=276 SMA)
    - **Best Motor function:**
        - Missingness 27.9%, 101 patients (36.6%) achieved "sitter" and 33 (12%) "walker" status.
        - 75 patients (27.2%) achieved "sitting without support", 51 (18.5%) achieved "rolling onto their side", 7.2% were able to "stand with assistance", 6.5% to "walk with assistance", 2.9% to "walk without assistance" and 1.8% to "walk 10m without assistance".
        - The CHOP-INTEND best score median was 44 [33, 54].
    - **Median event-free survival** (death or permanent ventilation) was 10 [6, 24] months.
    - **PRO** was 64.5 [48.8, 80.1] for the "Best score for Spain PROFuture Mobility and Independence PRO" and non-estimable for the "Best score for Belgium ACTIVLIM PRO".

In the SMA type 2 population, an improvement in "Best functional status" and "Best achieved motor milestones" has been observed after patients started treatment suggesting a positive effect of DMT on disease progression for SMA type 2 patients.

- **In never treated patients (N=361)**
    - **Best Motor function**:
        - Missingness 97.8%, 7 patients (1.9%) achieved "roll onto side", less than 5 achieved "Hold head without support".
        - CHOP-INTEND, RULM and HFMS(-E) best score median were non-estimable (<5 cases).
    - **Median event-free survival** (death or permanent ventilation) was 219 [156, 515] months.
    - **PRO** was 56.9 [51, 64.9] for the "Best score for Spain PROFuture Mobility and Independence PRO" and -8.1 [-8.1, -8.1] for the "Best score for Belgium ACTIVLIM PRO".

- **In treated patients** (**N=**540):
    - **Best Motor function**:
        - Missingness 8.5%, 329 patients (60.9%) achieved "sitter" and 133 (24.6%)

"walker" status and only 5.9% remaining "non-sitters".

- 205 patients (38.0%) achieved "sitting without support", 86 (15.9%) "walk with assistance", 13.9% "crawl", 7.8% "stand with assistance", 3% "walk 10m without assistance" and 3% "walk without assistance"
- CHOP-INTEND, RULM and HFMS(-E) best score median were 46 [35, 57.5], 17 [10, 24] and 12.5 [4, 31.2], respectively.

- **Median event-free survival** (death or permanent ventilation) was 143 [83, 246] months.
- **PRO** was improved with 50 [28.2, 66.3] for the "Best score for Spain PROFuture Mobility and Independence PRO" and -6.6 [-8.1, -3.7] for the "Best score for Belgium ACTIVLIM PRO".

In the SMA type 3 population, an improvement in "Best functional status" and "Best achieved motor milestones" has been observed after patients started treatment suggesting a positive effect of DMT on disease progression for SMA type 3 patients.

- **In never treated patients (N=299)**
  - **Best Motor function:**
    - Functional status and achieved motor milestones were not reported
    - CHOP-INTEND, RULM and HFMS(-E) best score median were non-estimable, 33 [23.2, 37] and 51 [14.5, 60], respectively.
  - **Median event-free survival** (death or permanent ventilation) was 532 [393.5, 588.5] months
  - **PRO** was 42 [27.4, 50] for the "Best score for Spain PROFuture Mobility and Independence PRO" and -3.5 [-8.1, -2.6] for the "Best score for Belgium ACTIVLIM PRO".
- **In treated patients** (N= 476)
  - **Best Motor function:**
    - Missingness 5.5%, 418 patients (87.8%) achieved "walker" and only 1.5% remaining "non-sitters" status.
    - 302 patients (63.4%) were able to "climb stairs", 92 (19.3%) were able to "walk 10 metres without assistance", 22 (4.6%) to "walk without assistance"
    - CHOP-INTEND, RULM and HFMS(-E) best score median were 51 [28.5, 64], 35.5 [26.8, 37] and 50 [29.8, 58], respectively
  - **No** event (death or permanent ventilation) has been reported to estimate the **median event-free survival**.
  - **PRO** was improved with 10.9 [4.8, 27.7] for the "Best score for Spain PROFuture Mobility and Independence PRO" and 0.1 [-2.4, 2.8] for the "Best score for Belgium ACTIVLIM PRO".

11.1.3 Evolution of healthcare management:

In our study population, we had patients receiving their first **DMT** as early as 2014-2016 due to participants' early enrolment in clinical trials; this trend was observed in almost all registries, as data was collected historically prior to registry entry. An uptake of the available treatments was observed across all participants in all registries: the proportion of patients on at least one DMT increased steadily from 2.2% in 2014-2016, to as high as 68.4%, in 2021, with the approval of drugs in more countries and the adoption of standard SMA treatment protocols. Spinraza and Zolgensma usage was often reported among patients with SMA type 1, whereas a higher distribution of patients with SMA type 2 were treated with Evrysdi across all calendar periods. The number of patients treated with **more than one DMT** was low, starting from 2020 across all SMA types and treatment with a combination of Spinraza and Evrysdi, Zolgensma and Spinraza, and Zolgensma and Evrysdi were particularly very scarce across all calendar periods.

Data relating serious adverse events leading to hospitalisation associated with DMT usage were very limited across the calendar periods and SMA types, hence no interpretations were made.

With respect to the use of **ventilation**, we observed an increase in the use of any ventilation across calendar periods spanning from 2011 to 2020 across SMA types. Ventilation usage in SMA type 1 has evolved from 18.8% in 2011/13 to 57.0% in 2020, in SMA type 2 from 10.3% in 2011/13 to 32.2% in 2020.

With respect to patients using **wheelchairs**, more than 50% of participants overall had usage across all calendar periods. Wheelchair usage in SMA type 1 has evolved from 21.9% in 2011/13 to 62.2% in 2021. In SMA type 2, usage increased slightly from 69.7% in 2011/2013 to 77.2% in 2021.

Muscular physiotherapy was similarly reported (36.9% overall) across all SMA types and others rehabilitative interventions (i.e., **respiratory physiotherapy, contracture management, spinal brace** and **speech therapy)** have been more reported in SMA type 1 patients than in SMA type 2 and than in SMA type 3.

Feeding tube usage was most common in patients with SMA type 1. Usage in SMA type 1 increased from 25.0% (n=16) in 2011/13 to 40.6% (n=103) in 2021, and in SMA type 2 from 4.6% 2011/2013 (n=8) to 6.0% (n=40) in 2021.

11.2. Limitations

These findings and limitations have been taken into account when interpreting the study results.

Feasibility phase:

Quality and completeness of the registry data:
A preliminary assessment of SMA registries part of the TREAT-NMD network was conducted (please refer to the full description and summary of the main findings in the feasibility report in Appendix D) to select fit for purpose registries. As a result, 7 registries were recommended for the study and 6 were finally included. This SPIFD framework was used to select registries because it operationalizes principles with respect to data reliability, relevance and accessibility. The final selection of registries was made based on the responses from both pre-feasibility and feasibility questionnaires.

A summary of the main findings for each registry included in the study (based on the pre-analysis phase) is presented below.

The Belgian registry was recommended for its apparent good comprehensiveness of records for all data elements, as well as for administrative information and quality requirements. Patients follow up is greater than 5 years. The 3 disease modifying therapies were available in the country at the time of the feasibility assessment. Spinraza has been available since 2018, Zolgensma since 2021 and Evrysdi since June 2022. Approximately 73%, 21% and 2% of patients of the Belgian registry have received Spinraza, Evrysdi and Zolgensma respectively. Comorbidities and PROs were collected in the registry database. Non-medicinal product therapies and support were not collected. No specific process exists to collect SAEs.

The Czech and Slovak registry was recommended based on its apparent comprehensiveness of records for the majority of data elements and very good administrative information and quality requirements. The registry has the highest number of patients among clinician-based registries. Spinraza has been available since 2017, Zolgensma since 2020 and Evrysdi since 2021. Approximately 80% of patients in the registry have received a DMT with Spinraza being the most administered. However, dosing and administration dates for DMTs were missing. The motor function test was partially reported as well as scoliosis data. Orthopaedic disorders were not collected. Date of death was recorded but the cause of death was missing for 95% of records. Comorbidities are well reported. The percentage of records for SAEs was extremely low, nonetheless each comorbidity, hospitalisation and death could be reported as a SAE in the database. The registry did not collect any PRO.

The Swedish registry was recommended for its apparent good comprehensiveness of records for all data elements as well as for administrative information and quality requirements. Founded in 2010, the Swedish registry is a national registry with patient follow-up greater than 5 years. The 3 DMTs were available in the country. Spinraza has been available since 2017 and Zolgensma and Evrysdi have been available since February 2022. As of September 2022, 59% of patients in the Swedish registry have received Spinraza and stopped receiving it with the stopping reasons of elective choices (85% of the reasoning responses) and loss of DMT response (15% of the responses). Comorbidities were collected in the database; however, SAEs and PROs were reported only for a small number of patients.

The Spanish registry was recommended considering the overall apparent data quality, very good administrative information and quality requirements as well as the future collection of PRO (PROfuture questionnaire) at the time of feasibility assessment. The registry started collecting data in 2015. All SMA patients in the registry have a confirmed 5q diagnosis and their consent has been uploaded in the database. The average patient follow-up in the registry was greater than 5 years. Spinraza has been available since 2018 and Zolgensma since 2021, both were financed through the reimbursement pricing system with some restrictions. Evrysdi was not yet available at the time of feasibility assessment. Dosage of DMTs was not collected in the registry. The patient motor function was not well reported, start date of wheelchair usage, motor function test and muscle contractures were not collected. Enteral nutrition and thoraco-pulmonary disorders were well reported. Regarding the height and weight of patients, the registry should start collecting these variables after discussion with their internal advisory committee. Comorbidities were collected in free text and the registry had no record of diagnosis date for comorbidities in the database. SAEs were not collected.

The German & Austrian registry was recommended considering the high number of patients included, overall data quality, very good administrative information and quality requirements. The registry started collecting data in 2008, consequently the average patient follow-up in the registry is greater than 6 years. The registry had the highest number of patients including the highest number of patients with a genetically confirmed 5q diagnosis among all patient-based registries. DMTs are covered by the public health insurance in Germany and Austria. Spinraza has been available since 2017, Zolgensma since 2020 and Evrysdi since March 2021. Approximately 40%, 2% and 11% of patients in the registry have received Spinraza, Zolgensma or Evrysdi respectively. The dosage of DMTs was not collected.

The SMA characteristics (symptom onset date) as well as the motor ability status were reported for half of the patients. More than half of patients had a record of their motor function (wheelchair usage and frequency, start date of wheelchair usage and muscle contractures), however motor function tests were not collected. Scoliosis was well reported although Cobb Angle value was not collected. Pulmonary function tests were reported, as well as the invasive and non-invasive ventilation usage and the need for airway clearance assistance. Death and cause of death were not collected. More than half of patients had one or several weight and height values recorded in the database. Comorbidities and their start date were collected. SAE and PRO were not collected.

The UK & Ireland registry was recommended considering the number of SMA patients with genetic confirmation was in the range of the Spanish registry. This registry had much less 5q SMA patients than the German & Austrian registry. The UK & Ireland registry received a favourable opinion of the ethics committee to begin collecting data in 2007; the average patient follow up was greater than 5 years. Spinraza has been available since 2019, Zolgensma since 2021 and Evrysdi since 2022. Less than half of patients in the registry had an administration of DMTs recorded. The dosage of DMTs was not collected.
The SMA clinical characteristics (symptom onset date) was reported for approximately 44% of patients with a genetic SMA confirmation which is lower than the percentage of other patient-based registries. The motor ability status was poorly reported (only 16% records). Motor function tests were not collected. Pulmonary function and hospitalizations, which were critical information, were not well reported. Overall, the UK & Ireland registry had less information on SMA clinical characteristics, functional status, and scoliosis diagnosis, and much less information on ventilation usage and hospitalisation information compared to the registry in Germany & Austria.

Logistical challenges with accessing registries: Some registries had timeline issues and delays in delivering the data due to ethical approval and contracting challenges. It was the case for the registry in Switzerland that was finally not included in the study due to lag time in the contracting process and data sharing.

Patient enrolment in registries: Participation and involvement in both physician- and patient-based registries is voluntary and therefore, not all SMA patients treated or never treated might be included in these registries and hence, in this study. Also, albeit there are no direct benefits (e.g., incentives) to patients to be part of registries, the patients get awareness thanks to the exposure to information like innovations, clinical trials, drug development, part of SMA community etc. Therefore, potential selection and information biases cannot be excluded.

Post-analysis phase:

Quality and completeness of the registry data:

Once data was analysed, we observed that the extent of missing data was higher than predicted during feasibility for some variables; in particular for the “age at symptom onset”, “number of SMN2 copies", “reason for and method of genetic testing” and the “duration of the disease”. Missingness was notably higher in never treated patients (e.g., “Best functional status” and “Best achieved motor milestones”), suggesting a less accurate follow up of such patients in registries.

One important date requested in the study protocol was “SMA diagnosis date”. Unfortunately, this is not directly captured within the TREAT-NMD GRP. One possible proxy is the “genetic report date”. It was assumed that “genetic report date” is the date when genetic diagnosis was confirmed. However, this may not be the case as physicians, or patients, might have entered a date from a hospital letter relating to their visit, rather than the true genetic report date. As a side note, the TREAT-NMD GRP allows patients to

provide multiple records for genetic reports. In the case where multiple genetic report dates were available for a specific patient, the earliest genetic report date has been used.
"Presymptomatic" is also not collected directly in the SMA type variable within the TREAT-NMD GRP. Thus, patients selecting "Asymptomatic to Symptom onset" and "Yes, to Genetic confirmation" have been classified as "presymptomatic".

DMTs in the context of SMA have been made available on the market recently (2017, 2020 and 2021, Spinraza, Zolgensma and Evrysdi, respectively), resulting in a limited follow-up duration in the registries after treatment start. Longer duration of follow-up might be required to make conclusive and robust observations of disease progression in the context of treatment initiation.

The lack of data completeness we have observed, especially for motor and functional status variables, results in an incomplete picture of this patient population and may have resulted in limited ability to identify post-diagnostic outcomes of interest or patient prognostic characteristics that may influence the treatment decision (initiation, stop, combination). This can notably apply to variables for patients entered in the registry later after onset of symptoms or diagnosis, or treatment initiation. Also, as registries differ in terms of size and data quality, large registries with lower data quality may have negatively impacted the study results (although data considered of poor quality at the feasibility phase were not included in the analyses).

Heterogeneity and sample size across registries:

The use of multiple registries in rare disease provides complementary information. In our study, 6 registries, either physician-based (Belgium, Czech Republic & Slovakia and Sweden) or patient-based (Spain, UK & Ireland and Germany & Austria) with various sample sizes and with some data heterogeneities have been combined. In total, 2188 patients with 7 types of SMA have been pooled, coming from the Germany and Austria registry (31.8%), 18.0% from the UK and Ireland, 15.9% from Czech Republic, 14.6% from Spain, 11.7% from Belgium and 8.0% from Sweden. Pooling all heterogenous registries may have introduced imbalances and different weights in the descriptive statistics that may have impacted artifactually the percentages and estimates.

Report of AESI, Deaths and lost to follow up:

We observed a very low number of SAESI globally, with less than 5 events of interest reported in the study. The low rate of SAESI points towards the underreporting of SAESIs in registries and the need to increase efforts to identify and report SAESIs in relation to DMTs. Several reasons for this underreporting are possible. Firstly, SAESIs are often required to be reported in multiple locations to different interested parties, and therefore patients or clinicians may not also update registry records as they believe data to already be reported elsewhere. Secondly, SAESIs can result in rapid acceleration of disease severity or prolonged hospitalisation, resulting in missed clinician appointments in which registry data is collected. Missing data concerning AEs is indicative of the fact that registry datasets have not been originally developed for monitoring of safety of medicines.

We observed a very low number of deaths (less than 5 per quarter). In such disease registries, without any linkages, most historical deaths may not have been reported. In particular, patients with SMA 1 known to have (or used to have) very short life span may not have been included in the registry data.

We observed, overall, 24.5% of patients were lost to follow-up across all registries (5.0% among treated patients and 55.4% among "Never treated" patients). Patients can be lost to follow-up for several reasons, including significant progression of disease severity or death. For example, patient death is not collected comprehensively in registries, therefore high proportions of deceased patients may appear lost to

follow-up. Another reason patients can be lost to follow-up is if the patient is missing appointments or is under the care of an alternative healthcare provider. The highest rates of loss to follow-up was observed in the "never treated" group of patients. This might illustrate that this group have less interactions with the healthcare system, or that these patients deteriorate rapidly. Loss to follow-up could introduce selection and information biases, especially as it differs between treated and never treated patients.

COVID-19 concomitant context:
Finally, the study period overlapped with the outbreak of COVID-19. COVID-19 was first present in Europe in early 2020; this was close to the availability of Zolgensma, and after the introduction of Spinraza. As exploratory ITS analyses were concerned, the outcomes of interest (i.e., death or ventilation) are also known as direct consequences of COVID-19. Accounting for COVID-19 in ITS modelling was not possible due to the fact that the introduction of DMTs had a large overlap with the emergence of COVID-19 across Europe and the available data were not able to distinguish the effects of COVID-19 from DMT. Thus, the interpretation of trends in ITS results should consider that 1/COVID-19 may lead to patient's death, or a requirement for full-time ventilator use, especially for those with pre-existing health conditions as SMA patients, 2/ due to the additional strain on healthcare professionals, keeping registry data up to date may not have been a priority, especially early on in the pandemic and 3/ a decrease in the number of SMA patients receiving full time ventilation/composite after Spinraza introduction may be also due to the lack of ventilators available. Also, the exploratory ITS analysis was not correcting for multiple testing (e.g., Bonferroni correction). As very few p-values have been close to the threshold of 5%, it was assumed this likely would not cause any drastic changes to conclusions.

Quality of life (QoL) using patient-reported outcomes (PROs):

PROs were available in Belgium and Spain registries only, between 2018-2021 and 2020-2023 respectively. PROFuture, used by the Spanish registry, has been validated in adults, but not yet in children. In Belgium, ACTIVLIM has been validated in both children and adults. Overall, the PRO availability ranged between 16.8% and 43.5% in Spain and between 48.6% and 68.8% in Belgium, and each patient had on average only one available record of PRO. Thus, the observed improvement of PRO scores at population level, once treated by DMTs, should be interpreted as trends only.

11.3. Interpretation

Description of registry specificities in terms of SMA population capture

The three clinician-based registries (Belgium, Czech Republic & Slovakia and Sweden) represented 779 patients (35.6%) and the 3 patient-based registries (Germany & Austria, Spain, UK & Ireland) 1409 patients (64.4%).

Registries have been implemented at different times resulting in various lengths of history and data availability: from 2008 in Germany and UK and Ireland, 2010 in Sweden, 2011 in Czech republic, 2015 in Spain and 2018 in Belgium.

The **features of registries were similar** and the data consistently reported across the 6 registries albeit **some heterogeneities have been observed**:

- The Czech Republic reported a higher proportion of SMA 1 (27.6%), Spain a higher proportion of SMA 2 (48%), and Sweden a higher proportion of SMA 3 (40.6%)
- Slightly more male than female patients included in the Spain, and UK and Ireland registries

- Spain and Sweden registries had 100% patient retention
- In Spain, a high proportion of SMA type 1 patients (19 patients, 26.8%) and SMA type 2 (55 patients, 35.9%) were classified as “Walkers” at their best functional status. This might be due to a different definition of Spanish clinicians of "walk with assistance", and "walk without assistance". Another potential explanation may be access to orthotic aids. Countries in which patients have greater or easier access could lead to higher numbers of patients able to walk with assistance, which would increase the proportion of walkers in that country.
- *In this project, the definition of a "Walker", was a patient that: "walk with assistance", "walk without assistance", "walk 10 metres without assistance", or "climb stairs.” However, the Spanish registry internally defines a walker as: “Someone who can walk at least 10 metres.” Therefore, those who walk with assistance or without assistance but don't reach the 10 metres mark would not be considered walkers in the Spanish registry, but are categorised as such in this project.*
- The UK and Ireland registry had the highest amount of missing data for the genetic report data, followed by the Sweden registry while this variable was well recorded in all the other registries.
- PRO data were available only in Spain and Belgium, with very few records per patient

Missingness for some variables was high across all registries, in particular for the “reason for and method of genetic testing” and the “duration of the disease”.

The **MLPA**, which is a gold standard for SMA diagnosis (31), was also observed as the most common method used for genetic testing across all SMA types and registries (24.1%).

As previously published (32), the **age at onset of symptoms** for patients with SMA type 1 was less than 6 months old, 6-18 months old for patients with SMA type 2 and 2-6 years old for SMA type 3 across all the registries.

With respect to the **screening method**, across all registries, most patients were not identified as a result of a screening but based on symptoms. Standard “newborn screening” being the agreed appropriate tool to ensure timely diagnosis, the findings from this study point to the lack of such systemic disease management strategy. (33). Nevertheless, for SMA type 1 patients, and across all registries, the duration between genetic report and registry entry were closer in time (22.6 months) than for SMA type 2 (82.6 months) and SMA type 3 (90.4 months), suggesting a more accurate enrolment and follow up amongst the most severe SMA patients.

Among all patients treated with at least one **DMT** (61.3%), some started receiving treatment prior to their first marketing authorization, which corresponded to treatment intakes during clinical trials (this has been confirmed by TREAT-NMD and Registry owners). Across all registries, the DMT usage increased since the marketing authorization and peaked in 2021-2022. Treatment with Spinraza, first on the market since 2017, was common across calendar periods and with the highest proportion of patients treated with Spinraza in 2021. Patients with SMA type 1 had the highest percentage of patients treated with Spinraza. Treatment with Evrysdi was less common than Spinraza, with the highest percentage observed in 2022 and Evrysdi was relatively more common among SMA type 2 patients. Usage of Zolgensma was less frequent across all SMA types and across all registries. Treatment with more than 1 DMT was rarely reported across all SMA types.

Natural history and impact of DMT treatments on disease progression:

Overall, in order to assess the impact of DMTs on disease progression, we focused on some key elements such as “**Best functional status”** and **“Best achieved motor milestones”** and their improvement during treatment. The improvements observed once patients are under treatment suggest positive effects of DMT on disease progression for SMA type 1, SMA type 2 and SMA type 3 patients, however no formal

comparison was attempted. In addition, from exploratory ITS, after the introduction of Spinraza (i.e., after 01-07-2017), we observed that the number of SMA type 1 and SMA type 2 patients first receiving full time ventilation was significantly reduced. Improvement of healthcare delivery over time can also be an explanation for this finding.

In SMA type 1 patients:

Studies show that 50% of SMA type 1 patients will have died or required permanent daily non-invasive ventilation support by 10.5 months of age and 92% by 20 months of age. (34) The classic clinical phenotype of untreated SMA type 1 patients is characterised by motor weakness and regression within 6 months of life, followed by respiratory failure and death. (35,36) Observational studies were also able to describe the natural history of SMA type 1 patients while focusing on meaningful outcomes used in clinical trials. (34,37) These studies showed that among never treated SMA type patients, none of them achieved independent sitting or other more advanced motor milestones. Functional status and achieved motor milestones have not been reported in the current study in SMA 1 patients who were never treated. In contrast, in SMA 1 treated patients, 36.6% achieved “sitter” status and 12% achieved “walker” status. Further, more than a quarter (27.2%) of treated patients achieved “sitting without support”, while 18.5% retained “rolling onto their side” as their best achieved motor milestone. Higher motor milestones were also achieved by these patients, including walking with assistance (6.5%), walking without assistance (2.9%), and walking 10 metres without assistance (1.8%). The surprisingly higher percentages observed in our study could be explained by differences in the definition of walkers with other published studies (e.g., the case of Spain as described above - among the 33 (12%) walkers, 19 come from Spain) or misclassification of patients in the different SMA types following the number of SMN2 copies rather than the phenotype (patients with 2 copies = SMA1; patients with 3 copies = SMA2 and patients with 4 copies = SMA type 3).

An open-label study of Evrysdi in patients with SMA type 1, 1-7 months of age at enrolment, assessed the efficacy and safety of daily administration of Evrysdi as compared to untreated patients. (38) The authors reported that treatment with Evrysdi resulted in a higher percentage of patients who achieved better motor milestones and improvements in motor functions compared to untreated historical controls. In our descriptive study, the trend in improvement of “best motor milestones” in SMA type 1 patients treated with Evrysdi was similar.

In SMA type 2 and 3 patients:

The SUNFISH trial (39), which looked at the two-year efficacy and safety of risdiplam, reported clinically relevant gains in motor function in SMA 2 and 3. Other published observational research literature (37) also shows that untreated patients with SMA type 2 could sit independently but not walk, whereas untreated patients with SMA type 3 develop independent walking. In our study, very few functional status measurements have been reported in SMA 2 and SMA 3 never treated patients. In contrast, in the overall treated SMA 2 patients, 60.9% achieved “sitter” status and 24.6% achieved “walker” status. Further, more than two thirds (38.0%) of treated patients achieved sitting without support. Higher motor milestones were also achieved by these patients, including walking with assistance (15.9%), “crawl” (13.9%), “stand with assistance” (7.8%) walking without assistance (3.0%), and walking 10 metres without assistance (3.0%). In treated SMA 3 patients, 87.8% achieved “walker” status and 63.4% of treated patients were able to climb stairs and 19.3% were able to walk 10 metres without assistance.

Finally, the decreasing proportion of scoliosis in SMA type 2 likely reflects that patients are not reported with scoliosis after spinal fusion in some registry.

SMA Pre-symptomatic patients:
Only 8 patients have been reported as pre-symptomatic or having been identified by newborn genetic screening (NBS). However, some Germans authors reported 47 patients identified by NBS in Germany and Belgian authors reported 9 cases (40,41), suggesting an underreporting of presymptomatic patients in our registries from the same countries. It is thus very likely that these patients have been reported in the different types following the number of SMN2 copies (patients with 2 copies = SMA1; patients with 3 copies = SMA2 and patients with 4 copies = SMA type 3). This could also explain the high proportion of SMA type 1 walkers after treatment (12%) (which is nearly never reported in the literature) or the more intriguing proportion of non-sitters at genetic report in SMA type 3 (12.4%) - which normally never happens or very rarely.(32)

Healthcare management and standard of care:

Over the last decade, there has been increasing evidence of improvements in management of the disease progression of all SMA patients (7,42). Such findings have also been identified in the study, with a high rate of screening using MLPA or with more than 50% of participants using wheelchairs across the calendar period or also, we did see an increase in the use of any ventilation across calendar periods spanning from 2011 to 2020. Those results reflect the adapting strategies as standard of care across a wide range of clinical profiles of SMA patients (43,44).

11.4. Generalisability

The SMA patients included in this study represent a total of 6 registries from 9 countries across Europe/UK, having a high external validity. In light of all registries that exist across the Europe/UK, conducting a study combining together multiple data sources represents a significant effort to leverage information across existing registries, initially assessed for good data quality and with wide geographical coverage. The results of this study and the capacity of participating registries to capture important elements may have been influenced by different factors, such as organisation of the national healthcare systems and their personal attitudes towards the integration of registries into clinical practices. In addition, variations in standard of care among participating countries may have had an impact on the extent of recorded patient outcomes, and as such, may not be generalizable to populations in other countries.

Moreover, patients' treatment and their disease progression as a result of available treatment options may differ from other EU countries and beyond, such as Canada, where treatment availability is limited. (45) Spinraza was recently approved by the EMA (May 2017) and the US Food and Drug Administration (December 2016) (45) and is now reimbursed in several European countries and in the USA. However, in Canada, the drug did not pass the price negotiation for the treatment, as the Canadian Agency for Drugs and Technologies in Health recommended against reimbursement and access to Spinraza for SMA patients. As such, treatment patterns and information on clinical characteristics, including changes in motor milestone status or any other clinical indicators may not be generalizable to other patients in countries where the drugs are not reimbursed. (46)

In the TREAT-NMD network, it is encouraged that all available data are entered in registries, which includes all available data from all visits in clinician-based registries and all available data whenever possible in patient registries. However, an important consideration is the potential for enrolment bias, which could be an issue if patients are enrolled differently and maintained within the registries through regularly scheduled appointments with doctors or nurses, which vary across countries. Thus, patients in this study might be different from other registries on SMA patients that employ different techniques for patient retention across other various geographical locations. We are not aware of any incentives used to

maintain patients within the registries and as such, we cannot comment on the extent to which this bias is at play in this longitudinal cohort of patients.

We would recommend further research projects with robust comparative designs and a more limited data set on some key pre-defined motor functions; to be started by a pilot in a few voluntary registries to assess the accuracy and quality of the required data.

Lessons learned

The use of multiple registries in rare disease provides complementary information to answer regulatory research questions. From 16 registries pre-identified across the TREAT-NMD network, we recommended 7 registries and finally 6 (from 9 countries) were considered the most fit-for-purpose for this specific study. This large pan European/UK study is the first of its kind to evaluate natural disease progression, clinical, healthcare management and treatment patterns from multiple disease-specific registries across Europe, with data collected by physicians or patients depending on the country, in the context of rare SMA disease. It offers a unique opportunity to compare patients' clinical profiles in the context of emerging treatment options and healthcare management changes, such as the introduction of systematic newborn genetic screening (NBS) in Germany (October 2021) and Belgium (March 2021). (47,48) However, this could not be captured in registries as the patients identified by NBS were not really recorded as such.

The quality and completeness of the registry data have been assessed through a feasibility study based on a fit for purpose questionnaire sent to registry owners. The questionnaire was designed according to the study objectives and the required key outcomes (age, type of SMA, medications, disease characteristics, disease outcomes etc) and by using EMA Guideline on registry-based studies, REQueST tool items and FAIR principles. At this feasibility phase, the completeness of data was not based on accurate quantitative counting rather on the registry owner's judgement. Once data was analysed, we observed that the extent of missing data was important for some variables. At the feasibility phase, further quantitative counting and higher granularity in defining the required data should be considered in the future.

The main limitations for collaboration with registries were tight timelines for feasibility and data sharing to TREAT-NMD, no systematic data quality assurance processes in place and data missingness related to study-specific research questions. In 2015, the Patient Registries Initiative was established with the aim to support a systematic and standardised approach for registry contribution to medicines assessment, especially in the context of PASS and post-authorization effectiveness studies. Moving forward, registry reporting, quality assurance processes and governance will need to be put in place to ensure further development of individual registries in order to support their use and contribution to medicines' regulatory assessments. (49)

In addition, complete data collection on critical disease variables is crucial; primary medication information is essential and should include the start and the stop date where applicable. (50) In the registries that we included for participation, we observed a high rate of data completion for the start date of treatment (only 20 patients flagged as "treated", did not have a start date recorded) and generally many variables were better recorded in the treated patients than never treated. Furthermore, PROs are of increased interest and importance to stakeholders, and as reported in this study, only two of the participating registries were able to contribute with PRO information; out of the two (Spain and Belgium), the mean number available of each record of each PRO was only around 1. Thus, better efforts are needed to ensure that sufficient information with respect to important and clinically validated PROs is collected on a regular basis and with good quality and completeness.

The absence of recorded AESIs points to the underreporting of special AEs in registries; better efforts to report AEs related to DMTs or alternative solutions, such as linkage are needed to ensure the suitability of registries to participate in safety and comparative effectiveness studies. As such, we were not able to draw

any descriptive comparisons between different groups due to the lack of data on such events. The low recorded rate may also indicate little interest in the topic or that registries might have not been originally developed for routine data collection on AEs, and consequently, for monitoring of safety medicines. Improvements in processes related to reporting of such adverse events is crucial for future safety research.

In this study, we observed a high degree of missingness for some important clinical motor indicators. Also, given the elevated attrition rate observed in some registries, retention of participants is of crucial importance. These two observations point to one of the key factors identified as needed to facilitate the use of registries for supporting regulatory assessments: sustainability. (50) Registry funding and support may have been limited in the participating registries in this study, especially during the COVID-19 period, and as such, may have caused difficulties in maintaining reliable quality assurance processes and staff training. Given that data entry is often done on a voluntary basis and manually by clinical staff directly, registry sustainability is critical for long-term development of registries. Also, these different elements plead for a common dictionary (e.g., common minimal SMA data model, common definition for the collection of key criteria and/or clinical judgement) for registries across Europe. Finally, linkage of such SMA registries with other data sources available at a country level (e.g., EHR, claims, spontaneous reports, , mortality register) should also be considered in a larger vision of possible usages and beneficials (i.e., early clinical research, clinical development, regulatory, HTA and Payers decisions).

Finally, the logistical challenge related to statistical analyses has been of importance. The complexity of describing cohorts from registry-based data when there are many subgroups and the population is dynamic (i.e., stratified cohort with varied and changing denominators over calendar time) should not be underestimated.

12. OTHER INFORMATION

13. CONCLUSIONS

This large pan European/UK study is the first of its kind to evaluate natural disease progression, clinical, healthcare management and treatment patterns in SMA disease across multiple European registries . The study used data collected in SMA from patients enrolled across 6 patient- and clinician-based registries in 9 European countries (Belgium, Sweden, Czech Republic & Slovakia, Germany & Austria, Spain, and UK and Ireland) as part of the TREAT-NMD network.

The results were globally consistent with existing studies evaluating the natural history and progression of the SMA disease. Clinically relevant gains in motor function were observed in SMA 1, SMA 2 and SMA 3 treated patients per DMTs, although due to lack of comparison, no definite conclusion could have been drawn.

Improving the data accuracy and quality, reducing the missingness, and standardisation of definition of variables and having a common set of important data to be collected could help greatly answering key questions for the SMA community and for regulatory decision making. These different elements plead for a common data model for SMA Registries across Europe with Regulators for contributing to its definition.

Our study exemplified that the use of multiple registries in rare disease provides complementary information and new avenues to answer regulatory research questions.

14. REFERENCES

1. Schorling DC, Pechmann A, Kirschner J. Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. J Neuromuscul Dis. 2020;7(1):1–13.
2. Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol. 2012 May;11(5):443–52.
3. Hahnen E, Forkert R, Marke C, Rudnik-Schöneborn S, Schönling J, Zerres K, et al. Molecular analysis of candidate genes on chromosome 5q13 in autosomal recessive spinal muscular atrophy: evidence of homozygous deletions of the SMN gene in unaffected individuals. Hum Mol Genet. 1995 Oct;4(10):1927–33.
4. Alías L, Bernal S, Fuentes-Prior P, Barceló MJ, Also E, Martínez-Hernández R, et al. Mutation update of spinal muscular atrophy in Spain: molecular characterization of 745 unrelated patients and identification of four novel mutations in the SMN1 gene. Hum Genet. 2009 Feb;125(1):29–39.
5. Mendonça R de H, Matsui C, Polido GJ, Silva AMS, Kulikowski L, Torchio Dias A, et al. Intragenic variants in the SMN1 gene determine the clinical phenotype in 5q spinal muscular atrophy. Neurol Genet. 2020 Oct;6(5):e505.
6. Pierzchlewicz K, Kępa I, Podogrodzki J, Kotulska K. Spinal Muscular Atrophy: The Use of Functional Motor Scales in the Era of Disease-Modifying Treatment. Child Neurol Open. 2021 Dec;8:2329048X211008725.
7. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103–15.
8. Wijngaarde CA, Stam M, Otto LAM, van Eijk RPA, Cuppen I, Veldhoen ES, et al. Population-based analysis of survival in spinal muscular atrophy. Neurology. 2020 Apr 14;94(15):e1634–44.
9. G B, K G, M D, A K, R E, N H, et al. Prognostic Factors and Treatment-Effect Modifiers in Spinal Muscular Atrophy. Clinical pharmacology and therapeutics [Internet]. 2021 Dec [cited 2022 Nov 10];110(6). Available from: https://pubmed.ncbi.nlm.nih.gov/33792051/
10. Coratti G, Pera MC, Lucibello S, Montes J, Pasternak A, Mayhew A, et al. Age and baseline values predict 12 and 24-month functional changes in type 2 SMA. Neuromuscul Disord. 2020 Sep;30(9):756–64.
11. Loeber JG, Platis D, Zetterström RH, Almashanu S, Boemer F, Bonham JR, et al. Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010. Int J Neonatal Screen. 2021 Mar 5;7(1):15.
12. EMA. European Medicines Agency. 2018 [cited 2022 Oct 13]. Spinraza. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/spinraza
13. Al-Zaidy SA, Mendell JR. From Clinical Trials to Clinical Practice: Practical Considerations for Gene Replacement Therapy in SMA Type 1. Pediatr Neurol. 2019 Nov;100:3–11.
14. EMA. European Medicines Agency. 2020 [cited 2022 Nov 10]. Zolgensma. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma
15. Ratni H, Ebeling M, Baird J, Bendels S, Bylund J, Chen KS, et al. Discovery of Risdiplam, a Selective Survival of Motor Neuron-2 (SMN2) Gene Splicing Modifier for the Treatment of Spinal Muscular Atrophy (SMA). J Med Chem. 2018 Aug 9;61(15):6501–17.
16. EMA. European Medicines Agency. 2021 [cited 2022 Oct 13]. Evrysdi. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/evrysdi
17. Eckstein S, editor. Clinical investigation of medicinal products in the paediatric population. In: Manual for Research Ethics Committees [Internet]. 6th ed. Cambridge University Press; 2003 [cited 2022 Dec 23]. p. 420–8. Available from: https://www.cambridge.org/core/product/identifier/CBO9780511550089A069/type/book_part
18. 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. Journal of Comparative Effectiveness Research. 2022 Apr;11(5):347–70.
19. Mercuri E, Baranello G, Boespflug-Tanguy O, De Waele L, Goemans N, Kirschner J, et al. Risdiplam in types 2 and 3 spinal muscular atrophy: A randomised, placebo-controlled, dose-finding trial followed by 24 months of treatment. Eur J Neurol. 2022 Jul 15;
20. Klil-Drori AJ, Coulombe J, Suissa S, Hirsch A, Tagalakis V. Temporal trends in outpatient management of incident pulmonary embolism and associated mortality. Thromb Res. 2018 Jan;161:111–6.
21. Pazzagli L, Linder M, Zhang M, Vago E, Stang P, Myers D, et al. Methods for time-varying exposure related problems in pharmacoepidemiology: An overview. Pharmacoepidemiol Drug Saf. 2018 Feb;27(2):148–60.
22. Pazzagli L, Linder M, Reutfors J, Brandt L. The use of uncertain exposure-A method to define switching and add-on in pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2022 Jan;31(1):28–36.
23. Abrahami D, Yin H, Yu OHY, Pollak MN, Azoulay L. Incretin-based Drugs and the Incidence of Colorectal Cancer in Patients with Type 2 Diabetes. Epidemiology. 2018 Mar;29(2):246–53.
24. Rodriguez-Torres RS, Uher D, Gay EL, Coratti G, Dunaway Young S, Rohwer A, et al. Measuring Fatigue and Fatigability in Spinal Muscular Atrophy (SMA): Challenges and Opportunities. Journal of Clinical Medicine. 2023 Jan;12(10):3458.
25. Vandervelde L, Van den Bergh PYK, Goemans N, Thonnard JL. ACTIVLIM: a Rasch-built measure of activity limitations in children and adults with neuromuscular disorders. Neuromuscul Disord. 2007 Jun;17(6):459–69.
26. Domine MC, Cattinari MG, de Lemus M, Castellano IP, Ñungo-Garzón NC, Sevilla-Mantecón T, et al. Physical fatigue and perceived fatigability in adolescents and adults with spinal muscular atrophy: A pilot study. Neurology Perspectives. 2022 Oct 1;2(4):199–208.
27. Guideline on registry-based studies [Internet]. [cited 2022 Nov 10]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf
28. REQueST tool [Internet]. [cited 2022 Oct 13]. Available from: https://www.eunethta.eu/wp-content/uploads/2019/10/EUnetHTAJA3_Vision_paper-v.0.44-for-ZIN.pdf
29. Gatto NM, Reynolds RF, Campbell UB. A Structured Preapproval and Postapproval Comparative Study Design Framework to Generate Valid and Transparent Real-World Evidence for Regulatory Decisions. Clinical Pharmacology & Therapeutics. 2019;106(1):103–15.
30. Pera MC, Coratti G, Berti B, D'Amico A, Sframeli M, Albamonte E, et al. Diagnostic journey in Spinal Muscular Atrophy: Is it still an odyssey? PLoS One. 2020;15(3):e0230677.
31. Hassan HA, Fahmy NA, El-Bagoury NM, Eissa NR, Sharaf-Eldin WE, Issa MY, et al. MLPA analysis for molecular diagnosis of spinal muscular atrophy and correlation of 5q13.2 genes with disease phenotype in Egyptian patients. Egyptian Journal of Medical Human Genetics. 2022 Dec 5;23(1):156.
32. Chabanon A, Seferian AM, Daron A, Péréon Y, Cances C, Vuillerot C, et al. Prospective and longitudinal natural history study of patients with Type 2 and 3 spinal muscular atrophy: Baseline data NatHis-SMA study. PLoS One. 2018;13(7):e0201004.
33. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, Gripp KW, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2023 Oct 10]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1352/
34. Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014 Aug 26;83(9):810–7.

35. Thomas NH, Dubowitz V. The natural history of type I (severe) spinal muscular atrophy. Neuromuscul Disord. 1994;4(5–6):497–502.
36. McGrattan KE, Graham RJ, DiDonato CJ, Darras BT. Dysphagia Phenotypes in Spinal Muscular Atrophy: The Past, Present, and Promise for the Future. Am J Speech Lang Pathol. 2021 May 18;30(3):1008–22.
37. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. Natural history of infantile-onset spinal muscular atrophy. Annals of Neurology. 2017 Dec 1;82(6):883–91.
38. Darras BT, Masson R, Mazurkiewicz-Bełdzińska M, Rose K, Xiong H, Zanoteli E, et al. Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls. New England Journal of Medicine. 2021 Jul 29;385(5):427–35.
39. Oskoui M, Day JW, Deconinck N, Mazzone ES, Nascimento A, Saito K, et al. Two-year efficacy and safety of risdiplam in patients with type 2 or non-ambulant type 3 spinal muscular atrophy (SMA). J Neurol. 2023 May;270(5):2531–46.
40. Kölbel H, Kopka M, Modler L, Blaschek A, Schara-Schmidt U, Vill K, et al. Impaired Neurodevelopment in Children with 5q-SMA - 2 Years After Newborn Screening. J Neuromuscul Dis. 2023 Oct 31;
41. Boemer F, Caberg JH, Beckers P, Dideberg V, di Fiore S, Bours V, et al. Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium. Sci Rep. 2021 Oct 7;11:19922.
42. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018 Mar;28(3):197–207.
43. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. 2007 Aug;22(8):1027–49.
44. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103–15.
45. Gidaro T, Servais L. Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps. Dev Med Child Neurol. 2019 Jan;61(1):19–24.
46. Canada rejects Biogen's Spinraza for reimbursement for adults [Internet]. [cited 2023 Sep 26]. Available from: https://www.fiercepharma.com/pharma/canada-recommends-against-reimbursement-biogens-spinraza-adults
47. Müller-Felber W, Blaschek A, Schwartz O, Gläser D, Nennstiel U, Brockow I, et al. Newbornscreening SMA - From Pilot Project to Nationwide Screening in Germany. J Neuromuscul Dis. 2023;10(1):55–65.
48. Berthomier A. Newborn screening for SMA becomes official in Belgium [Internet]. Institut de Myologie. 2021 [cited 2023 Nov 10]. Available from: https://www.institut-myologorg/en/2021/10/20/newborn-screening-for-sma-becomes-official-in-belgium/
49. European Medicines Agency. Initiative for patient registries - strategy and pilot phase. EMA/176050/2014 [Internet]. 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195576.pdf. Accessed 29 September 2023.
50. McGettigan P, Olmo CA, Plueschke K, Castillon M, Zondag DN, Bahri P, et al. Patient Registries: An Underused Resource for Medicines Evaluation: Operational proposals for increasing the use of patient registries in regulatory assessments. Drug Safety. 2019;42(11):1343.
51. Vandervelde L, Van den Bergh PYK, Goemans N, Thonnard JL. Activity limitations in patients with neuromuscular disorders: a responsiveness study of the ACTIVLIM questionnaire. Neuromuscul Disord. 2009 Feb;19(2):99–103.

52. Trundell D, Skalicky A, Staunton H, Hareendran A, Le Scouiller S, Barrett L, et al. Development of the SMA independence scale-upper limb module (SMAIS-ULM): A novel scale for individuals with Type 2 and non-ambulant Type 3 SMA. J Neurol Sci. 2022 Jan 15;432:120059.

15. APPENDICES

Appendix A. Additional information

Supplementary Table 1. Years of availability of different disease modifying treatments (DMTs) in the 6 selected study registries.

Medication and year of availability	Sweden	Czech Republic & Slovakia	Belgium	Switzerland	Spain	Germany & Austria
Spinraza availability						
2017	1*	1	-	1	-	1
2018	2	2	1	2	1	2
2019	3	3	2	3	2	3
2020	4	4	3	4	3	4
2021	5	5	4	5	4	5
2022	6	6	5	6	5	6
Zolgensma availability						
2017	-	-	-	-	-	-
2018	-	-	-	-	-	-
2019	-	-	-	-	-	-
2020	-	1	-	-	-	1
2021	-	2	1	1	1	2
2022	1	3	2	2	2	3
Evrysdi availability						
2017	-	-	-	-	-	-

2018	-	-	-	-	-	-
2019	-	-	-	-	-	-
2020	-	-	-	-	-	-
2021	-	1	-	1	-	1
2022	1	2	1	2	-	2

* For each year, the cell value represents the total number of years the drug has been available on the market in the specific country of interest. If a value is missing, this is indicative of the medication being unavailable in a specific country in a specific year. Note that as of 2022, Evrysdi has still not been made available in Spain.

Appendix B. PRO Questionnaire: Spain

CUESTIONARIO "FATIGA FÍSICA Y FATIGABILIDAD PERCIBIDA" DE FUNDAME

Fatiga física y Resistencia

Durante el último mes:	Nunca o casi nunca	A veces	Siempre o casi siempre
1. ¿Ha necesitado descansar a menudo durante el día o por periodos de tiempo largos por sentirse cansado?			
2. ¿Ha necesitado seleccionar sus actividades durante el día para poder hacer lo que querías?			
3. ¿Ha tenido problemas para mantener la postura durante el día, por sentirse cansado?			
4. ¿Ha habido actividades que ha podido realizar por la mañana y que no ha podido realizar por la tarde o por la noche (la energía se ha ido agotando a lo largo del día)? *			
5. Si ha realizado un esfuerzo mayor de lo habitual, ¿el cansancio le dura hasta el día siguiente?			

Figura 1. Cuestionario "Fatiga física y Resistencia"

Fatigabilidad percibida en miembros superiores

Durante el último mes, ¿cuánta dificultad ha tenido en completar con éxito las siguientes actividades que incluyen movimientos repetitivos y continuados?	Imposible	Difícil	Me cuesta un poco	Fácil
6. Tomar notas en papel				
7. Mandar mensajes de texto				
8. Peinarse				
9. Comer solo				
10. Cepillarse los dientes				

Figura 2. Cuestionario "Fatigabilidad percibida en miembros superiores"

Appendix C. PRO Questionnaire: Belgium

Université catholique de Louvain
Unité de Réadaptation et de Médecine Physique

INSTRUCTIONS FOR THE ACTIVLIM QUESTIONNAIRE

The ACTIVLIM questionnaire

The ACTIVLIM questionnaire was developed as a measure of activity limitations in children and adults with **neuromuscular disorders** (Vandervelde et al, Neuromuscul Disord, 2007). Activity limitations are defined as difficulties a patient may have in executing activities of daily living. The questionnaire includes 22 items that are daily activities. Among these 22 items, 4 are specifically designed for child evaluation, 4 for adult evaluation, and the remaining 14 items are common to all patients. ACTIVLIM was built either on the perception of the parents of the affected children or on the perception of the adult patients themselves. This perception concerns the difficulty in performing each activity of the questionnaire. The 22 items of ACTIVLIM defined a valid, reliable and reproducible scale. ACTIVLIM was originally developed using the Rasch measurement model. It allows to convert ordinal scores into linear measures located on a unidimensional scale.

Evaluation

*For a **child** evaluation (between 6 and 15 years-old):*
The **parents** fill in the questionnaire by estimating their child's difficulty or ease in performing each activity.

*For an **adult** evaluation (more than 16 years-old):*
The **patient** fills in himself the questionnaire by estimating their own difficulty or ease in performing each activity.

The activities should be done:

- **Without technical or human help** (even if the patient actually uses help in daily life)
- Irrespective the limb(s) actually used to achieve the activity
- Whatever the strategy used (any compensation is allowed)

Three responses are presented. These assess the perception of the difficulty/ease depending on whether the activity is "impossible", "difficult" or "easy". Activities not attempted in the last 3 months are not scored and entered as missing responses (to tick the question mark).

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium.
www.rehab-scales.org

Appendix D - Stand-alone Document - Feasibility Report

Please note that the full feasibility report (including Description of different data sources) is available in a stand-alone document, submitted with this report.

Appendix E - Stand-alone Document - Statistical Analysis Plan

Please note that the SAP (Appendix E1) and addendum (Appendix E2) is available in a stand-alone document, submitted with this report.

Appendix F- Stand-alone Document - ITS Analyses Report

Please note that the exploratory analysis is available in a stand-alone document, submitted with this report.

Appendix G - Stand-alone Document - Supplementary Tables

Please note that the supplementary tables are available in stand-alone documents, submitted with this report.

Appendix G1 - Objective 0 (Preliminary) Results 2024_03_13

Appendix G2 - Objective 1 (Natural History) Results 2024_1_26

Appendix G3 - Objective 2 (Healthcare) Results 2024_03_13

Appendix G4 - Supplementary Results Objective 1 (Natural History) 2024_1_26

Appendix G5 - Supplementary Results Objective 2 (Healthcare) 2024_03_13

Approval page

Non-interventional registry-based Study – Study Report

A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs).

Protocol: EUPAS50476

PRINCIPAL INVESTIGATOR: Nicolas Deltour, VP Real World Strategy - Coordinating/Principal Investigator for Aetion; Pr Laurent Servais, Professor of Paediatric Neuromuscular Diseases, University of Oxford - Medical responsible party and Principal Investigator for TREAT-NMD

Version Date : Version 5.1 - 5 April 2024

The following people have reviewed the Report and given their approval

Name, title	Signature	Date
Pr Laurent Servais	[redacted]	08 APR 2024

Name, title	Signature	Date
Nicolas Deltour	[redacted]	11.04.2024

Appendix D Feasibility report

Non-interventional registry-based Study
Protocol: EUPAS50476

A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs).

Table of contents

List of abbreviations

Abbreviation	Definition
BNMDR	Belgian Neuromuscular Diseases Registry
CDW	Central Data Warehouse
CSMA	Children with Spinal Muscular Atrophy
ddPCR	Droplet Digital Polymerase Chain Reaction
DMT	Disease Modifying Therapy
DNA	DeoxyriboNucleic Acid
EEA	European Economic Area
EMA	European Medicine Agency
FFP	Fit-For-Purpose
HRM	High Resolution Melting
ISO	International Organization for Standardization
MLPA	Multiplex Ligation-dependent Probe Amplification
NMD	NeuroMuscular Disorders
NMiS	*Neuromuskulära sjukdomar i Sverige* Swedish National Registry for Neuromuscular disorder
PRO	Patient Reported Outcome
RFLP	Restriction Fragment Length Polymorphism
SAE	Serious Adverse Event
SMA	Spinal Muscular Atrophy
SPIFD	Structured Process to Identify Fit-for-Purpose Data framework
Swiss-Reg-NMD	Swiss Registry for Neuromuscular Disorders
qrtPCR	Quantitative Reverse Transcription Polymerase Chain Reaction
UK	United Kingdom

1. Rationale and Background

TREAT-NMD is a global registry network launched in 2007 for the neuromuscular field that provides an infrastructure to ensure the most promising new therapies reach patients as quickly as possible across multiple diseases. The global registry network is composed of Member Registry Curators including Patient Representatives, and supported by the TREAT-NMD Ethic Board Representatives. The TREAT-NMD spinal muscular atrophy (SMA) original core dataset containing 23 data items was established in 2008 when the main purpose of the registries was clinical trial readiness and recruitment. The TREAT-NMD SMA dataset was expanded in 2018 and the subsequent version 2 was released, with 120 data items in the new version. TREAT-NMD currently has 26 SMA registries (19 in Europe) as part of the network with an estimated 4,800 patients. The TREAT-NMD Registry Network is made up of SMA clinician, patient reported and dual reported registries.

By becoming members, the Registries are also signing up to The Charter which sets some criteria and standards on which Registries need to meet which include collecting the core datasets, data transfer and attending annual meetings.

The purpose of the TREAT-NMD Central Data Warehouse (CDW) is to collect data in a harmonised way by using the SMA Core dataset, to build a natural pool of data and allow for better data analysis. The core data model was developed through extensive stakeholder engagement with registry curators, physicians, physiotherapists, patient representatives and industry representatives.

Recently, the European Medicines Agency (EMA) approved three disease modifying therapies (DMT) for SMA: nusinersen (Spinraza®), onasemnogene abeparvovec-xioi (Zolgensma®), and risdiplam (Evrysdi®). Since the approval of these new treatments for SMA, studies have reported disease trajectories that significantly differ from the known natural history of SMA[1]. Considered together with the limited evidence on the long-term safety and efficacy available at drug approval due to the rarity of disease, the EMA, to address the Committee for Advanced Therapies' needs, asked to investigate SMA patients' course of the disease and the standards of SMA care delivery, as well as to explore use, effectiveness and safety of these DMTs in real-world settings. In order to inform the related study protocol (refer to Section 2 for study objectives), a fit-for-purpose (FFP) assessment of registries part of TREAT-NMD network was performed.

2. Study Objectives

The specific research question is to investigate SMA patients' course of disease and standards of care delivery over time in at least 5 European countries including at least 4 Member States of the European economic area (EEA).
A preliminary objective will assess potential heterogeneity in the management care or reporting across participating registries:

- First objective: To describe the natural history of SMA (the disease and its progression) based on patients' characteristics, post-diagnosis outcomes of interest and quality of life.
- Second objective: To describe the diagnosis methods, medicinal and non-medicinal management care and the use, effectiveness and safety of DMTs.

3. Feasibility Objectives

This FFP assessment aimed to identify FFP registries within the TREAT-NMD network that could be leveraged for the SMA study.

The feasibility objectives were as follows:

- To conduct a preliminary assessment among registries part of TREAT-NMD network located in Europe and Middle East to assess administrative information and general registry metrics in order to recommend registries for FFP data assessment.
- To conduct a FFP data assessment as per study objectives (refer to Section 2) among selected candidate data sources to assess and recommend registries for the study.

4. Methods

A preliminary assessment was conducted using a pre-feasibility questionnaire (refer to Section 4.1 for further details) to select registries for FFP data assessment (refer to Section 4.2 for further details). A feasibility questionnaire was sent to the registries identified during pre-feasibility for further assessment (refer to Section 4.3 for further details). The final selection of registries was made based on the responses of both pre-feasibility and feasibility questionnaires. The pre-feasibility and feasibility questionnaires were developed based on the EMA guideline on registry-based studies[2], the Request tool[3] and the Structured Process to Identify Fit-for-Purpose Data framework (SPIFD)[4]. The SPIFD framework outlines a systematic approach to evaluating data sources to ensure their fitness for addressing regulatory-grade research using observational data. This framework operationalizes principles with respect to data reliability, relevance and accessibility. Reliability is demonstrated when data are valid, consistent, and complete such that they accurately represent the healthcare concept of interest. Relevance is demonstrated through the ability to capture key variables (e.g., exposure, outcome) and contribute sufficient sample size and follow-up. Accessibility is demonstrated in the ability to effectively contract, collect, and analyse the data. SPIFD-based feasibility assessments support the choice of a robust data source in which to conduct an observational study.

4.1. Pre-feasibility

The pre-feasibility questionnaire leverages the items defined in the checklist for evaluating the suitability of registries for registry-based studies of the EMA guideline[2].

Items included in the pre-feasibility questionnaire were as follows:

- Country
- Clinician-based registry or Patient-based registry or both
- Funding sources
- Registry governance
- Registry start date
- Last data available
- Coverage of the registry (e.g., national, regional, local)
- Type of SMA included (e.g., only specific genetic variant, any variants)
- Adults or Children or both included in registry
- Total number of patients with SMA in registry

- Approximate number of new SMA patients entering the registry per year (on average)
- Approximate number of SMA patients lost per year (on average)
- Consent for research purposes
- Quality requirements: capability and experience in data management (cleaning, verification) & analysis, quality planning/control/assurance process, audit practice
- Ethics committee/Review Board approval
- Data privacy
- Data corresponding to the ""TREAT-NMD Core dataset version 2 for SMA"" dataset
- Inclusion in the registry from diagnosis
- Longitudinality of patient data
- Average time between 2 follow up visits
- Completeness of information

4.2. Identification and reduction of data source options

Based on the responses to the pre-feasibility questionnaire obtained from the registries, registries were selected for feasibility assessment. The reasons for the exclusion of registries are described in Section 5.1. Pre-feasibility results (corresponding to the Step 2 of SPIFD).

4.3. Conduct detailed data feasibility assessment

Operationalization and ranking of minimal criteria required to answer the research question was used to develop the feasibility questionnaire (corresponding to the Step 1 of SPIFD).
The feasibility questionnaire included questions regarding the core data elements (except pregnancy) listed in the EMA guideline for registry based studies.
The data elements part of feasibility assessment were based on required data to achieve the main study objectives and were further categorised as follows. The “Need to have” data elements were defined based on important disease management information and disease outcomes (such as genetic information and SMA status, DMT information, hospitalisation, pulmonary disorder, etc.), and to allow stratifications as planned in the study protocol. Other data elements that were identified as less critical for the conduct of the study were classified as “Nice to have”.

“Need to have” data elements are as follows:

- Patient demographics
  - Age
  - Sex
  - Geography
- Diagnosis of SMA
  - Type of SMA
  - Age at onset
  - Functional status (non sitter/sitter/walker)
  - Genetic testing results
- Treatment characteristics
  - Disease modifying therapies
- Outcomes
  - Hospitalisations
  - Vital status
  - Thoraco-pulmonary disorders

    - Feeding tube
    - Wheelchair
    - Motor function
    - Scoliosis & hip disorders

"Nice to have" data elements are as follows:

- Patient demographics
    - Height & weight
- Diagnosis of SMA
    - Genetic methods (initially not assessed to reduce registry burden - not identified as critical for the study conduct; added as follow-up request)
- Treatment characteristics
    - Non-medicinal therapies
    - Comedications (not assessed to reduce registry burden - not identified as critical for the study conduct)
    - Immunisation (not assessed to reduce registry burden - not identified as critical for the study conduct)
- Clinical characteristics
    - Comorbidities
- Patient reported outcomes (PROs)
- Outcomes
    - Serious adverse events

The SPIFD framework generates a ranking for data elements considered in the assessment. The FFP heatmap presents the FFP fitness score of each data source for each data element. A score of 1 (*low fitness*) to 5 (*high fitness*) is assigned to each data element. The FFP fitness score is detailed in the SPIFD framework[4].

For this feasibility assessment, the score is based on the percentage of missingness or completeness of records for each data element or/and based on qualitative data (as shown in Figure 1 below).

Ranking	1	2	3	4	5
Legend	Very few patients / items with a value recorded (<25%)	Less than half of patients /items with a value recorded (25-50%)	More than half of patients /items with a value recorded (50-75%)	Majority of patients / items with a value recorded (75-95%)	Nearly all patients /items with a value recorded (95-100%)

Figure 1. Ranking of data elements

For data elements for which completeness of records cannot be used, the score was based on the qualitative data provided by the registry (refer to Table 1 below).

Table 1. Data type used for registries ranking

Quantitative data	Quantitative and qualitative data	Qualitative data
● Demographics ● SMA characteristics ● Functional status (=Motor ability status) ● Motor function test ● Wheelchair usage ● Feeding tube ● Scoliosis ● Thoraco-pulmonary disorders	● Hospitalizations ● Living status ● Comorbidities ● SAEs ● PROs ● DMTs	● Non-medicinal product therapies and aid ● Administrative information and Quality requirements

DMT: disease modifying therapy; PRO: patient reported outcome; SAE: serious adverse event

5. Results

The results from the pre-feasibility and feasibility assessment are presented in Section 5.1 and Section 5.3, respectively. A description of each registry which completed the pre-feasibility assessment is presented in Section 5.2.

5.1. Pre-feasibility results

A total of 19 registries from the TREAT-NMD network across 20 countries were contacted across Europe and the Middle East region. These registries have an active TREAT-NMD membership. The registries included in the pre-feasibility are listed in Table 2.

Table 2. List of registries included in the pre-feasibility

European registries	Bulgaria, Czech Republic & Slovakia, Croatia, Hungary, Latvia, Slovenia, Belgium, Germany & Austria, Spain, Sweden, Denmark, Poland, UK and Ireland
Non-EEA registries	Georgia, Turkey (3), Ukraine, Switzerland

EEA: European Economic Area

After reaching out to the 19 registries, all registries except the Istanbul University registry (Turkey) provided a first feedback. Thus, this registry was excluded.
The Danish registry was extremely busy and did not complete the pre-feasibility assessment. The Polish registry had limited resources due to the conflict in Ukraine. These 2 registries were also excluded.

The pre-feasibility assessment was completed by 16 registries (84% response rate). Among those, the Swedish registry completed the pre-feasibility and feasibility assessment altogether.
The main results of the pre-feasibility are summarised in Table 3 below.

Table 3. Pre-feasibility results

Country	Registry start date	SMA patient count	Data follow-up	Frequency of visits	Data quality process	Audit practice	Patient-level data sharing	Ethics/ Review board approval needed
Bulgaria	2014	93	3-4 years	Treated patients: 6 months Others: 1 year	No	No	No	No
Czech Republic & Slovakia	2011	317	3 years	5 months	Yes	Yes	Yes	No
Croatia ✦	2017	43	≥5 years	< 6 months	Yes	Yes	No	Yes
Georgia✦	2019	51	3-4 years	6 months	No	No	Yes	Yes
Hungary	2008	161	1 year	6 months, less for treated patients	No	No	Yes	No
Latvia	2016	38	≥5 years	6 months paediatric 1 year adults	No	No	Yes	No
Slovenia	2017	37	≥5 years	1 year	Yes	No	Yes	Yes
Turkey Kukas✦	2009	65	1 year	6 months	Yes	Unknown	Yes	Yes
Turkey Lukam	2020	60	3-4 years	6 months	No	No	Yes	No
Ukraine	2007	360	4-5 years	1 year	Yes	No	Yes	Yes
Belgium	2018	272	≥5 years	6 months	Yes	No	Yes	Yes
Germany & Austria	2008	893	≥5 years	1 year	Yes	Yes	No*	Yes
Spain	2015	273	≥5 years	< 6 months	Yes	Yes	Yes	Yes
Sweden	2010	177	≥5 years	6 to 12 months	Yes	Yes	Yes	Yes
Switzerland	2008	137	4 years	Treated patients: 4 months Others: 1 year	Yes	No	Yes	Yes
UK & Ireland	2007	566	≥5 years	6 months for paediatric and patients treated with nusinersen or risdiplam. Others: 1 year	Yes	Yes	Yes	Yes

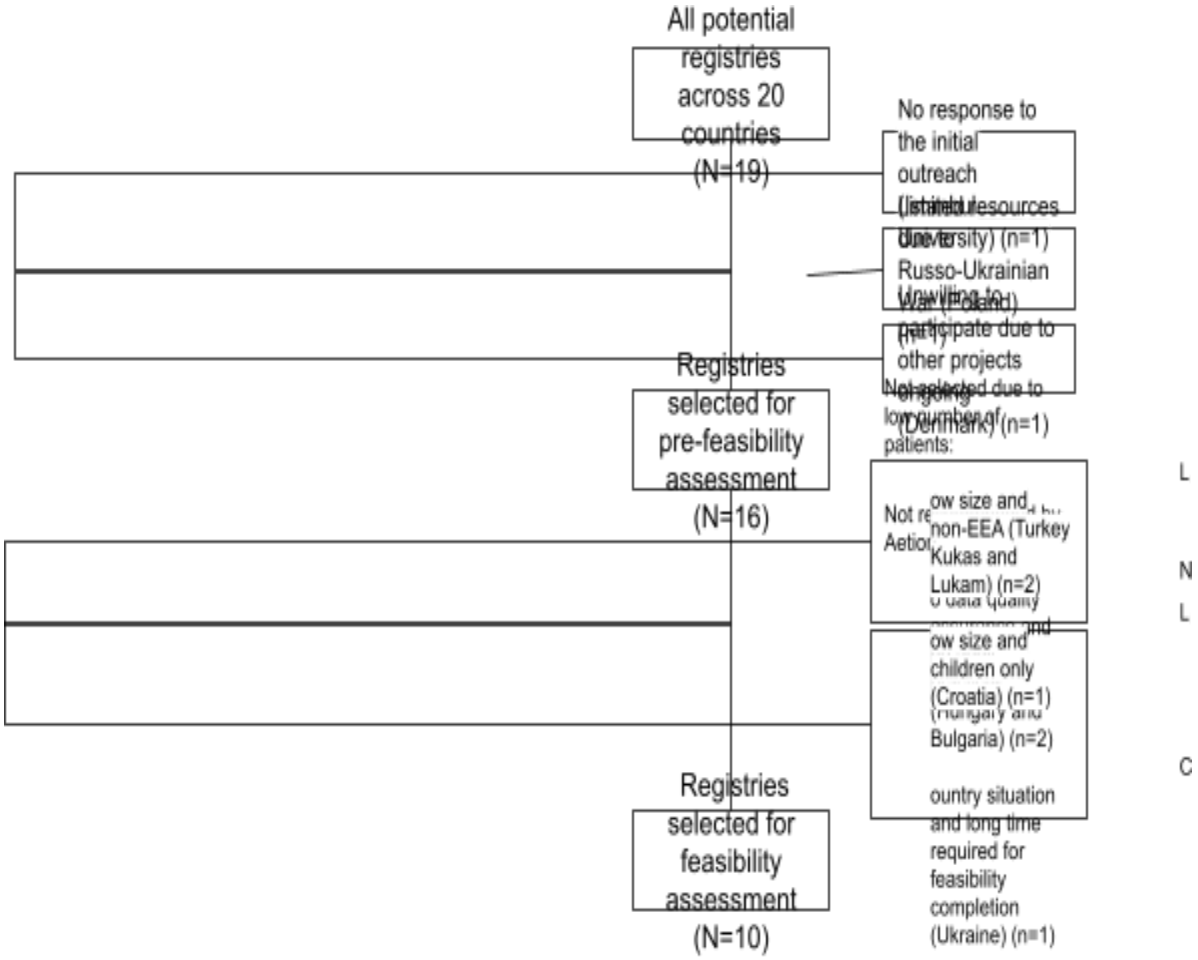
✦ Children registries; *Non-European economic area countries*; **Patient-based registries**

*Germany & Austria registry has the capabilities to run analysis locally

The registry in Croatia was not selected due to the low number of SMA patients (n=43) being children only, and the fact that patient-level data cannot be shared.
The 2 registries in Turkey (Kukas and Lukam) were not selected due to their relatively low size and not being part of the EEA. The Kukas registry includes 65 patients and most of them are children. The Lukam registry includes 60 patients, both adults and children.
Bulgaria and Hungary were not recommended by Aetion due to a lack of capability and experience in data quality assurance and audit practices, and not being able to share patient-level data for Bulgaria and having only 1 year of longitudinal data for Hungary. Ukraine was excluded due to the ongoing conflict and the long time estimated to complete the feasibility assessment (6 months).

The selection process of registries for the feasibility assessment is presented in Figure 2.
The registries selected for the feasibility assessment are:

- Patient-based registries: Spain, Germany & Austria, and UK & Ireland
- Clinician-based registries: Belgium, Czech Republic & Slovakia, Latvia, Sweden, Georgia, Switzerland, Slovenia



EEA: European Economic Area

Figure 2: Attrition of Registries for Feasibility assessment

5.2. Registry description

5.2.1. Belgium

The Belgian Neuromuscular Diseases Registry (BNMDR)[5] is a national clinician-based registry which started in 2008 (and restructured in 2018), with 272 adults and children SMA patients included as of June 2022. This registry is funded by the National Health Insurance (Belgium National Institute for Health and Disability Insurance). The registry is governed by a Steering Committee that meets annually. This committee includes representatives of experts (physicians), patients organisations, one representative of the National Health Insurance and two representatives of Sciensano who manages the registry (a public research institution established in 2018). During the annual meeting, data collected and evolution of the project are being discussed. A Scientific Committee composed by experts from participating centres (physicians) is also in place. This committee can meet more regularly to support decision making on scientific aspects.

A dedicated quality team is responsible for managing Sciensano's quality management system. They ensure that all services comply with quality standards in order to guarantee the accuracy of the analysis results that they issue and the reliability of the opinions or conclusions that they formulate. The quality standards applied within Sciensano are ISO 15189, 17025 and 17043.

At the beginning of each project, documents such as study protocol and report, statistical analysis plan and data management plan are created and regularly updated.

Registry patient-level data are de-identified and can be shared with TREAT-NMD. Patients followed over different centres can be identified and most complete data are being kept in the registry. A data validation process is in place to avoid the entry of aberrant data within the form completed by data providers/physicians. In addition, statistics are being run on the registry data and compared to historical checks once a year (e.g., description such as counts, distribution, percentages of key characteristics). If discrepancies are identified, queries are being raised for aberrant data. Missing data are checked once a year and trends checked with data providers/physicians in order to improve completion (e.g., unavailability of source data or changing to mandatory fields).

5.2.2. Bulgaria

The Bulgarian SMA registry is a national clinician-based registry which started in 2014, with 93 children and adults SMA patients included as of June 2022. This registry does not have funding sources. The registry is governed only by the clinicians in the Expert centre for hereditary neurologic and metabolic disorders. Registry patient-level data cannot be shared with TREAT-NMD. All registry items are being checked against medical records by a physician or a (research) nurse once a year. Queries are being raised to ask for completion of missing information by contacting the patient or checking medical documentation.

5.2.3. Croatia

The Croatian registry for paediatric NMD is a national clinician-based registry which started in 2017, with 43 children SMA patients included as of June 2022. This registry receives funds via TREAT-NMD. The registry does not have a governing body in place. Registry patient-level data are de-identified and can be shared with TREAT-NMD. The registry performs quality checks notably verifying patient duplicates and has audit practice.

5.2.4. Czech Republic & Slovakia

The REaDY is a national clinician-based registry which started in 2011 covering both Czech Republic and Slovakia. It was developed by the Institute of Biostatistics and Analyses, with 317 adults and children SMA patients included as of May 2022. This registry is funded by the pharmaceutical industry. The

registry has been endorsed by ethical committees and regulatory authorities in both Czech and Slovak Republics.
Quality documentation for the registry implementation is available: data management plan and data validation plan. In addition, a validation process is set up within the database with data quality control by the system. Each eCRF adjustment is discussed and approved by a study guarantor.
Registry patient-level data are de-identified and can be shared with TREAT-NMD. Data verification statistics are run on the data upon request such as checking date/integer ranges or checking correct data types. No specific actions are put in place to improve missingness.

5.2.5. Georgia

The Georgian paediatric NMD registry is a national clinician-based registry which started in 2019, with 51 children SMA patients included as of June 2022. This registry receives funds from the TGDOC registry bursary and the Georgian Association of Child Neurologists and Neurosurgeons. The registry did not specify whether they have a governing body in place. Registry patient-level data are de-identified and can be shared with TREAT-NMD. The registry has clinical trial-specific documentation and procedures when performed at their hospital. All registry items are being checked against medical records by a physician or a (research) nurse every 3 to 6 months. Missing data are being checked every 3 to 6 months and queries raised for completion. Missing data are completed as much as possible during follow-up visits with the patients.

5.2.6. Germany & Austria

The SMA-Patient registry for Germany and Austria (*DMD- und SMA-Patientenregister für Deutschland und Österreich*) is a patient-based registry which started in 2008, with 893 adults and children SMA patients included as of June 2022. This registry is operated by the Friedrich Baur Institut in Munich University Hospital (Germany)[6], dedicated to patient care and cutting-edge research in the field of neuromuscular disorders (NMD). This registry is funded by research project sponsors. The registry is governed by an independent oversight committee.
Registry patient-level data are de-identified and can only be shared with TREAT-NMD at an aggregated level. Registry participants provide a copy of human genetic findings which are reviewed at the centre and added to the participant's dataset. All participants are asked at least once per year to review and add genetic reports to the dataset for timeliness and completeness. Missing data are checked every 6 months and query raised to ask for completion.

5.2.7. Hungary

The Hungarian SMA/DMD Registry is a national patient-based registry which started in 2008, with 161 adults and children SMA patients included as of June 2022. This registry does not have any funding sources. The registry belongs to the Semmelweis University and has been endorsed by the National Ethics Committee. Registry patient-level data are de-identified and can be shared with TREAT-NMD.

5.2.8. Latvia

The NMD registry in Latvia (*NMS datu kolekcija*) is a national clinician-based registry which started in 2016, with 38 adults and children SMA patients included as of June 2022. This registry is funded by the hospital. This registry does not have any governing body in place. Registry patient-level data are de-identified and can be shared with TREAT-NMD. All registry items are being checked against medical records by a physician or a (research) nurse once a year. Missing values as left in the registry with no further action.

5.2.9. Slovenia

The Slovene registry of children with NMD is a national clinician-based registry which started in 2017, with 37 children SMA patients included as of June 2022. This registry does not have any funding source. This registry does not have any governing body in place. Patient duplicates are being verified. Registry patient-level data are de-identified and can be shared with TREAT-NMD.

5.2.10. Spain

The *Registro Nacional de Pacientes de la Fundación Atrofia Muscular Espinal* (FundAME) is a national patient-based registry which started in 2015, with 273 adults and children SMA patients included as of June 2022. This registry is funded by FundAME[7]. The registry governing bodies are as follows: 2 curators, 1 data manager who is responsible for the registry, 1 patient representative and 1 financial & administrative responsible.

The following information is being described into a protocol: curation method, responsibilities, instructions and resources during the different phases including promotion and training activities within the patient registry.

Required data changes and dataset modifications are documented. Currently the data is migrating to a new platform, hence documentation will be updated.

Registry patient-level data are de-identified and can be shared with TREAT-NMD. The following items are being checked against medical records by a physician or a (research) nurse: SMN1 data, SMN2 data and forced vital capacity. All other items are curated by a SMA specialist healthcare professional. Data is being verified every time there's a data modification or update in every patient. Patients are encouraged through contacts or phone calls to complete missing data or send medical reports.

5.2.11. Sweden

The Swedish National Registry for NMD (*Neuromuskulära sjukdomar i Sverige* - NMiS) is a national clinician-based registry which started in 2010, with 177 adults and children SMA patients included as of September 2022. This registry is funded by the government. The registry is governed by a Steering Committee composed by 2 representatives of patient organisations.

The quality standards applied for the platform used by the NMiS-registry are following ISO 13485:2016. It covers NMiS-registry on a general level regarding platform development, risk analysis, maintenance, etc.

Registry patient-level data are de-identified and can be shared with TREAT-NMD. A data verification process is in place where all registry items are being checked against medical records by a physician or a (research) nurse once a year. Queries are being raised to ask for completion of missing information. In order to improve completion of missing data, helptext, automatic reminders and mandatory fields are also put in place in the registry.

5.2.12. Switzerland

The Swiss Registry for NMD (Swiss-Reg-NMD) is a national clinician-based registry which started in 2008, with 137 adults and children SMA patients included as of June 2022. This registry is funded by patient organisations, foundations and the pharmaceutical industry. The governing bodies of the Swiss-Reg-NMD are the Steering Committee and the Executive Office. The Steering Committee is currently composed of a group of 7 specialised physicians. It is the Swiss-Reg-NMD legal representative superordinate organ and acts as a supervisory authority. Among other things, the Steering Committee defines the objectives, the research questions and the dataset of the Swiss-Reg-NMD. The tasks of the Executive Office include management and legal issues, data collection and storage, data quality check, communication with different stakeholders, finances, research and collaborations.

The Swiss-Reg-NMD is currently planning and discussing with interested parties the involvement of patient representatives in the registry work.

Specific guidelines and agreements regulate data collection, data use and dissemination, responsibilities, time schedules, and goals within the Swiss-Reg-NMD.
Registry patient-level data are de-identified and can be shared with TREAT-NMD. Data completeness and quality checks (consistency over time) are being conducted at first data entry and every 6 months. Queries on missing or discrepant data are raised and discussed with the treating physician. Missing data can be collected during on site visits.

5.2.13. Turkey - KUKAS

The KUKAS registry in Turkey is a local clinician-based and patient-based registry, with 65 children (and few adults) SMA patients included as of June 2022. This registry does not have any funding source. The registry does not have any governing body in place. Patients' families are able to register however if they do not come to visit the local clinic for assessments and sign a consent form their registration is not confirmed.
Registry patient-level data are de-identified and can be shared with TREAT-NMD.

5.2.14. Turkey - LUKAM

The LUKAM registry in Turkey is a local clinician-based registry which started in 2020, with 60 children and adults SMA patients included as of June 2022. This registry does not have any funding source. The registry governance is directed by Prof. Karaduman who is a very experienced clinician in the registry and connected with the association of DMD families in Turkey. Also, she is a member of the oversight committee of TREAT-NMD. Registration of patients is performed using Turkish ID numbers to avoid duplicates.
Registry patient-level data are de-identified and can be shared with TREAT-NMD.

5.2.15. UK & Ireland

The UK SMA Patient Registry[8] is a patient-based registry which started in 2007 covering the United Kingdom and Ireland, with 566 adults and children SMA patients included as of June 2022. This registry is funded by Biogen, through its funding of Adult SMA REACH. This registry is governed by an independent steering committee. This includes representation from three patient organisations, SMA UK, MDUK and TreatSMA. Enrolment is patient-initiated and achieved online through the registry website (www.sma-registry.org.uk). Patients become aware of the registry through patient organisations, through the clinical studies Adult SMA REACH and SMA REACH UK (paediatric) and through distribution of registry information leaflets from their neuromuscular clinic.
The patient registry has a study Protocol in place but does not have a quality plan document. Registry patient-level data are de-identified and can be shared with TREAT-NMD. Data management is performed by the registry coordinator. Patients are requested to share a copy of their genetic report with the registry, enabling the registry coordinator or medical staff to verify their eligibility upon receipt. Duplicate registrations are routinely investigated and removed, following contact with the patient. Data is regularly reviewed by the curator and any anomalies are followed-up with the patient. Periodic follow-ups with patients are performed to request missing data, notably genetic reports. This is through both targeted and more general communications. All database entries and contacts are traceable through an audit trail. Self-audit is performed approximately every two years.

5.2.16. Ukraine

The Children with Spinal Muscular Atrophy (CSMA) is a national clinician-based and patient-based registry which started in 2007, with 360 adults and children SMA patients included as of June 2022. This registry is auto-funded. The governing bodies of the CSMA are the curators of the registry, including patient organisation representatives. There is no external independent committee.

Registry patient-level data are de-identified and can be shared with TREAT-NMD. RThe registry curators perform data quality checks each time a new record is created (by the patient or by their doctor). Duplication of patients is also checked.

5.3. Feasibility results

Among the 10 countries selected for the feasibility assessment, Slovenia declined participation. Bulgaria provided their feasibility assessment even though this registry was not initially recommended. The Bulgarian registry received as all registries the initial set of feasibility assessment without further request for completion; hence their response was not expected. Nonetheless it is included in this report for comprehensiveness.

The following registries were included in the feasibility assessment:

- Patient-based registries: Spain, Germany & Austria, and UK & Ireland
- Clinician-based registries: Belgium, Czech Republic & Slovakia, Latvia, Sweden, Georgia, Switzerland, Bulgaria.

5.3.1. Administrative information and Quality requirements

The below Table 4 summarises administrative information and quality requirements for each registry. The overall assessment is based on the number of item requirements met (refer to Figure 3 below). The ranking is as follows: 5=all items met, 4=nearly all met, 1=very few or none met.

Further details on data quality checks performed by each registry are further described in Section 5.2 (Registry description).

Item in the Pre-Feasibility assessment	Question to the registry
Ethics committee/Review board approval	Is there an Ethics committee/Review Board approval needed to get access to the registry data for research purposes?
Governance and transparence (steering committee or governance body in place)	Please specify whether an independent steering committee or a governing body and a data quality team with specified responsibilities are in place. These should include patient representation.
Patient-level data sharing for central study analysis	Does current patient/parent consent cover de-identified patient-level data sharing for research purposes? If yes, please specify whether patient-level data can be provided to TREAT-NMD.
Financing (funding)	What are the funding sources?
Data cleaning (capability/experience)	Can you specify if you have/plan to have: Capability (and experience) for data cleaning, extraction, transformation and analysis?
Quality assurance (quality control, data verification)	Can you specify if you have/plan to have: Process in place for quality planning, control, assurance and improvement ? Data verification (method and frequency of verification) notably risk of patient duplication (i.e. patient being followed in different centres) ?
Auditing practice	Can you specify if you have/plan to have: Auditing practice?

Figure 3. Administrative information and Quality requirements items considered

Table 4. Administrative information & Quality requirements for each registry included in the feasibility assessment

Items	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Ethics committee/review board approval	Obtained	In progress*	Obtained	Obtained	In progress*	In progress*	Not required	No follow-up	No follow-up	No follow-up
Governance and transparency (steering committee or governance body in place)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Patient-level data sharing for central study analysis	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Financing (funding)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Data cleaning (capability/experience)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Quality assurance (quality control, data verification)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Auditing practice	Yes	Yes	Yes	No	Yes	No	Yes	No	No	No
Overall Qualitative assessment (item requirements met)	4	5	5	4	5	4	5	1	1	1

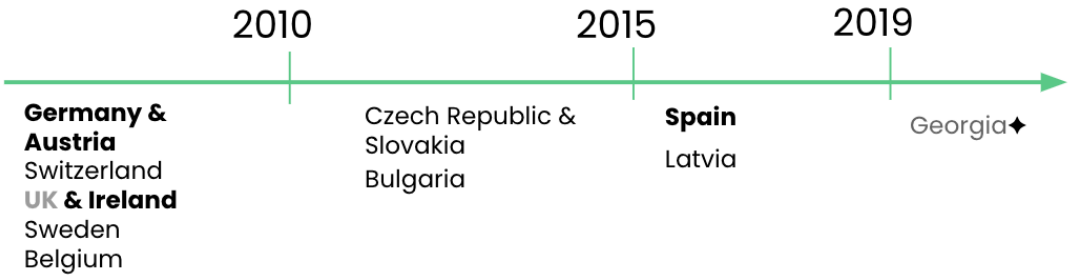
UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

*For Spain, Sweden and Switzerland registries, there are awaiting the final protocol to request Ethics committee approval.

5.3.2. Patient population covered

5.3.2.1. Start date of registry

All registries selected for the feasibility assessment started collecting data before 2019 (except Georgia).



UK: United Kingdom. Note: Belgium registry was restructured in 2018

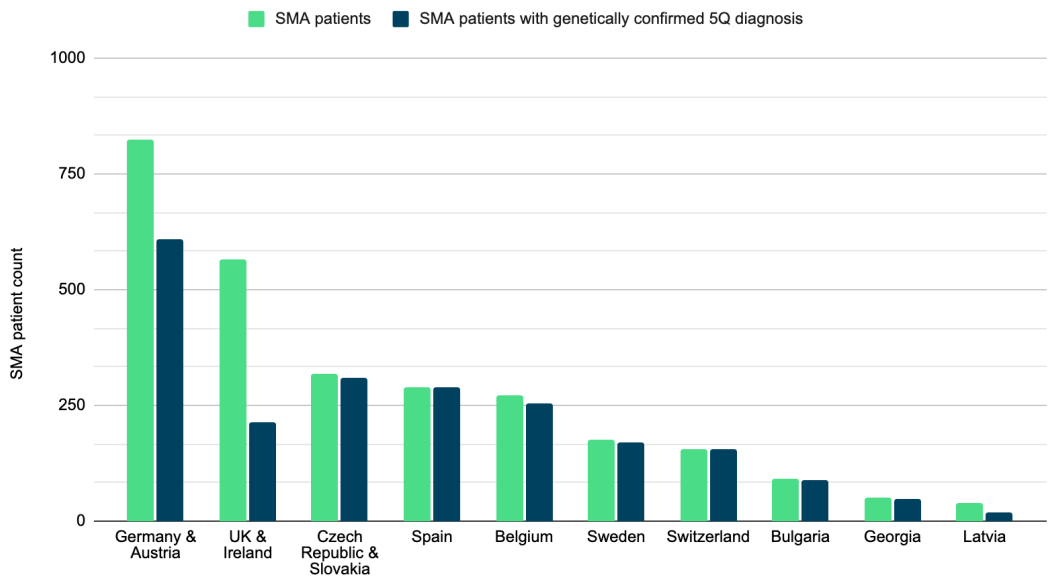
Figure 4: Registry start date

5.3.2.2. Size of registry

The Figure 5 below presents the SMA patient count per registry as of September 2022.

For both registries in Germany & Austria and the UK & Ireland, a difference can be observed between the number of patients in the registry and those with a genetically confirmed 5Q diagnosis.
The German & Austrian registry is actively following-up with patients to submit their reports, nonetheless the registry should rely on their willingness to do so.
In the UK & Ireland registry not all patients have a copy of their genetic test report. If they have one, patients are encouraged to share it with the registry. If they do not have a copy, the registry asks to share their clinic details, so that the registry can approach the clinic and request a copy. There is mixed success at receiving reports through this route. This registry includes older patients who probably received a diagnosis from their physician before genetic testing for SMA had been developed. There was no treatment available until 2017 and it is probable that some of these patients had not been offered genetic testing to confirm their diagnosis.

For the Spanish registry, the numbers are similar due to an update campaign run by the Spanish registry during summer 2022 to obtain the genetic report from all the patients included in the registry.
The clinician-based registries have lower amounts of SMA patients but nearly all patients have a genetic confirmation of their diagnosis.

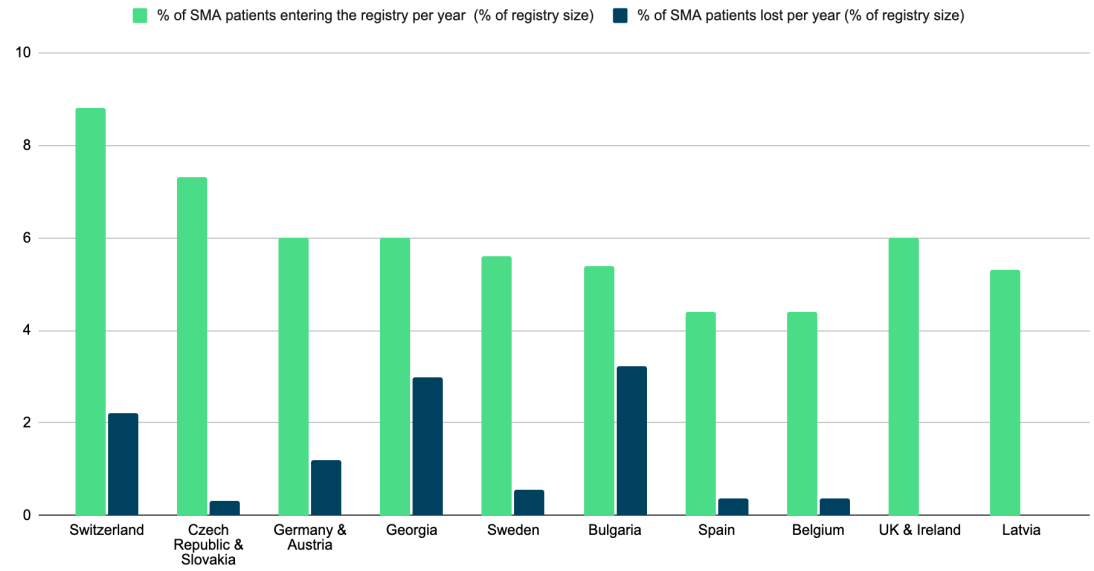


SMA: spinal muscular atrophy; UK: United Kingdom.

Figure 5: SMA Patient count per registry (September 2022)

Figure 6 presents the percentage of patients' entry and loss per year based on the total number of patients in each registry.

The percentages of SMA patients entering the registry per year is higher than the number of patients lost per year. In Switzerland, each year, the registry size grows by approximately 6,5%. The percentage of patients entering the registry per year is 8,5% of the registry size and the percentage of patients lost per year is approximately 2% of the registry size. The percentage of patients lost per year is unknown for the UK & Ireland and for Latvia.



SMA: spinal muscular atrophy; UK: United Kingdom.

Figure 6: Percentage of SMA patients' entry and loss per year across registries (September 2022)

Table 5 summarises the availability of DMT per country. Spinraza is available in all the countries with a registry selected for FFP assessment except in Georgia. Zolgensma has been available in Sweden since February 2022 and is not available in Bulgaria and Georgia. Evrysdi is only available from 2022 in half of the countries selected for FFP assessment and is not yet available in Spain and Ireland.

Table 5. Year of availability of SMA disease modifying therapy across registries

Year	2017	2018	2019	2020	2021	2022
Spinraza availability	• Germany & Austria • Sweden • Switzerland • Czech republic & Slovakia	• Spain • Belgium	• Bulgaria • Latvia • UK & Ireland			
Zolgensma availability				• Germany & Austria • Czech Republic & Slovakia	• Belgium • Spain • Switzerland • UK & Ireland	• Sweden
Evrysdi availability					• Germany & Austria • Switzerland • Czech Republic & Slovakia • Georgia	• Sweden • Belgium • Bulgaria • Latvia • UK (not Ireland)

SMA: spinal muscular atrophy; UK: United Kingdom.

5.3.2.3. Type of SMA and Genetic testing focus

Table 6 summarises the type of SMA recorded and genetic testing information availability in each registry. There are almost no type 0 across all registries, and all have patients with SM2 copy. Details on the methods of SMA testing collected in each registry are presented in Section 5.3.4 on "Nice to have" data elements.

Table 6. Type of SMA and SMA genetic testing

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
SMA patients • Type 0 • Type 1,2,3,4 • Undetermined • Pre-symptomatic	• 0 • 814 • 1 • 1	• 0 • 289 • 0 • 0	• 0 • 474 • 1 • 0	• 0 • 257 • 0 • 13	• 0 • 171 • 3 • 0	• 2 • 153 • 1 • 3	• 1 • 315 • NA • 1	• 0 • 46 • NA • NA	• 0 • 48 • 3 • 0	• 0 • 20 • 0 • 1
Genetically confirmed 5q SMA patients (patients with genetic testing)	610	289	215	254	171	156	309	90	48	20
Patients with SMN2 copy number recorded	377	263	78	212	148	128	273	46	48	20
Patients with SMN1 gene mutation type	-	289	-	254	157	145	294	45	48	20

SMA: spinal muscular atrophy; UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.
Note: The following methods of SMA testing can be selected RFLP, HRM, MLPA, DNA sequencing, qrtPCR, ddPCR (source: TREAT-NMD version 2 dataset)

5.3.2.4. Duration of follow-up

All registries have an average duration of follow up greater than 3 years.
The registries with an average duration of follow up between 3 and 4 years are: Bulgaria, Czech Republic & Slovakia, Georgia and Switzerland.
The registries with an average duration of follow-up greater than 4 years are Latvia, Belgium, Spain, Sweden, UK & Ireland, Germany & Austria.

For each registry that will be included in the study, the maximum available data will be used in order to maximize the follow-up time during which disease progression metrics and post-diagnosis outcomes will be evaluated.

5.3.3. "Need to have" data elements

The "Need to have" data elements (refer to Section 4.3 for further details on selection of these data elements) were classified in 3 categories: patient characteristics, DMT and outcomes. Patient characteristics and outcomes encompass several subcategories, where DMT has only one. The ranking of each subcategory, summarised in the below Table 7, is further detailed in this chapter and corresponds to an average ranking based on corresponding data elements ranking.
Overall, among clinician-based registries in Belgium, Sweden, Switzerland and Czech Republic & Slovakia are ranking the highest across the 3 categories. Among patient-based registries Spain ranks similarly to these clinician-based registries. The 2 other patient-based registries have quite similar overall rankings. Nonetheless, the registry in Germany & Austria has better SMA clinical characteristics, functional status and scoliosis diagnosis information, and much better on ventilation usage and hospitalisation information compared to the UK & Ireland registry.

Table 7. Ranking of "Need to have" data elements across registries

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Patient characteristics										
Demographics	5	5	5	5	5	5	5	5	1	1
SMA characteristics	3	5	2	4	3	4	4	3	5	3
Functional status (=Motor ability status)	2	4	1	2	5	4	4	3	4	3
DMT										
DMTs information	2	3	2	5	5	3	3	5	2	1
Outcomes										
Motor function test				4	5	5	3	1	4	3
Wheelchair usage	4	5	4	5	5	5	4	3	2	3
Feeding tube	4	5	5	5	5	3	5	5	1	1
Scoliosis	3	3	2	5	5	3	3	4	4	1
Thoraco-pulmonary disorders	3	4	2	5	5	4	5	4		1
Hospitalizations	4	2	1	5	5	4	4	1	2	2
Living status	1	4	1	5	5	4	3	5	4	1

DMT: disease modifying therapy; SMA: spinal muscular atrophy; UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

5.3.3.1. Patient characteristics

Table 8 below summarises the patient characteristics information available across registries. Demographics include age at diagnosis and sex. These 2 data elements are mandatory to collect in Germany & Austria, UK & Ireland and Sweden. They are well captured in all other registries except for Georgia and Latvia.

SMA characteristics include the symptom onset date which means the date when the patient started presenting symptoms of the disease. The collection of this information varies across registries. UK & Ireland is the one with the lowest percentage of value recorded since this data element is recorded for 43% of patients with a 5q SMA diagnosis. For Czech Republic & Slovakia, the age (in years) at symptom onset is collected instead of the symptom onset date. For patients with an onset that started before 3 years old, the age of onset is recorded in months.

The functional status (=Motor ability status) is defined by one or several of these motor skills assessment: Hold head without support, roll onto side, sit without support, crawl, stand with assistance, stand without assistance, walk with assistance, walk without assistance, walk 10 metres without assistance, climb stairs, useful function of hands, reach overhead when seated, raise hands to mouth when seated.

Table 8. Patient characteristics information across registries

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Demographics • Age at diagnosis • Sex	5	5	5	5	5	5	5	5	1	1
SMA clinical characteristics • Symptom onset date	3	5	2	4	4	4	5	3	5	3
Registry entry date	5	5	5	4	5	5	5	5	4	3
Functional status (=Motor ability status)	2	4	1	2	5	4	4	3	4	3

SMA: spinal muscular atrophy; UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

5.3.3.2. Disease modifying therapies (DMT)

Table 9 below summarises DMT information available across registries. The DMT administration date is generally very well recorded across all registries except in Czech Republic & Slovakia, Georgia and Latvia. The DMT dosage is poorly recorded or not recorded except for Belgium, Sweden and Bulgaria.

Table 9. Disease modifying therapy (DMT) information across registries

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
DMTs (% of patients with a value recorded for DMT) 1/ Spinraza 2/ Zolgensma 3/ Evrysdi	n=342 (56%) 1/ 71% 2/ 4% 3/ 20%	n~ 76%	n=90 (42%) 1/ 27% 2/ 4% 3/ 32%	Total treated unknown 98% records 1/ 73% 2/ 2% 3/ 21 %	n=113 (64%) 1/ 92% 2/ 4% 3/ 14%	Total treated unknown 77% records	Total treated unknown 80% records 1/ 62% 2/ 9% 3/ 15%	Total treated unknown 100% records 1/ 25% 2/ NA 3/25%	Total treated unknown 1/ NA 2/ 4% 3/ 69%	Total treated unknown 1/ 21% 2/ 0% 3/ 5%
Administration date if DMT recorded	5	5	5	5	5	5	3	5	2	1
Dosage recorded	Not collected	Not collected	Not collected	5	5	1	3	5	2	1
Administration status stopped recorded if administration status start is recorded	n=63/314	Unknown	n=2/59	Unknown	n=17/104 Spinraza n=04/16 Evrysdi	80% records	5% records	100% records	n=14/35	Unknown

DMT: disease modifying therapy; UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

5.3.3.3. Outcomes

- **Motor Function**

Table 10 below summarises the motor function information available across registries. The wheelchair usage and frequency of usage are well reported for all registries except for the Georgian registry. The type of wheelchair (manual or electric) is not reported in Belgium, Germany & Austria, Switzerland, UK & Ireland, Georgia, Latvia hence this variable was not included in the feasibility assessment.
In Czech Republic & Slovakia, the patient's age at the start of wheelchair usage is recorded.
In Spain, the start date of wheelchair usage is not collected. Wheelchair usage is collected at several time points (sometimes/permanent).
Motor function test is not available in all patient-registries and poorly reported in Bulgaria.

Table 10. Motor function information across registries

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Wheelchair usage and frequency	4	5	4	5	5	5	4	3	2	3
Start date of wheelchair usage	3	Not collected	4	2	5	1	4	3	2	1
Motor function test	Not collected	Not collected	Not collected	4	5	5	3	1	4	3
Muscle contracture	3	1	2	5	5	5	5	1	5	3

UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

- **Nutrition/Feeding tube**

Table 11 below summarises information on nutrition collected across registries.

Table 11. Nutrition information across registries

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Feeding tube usage • Y/N option • Pre-selected answers • Other	Other	Y/N option	Other	Pre-selected answers	Pre-selected answers	Pre-selected answers	Pre-selected answers	Y/N option	Y/N option	Pre-selected answers
Feeding tube usage recorded (%)	4*	5	5*	5	5	3	5	5	1	1
G-tube or gastrostomy	4*	5	5*	3	5	4	5	5	Not collected	1

*For Germany & Austria and UK & Ireland(i.e. nasogastric tube vs G-tube) cannot be distinguished.
UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

- **Orthopaedic disorders**

Table 12 below summarises information on scoliosis and hip disorder collected across registries.

Table 12. Scoliosis and hip disorder information across registries

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Scoliosis	3	3	2	4	4	3	3	4	4	1
Diagnosis	3	3	2	5	5	4	4	4	4	1
Cobb Angle value (CAV)	Not collected	Not collected	Not collected	3	3	2	2	1	Unknown	1
Surgery	5	5	5	5	5	3	3	5	Unknown	1
Hip disorder : surgical treatment	1	1	1	1	1	Not collected	Not collected	5	1	1

UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

- **Thoraco-pulmonary disorders**

Table 13 below summarises information on pulmonary function collected across registries.

Table 13. Pulmonary function information across registries

Data elements	Germany & Austria	Spain	UK & Ireland	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Thoraco-pulmonary disorders	3	4	2	5	5	4	5	4		1
Forced Vital Capacity	Not collected	4	Not collected	4	5	5	4	2	5	2
Airway clearance assistance	3	4	2	4	5	3	5	3	Unknown	2
Non invasive ventilation usage	4	5	2	5	5	4	5	5	Unknown	1
Invasive ventilation usage	4	5	1	5	5	4	5	5	Unknown	1

UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

- **Hospitalisation and survival**

Table 14 below summarises information on living status and hospitalisations collected across registries.
All patients in the German & Austrian registry are supposed to be alive. Many are lost to follow-up and thus may be deceased, but remain in the registry until notification of their death. Deceased patients are generally removed from the registry.
In Spain, the cause of death is known for some patients but is not coded; death certificates are not collected.

Table 14. Hospitalisation and vital status information across registries

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Living status, date and cause of death	1*	4	1	5	5	4	3	5	4	1
Hospitalisation reason (acute or planned hospitalisation) and date recorded	4	2	1	5	5	4	4	1	2	2

* All patients in the German & Austrian registry are supposed to be alive. Deceased patients are generally removed from the registry.
UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

5.3.4. “Nice to have” data elements

The “Nice to have” data elements (refer to Section 4.3 for further details on selection of these data elements) ranking is summarised in the Table 15 below.

Non-medicinal product therapies and aid ranking is based on qualitative information on the use of rehabilitative interventions in each registry.

PROs ranking is based on qualitative information on the use of PROs assessing different dimensions which are different from the patient's global impression of change/improvement.

The Spanish registry does not collect height and weight, they will evaluate the possibility of starting to collect it with their internal advisory committee.

Table 15. Ranking of "Nice to have" data elements

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Height and Weight	3		2	4	4	3	4	3	1	1
Non-medicinal product therapies and aid	4	5	4		4	4	3		1	3
Comorbidities*	2	1	2	5	5	2	4	1	2	1
SAEs				1	1	2	1	1	1	1
PROs			1	4	1					3
Genetic testing methods	1		1	4	4		1	3	5	3

PROs: patient reported outcomes; SAE: serious adverse events; UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

5.3.4.1. Major non-medicinal product therapies and aid/support

Table 16 below summarises the use of rehabilitative interventions in each registry.

Table 16. Rehabilitative interventions usage across registries

Rehabilitative interventions usage	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Physiotherapy sessions (e.g., stretches)	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Respiratory physiotherapy	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes
Orthoses usage	No	Yes	No	No	Yes	Yes	Yes	No	No	Yes
Spinal brace	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes
Speech therapy	Yes	Yes	Yes	No	Yes	No	No	No	No	No
Occupational therapy	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes
Others	Contracture management using orthotics, Hydrotherapy, home programme and massage	Home programme, Massage, Hydrotherapy	Contracture management using orthotics, Hydrotherapy, Home programme, massage	No	Home programme Hydrotherapy	Hydrotherapy	Hydrotherapy	No	No	No

UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

5.3.4.2. Comorbidities and serious adverse events (SAEs)

Table 17 below summarises the comorbidities and SAEs collected in each registry. All registries collect comorbidities, nonetheless patient based registries collect them for a lower range of the population. Among clinician based registries Belgium, Sweden and Czech Republic & Slovakia are ranking the highest.

Table 17. Comorbidities and Serious adverse events collected across registries

Data elements	Germany & Austria	Spain	UK & Ireland	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Comorbidities	2	1	2	5*	5*	2	4*	1	2	1
SAEs	Not collected	Not collected	Not collected	1	1	2	1	1	1	1

*Comorbidities recorded in ICD-10 codes, others are recorded in free text then coded before data transfer
SAEs: serious adverse events; UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

5.3.4.3. Patient reported outcomes (PROs)

The below Table 18 summarises whether registries collect PROs locally with estimated completion where available. PROs are generally poorly collected except for Belgium.

Table 18. Patient reported outcomes (PROs) collected in each registry

Patient based registries	Clinician based registries
● Germany & Austria: No PROs ● Spain: Profuture Questionnaire currently in validation phase ● UK & Ireland: EQ-5D-L, EQ-5D-Y, SMA Independence Scale (non-ambulant), Global Impression of Change (implemented in April 2022 - 17% completion)	● Belgium: ACTIVLIM (completed 1/year by patients between 6 and 80 years old - 74% recorded) ● Sweden: EQ-5D-5L (15 % recorded), EQ-5D-3L, EQ-5D-Y ● Switzerland: Patient Global Impression of Improvement, planned SMA Independence Scale ● Bulgaria: No PROs ● Czech Republic & Slovakia: No PROs ● Georgia: No PROs ● Latvia: PEDI and PEDSQL (for 75% of patients)

5.3.4.4. Genetic methods testing

Table 19 below summarises the genetic methods tested information collected in each registry.
Despite having all genetic reports for patients entered into the Spanish registry, the registry is not collecting this information in their data model. Retrieving this additional information from the genetic reports represents a burden for the Spanish registry.

Table 19 . Genetic methods testing information across registries

Data elements	**Germany & Austria**	**Spain**	**UK & Ireland**	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia ✦	Latvia
Genetic method testing	1	Not collected	1	4	4	Not collected	1	3	5	3
Methods	RFLP HRM MLPA DNA sequencing qrtPCR ddPCR	Not collected	RFLP MLPA DNA sequencing qrtPCR Next Generation Sequencing for Whole Exome Sequencing Whole Genome Sequencing sspC gene analysis Fluorescent STS gene analysis	RFLP MLPA DNA sequencing qrtPCR ddPCR	MLPA DNA sequencing	Not collected	MLPA qrtPCR	MLPA	MLPA qrtPCR	RFLP MLPA qrtPCR

ddPCR: droplet digital polymerase chain reaction; DNA: deoxyribonucleic acid; HRM: high resolution melting; MLPA: multiplex ligation-dependent probe amplification; RFLP: restriction fragment length polymorphism; qrtPCR: quantitative reverse transcription polymerase chain reaction; UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

6. Discussion

A summary of the main findings for each registry participating in the feasibility assessment is provided below.

6.1. Clinician-based registries

The **Swedish registry** is highly recommended for its very good completeness of records for all data elements as well as for administrative information and quality requirements. Founded in 2010, the Swedish registry is a national registry with patient follow-up greater than 5 years. The 3 DMTs are available in the country. Spinraza has been available since 2017 and Zolgensma and Evrysdi have been available since February 2022. As of September 2022, 59% of patients in the Swedish registry are receiving or have received Spinraza and stopped receiving it. Comorbidities are collected in the database however SAEs and PROs are reported only for a small number of patients.

The **Belgian registry** is highly recommended for its very good completeness of records for all data elements as well as for administrative information and quality requirements. The registry collects data on SMA patients since 2015. Patient follow up is greater than 5 years. The 3 disease modifying therapies are available in the country. Spinraza has been available since 2018, Zolgensma since 2021 and Evrysdi since June 2022. Approximately 73%, 21% and 2% of patients of the Belgian registry are currently or have received Spinraza, Evrysdi and Zolgensma respectively. Comorbidities and PROs are collected in the registry database. Non medicinal product therapies and support are not collected. No specific process exists to collect SAEs in the Belgian registry.

The **Swiss registry** is recommended based on its good completeness of records for the majority of data elements and very good administrative information and quality requirements. The registry started in 2008 and went through a restructuring process in 2018. The first completed dataset entered in the database was in 2018 so the patient follow up is around 4 years. Approximately 80% of patients in the registry are receiving or have received a DMT. Spinraza has been available since 2017 and Zolgensma and Evrysdi since 2021. Dosage of DMTs is not recorded in the Swiss registry. Orthopaedic disorders are not collected and data regarding scoliosis and nutrition (feeding tube) are missing. Comorbidities and SAEs are reported only for a small number of patients.

The **Czech and Slovak registry** is recommended based on its good completeness of records for the majority of data elements and very good administrative information and quality requirements. The registry started collecting data in 2011 and has the highest number of patients among clinician-based registries. Spinraza has been available since 2017, Zolgensma since 2020 and Evrysdi since 2021. Approximately 80% of patients in the registry are receiving or have received a DMT with Spinraza being the most administered. However, dosing and administration dates for DMTs are missing. The motor function test is partially reported as well as scoliosis data. Orthopaedic disorders are not collected. Date of death is recorded but the cause of death is missing for 95% of records. Comorbidities are well reported. The percentage of records for SAEs is extremely low nonetheless each comorbidity, hospitalisation and death can be reported as a SAE in the database. The registry does not collect any PROs.

The **Bulgarian registry** was deprioritized due to the lack of quality assurance processes and low to medium completeness of data elements compared to other clinician-based registries.
The registry started collecting data in 2014. Spinraza has been available since 2019 and Evrysdi since March 2022 in Bulgaria. Zolgensma is not available in the country. Motor function tests, hospitalizations, comorbidities, SAEs are missing. PROs and rehabilitative interventions usage are not collected.

The **Latvian registry** and the **Georgian registry** were deprioritized due to the low number of SMA patients included in the registries, the absence of a governance structure, the lack of quality assurance processes and the lower completeness of data elements compared to other clinician-based registries.
The Latvian registry started in 2016 and includes 38 patients. Only 20 patients in the registry have a 5Q SMA diagnosis. The Georgian registry started in 2019 and includes 51 patients. Both registries have no records of the age and sex of patients. Spinraza and Zolgensma are not available in Georgia, only Evrysdi is available since 2021. In Latvia, Spinraza is available since 2019 and Evrysdi since February 2022, Zolgensma is not yet available. The date of administration and dosage of available DMTs are missing. The outcomes (feeding tube, scoliosis, thoraco-pulmonary disorders etc.) as well as the "Nice to have" data elements are poorly to moderately reported, except for genetic testing methods in Georgia.

6.2. Patient-based registries

The **Spanish registry** is recommended considering the overall good data quality, very good administrative information and quality requirements as well as the future collection of PROs.
The registry started collecting data in 2015 and the database is currently being renovated. All SMA patients in the registry have a confirmed 5q diagnosis and their consent uploaded in the database.
The average patient follow up in the registry is less than 5 years. Spinraza has been available since 2018 and Zolgensma since 2021, both are financed through the reimbursement pricing system with some restrictions. Evrysdi is not yet available. Dosage of DMTs is not collected in the registry. The patient motor function is not well reported, started date of wheelchair usage, motor function test and muscle contractures are not collected. Enteral nutrition and thoraco-pulmonary disorders are well reported. Regarding the height and weight of patients, the registry will start collecting these variables after discussion with their internal advisory committee. Comorbidities are collected in free text and the registry has no records of diagnosis date for comorbidities in the database. SAEs are not collected. The registry and its renovation is fully financed by the foundation FundAME which develops a research project called PROfuture collecting PROs. The PROfuture questionnaire is currently in the validation phase and will be soon available in the database.

The **German & Austrian** registry is recommended considering the high number of patients included, overall good data quality, very good administrative information and quality requirements. The registry started collecting data in 2008 consequently the average patient follow up in the registry is greater than 6 years. The registry has the highest number of patients including the highest number of patients with a 5q diagnosis genetically confirmed among all registries. All patients included in the registry have given their consent for the use of their deidentified data for research purposes. DMTs are covered by the public health insurance in Germany and Austria. Spinraza has been available since 2017, Zolgensma since 2020 and Evrysdi since March 2021. Approximately 40%, 2% and 11% of patients in the registry have received or are currently receiving Spinraza, Zolgensma or Evrysdi respectively. The dosage of DMTs is not collected.
Regarding the "need to have" data elements, the patient SMA characteristics (symptom onset date) as well as the motor ability status are reported for half of the patients included in the registry. More than half of patients have a record of their motor function (wheelchair usage and frequency, start date of wheelchair usage and muscle contractures) however motor function tests are not collected. Scoliosis is well reported although Cobb Angle value is not collected. Pulmonary function tests are reported as well as the invasive and non-invasive ventilation usage and the need for airway clearance assistance. Death and cause of death are not collected.
In regards to the "nice to have data elements", more than half of patients have one or several weight and height values recorded in the database. Comorbidities and their start date are collected. SAEs and

PROs are not collected.

The **UK & Ireland** registry is recommended considering the number of SMA patients with genetic confirmation is in the range of the Spanish registry. This registry has much less 5q SMA patients than the German & Austrian registry. The UK & Ireland registry received a favourable opinion of the ethics committee to begin collecting data in 2007; the average patient follow up is greater than 5 years. All patients included in the registry have given their consent for the use of their deidentified data for research purposes. Spinraza has been available since 2019, Zolgensma since 2021 and Evrysdi since 2022. Less than half of patients in the registry have had an administration of DMTs recorded. The dosage of DMTs is not collected.
Regarding the “need to have” data elements, the SMA clinical characteristics (symptom onset date) is reported for approximately 44% of patients with a genetic SMA confirmation which is lower than the percentage of other patient-based registries. The motor ability status is poorly reported (only 16% records). Motor function tests are not collected. Pulmonary function and hospitalizations, which are critical information, are not well reported. Overall, the UK & Ireland registry has less information on SMA clinical characteristics, functional status and scoliosis diagnosis, and much less information on ventilation usage and hospitalisation information compared to the registry in Germany & Austria. These limitations will need to be taken into account when interpreting the study results.

The overall registry assessment is summarised in the Table 20 below.

Table 20. Overall registry assessment

Registry (n=SMA 5Q diagnosis)	**Germany & Austria** (n=610)	**Spain** (n=289)	**UK & Ireland** (n=215)	Belgium (n=254)	Sweden (n=171)	Switzerland (n=146)	Czech Rep. & Slovakia (n=309)	Bulgaria (n=90)	Georgia ✦ (n=48)	Latvia (n=20)
Longitudinal patient data	≥5 years	<5 years	≥5 years	≥5 years	≥5 years	4 years	3 years	3-4 years	3-4 years	≥5 years
"Need to have" data elements										
Patient characteristics	4	4	3	4	5	4	5	4	3	2
DMTs	2	3	2	5	5	3	3	5	2	1
Outcomes	3*	4*	2*	5	5	4	4	3*	2	2
"Nice to have" data elements	2	1	2	3	3	2	2	1	2	2
Administration & Quality	4	5	5	4	5	4	5	1	1	1

*absence /very limited motor function

DMT: disease modifying therapy; SMA: spinal muscular atrophy; UK: United Kingdom. ✦children-only registry; bold characters represent patient-based registries.

7. Conclusion

To support the research questions and after FFP assessment of each registry and considering the need to get at least 5 registries included in the study, Aetion recommends including 4 clinician-based registries (Belgium, Sweden, Switzerland and Czech Republic & Slovakia) and 3 patient-based registries (Spain, Germany & Austria, and UK & Ireland).

8. References

1. Schorling DC, Pechmann A, Kirschner J. Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. J Neuromuscul Dis. 2020;7(1):1-13. doi: 10.3233/JND-190424.
2. Guideline on Registry-based studies, EMA, EMA/426390/2021 Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf (Accessed : October, 21, 2022).
3. REQueST Tool and its vision paper, EUnetHTA, Available at: https://www.eunethta.eu/request-tool-and-its-vision-paper/ (Accessed : October, 21, 2022).
4. Gatto, NM et al. (2022). The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework. Clin. Pharmacol. Ther., 111(1), 122-134. https://doi.org/10.1002/cpt.2466
5. Belgian Neuromuscular Diseases Registry (BNMDR), Sciensano, Available at : https://www.sciensano.be/en/belgian-neuromuscular-diseases-registry-bnmdr (Accessed : October, 21, 2022).
6. DMD and SMA Patient Registry, About the register, Treat-NMD, Available at: https://www.treat-nmd.de/register/general/index.de.html (Accessed : October, 21, 2022).
7. Registro de pacientes (investigación), FundAME, Available at : https://www.fundame.net/registro-de-pacientes-investigacion/ (Accessed : October, 21, 2022).
8. General information, UK SMA Patient Registry, Available at https://www.sma-registry.org.uk/, (Accessed : October, 21, 2022).

Appendix E - Statistical Analysis Plan

Non-interventional registry-based Study
Protocol: EUPAS50476

A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs).

Statistical Analysis Plan

A registry-based cohort study on Spinal Muscular Atrophy (SMA) disease

SAP version identifier	Version 1.7
Date of last version of SAP	26 April 2023
Active substance	Not applicable
Medicinal product	Not applicable
Product reference	Not applicable
Procedure number	EMA/2020/46/TDA/11, Lot 5 (Pharmacoepidemiological research)
Marketing authorization holder(s)	Not applicable
Framework contractor	Aetion Germany GmbH
Framework contractor contact person	Pierre Engel Senior Director, Business Development (EU) pierre.engel@aetion.com
Joint PASS	No
Country(-ies) of study	Belgium, Czech Republic and Slovakia, Germany and Austria, Spain, Sweden, United Kingdom and Ireland
Author	Rhian Davies Senior Statistician, Jumping Rivers rhian@jumpingrivers.com

Table of contents

2. List of abbreviations

Abbreviation	Description
AE	Adverse Event
AT	As Treated
CDW	Central Data Warehouse
CED	Cohort Entry Date
DMT	Disease Modifying Therapy
EMA	European Medicines Agency
EU	European Union
GRP	Global Registry Platform
INN	International Nonproprietary Names
ITS	Interrupted Time Series
ITT	Intention to Treat
PPRL	Privacy-Preserving Record Linkage
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SAESI	Serious adverse events of special interest
SAP	Statistical Analysis Plan
SMA	Spinal Muscular Atrophy
SMN1	Survival of Motor Neuron 1
SMN2	Survival of Motor Neuron 2
TGDOC	TREAT-NMD Global Data Oversight Committee

3. Responsible parties

Organisation	Key person	Position	Role
Aetion Germany GmbH	Emmanuelle Jacquot	Senior Director, Science	Principal Investigator
	Coralie Lecomte	Senior Director Data Science, Pharmacoepidemiologist	Feasibility assessment
	Elodie Boin	Scientist, Scientific Data Insights	Feasibility assessment
	Anabel Ferreras	Senior Project Director	Project management
	Siyana Kurteva	Senior Scientist	Science Analyst
TREAT-NMD	John McKenna	Head of Projects & Risk	Project management
	Seung Lee	Project Manager	Project management
	Neil Bennett	Research and communication manager	Registry and communication support
	Marcel Heidemann	Data processor	Data management and analyst
	Colin Gillespie	Senior Biostatistician	Data analyst
	Rhian Davies	Senior Statistician	Data analyst
	Pr. Laurent Servais	Professor of Paediatric Neuromuscular Diseases, University of Oxford	Principal investigator for TREAT-NMD

4. Introduction

4.1 Background

Spinal muscular atrophy (SMA) is a rare recessive progressive neurodegenerative disorder. The age of onset is highly variable from birth to adulthood, leading to a broad phenotypic spectrum. Since the approval of new treatments for SMA, studies have reported disease trajectories that significantly differ from the known natural history of SMA. This study uses patient registry data from seven registries to investigate SMA patients' course of the disease with and without these new therapies, and the SMA standards of care delivery including the newly available disease-modifying therapies in real-world settings.

4.2 Design of the study

The study will be a non-interventional, primarily descriptive, retrospective cohort study of SMA patients using seven registries (spanning ten countries) from the TREAT-NMD federated network. The study period will start on each registry start date and end on 30 November 2022 (or latest data available per registry). Patients will be followed from the registry entry date until the earliest of end of study, or death, or loss to follow-up. Please refer to section 8.3.1 for the censoring criteria when describing disease modifying therapies (DMT) patterns of use.

4.3 Aims and planned analyses

There are four main analyses planned: three descriptive summaries and one exploratory analysis. The descriptive summaries will be stratified by certain key properties, as detailed in Table 1.

Table 1: Breakdown of stratifications and time periods for each analysis

Analysis	**Stratifications**	**Time Period/Axis**
Preliminary analysis	• Registry ○ SMA type	Calendar year

SMA natural history and disease progression	• SMA Type
	  ○ DMT
	  ■ Class of age at symptom onset
	  ■ SMN2 copy number
	  ■ Functional status at age of symptom onset
	  ■ Achieved motor milestone at age of symptom onset
		Class of current age

Analysis	Stratifications	Time Period/Axis

Description of SMA healthcare management over time	• Registry
	  ○ SMA type
	  ○ SMN2 copy number
	  ○ Functional status at age of symptom onset
		Calendar year

Exploratory Analysis	NA	NA

4.4 Sample size

A feasibility assessment was conducted in the European registries of the TREAT-NMD network. Based on this feasibility assessment and the seven selected registries, the projected minimum number of patients with genetically confirmed 5q SMA are presented in Table 2.

Table 2: Projected minimum number of patients with genetically confirmed 5q SMA

	Belgium	Sweden	Czech Republic & Slovakia	Germany & Austria	Spain	United Kingdom & Ireland
Patients with genetically confirmed 5q SMA, n	254	171	309	610	289	215
Patients receiving at least one DMT, %	100%	64%	80%	56%	100%	42%
Average length of follow-up	≥5 years	≥5 years	3 years	≥5 years	≥5 years	≥5 years

5. Populations

5.1 Eligibility criteria

The primary study population will include all SMA patients entered in each of the registries selected for the study between registry entry date and 30 November 2022, that meet the following eligibility criteria:

- Patients with genetically confirmed 5q SMA
- Patients with the month and the year of their birth available.

To assess the different objectives, three main cohorts will be studied:

- All patients (ALL): to study management care changes overtime and differences across European countries/registries.
- Untreated patients (UNTREATED): to study the natural history of SMA.
- Treated patients (TREATED): to study the effectiveness and safety of DMT.

A patient will be included in the UNTREATED cohort before initiation of a DMT, then the patient will be considered to be in the overall TREATED cohort at initiation of 1st DMT. Exposure categories will be constructed in a way that allows patients to switch from the untreated group to the different treatment exposure regimens based on the individual's DMTs. Patients will also be followed across different treatment exposure regimens if they switch from one DMT to another or have an add-on therapy. Patients will start contributing to the TREATED cohort when they have received at least one of the DMTs of interests:

- Nusinersen (Spinraza®)
- Onasemnogene abeparvovec-xioi (Zolgensma®)
- Risdiplam (Evrysdi®)

Please see exposure definition in section 8.3 for more details.

6. Data sources

TREAT-NMD is a global registry network launched in 2007 for the neuromuscular field that provides an infrastructure to ensure the most promising new therapies reach patients as quickly as possible across multiple diseases. The global registry network is overseen by TGDOC - a committee of 3 Chairs, Member Registry Curators and Patient Representatives, supported by the TREAT-NMD Ethics Committee members as required.

TREAT-NMD currently has 28 Core SMA registries (16 in Europe) and includes clinician-, patient-, and dual-reported registries. Collectively, the registries collect data on approximately 6,000 patients (4,778 in Europe).
Registries joining the network agree to abide by the TGDOC Charter, which sets some criteria and standards Registries should meet - including collecting a TREAT-NMD core dataset, sharing data, and attending annual meetings.

The TREAT-NMD SMA core dataset containing 23 data items was established in 2008 when the main purpose of the registries was clinical trial readiness and recruitment. The dataset was

expanded significantly through a process (started in 2018) that involved extensive stakeholder engagement with registry curators, physicians, physiotherapists, patient representatives and industry representatives. The current dataset includes 120 data items.

Data from all Registry Members can be collated in the TREAT-NMD Central Data Warehouse (CDW) to build a harmonised pool of data and allow for better data analysis.

The final list of registries contributing data to this project has been determined after fit-for-purpose data feasibility assessment.

7. Data management processes

The SMA Registries are currently implementing or actively collecting the latest dataset v2 largely displayed in section 9.3.2 of the study protocol and which can be found in the TREAT-NMD Core Datasets. This is part of their membership commitment to the TREAT-NMD Global Data Oversight Committee (TGDOC). Data from different registries is collated in the TREAT-NMD central data warehouse (CDW), which carries out validation checks before making data available for analysis.

Registries can share data with the CDW regularly, or in response to a specific request. For the purpose of this study, a date on which all data should be transferred by, is 17th March 2023.

Core Member Registries collect and process data according to the national or international laws and best practices that apply to each of them respectively (in particular, accuracy and minimization of missing data; informed consent concerning use of the data for research; right of the patients to withdraw consent etc).

Several processes are in place to ensure data quality:

- The TREAT-NMD PPRL Generator is a tool developed for use within the Global Registry Network to generate a unique record string based on demographic information. The purpose of the PPRL tool is twofold:
    - de-identification of data: patient data is de-identified by registries using the PPRL tool. This allows patient level data to be shared without revealing identifying information to TREAT-NMD.

  For registries using TREAT-NMD Global Registry Platform, creation of an export file to transfer data to the CDW will automatically include the patients' PPRLs. Registries using

different platforms will be provided with the TREAT-NMD PPRL Generator for local use.

- Before data is transferred to TREAT-NMD, all safety monitoring instances are checked by a curator for accuracy and will be corrected before being transferred.
- Deidentified data uploaded to the CDW is initially stored in a holding area. Whilst the de-identified data is in the holding area, the individuals' record will be checked via automatic process, for any validation errors and also by the TREAT-NMD data analyst. Any automatic validation errors that are not within a small tolerance will be returned to the registry curator for another check of the data content. If the data has passed the automatic process validation or the error is within a small tolerance, then the data will be approved by the data analyst and released into the CDW for storage and future analysis.
- Once the data is in the CDW the data analyst will then analyse the data for data quality-management purposes and future uses of the data, whether that is for enquiries or post marketing activities.

No auditing practices are in place between TREAT-NMD and the Registries.

Data is intended to be collected by the registries at regular intervals (at least every 12 months). The data collection (reference) period begin and end dates are set at each visit/data-collection. Begin date specifies the beginning of the period to which the question refers; end date specifies the end of the period to which the question refers.

The data collection period should cover:

- The year before registry entry for the first visit
- The period between the last update (last visit) to the date of data entry (current visit).

Historical data may be also collected by registries, notably for longitudinal data or when data entry is not at diagnosis. The date stamp in this case should usually be the date when the clinical examination or test has been done.
Certain events are collected by the registries over the data collection period as "currently", "previously" or "never" occurred over the period of interest. These events are then mapped by TREAT-NMD as:

- "Currently" when the event is current,
- "Previously when it has been previously the case, but is not currently
- "Never" when it has never been the case
- "Sometime" when it has been the case at some time but it is unknown whether it is currently the case
- Not currently when it is currently not the case but it is unknown whether it has previously been the case.

In addition, start and stop dates of events (e.g hospitalisation, comorbidities, or invasive ventilation when reported as previously occurred or currently occurring) are also reported, as well as ongoing date when the condition is known to hold.

Comorbidities, cause of deaths or of hospitalisations are reported using dropdown lists with prespecified events or may also be reported and will be coded by the curator of the registry using ICD-10 codes.

For any drugs or classes of drugs which have been identified as relevant co-medications but which are not included in the predefined list of drugs in the TREAT-NMD core dataset (items "Allopathic drug" and "Allopathic drugs"), the values of the items "Other allopathic drug" and "Other allopathic drugs" will be searched for the INNs of the respective drugs.
Operational definitions for the presence and/or occurrence for each outcome will be further detailed in the SAP as it will differ according to the nature of the outcome and the availability of data.

8. Stratifications

The data will be stratified in a combination of ways as detailed in Table 1. The following stratifications will be considered:

- Registry
- SMA Type
- DMT
- Class of age at symptom onset
- SMN2 copy number
- Functional status at symptom onset date
- Achieved motor milestone at symptom onset date
- Time period

Please note that SMA type includes a category of “presymptomatic” patients (see section 8.2). As the identification method needed to be classified as presymptomatic occurs through newborn screening, the “presymptomatic” category is also included as part of the age of symptom onset (see section 8.4).

8.1 Registry

Where the data is stratified by registry, it will be split into ten groupings: the seven registries, plus three groupings of those same registries. The three groupings will be patient-reported registries, clinician-reported registries, and all registries combined.

8.2 SMA type

The types of SMA which will be considered will be Presymptomatic, 1, 2, 3, and 4 and "other". The corresponding variable in the TREAT-NMD database is SMA Type. SMA types 3a and 3b will be simplified and re-coded as SMA type 3 to help with sample size. Presymptomatic is not collected directly in the SMA type variable. Patients selecting *Asymptomatic* to Symptom onset, and *Yes* to Genetic confirmation will be classified as presymptomatic. *Genetic confirmation* includes diagnosis made as a result of screening such as family screening, newborn screening and prenatal screening.
According to the feasibility assessment, only three patients overall had SMA type 0. SMA type was undetermined in 10 patients by the selected registries. These will be grouped into an "other" category.

When different types have been reported for the same patient, the last reported type will be considered to define the SMA type of this patient.

8.3 DMT Exposure

8.3.1. Construction of Exposure Variables:

Patient exposure will be defined according to the information collected in the registry.
The exposure of interest are:

- Treated with at least one DMT (this will serve to create an overall exposure category representing all patients who were treated regardless of the treatment or combination of treatments received during the follow-up).
- Treated with nusinersen (Spinraza®), and possible combinations with Spinraza®.
- Treated with onasemnogene abeparvovec-xioi (Zolgensma®), and possible combinations with Zolgensma®.
- Treated with risdiplam (Evrysdi®), and possible combinations with Evrysdi®

Treated with at least one DMT or possible treatment combinations will be defined using the following fields available within the TreatNMD network:

- The "DMT received field" indicator (e.g.,: "Yes")

- A field indicating the name of the specific DMT taken (nusinersen (Spinraza®), onasemnogene abeparvovec-xioi (Zolgensma®), and risdiplam (Evrysdi®)
- A field indicating the corresponding start date (or a single administration date for Zolgensma®)

All three fields will need to be specified for the individual to be considered as exposed to a given DMT and flagged as a treated patient.

8.3.2. Exposure Definition:

In all the analyses, a time-varying exposure, where the exposure status of a patient is updated based on the current treatment that the patient is on, will be used to model the use of DMTs, alone or in combination, with each other, during the follow-up period. (1)(2)(3)(4). This exposure definition accounts for the dynamic treatment landscape and allows patients to discontinue their initial pharmacological treatments, switch treatment or start add-on therapies and consequently be exposed to multiple pharmacological treatments at the same time. This approach will have patients contributing person-time in different mutually exclusive categories, whether it is an exposure to a single treatment or a category that combines two treatments (in case of concomitant use). The possible combinations of use will be constructed based on combinations seen in the registries' data. For all patients, end of follow-up will be the earliest of date of death or end of follow-up / end of data (censoring at last available information in lost-to follow-up patients).

The SMA natural history and disease progression analysis will be stratified by DMT exposure categories. The possible cohorts will consist of:

- Untreated
- Treated (Any DMT)
- Nusinersen (Spinraza®)
- Onasemnogene abeparvovec-xioi (Zolgensma®)
- Risdiplam (Evrysdi®)
- Zolgensma + Spinraza
- Zolgensma + Evrysdi
- Evrsydi + Spinraza

The *Treated* cohort consists of patients who have been exposed to any DMTs. Patients will be classified as *Untreated* until they receive their first DMT, and then will be classified as *Treated* from that time point onwards until there is an observed change in their treatment exposure status during the follow-up resulting in treatment discontinuation. If a treatment discontinuation is observed with Evrysdi and Spinraza (treatment discontinuation is not applicable for Zolgensma

therapy, which assumes an never/ever exposure definition, see Section 8.3.2 for more details), then the patient will switch back to contribute person-time to the *Untreated* category as per the time-varying exposure definition (please see Section 8.3.2 and Table 3 below for more operational details on this). Please refer to treatment discontinuation rules below for how treatment periods will be constricted. Depending on the type of DMT received, patients will be categorised in various categories of monotherapy or/and treatment combination categories. Sankey plots will be used to visually display the different treatment patterns of use and treatment switches.

Treatment discontinuation/treatment switch will be defined as follows, depending on the type of DMT used:

- For onasemnogene abeparvovec-xioi (Zolgensma®), a patient is considered exposed from the first administration with a single-dose infusion until the end of follow-up. Given the nature of the onasemnogene abeparvovec-xioi (Zolgensma®) treatment where the effect of the single-dose gene therapy is considered irreversible, there will be no treatment discontinuation rule created and the analytical approach here will carry forward the initial exposure status; once the patient is exposed, they will be always considered exposed to this type of therapy. In case where the patient had an add-on therapy with either 1) nusinersen (Spinraza®) or 2) risdiplam (Evrysdi®), this patient will be counted (contribute person-time) in the respective category that combines Zolgensma and the add-on therapy: Zolgensma + Spinraza, or Zolgensma + Evrysdi.
- For nusinersen (Spinraza®), patients are considered exposed to the treatment from the first administration date to the stop date (exposure will be updated on the last ongoing date if no stop date is reported), which will correspond to the:
    - 2 months after the loading dose administration period,
    - 6 months after the maintenance administration period (as maintenance dose should be administered every 4 months).
- For risdiplam (Evrysdi®) that should be taken daily, patients are considered exposed from the first intake date to the stop date (exposure status will be updated on the last ongoing date if no stop date is reported or the last ongoing date if no stop date is reported) + 1 month.
- Subsequent treatment switches will be defined as the switch from the first (or previous) DMT the patient was initiated.
- The number of patients who have been treated with more than one DMT will be reported in each of the respective categories as they appear in the registries' data (n,%).

In each of the possible exposure categories (monotherapy or combination therapy), patients will be followed-up until the earliest of death or end of data availability.

Table 3 provides a graphical representation of how the modelling for the different hypothetical patient scenarios and treatment patterns will be considered, in light of a treatment switch, discontinuation or add-on therapy. Please note that for simplicity, we did not present every possible combination of medications, but these will be considered in the final analyses. In addition, the dates below are hypothetical and not taken from the real-world setting but provided only for illustrative purposes.

Table 3. An example of how modelling for different hypothetical exposures will be modelled accounting and allowing for treatment switches, add-on therapies and discontinuations.

Patient ID	DMTs	Start date (dd/mm/yy)	Stop date (dd/mm/yy)	Overall exposure	Onasemnogene abeparvovec-xioi (Zolgensma®)	Nusinersen (Spinraza®)	Spinraza + Evrysdi	Zolgensma + Spinraza	Zolgensma + Evrysdi	Risdiplam (Evrysdi®)
1	Onasemnogene abeparvovec-xioi (Zolgensma®) (one-time administration)	01-12-2020	NA[1]	1	1	0	0	0	0	0
1	Risdiplam (Evrysdi®)	01-12-2021	30-01-2022	1	0	0	0	0	1	0
2	Nusinersen (Spinraza®) loading administration	12-01-2020	12-03-2020	1	0	1	0	0	0	0
2	Nusinersen (Spinraza®) maintenance administration	02-12-2020	08-12-2020	1	0	1	0	0	0	0
2	Risdiplam (Evrysdi®)	03-18-2021	03-07-2021	1	0	0	0	0	0	1
3	Risdiplam (Evrysdi®)	02-01-2020	03-10-2020	1	0	0	0	0	0	1
3	Nusinersen (Spinraza®)	03-08-2020	03-10-2020	1	0	0	1	0	0	0
4	Nusinersen (Spinraza®)	04-04-2021	04-06-2021	1	0	1	0	0	0	0
4	Onasemnogene abeparvovec-xioi (Zolgensma®)	14-08-2022	NA	1	0	0	0	1	0	0

[1]Patients on Zolgensma therapy will be considered exposed to Zolgensma throughout the follow-up period. The stop date will correspond to the end of follow-up, which will be the earliest of date of death or end of available data.

8.3.3 Illustrative examples:

Patient ID 1: As this patient received Zolgensma as their initial treatment, they will begin contributing person-time to the Zolgensma exposure category until the start of their add-on therapy with Evrysdi. From that moment on, this patient would start contributing person-time in the treatment exposure category that combines Zolgensma and Evrysdi. If there is an observed treatment discontinuation with Evrysdi, based on the discontinuation rule specified above, then that patient will stop contributing person-time to the combination therapy (will no longer be counted in this group) and switch back to the Zolgensma only treatment category (given the "once exposed, always exposed" definition for this type of DMT), where, from this moment on, they will be counted only in the monotherapy exposure group of Zolgensma until a subsequent add-on therapy, if any, is observed.

Patient ID 3: As this patient initiated treatment on Spinraza, they will be considered exposed to monotherapy with Spinraza until the moment when they switch to monotherapy with Evrysdi, as of which, patient will start contributing person-time to the exposure category of Evrysdi monotherapy (as in the case of this patient, there is no drug overlap between the two DMTs as per the above-mentioned discontinuation rules).

8.4 Class of age at symptom onset

This stratification will consider the patients, as grouped by their age when symptoms began. The age classes are categorical and will be defined as follows:

- Presymptomatic
- Prenatal
- < 1 month
- [1 - 3 months)
- [3 - 6 months)
- [6 - 18 months)
- [1.5 - 2 years)
- [2 - 6 years)
- [6 - 11 years)
- [11 - 18 years)
- 18 years +
- Missing
- All

8.5 SMN2 copy number

This comes from the SMN2 copy number variable in the TREAT-NMD database. This is usually reported as an integer, for example, "3". However, in some cases, there may only be a range (3-5)

or a lower bound (4+) reported. Any non-integer values or missing SMN2 copies will be collated in an “Other” category for the stratifications. The possible categories will be:

- 0
- 1
- 2
- 3
- 4
- >4
- Other
- Missing

8.6 Functional status at symptom onset

Functional status is not collected directly within the TREAT-NMD database, but is instead derived from the motor milestones according to the highest class where at least an item is reached.

The categories considered will be:

- **Walker**: Patients who can walk with assistance, walk without assistance, walk 10 metres without assistance, or climb stairs.
- **Sitter**: Non-walkers, who can “sit without support,” “crawl,” “stand with assistance,” or “stand without assistance.”
- **Non-sitter**: Patients who do not meet the Walker or Sitter requirements, but have some data for motor milestones
- **Unknown**: No data on motor milestones

8.7 Achieved motor status at symptom onset

Motor status is collected in the Motor ability variable. The possible values that we will consider are:

- Climb stairs
- Walk 10 metres without assistance
- Walk without assistance
- Walk with assistance
- Stand without assistance
- Stand with assistance

- Crawl
- Sit without support
- Roll onto side
- Hold head without support
- Unknown

There may be multiple observations of achieved motor status for each patient. In the case of multiple observations, the highest value will be taken, and also the most recent. The highest will be calculated based on the ordering in the above list (top-to-bottom).

8.8 Time Period

Certain indicators will also be stratified by a time period to show possible changes over time. In the preliminary analysis and the SMA healthcare management analysis the time period will be calendar year. In the SMA natural history and disease progression the time period will be the current class of age. These time periods are described in more detail below.

8.8.1 Calendar period

For the preliminary analysis and SMA healthcare management analysis, the time periods have been chosen to reflect the availability of DMTs and the publication of standards of care guidelines. Since the first international consensus statement on care was published in 2007 and updated in 2017, and the first DMT was approved in 2017, the following time periods will be used.

- Before 2011
- 2011 - 2013
- 2014 - 2016
- 2017
- 2018
- 2019
- 2020
- 2021
- 2022

8.8.2 Current class of age

For the SMA natural history and disease progression, certain indicators will be reported by the age of the patient when they report that statistic - their “current class of age”. The bounds for these ages are given below.

- < 1 month
- [1 - 3 months)
- [3 - 6 months)
- [6 - 18 months)
- [1.5 - 2 years)
- [2 - 6 years)
- [6 - 11 years)
- [11 - 16 years)
- [16 - 21 years)
- [21 - 31 years)
- [31 - 41 years)
- [41 - 51 years)
- [51 - 61 years)
- > 60 years
- Missing
- All

9 Data handling

In this section, we will discuss general data handling that affects both the descriptive analysis and the exploratory analysis. The two analyses are then described in more detail in sections 10 & 11 respectively.

9.1 Data Validation

Data validation is handled during the data ingestion into the TREAT-NMD CDW as described in the Section 7. Unit tests will be written to ensure the validity of the R scripts, and all coding will be assessed by two analysts as described in Section 9.9.

9.2 Missing data

Missing data for each variable will be counted, overall, by registry and by SMA type. No imputation of explicitly missing values is planned. Missing data due to loss to follow-up will result in an individual's data being censored. Missing data are assumed to be missing-at-random (MAR), with no significant differences seen between registries.

9.3 Limitations of the descriptive analysis

The descriptive statistics are simple statistical summaries such as count and means. The limitations of these simple summaries are minimal, although the mean can be skewed by extreme values within the population.

9.4 Loss to follow-up

Lost to follow-up will be defined as patients with last available data > 24 months in absence of death.

9.5 Key date variables

There are three date variables of key importance which feed into a number of indicators across the analyses, symptom onset, diagnosis date and registry entry,

9.5.1 Symptom onset

We suspect this date we will be fairly straight forward and should be well represented within the data. This is a defined, required variable within the TREAT-NMD Global Registries Platform.

9.5.2 Diagnosis date

One date requested within the study protocol is *diagnosis date*. Unfortunately, this is not something directly captured within the TREAT-NMD GRP. One possible proxy is the *genetic report date*, however, there can be some issues with this variable. We assume that this date is the date that a genetic diagnosis was confirmed, but this may not be the case as patients might have entered a date from a hospital letter relating to their diagnosis, rather than the true genetic report date. It may also be a missing variable for some records. We do not know how many at present. As a side note, The TREAT-NMD GRP allows patients to provide multiple records for genetic diagnosis reports. In the case where multiple genetic report dates are given for a patient, we will use the earliest genetic report date.

9.5.3 Registry entry

Another date referred to in the protocol is *registry entry*. This is not a variable which is collected within the TREAT-NMD GRP. We will derive this from an earliest longitudinal date stamps or timestamps variable, based on the earliest date we observe for a patient. Note that this assumes that longitudinal data is never added retrospectively; this assumption will be verified on the data received

9.6 ICD codes

A number of indicators relate to co-morbidities and SAESI which will require ICD-10 codes for mapping. The co-morbidities and SAESIs which require ICD-10 codes as are follows:

SAESI:

- Thrombocytopenia and coagulation abnormalities
- Renal toxicity
- Hydrocephalus
- Meningitis
- Hypersensitivity reactions
- Cutaneous vasculitis
- Hepatotoxicity
- Cardiac adverse event

Other relevant comorbidities:

- Osteoporosis
- Fractures
- Pulmonary infections
- Sleep apnea
- Pneumothorax
- Atrial or ventricular defect
- Diabetes
- Vertebral fracture
- Non-vertebral fractures
- Bronchopulmonary infections
- Gastrostomy

The mapping of these ICD-10 codes are described in Appendix III. For indicator 2.95, causes of death, ICD-10 codes will be reported at the four-digit ICD-10 code level (labelled) and all codes above that hierarchically.

9.7 Pooled analysis for registries

Some analyses require data to be pooled across all registries. This is in order to increase the sample size, and provide a representative summary across the full population. The registries from Belgium, Sweden, Czech Republic & Slovakia, Spain and the United Kingdom and Ireland will provide patient-level data to the TREAT-NMD Central Data Warehouse for central analysis. Data will be formatted to a common structure to facilitate the analysis.

However, the Germany & Austrian NMD Registry cannot share patient-level data. These registries will therefore be analysed separately by a different analysis team.

To ensure that the analyses are comparative, the same raw data will be collected and the same variables derived via the use of R scripts. The same R scripts will be used to perform the analysis, regardless of registry, with in-built sanity checks to ensure robustness across analyses. This will ensure that the process is standardised and repeatable, regardless of the registry.

9.8 Statistical packages

All data analysis will be performed using the statistical programming language R, version 4.2. The analysis will use several R packages which are downloaded and installed from the Comprehensive R Archive Network (CRAN). Each R package has been considered for stability and suitability.

9.9 Reproducibility and version control

Ubuntu, R and the associated R packages are all popular and commonly used open-source, freely available pieces of software. All scripts will be stored on gitlab.com under the Jumping Rivers account and mirrored to the TreatNMD Git server. No user will be able to push to the main branch directly. All code merged into the main branch will require two approvals from other developers. All developer roles will be detailed in the CODEOWNERS file.

The {renv} framework will be used to fully specify the R packages (with associated version numbers) to ensure future reproducibility. A continuous integration process will be launched when the code is committed to the Git repository. This will use the packages specified via {renv}, a docker image and a dummy but representative data set to test the code. Code that is merged into the main branch must pass this continuous integration step. In addition to code reproducibility, code style and documentation will be enforced via the {lintr} package.
Key git commits will be tagged to allow for code versioning.

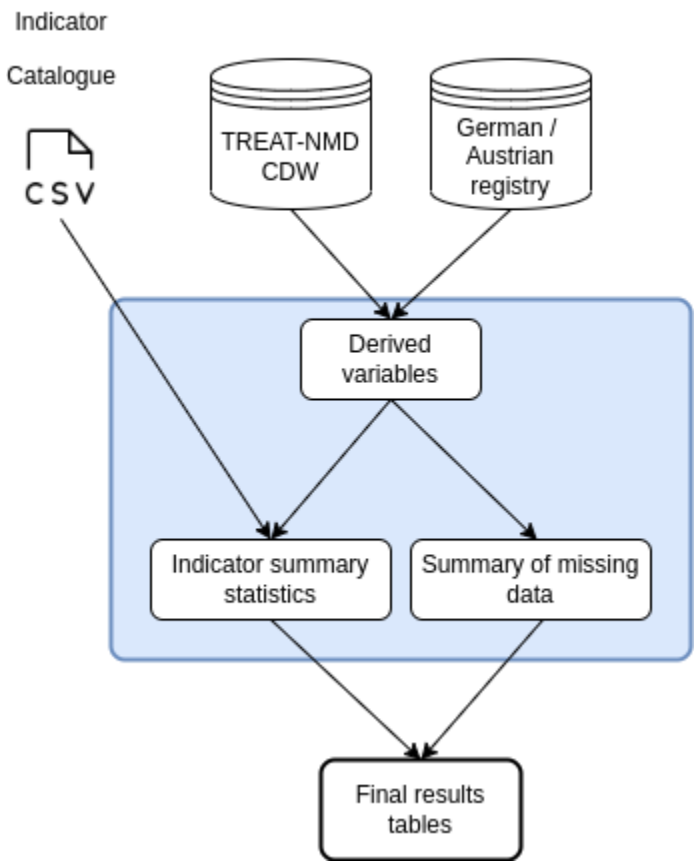
9.10 COVID-19

The study period overlaps with the outbreak of COVID-19. A number of the outcomes of interest in this study relate to death or ventilation. Known consequences of COVID-19 are ventilation and death. The effect that COVID-19 had on SMA patients and the progression of the disease has not been fully studied and is not well understood. We will not attempt to incorporate the COVID-19 outbreak into our analysis.

10. Descriptive analysis

10.1 Analysis flow

An overview of the stages of the analysis for the descriptive analyses are given below. The processes in the blue box will need to be repeated twice. Once for the registries whose data is available to be shared with the external analysts via the TREAT-NMD CDW, and separately for registries with restricted access (Germany & Austria). These indicator summaries will then be combined across all registries (where appropriate) to create the final results table.



10.2 Reporting statistics

In the descriptive statistics, there are two types of indicators, categorical and continuous.
When reporting categorical data, we will present the counts for each category of interest, and the percentages (n, %).

For the continuous indicators, we will report the mean and the standard deviation (mean, sd)In addition, medians and upper and lower quartiles will be provided for continuous indicators which

are reported at a per-registry level. However, it is not possible to provide medians and quartiles for aggregated registries as the analysis team will not have access to the record-level data for Germany, only predefined statistical summaries.
For example, we will be able to provide the mean and median age at death in months for individual registries (Spain etc.), but we can provide the mean only for “All registries”.

All numbers will be reported to one decimal place. Percentages will be calculated with missing values included in the denominator. Sample sizes will be reported.

To preserve patient confidentiality, cells with a number of patients or events below five will be merged with another relevant category.

10.3 Preliminary analysis

The preliminary analyses aims to assess the heterogeneity of management of care or reporting over time within each registry and between registries. All indicators will be stratified by registry and by SMA type. The study population will be all patients, across the entire study period.

The indicators and their related variables are given in Table 4.

Table 4: Indicators for Preliminary Analysis

ID	Description	Relevant columns in dataset	Time axis
1.01	Calendar year of registry entry (n, %)	Derived	No
1.02	Calendar year of death (n, %)	Date of death	No
1.03	Sex (n, %)	Sex	No
1.04	Class of age at symptom onset (n, %)	Derived from Symptom onset date	No
1.05	Best functional SMA status (n, %)	Derived from Motor ability	No
1.06	Best achieved motor milestone (n, %)	Motor ability	No
1.07	SMN1 gene mutation type (n, %)	SMN1 variant	No
1.08	Number of SMN2 copies (n, %)	SMN2 copy number	No
1.09	Methods used for genetic testing (n, %)	SMN1 testing method	No
1.10	Duration of follow up (registry entry to death, end of data or loss to follow-up) (mean, sd, median, IQR)	Derived	No

ID	Description	Relevant columns in dataset	Time axis
1.11	Duration of SMA (from onset of symptoms to death, end of data or loss to follow-up, in months) (mean, sd, median, IQR)	Derived	No
1.12	Duration between two consecutive visits collected in the registry (mean, sd, median, IQR)	Derived	No
1.13	Duration between genetic report date and registry entry (mean, sd, median, IQR)	Derived	No
1.14	Reason for genetic testing (n, %)	Screening	Calendar period
1.15	Age at onset of SMA symptoms (mean, sd, median, IQR)	Symptom onset date	Calendar period
1.16	Age at genetic report date (mean, sd, median, IQR)	Genetic report date	Calendar period
1.17	Age at registry entry (mean, sd, median, IQR)	Derived	Calendar period
1.18	Age at death (mean, sd, median, IQR)	Date of death	Calendar period
1.19	Lost to follow-up (n, %)	Derived	Calendar period
1.20	Treated with at least one DMT (n, %)	DMT	Calendar period
1.21	Treated with more than one DMT (n, %)	DMT	Calendar period
1.22	Treated with nusinersen (Spinraza®) (n, %)	DMT	Calendar period
1.23	Treated with onasemnogene abeparvovec-xioi (Zolgensma®) (n, %)	DMT	Calendar period
1.24	Treated with risdiplam (Evrysdi®) (n, %)	DMT	Calendar period
1.25	Invasive ventilation (n, %)	Invasive ventilation episode	Calendar period
1.26	Non-invasive ventilation (n, %)	Non-invasive ventilation episode	Calendar period
1.27	Feeding tube usage (n, %)	Feeding tube usage episode	Calendar period

ID	Description	Relevant columns in dataset	Time axis
1.28	Wheelchair usage (n, %)	Wheelchair usage episode	Calendar period
1.29	At least one reported measure by available motor function scale or test, and by at least one PRO (n, %)	Motor ability & PRO	Calendar period
1.30	At least three reported measure by available motor function scale or test, and by at least one PRO (n, %)	Motor ability & PRO	Calendar period
1.31	Available number of records of each motor function scale by patient (mean, sd, median, IQR)	Motor ability & PRO	Calendar period
1.32	Available number of records of each PRO by patients (mean, sd, median, IQR)	Motor ability & PRO	Calendar period

10.4 SMA natural history and disease progression

SMA natural history will be described in the untreated and treated cohorts according to the patient's current age. Statistics will be summarised over the entire study period. The results will be stratified in the following manner:

- SMA Type
  - DMT (including a category for overall untreated patients)
    - Class of age at symptom onset
    - SMN2 copy number
    - Functional status at age of symptom onset
    - Achieved motor milestone at age of symptom onset

The indicators and their related variables are given in Table 5.

Table 5: Indicators for the SMA natural history and disease progression analysis

ID	Description	Relevant columns in dataset	Time axis
2.01	Sex (n, %)	Sex	None

ID	Description	Relevant columns in dataset	Time axis
2.02	Registry (n, %)	Metadata	None
2.03	Age at symptom onset (mean, sd)	Derived from Symptom onset date	None
2.04	Reason for genetic testing (n, %)	Screening	None
2.05	Method used for genetic testing (n, %)	SMN1 testing method	None
2.06	SMN1 variant (n, %)	SMN1 variant	None
2.07	Functional status at genetic report date (n, %)	Derived from Motor ability episode	None
2.08	Achieved motor milestone at genetic report date (n, %)	Motor ability episode	None
2.09	Best functional status (n, %)	Derived from Motor ability episode	None
2.10	Best achieved motor milestone (n, %)	Motor ability episode	None
2.11	Best functional status before treatment (n, %)	Derived from Motor ability episode	None
2.12	Best functional status after treatment (n, %)	Derived from Motor ability episode	None
2.13	Best achieved motor milestone before treatment (n, %)	Motor ability episode	None
2.14	Best achieved motor milestone after treatment (n, %)	Motor ability episode	None
2.15	Height (mean, sd)	Height	Current Age
2.16	Weight (mean, sd)	Weight	Current Age
2.17	Age at first acquisition of -the best motor ability episodes (mean, sd)	Motor ability episode (early age record if multiple)	None

ID	Description	Relevant columns in dataset	Time axis
2.18	Age at first loss of the best motor ability episodes (mean, sd)	Motor ability episode (early age record if multiple)	None
2.19	Full-time or part time wheelchair use (n, %)	Wheelchair usage frequency	Current Age
2.20	Age at first full-time or part-time wheelchair usage (mean, sd)	Wheelchair usage frequency	None
2.21	No contracture, one contracture, more than one contractures (n, %)	Combination of 8 contracture variables	Current Age
2.22	Score for CHOP-INTEND at genetic report date (mean, sd)	Motor Measures	None
2.23	Best score for CHOP-INTEND (mean, sd)	Motor Measures	None
2.24	Most recent score for CHOP-INTEND (mean, sd)	Motor Measures	Current Age
2.25	Score for HFMS(-E) at genetic report date (mean, sd)	Motor Measures	None
2.26	Best score for HFMS(-E) (mean, sd)	Motor Measures	None
2.27	Most recent score for HFMS(-E) (mean, sd)	Motor Measures	Current Age
2.28	Score for RULM at genetic report date (mean, sd)	Motor Measures	None
2.29	Best score for RULM (mean, sd)	Motor Measures	None
2.30	Most recent score for RULM (mean, sd)	Motor Measures	Current Age
2.31	Score for HINE-2 at genetic report date (mean, sd)	Motor Measures	None
2.32	Best score for HINE-2 (mean, sd)	Motor Measures	None
2.33	Most recent score for HINE-2 (mean, sd)	Motor Measures	Current Age

ID	Description	Relevant columns in dataset	Time axis
2.34	Score for MFM32 at genetic report date (mean, sd)	Motor Measures	None
2.35	Best score for MFM32 (mean, sd)	Motor Measures	None
2.36	Most recent score for MFM32 (mean, sd)	Motor Measures	Current Age
2.37	Score for 6MWT at genetic report date (mean, sd)	Motor Measures	None
2.38	Best score for 6MWT (mean, sd)	Motor Measures	None
2.39	Most recent score for 6MWT (mean, sd)	Motor Measures	Current Age
2.40	Change between scores in HFSM-E in consecutive age classes (mean, sd)	Transformation of Motor Measures	Current Age
2.41	Change between scores in RULM in consecutive age classes (mean, sd)	Transformation of Motor Measures	Current Age
2.42	Change between scores in 6MWT in consecutive age classes (mean, sd)	Transformation of Motor Measures	Current Age
2.43	Age at report of (first) best CHOP-INTEND score (mean, sd)	Motor Measures	None
2.44	Age at report of (first) best HFMS(-E) score (mean, sd)	Motor Measures	None
2.45	Age at report of (first) best RULM right side score (mean, sd)	Motor Measures	None
2.46	Age at report of (first) best HINE-2 score (mean, sd)	Motor Measures	None
2.47	Age at report of (first) best MFM32 score (mean, sd)	Motor Measures	None
2.48	Age at report of (first) 6MWT best score (mean, sd)	Motor Measures	None

ID	Description	Relevant columns in dataset	Time axis
2.49	Ever diagnosed with scoliosis (n, %)	Scoliosis Diagnosis	Current Age
2.50	Cobb angle value <30°, 30-45°, >45° (n, %)	Convert numeric cobb angle into categories	Current Age
2.51	At least one use of spinal brace ever (n, %)	Rehabilitative Interventions	None
2.52	Surgery for scoliosis (n, %)	Scoliosis surgery performed	Current Age
2.53	Age at surgery for scoliosis (mean, sd)	Transformation of Scoliosis Surgery Date	None
2.54	Annual number of vertebral fracture by patient reported in cause of hospitalisation or as a comorbidity (mean, sd)	Hospitalisation acute reason code	None
2.55	Annual number of non-vertebral fractures by patient reported in cause of hospitalisation or as a comorbidity (mean, sd)	Hospitalisation acute reason code	None
2.56	Age at first reported vertebral fracture (mean, sd)	Hospitalisation acute reason code	None
2.57	Forced vital capacity percent (mean, sd)	Forced vital capacity percentage	Current Age
2.58	Forced vital capacity volume (n, %)	Forced vital capacity volume	Current Age
2.59	At least one episode of airway clearance assistance (n, %)	Airway Clearance Assistance	Current Age
2.60	At least one episode of any non-invasive ventilation (n, %)	Non-invasive ventilation episode	Current Age
2.61	At least one episode of full-time non-invasive ventilation (n, %)	Non-invasive ventilation episode	Current Age
2.62	At least one episode of part-time awake and sleeping non-invasive ventilation (n, %)	Non-invasive ventilation episode	Current Age

ID	Description	Relevant columns in dataset	Time axis
2.63	At least one episode of part-time sleeping non-invasive ventilation (n, %)	Non-invasive ventilation episode	Current Age
2.64	Age at start of first full-time non-invasive ventilation episode (mean, sd)	Non-invasive ventilation episode	None
2.65	At least one episode of any invasive ventilation (n, %)	Invasive ventilation episode	Current Age
2.66	At least one episode of full-time invasive ventilation (n, %)	Invasive ventilation episode	Current Age
2.67	At least one episode of part-time awake and sleeping invasive ventilation (n, %)	Invasive ventilation episode	Current Age
2.68	At least one episode of part-time sleeping invasive ventilation (n, %)	Invasive ventilation episode	Current Age
2.69	Age at start of first full-time invasive ventilation episode (mean, sd)	Invasive ventilation episode	None
2.70	P ulmonary infections reported in cause of hospitalisation or as a comorbidity (n, %)	Hospitalisation acute reason code	Current Age
2.71	At least one episode of respiratory physiotherapy (n, %)	Rehabilitative Interventions	None
2.72	At least one episode of feeding tube usage (n, %)	Feeding tube usage episode	Current Age
2.73	At least one episode of exclusive feeding tube usage (n, %)	Feeding tube usage episode	Current Age
2.74	At least one episode of supplementary feeding tube usage (n, %)	Feeding tube usage episode	Current Age

ID	Description	Relevant columns in dataset	Time axis
2.75	At least one gastronomy reported in cause of hospitalisation or as a comorbidity (n, %)	Hospitalisation acute reason code	Current Age
2.76	Age at first gastrostomy (mean, sd)	Hospitalisation admission date	None
2.77	At least one hospitalisation (n, %)	Hospitalisation admission date	Current Age
2.78	Annual number of hospitalisations (mean, sd)	Hospitalisation admission date	None
2.79	Event-free survival (death or permanent ventilation) (mean, sd)	Date of death or first full-time invasive ventilation or full-time non-invasive ventilation	None
2.80	Causes of death (n, %)	Cause of death code	None
2.81	Causes of hospitalisation (n, %)	Hospitalisation acute reason code	None
2.82	Incidence rate of each listed comorbidity	Comorbidity code	None
2.83	Score for Spain PROFuture Mobility and Independence PRO at genetic report date (mean, sd)	Patient-reported outcome measures	None
2.84	Best score for Spain PROFuture Mobility and Independence PRO (mean, sd)	Patient-reported outcome measures	None
2.85	Most recent score for Spain PROFuture Mobility and Independence PRO (mean, sd)	Patient-reported outcome measures	Current Age
2.86	Score for Belgium ACTIVLIM PRO at genetic report date (mean, sd)	Patient-reported outcome measures	None
2.87	Best score for Belgium ACTIVLIM PRO (mean, sd)	Patient-reported outcome measures	None
2.88	Most recent score for Belgium ACTIVLIM PRO (mean, sd)	Patient-reported outcome measures	Current Age

10.4.1 PROs

As indicated in Table 5 above, PRO scores from data contained in the Spanish (PROFuture) and Belgium (ACTIVLIM) registries will be included in the analyses of SMA natural history and disease progression. Upon data availability, PRO scores will be measured/reported: 1) at genetic report date, 2) as an overall best score, and 2) at the most recent score. Standard classifications will be used as reported in the literature for the PRO scores calculations. Specific registries' questionnaires used in the construction of each PRO score are included in the Appendix **IV & V**. Scores are generated by converting raw data into a linear measure of activity limitation using a Rasch model. PROFuture, used by the Spanish registry, has been validated in adults, but not yet children (5). ACTIVLIM has been validated in both children (6-15) and adults (16-80)(6).

10.5 Description of SMA healthcare management over time

Descriptive summary statistics of SMA diagnosis, healthcare management and its evolution over time will be studied in all patients, across the entire period and in the Calendar Period. The analysis in this section will be stratified in the following manner.

- Registry
    - SMA type
    - SMN2 copy number
    - Functional status at age of symptom onset

The indicators and their related variables are given in Table 6. Note that the population for this analysis varies between indicators.

Table 6: Description of SMA healthcare management over time

ID	Population	Description	Relevant columns in dataset	Time axis
3.01	All	SMN1 testing method (n, %)	SMN1 testing method	Calendar period
3.02	All	SMN2 testing method (n, %)	SMN2 copy number testing method	Calendar period
3.03	All	At least one DMT (n, %)	DMT	Calendar period
3.04	All	Taken the drugs listed as comedications at least once from registry entry (n, %)	Allopathic drug	Calendar period
3.05	All	Annual influenza vaccination (n, %)	Allopathic drug	Calendar period
3.06	All	At least one pneumococcal vaccination (n, %)	Allopathic drug	Calendar period

ID	Population	Description	Relevant columns in dataset	Time axis
3.07	All	Pneumococcal vaccination at least once every 5 years (n, %)	Allopathic drug	None
3.08	All	At least one episode of any ventilation (n, %)	Invasive ventilation episode or Non-invasive ventilation episode	Calendar period
3.09	All	At least one episode of feeding tube usage (n, %)	Feeding tube usage episode	Calendar period
3.10	All	At least one episode of wheelchair use (n, %)	Wheelchair usage episode	Calendar period
3.11	All	Age at first episode of any ventilation (invasive or non-invasive) (mean, sd, median, IQR)	Invasive ventilation episode or Non-invasive ventilation episode	Calendar period
3.12	All	Age at first episode of invasive ventilation (mean, sd, median, IQR)	Invasive ventilation episode	Calendar period
3.13	All	Age at first episode of feeding tube usage (mean, sd, median, IQR)	Feeding tube usage episode	Calendar period
3.14	All	Age at first episode of gastronomy (mean, sd, median, IQR)	Hospitalisation acute reason code	None
3.15	All	At least one episode of muscular physiotherapy ever (n, %)	Rehabilitative Interventions	None
3.16	All	At least one episode of respiratory physiotherapy ever (n, %)	Rehabilitative Interventions	None
3.17	All	At least one episode of contracture management using orthotics ever (n, %)	Rehabilitative Interventions	None
3.18	All	At least one episode of spinal brace ever (n, %)	Rehabilitative Interventions	None
3.19	All	At least one episode of speech therapy ever (n, %)	Rehabilitative Interventions	None
3.20	Treated	Age at first DMT (mean, sd)	DMT	Calendar period

ID	Population	Description	Relevant columns in dataset	Time axis
3.21	Treated	Patients who received more than one DMT (n,%)	DMT	Calendar period
3.22	Treated	Treated with nusinersen (Spinraza®) (n, %)	DMT	Calendar period
3.23	Treated	Treated with onasemnogene abeparvovec-xioi (Zolgensma®) (n, %)	DMT	Calendar period
3.24	Treated	Treated with risdiplam (Evrysdi®) (n, %)	DMT	Calendar period
3.25	Treated	Treated with nusinersen (Spinraza®) & onasemnogene abeparvovec-xioi (Zolgensma®) (n, %)	DMT	Calendar period
3.26	Treated	Treated with nusinersen (Spinraza®) & risdiplam (Evrysdi®) (n, %)	DMT	Calendar period
3.27	Treated	Treated with onasemnogene abeparvovec-xioi (Zolgensma®) & risdiplam (Evrysdi®) (n, %)	DMT	Calendar period
3.28	Treated	Treated with nusinersen (Spinraza®) & onasemnogene abeparvovec-xioi (Zolgensma®) & risdiplam (Evrysdi®) (n, %)	DMT	Calendar period
3.29	Treated	Age at initiation of nusinersen (Spinraza®) (mean, sd, median, IQR)	DMT	Calendar period
3.30	Treated	Age at initiation of onasemnogene abeparvovec-xioi (Zolgensma®) (mean, sd, median, IQR)	DMT	Calendar period
3.31	Treated	Age at initiation of risdiplam (Evrysdi®) (mean, sd)	DMT	Calendar period
3.32	onasemnogene abeparvovec	Adequate dose regarding weight at administration (n, %)	DMT dosage value	Calendar period

ID	Population	Description	Relevant columns in dataset	Time axis
	-xioi (Zolgensma®)			
3.33	onasemnogene abeparvovec -xioi (Zolgensma®)	Co-administration of corticosteroids (n, %)	DMT corticosteroid administration duration > 0	Calendar period
3.34	onasemnogene abeparvovec -xioi (Zolgensma®)	Anti-AAV9 antibody test before Zolgensam administration (n, %)	Anti-AAV9 antibody test date & DMT single administration date	Calendar period
3.35	onasemnogene abeparvovec -xioi (Zolgensma®)	Positive (>1:50) anti-AAV9 antibody test (n, %)	Anti AAV9 antibody test result	Calendar period
3.36	nusinersen (Spinraza®)	At least one adequate dose (12mg) (n, %)	DMT dosage value	Calendar period
3.37	nusinersen (Spinraza®)	Time between genetic report date and first administration (D0) (mean, sd)	DMT administration schedule deviation	None
3.38	nusinersen (Spinraza®)	Treatment duration defined as the time from initiation to last available administration date (discontinuation date, death, loss to follow-up, date of data-extraction if the last information indicates that nusinersen (Spinraza®) is ongoing) (mean, sd, median, IQR)	DMT episode	Calendar period
3.39	nusinersen (Spinraza®)	Ongoing nusinersen (Spinraza®) at their last reported dose (n, %)	DMT episode	Calendar period
3.40	nusinersen (Spinraza®)	Treatment discontinuation (n, %)	DMT episode	Calendar period
3.41	nusinersen (Spinraza®)	Reason for treatment discontinuation (n, %)	DMT stopping reason	Calendar period

ID	Population	Description	Relevant columns in dataset	Time axis
3.42	nusinersen (Spinraza®)	Treatment duration in patients with treatment discontinuation (mean, sd)	DMT episode	Calendar period
3.43	risdiplam (Evrysdi®)	At least one adequate dose regarding age and weight (n, %)	DMT dosage value	Calendar period
3.44	risdiplam (Evrysdi®)	Treatment duration defined as the time from initiation to last available administration date (discontinuation date, death, loss to follow-up, date of data-extraction if the last information indicates that risdiplam (Evrysdi®) is ongoing) (mean, sd, median, IQR)	DMT episode	Calendar period
3.45	risdiplam (Evrysdi®)	Ongoing risdiplam (Evrysdi®) at their last reported dose (n, %)	DMT episode	Calendar period
3.46	risdiplam (Evrysdi®)	Treatment discontinuation (n, %)	DMT episode	Calendar period
3.47	risdiplam (Evrysdi®)	Reason for treatment discontinuation (n, %)	DMT stopping reason	Calendar period
3.48	risdiplam (Evrysdi®)	Treatment duration in patients with treatment discontinuation (mean, sd)	DMT episode	Calendar period
3.49	Treated	At least one SAE reported in the registry related to any DMT (n, %)	Hospitalisation SAE or Comorbidity SAE	Calendar period
3.50	nusinersen (Spinraza®)	At least one SAE reported in the registry related to nusinersen (Spinraza®) (n, %)	Hospitalisation SAE or Comorbidity SAE	Calendar period
3.51	onasemnogene abeparvovec-xioi (Zolgensma®)	At least one SAE reported in the registry related to onasemnogene abeparvovec-xioi (Zolgensma®) (n, %)	Hospitalisation SAE or Comorbidity SAE	Calendar period
3.52	risdiplam (Evrysdi®)	At least one SAE reported in the registry related to risdiplam (Evrysdi®) (n, %)	Hospitalisation SAE or Comorbidity SAE	Calendar period

ID	Population	Description	Relevant columns in dataset	Time axis
3.53	Treated	Incidence rate of listed SAESI	Hospitalisation acute reason code matches defined ICD-10 list	Calendar period

The recommended dosing of onasemnogene abeparvovec-xioi (Zolgensma®) required for indicator 3.32 is given in Appendix I. The recommended dosing of risdiplam (Evrysdi®) required for indicator 3.43 is given in Appendix II.

11. Exploratory analyses

In addition to the descriptive analysis, we will further investigate objective two through exploratory comparative analysis. This analysis will investigate trends in post-SMA diagnosis outcomes with respect to the availability of DMTs using interrupted time series (ITS) analysis. ITS analysis is useful for investigating the effect of an intervention where randomisation is not suitable or possible.

11.1 Outcomes of interest

The three post-SMA diagnosis outcomes of interest are;

- Died in the quarter
- Have started using full-time ventilation (invasive or noninvasive) in that quarter
- Composite outcome; the total number of patients who have died in the quarter or started the use of full-time ventilation (invasive or noninvasive) in that quarter

These outcomes will be analysed separately - no efforts to model dependence between the three outcomes will be made.

11.2 Time-axis

Although the data is available to us monthly, the outcomes will be aggregated and analysed quarterly. Quarterly was chosen as it provides a good trade-off between maximising sample size per observation, whilst providing enough unique time points post-interruption to fit the model correctly. ITS requires a minimum of 8 observations (7) before and after the intervention to have sufficient power to estimate the regression coefficients.

11.3 Choice of the interruption points

For each outcome, two interruption points will be considered, relating to the EU marketing authorisation dates for Spinraza® and Zolgensma®. Since Evrysdi® was only recently authorised (March 2021), there will not be enough observations post-intervention to consider this interruption point. The interruption points have been chosen at the start of the next quarter following the market authorisation. For example, Spinraza® was authorised at the end of May 2017, we will consider the interruption point to be 01/07/2017 (the start of the next quarter.) The market authorisation dates and related interruption points are detailed in Table 7.

Table 7: Market authorisation dates for DMTs

DMT	Date of issue of marketing authorisation valid throughout the European Union	Interruption point
Spinraza®	30/05/2017	01/07/2017
Zolgensma®	18/05/2020	01/07/2020
Evrysdsi®	26/03/2021	NA

One question might be - why use a single intervention point of the EU market authorisation, rather than considering the availability of DMT per country of registry separately? A multiple baseline ITS approach was initially considered, allowing the interruption to vary across registries and considering the outcomes before and after a general “Time 0” rather than using calendar time.

However, due to the possible different rollout lag times across registries and the potential complications of COVID-19, it was decided to not allow different interruption points for different registries. Instead we will use the same, real, calendar time point for all registries. These are defined in Table 7.

11.4 Population of interest

For each analysis, the population will be all patients (regardless of treatment), who have SMA type 1 or 2. By restricting the population to just patients with the most severe type of SMA, we are ensuring that the underlying populations being compared share similar characteristics.

Moreover, given the severity of these two types of SMA, we also assume that uptake of newly available therapy options will be rapid after their market approval.

A natural question might be - why not run the analysis for the Spinraza® interruption point on just the population of patients treated with Spinraza®? The main reason this is not possible, is because the average life expectancy of patients with SMA type 1 or 2 was very short prior to the availability of DMTs. This means all patients who were in the registry 18 months or earlier than the introduction of Spinraza® will have likely died before getting the opportunity to use Spinraza® and therefore be excluded from the analysis. This would mean that we do not have the required number of observations before the interruption point to perform the modelling.
It would also be challenging to model the switching of DMTs appropriately within this framework. For these reasons, we will perform the analysis on the population of all patients, regardless of treatment.

11.5 Statistical Model

A Poisson GLM with log link function will be used to model the rates of the occurrence of each of the specified outcomes. We use a Poisson model as this is the classic choice for count data. We will use the base R function glm() to fit the models.
For each of the three outcomes, the linear predictor will be of the form

$$\log(\mu(t)) = \eta(t) = \beta_0 + \beta_1 t + (\beta_3 + \beta_4 t) \times I(t > t') .$$

Where $\mu(t)$ is the expected number of events at time t, β terms are unknown coefficients, t' is the interruption point and $I(t > t')$ is an indicator function returning 1 whenever $t > t'$ and 0 otherwise. $\mu(t)$ can be interpreted as the expected number of patients who died/ventilated/both in each quarter.

11.6 Model adequacy

Various checks will be performed to assess the appropriateness of the Poisson ITS model. The checks will answer the following assumptions

1. Is the Poisson model appropriate?
2. Is the choice of linear predictor appropriate?

For assumption 1 we will run the following diagnostic tests and, if the test indicates a potential violation of the assumption, investigate the potential alternative models as indicated in Table 8:

Table 8: Diagnostic tests and their implications

Diagnostic test	What is the test investigating?	Alternative course of action
Residual plot: plot $\hat{\eta}(t)$ against estimated residuals $\hat{\varepsilon}$ - look for any patterns in the plot	Whether the linear predictor is of an appropriate form.	Consider building in additional terms (e.g. quadratic) or transforming time to e.g. log(time) in the linear predictor.
Residual plot: plot $\hat{\eta}(t)$ against estimated residuals $\hat{\varepsilon}$ - look for any change in the variance of $\hat{\varepsilon}$ when plotted against $\hat{\eta}(t)$	Whether the estimated variance of the counts is reasonable. The mean and variance of a Poisson distribution are equal - this needs to be checked against the data.	Fit alternative models. As above, try zero inflated models or a different linear predictor. We can also try fitting a negative binomial model to account for overdispersion.
Test for over/under dispersion with dispersiontest() from the {AER} package.	Formalises the graphical check for over/under dispersion.	As above; investigate alternative models.
Check for zero inflation by fitting a zero inflated Poisson (ZIP)model. This can be done with the zeroinfl() function from {pscl}.	We will compare the fit of a standard Poisson model to a ZIP model via AIC. If the AIC of ZIP model is smaller than the standard Poisson, this suggests zero inflation is present.	Use the fitted zero-inflated model.
Check for autocorrelation via an autocorrelation plot	Investigating as to whether autocorrelation is present in the residuals of the time series. Autocorrelation will be deemed present if a statistically significant (at 5% level) is present in the plot. However, if the autocorrelation is mild, we may be able to ignore it.	Fit an alternative model such as an INGARCH(p, q) model. This will be possible for Poisson and Negative Binomial models, but not ZIP models.

11.7 Possible Limitations

Although ITS has many strengths, there are important limitations to be aware of. Firstly, estimating the level and slope parameters requires a minimum of 8 observations (1) before and after the intervention to have sufficient power to estimate the regression coefficients. Lack of randomisation means that drawing definitive answers about the effects of the treatment is limited. ITS cannot be used to make inferences about individual-level outcomes when the series is a set of population counts.

11.8 Results

The analysis will be performed for each of the six models:

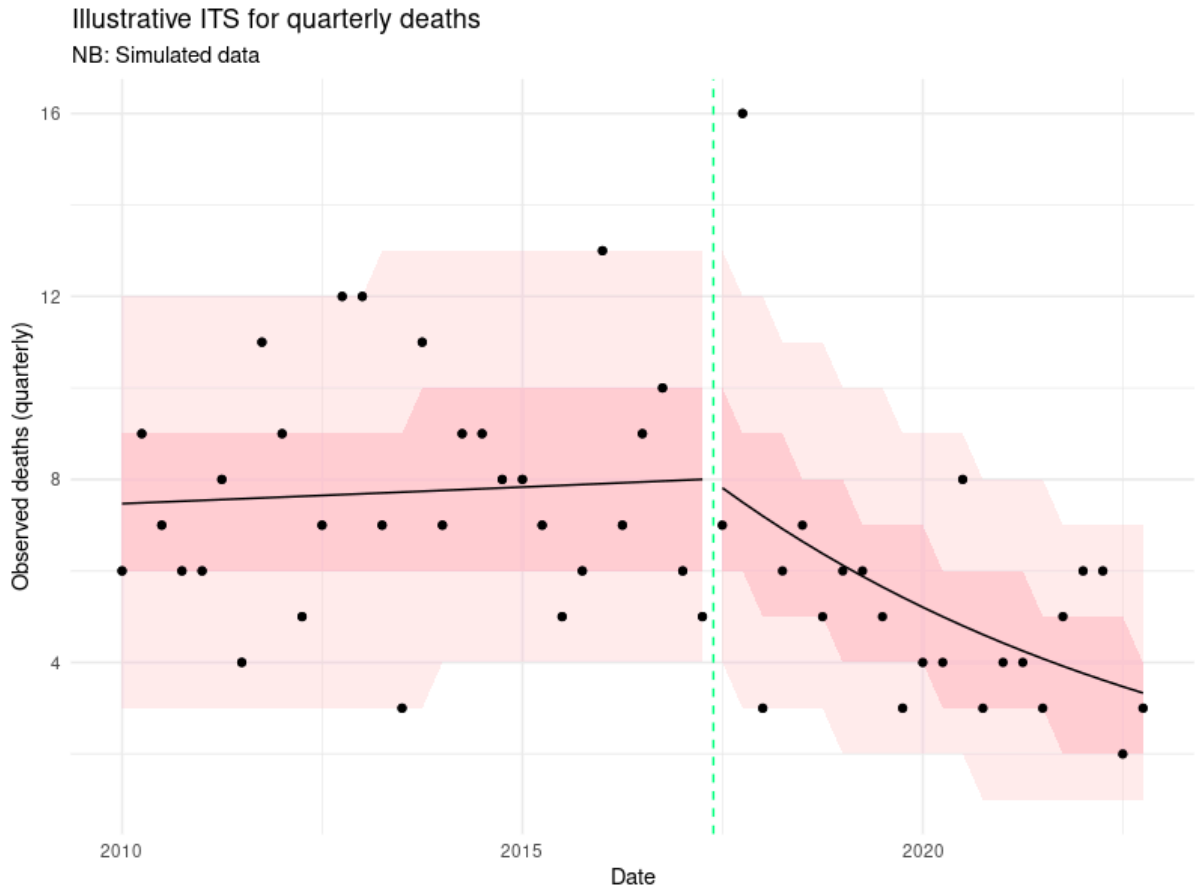
Outcome	**Interruption point**
Died in the quarter	01/07/2017
Started using full-time ventilation (invasive or noninvasive) in that quarter	01/07/2017
Composite outcome; the total number of patients who have died in the quarter or started the use of full-time ventilation (invasive or noninvasive) in that quarter	01/07/2017
Died in the quarter	01/07/2020
Started using full-time ventilation (invasive or noninvasive) in that quarter	01/07/2020
Composite outcome; the total number of patients who have died in the quarter or started the use of full-time ventilation (invasive or noninvasive) in that quarter	01/07/2020

For each of the above six scenarios we will report:

- The fitted model formulation
- A table of coefficients
- A plot of the fitted regression model pre/post intervention with 80% and 95% prediction intervals. See below figure for a simulated example.

The table of coefficients will report point estimates, 95% confidence intervals and p-values for the following parameters of the linear predictor:

- Slope parameter pre-interruption
- Intercept parameter pre-interruption
- Slope adjustment post-interruption
- Intercept adjustment post-interruption



References

1. Pazzagli, L., Linder, M., Zhang, M., Vago, E., Stang, P., Myers, D., Andersen, M., & Bahmanyar, S. (2018). Methods for time-varying exposure related problems in pharmacoepidemiology: An overview. Pharmacoepidemiology and drug safety, 27(2), 148–160. https://doi.org/10.1002/pds.4372
2. Pazzagli, L, Linder, M, Reutfors, J, Brandt, L. The use of uncertain exposure—A method to define switching and add-on in pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2022; 31(1): 28- 36. doi:10.1002/pds.5363

3. Abrahami, D., Yin, H., Yu, O. H. Y., Pollak, M. N., & Azoulay, L. (2018). Incretin-based Drugs and the Incidence of Colorectal Cancer in Patients with Type 2 Diabetes. Epidemiology (Cambridge, Mass.), 29(2), 246–253. https://doi.org/10.1097/EDE.0000000000000793
4. Klil-Drori, A. J., Coulombe, J., Suissa, S., Hirsch, A., & Tagalakis, V. (2018). Temporal trends in outpatient management of incident pulmonary embolism and associated mortality. Thrombosis research, 161, 111–116. https://doi.org/10.1016/j.thromres.2017.10.026
5. M.C. Domine, M.G. Cattinari, M. de Lemus, I.P. Castellano, N.C. Ñungo-Garzón, T. Sevilla-Mantecón, J.F. Vázquez-Costa (2022) Physical fatigue and perceived fatigability in adolescents and adults with spinal muscular atrophy: A pilot study. Neurology Perspectives 2: 199-208
6. Vandervelde L, Van den Bergh PY, Goemans N, Thonnard JL. ACTIVLIM: a Rasch-built measure of activity limitations in children and adults with neuromuscular disorders. Neuromuscul Disord. 2007 Jun;17(6):459-69. doi: 10.1016/j.nmd.2007.02.013. Epub 2007 Apr 11. PMID: 17433675.
7. Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. Acad Pediatr. 2013 Nov-Dec;13(6 Suppl):S38-44. doi: 10.1016/j.acap.2013.08.002. PMID: 24268083

Appendix I. Recommended dosing of onasemnogene abeparvovec-xioi (Zolgensma®)

Table 1 Recommended dosing based on patient body weight

Patient weight range (kg)	Dose (vg)	Total volume of dose [a] (mL)
2.6 – 3.0	3.3×10^{14}	16.5
3.1 – 3.5	3.9×10^{14}	19.3
3.6 – 4.0	4.4×10^{14}	22.0
4.1 – 4.5	5.0×10^{14}	24.8
4.6 – 5.0	5.5×10^{14}	27.5
5.1 – 5.5	6.1×10^{14}	30.3
5.6 – 6.0	6.6×10^{14}	33.0
6.1 – 6.5	7.2×10^{14}	35.8
6.6 – 7.0	7.7×10^{14}	38.5
7.1 – 7.5	8.3×10^{14}	41.3
7.6 – 8.0	8.8×10^{14}	44.0
8.1 – 8.5	9.4×10^{14}	46.8
8.6 – 9.0	9.9×10^{14}	49.5
9.1 – 9.5	1.05×10^{15}	52.3
9.6 – 10.0	1.10×10^{15}	55.0
10.1 – 10.5	1.16×10^{15}	57.8
10.6 – 11.0	1.21×10^{15}	60.5
11.1 – 11.5	1.27×10^{15}	63.3
11.6 – 12.0	1.32×10^{15}	66.0
12.1 – 12.5	1.38×10^{15}	68.8
12.6 – 13.0	1.43×10^{15}	71.5
13.1 – 13.5	1.49×10^{15}	74.3
13.6 – 14.0	1.54×10^{15}	77.0
14.1 – 14.5	1.60×10^{15}	79.8
14.6 – 15.0	1.65×10^{15}	82.5
15.1 – 15.5	1.71×10^{15}	85.3
15.6 – 16.0	1.76×10^{15}	88.0
16.1 – 16.5	1.82×10^{15}	90.8
16.6 – 17.0	1.87×10^{15}	93.5
17.1 – 17.5	1.93×10^{15}	96.3
17.6 – 18.0	1.98×10^{15}	99.0
18.1 – 18.5	2.04×10^{15}	101.8
18.6 – 19.0	2.09×10^{15}	104.5
19.1 – 19.5	2.15×10^{15}	107.3
19.6 – 20.0	2.20×10^{15}	110.0
20.1 – 20.5	2.26×10^{15}	112.8
20.6 – 21.0	2.31×10^{15}	115.5

[a] NOTE: Number of vials per kit and required number of kits is weight-dependent. Dose volume is calculated using the upper limit of the patient weight range.

Appendix II. Recommended dosing of risdiplam (Evrysdi®)

Age and body weight	*Recommended daily dose*
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

Appendix III. ICD Codes

Comorbidity	ICD-10 Code	ICD-10 Description
Thrombocytopenia and coagulation abnormalities	D65	Disseminated intravascular coagulation [defibration syndrome]
	D66	Hereditary factor VIII deficiency
	D67	Hereditary factor IX deficiency
	D68	Other coagulation defects
	D69	Purpura and other haemorrhagic conditions
Renal toxicity	N17.0, N17.1, N17.2, N17.3, N17.8, N17.9	Acute kidney failure
	N19	Unspecified kidney failure
	N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9	Unspecified nephritic syndrome
	N06.0, N06.1, N06.2, N06.3, N06.4, N06.5, N06.6, N06.7, N06.8, N06.9	Isolated proteinuria with specified morphological lesion
	N14.0, N14.1, N14.2, N14.3, N14.4	Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions
	N15.0, N15.1, N15.8, N15.9	Other renal tubulo-interstitial diseases
	R34 only	Anuria and oliguria (R34 only)
	R94.0, R94.1, R94.2, R94.3, R94.4, R94.5, R94.6, R94.7, R94.8	Abnormal results of function studies
Hydrocephalus	G91.0, G91.1, G91.2, G91.3, G91.8, G91.9	Hydrocephalus
	P91.7	Acquired hydrocephalus of newborn
	Q03.0, Q03.1, Q03.8, Q03.9	Congenital hydrocephalus
	P37.1	Congenital toxoplasmosis – Hydrocephalus due to congenital toxoplasmosis
Meningitis	G00.0, G00.1, G00.2, G00.3, G00.8, G00.9	Bacterial meningitis, not elsewhere classified
	G01	Meningitis in bacterial diseases classified elsewhere
	G02	Meningitis in other infectious and parasitic diseases classified elsewhere
	G03.8, G03.9	Meningitis due to other and unspecified causes
	A17.0	Tuberculous meningitis
	A20.3	Plague meningitis
	A39.0	Meningococcal meningitis

	A87.0, A87.1, A87.2, A87.8, A87.9	Viral meningitis
	B00.3	Herpesviral meningitis
	B01.0	Varicella meningitis
	B02.1	Zoster meningitis
	B26.1	Mumps meningitis
	B37.5	Candidal meningitis
	B38.4	Coccidioidomycosis meningitis
	B45.1	Cerebral cryptococcosis
	A01.01, A02.21, A27.81, A32.11, B06.02, B27.02, B27.12, B27.82, B27.92	Other meningtis related ICD-10-CM codes
Hypersensitivity reactions	T78.4	Allergy, unspecified
Cutaneous vasculitis	M31.0	Hypersensitivity angiitis
Hepatotoxicity	K71, K71.0, K71.1, K71.2, K71.3, K71.4, K71.5, K71.6, K71.7, K71.8, K71.9	Toxic liver disease
	K72.0, K72.1, K72.9	Hepatic failure, not elsewhere classified
	K75.2	Nonspecific reactive hepatitis
	K75.9	Inflammatory liver disease, unspecified
	R17.0, R17.9	Hyperbilirubinaemia, with or without jaundice, not elsewhere classified
Cardiac adverse event	I50.1, I50.2, I50.3, I50.4, I50.8, I50.9,	Heart failure
Osteoporosis	M80.0, M80.1, M80.2, M80.3, M80.4, M80.5, M80.8, M80.9,	Osteoporosis with pathological fracture
	M81.0, M81.1, M81.2, M81.3, M81.4, M81.5, M81.6, M81.8, M81.9	Osteoporosis without pathological fracture
	M82.0, M82.1, M82.8	Osteoporosis in diseases classified elsewhere
Fractures	S02.0, S02.1, S02.2, S02.3, S02.4, S02.5, S02.6, S02.7, S02.8, S02.9	Fracture of skull and facial bones
	S12.0, S12.1, S12.2, S12.3, S12.4, S12.5, S12.6, S12.7, S12.8, S12.9	Fracture of neck
	S22.0, S22.1, S22.2, S22.3, S22.4, S22.5, S22.8, S22.9	Fracture of rib(s), sternum and thoracic spine
	S32.0, S32.1, S32.2, S32.3, S32.4, S32.5, S32.7, S32.8	Fracture of lumbar spine and pelvis
	S42.0, S42.1, S42.2, S42.3, S42.4, S42.7, S42.8, S42.9	Fracture of shoulder and upper arm

	S52.0, S52.1, S52.2, S52.3, S52.4, S52.5, S52.6, S52.7, S52.8, S52.9	Fracture of forearm
	S62.0, S62.1, S62.2, S62.3, S62.4, S62.5, S62.6, S62.7, S62.8	Fracture at wrist and hand level
	S72.0, S72.1, S72.2, S72.3, S72.4, S72.7, S72.8, S72.9	Fracture of femur
	S82.0, S82.1, S82.2, S82.3, S82.4, S82.5, S82.6, S82.7, S82.8, S82.9	Fracture of lower leg, including ankle
	S92.0, S92.1, S92.2, S92.3, S92.4, S92.5, S92.7, S92.8, S92.9	Fracture of foot, except ankle
	T02.0, T02.1, T02.2, T02.3, T02.4, T02.5, T02.6, T02.7, T02.8, T02.9	Fractures involving multiple body regions
	T08	Fracture of spine, level unspecified
	T10	Fracture of upper limb, level unspecified
	T12	Fracture of lower limb, level unspecified
	T14.2	Fracture of unspecified body region
Pulmonary infections (Bronchopulmonary infections)	J09	Influenza due to identified zoonotic or pandemic influenza virus
	J10.0, J10.1, J10.8	Influenza due to identified seasonal influenza virus
	J11.0, J11.1, J11.8	Influenza, virus not identified
	J12.0, J12.1, J12.2, J12.3, J12.8, J12.9	Viral pneumonia, not elsewhere classified
	J13	Pneumonia due to Streptococcus pneumoniae
	J14	Pneumonia due to Haemophilus influenzae
	J15.0, J15.1, J15.2, J15.3, J15.4, J15.5, J15.6, J15.7, J15.8, J15.9	Bacterial pneumonia, not elsewhere classified
	J16.0, J16.8	Pneumonia due to other infectious organisms, not elsewhere classified
	J17.0, J17.1, J17.2, J17.3, J17.8	Pneumonia in diseases classified elsewhere
	J18.0, J18.1, J18.2, J18.8, J18.9	Pneumonia, organism unspecified
	J20.0, J20.1, J20.2, J20.3, J20.4, J20.5, J20.6, J20.7, J20.8, J20.9,	Acute bronchitis
	J21.0, J21.1, J21.8, J21.9	Acute bronchiolitis
	J22	Unspecified acute lower respiratory infection
	A20.2	Pneumonic plague
	A21.2	Pulmonary tularemia
	A31.0	Pulmonary mycobacterial infection
	A43.0	Pulmonary nocardiosis
	A48.1	Legionnaires' disease
	B01.2	Varicella pneumonia

	B05.2	Measles complicated by pneumonia
	B25.0	Cytomegaloviral pneumonitis
	B39.0	Acute pulmonary histoplasmosis capsulati
	B37.1	Pulmonary candidiasis
	B59	Pneumocystosis
	B38.0	Acute pulmonary coccidioidomycosis
	B38.2	Pulmonary coccidioidomycosis, unspecified
	B58.3	Pulmonary toxoplasmosis
	J85.1	Abscess of lung with pneumonia
	A01.03, A02.22, A37.01, A37.11, A37.81, A37.91, J15.211, J15.212, J15.29, B06.81, J10.00, J10.08, J11.00, J11.08, J12.81, J12.89, B77.81	Other Pulmonary related ICD-10-CM codes
Sleep apnea	G47.3	Sleep apnoea
	P28.3	Primary sleep apnoea of newborn
Pneumothorax	J93.0, J93.1, J93.8, J93.9	Pneumothorax
	P25.1	Pneumothorax originating in the perinatal period
Atrial or ventricular defect	Q21.0	Congenital malformations of cardiac septa
Diabetes	E10.1,E10.2, E10.3, E10.4, E10.5, E10.6, E10.8, E10.9	Type 1 diabetes mellitus
	E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.8, E11.9	Type 2 diabetes mellitus
	E12	Malnutrition-related diabetes mellitus
	E13.0, E13.1, E13.2, E13.3, E13.4, E13.5, E13.6, E13.8, E13.9	Other specified diabetes mellitus
	E14	Unspecified diabetes mellitus
Vertebral fracture	T08	Fracture of spine, level unspecified
	S12.0, S12.1, S12.2, S12.3, S12.4, S12.5, S12.6, S12.7, S12.8, S12.9	Fracture of neck
	S22.0, S22.1, S22.2, S22.3, S22.4, S22.5, S22.8, S22.9	Fracture of thoracic vertebra
	S22.1	Multiple fractures of thoracic spine
	S32.0	Fracture of lumbar vertebra
	S32.1	Fracture of sacrum
	S32.2	Fracture of coccyx
	S02.0, S02.1, S02.2, S02.3, S02.4, S02.5, S02.6, S02.7, S02.8, S02.9	Fracture of skull and facial bones
	S22.2, S22.3, S22.4, S22.5, S22.8, S22.9	Fracture of rib(s), sternum and thoracic spine

	S32.3, S32.4, S32.5, S32.6, S32.8, S32.9	Fracture of lumbar spine and pelvis
	S42.0, S42.1, S42.2, S42.3, S42.4, S42.7, S42.8, S42.9	Fracture of shoulder and upper arm
	S52.0, S52.1, S52.2, S52.3, S52.4, S52.5, S52.6, S52.7, S52.8, S52.9	Fracture of forearm
	S62.0, S62.1, S62.2, S62.3, S62.4, S62.5, S62.6, S62.7, S62.8	Fracture at wrist and hand level
	S72.0, S72.1, S72.2, S72.3, S72.4, S72.7, S72.8, S72.9	Fracture of femur
	S82.0, S82.1, S82.2, S82.3, S82.4, S82.5, S82.6, S82.7, S82.8, S82.9	Fracture of lower leg, including ankle
	S92.0, S92.1, S92.2, S92.3, S92.4, S92.5, S92.7, S92.8, S92.9	Fracture of foot, except ankle
	T02.0, T02.1, T02.2, T02.3, T02.4, T02.5, T02.6, T02.7, T02.8, T02.9	Fractures involving multiple body regions
	T10	Fracture of upper limb, level unspecified
	T12	Fracture of lower limb, level unspecified
	T14.2	Fracture of unspecified body region
Bronchopulmonary infections	Combined with pulmonary infections as Prof Servais confirmed there is no difference.	
Gastrostomy	Z93.1	Gastrostomy status

Appendix IV. PRO Questionnaire: Spain

CUESTIONARIO "FATIGA FÍSICA Y FATIGABILIDAD PERCIBIDA" DE FUNDAME

Fatiga física y Resistencia

Durante el último mes:	Nunca o casi nunca	A veces	Siempre o casi siempre
1. ¿Ha necesitado descansar a menudo durante el día o por periodos de tiempo largos por sentirse cansado?			
2. ¿Ha necesitado seleccionar sus actividades durante el día para poder hacer lo que querías?			
3. ¿Ha tenido problemas para mantener la postura durante el día, por sentirse cansado?			
4. ¿Ha habido actividades que ha podido realizar por la mañana y que no ha podido realizar por la tarde o por la noche (la energía se ha ido agotando a lo largo del día)? *			
5. Si ha realizado un esfuerzo mayor de lo habitual, ¿el cansancio le dura hasta el día siguiente?			

Figura 1. Cuestionario "Fatiga física y Resistencia"

Fatigabilidad percibida en miembros superiores

Durante el último mes, ¿cuánta dificultad ha tenido en completar con éxito las siguientes actividades que incluyen movimientos repetitivos y continuados?	Imposible	Difícil	Me cuesta un poco	Fácil
6. Tomar notas en papel				
7. Mandar mensajes de texto				
8. Peinarse				
9. Comer solo				
10. Cepillarse los dientes				

Figura 2. Cuestionario "Fatigabilidad percibida en miembros superiores"

Fatigabilidad percibida en musculatura axial para pacientes no ambulantes

Durante el último mes, ¿ha podido hacer los siguientes movimientos varias veces con la misma fuerza y rapidez?	Imposible	Difícil	Me cuesta un poco	Fácil
11. Enderezarse en el asiento cuando se tiene la cabeza apoyada				
12. Mantener la posición de la cabeza				
**Repetir movimientos concretos cuando se está jugando.				

Figura 3. Cuestionario "Fatigabilidad percibida en musculatura axial para pacientes no ambulantes".

Fatigabilidad percibida en miembros inferiores para pacientes ambulantes

Durante el último mes, ¿ha podido hacer los siguientes movimientos varias veces con la misma fuerza y rapidez?	Imposible	Difícil	Me cuesta un poco	Fácil
13. Subir un tramo entero de escaleras				
14. Mantener el ritmo cuando anda				
15. Levantarse del asiento o de la cama				
16. Entrar o salir del coche				

Figura 4. Cuestionario "Fatigabilidad percibida en miembros inferiores para pacientes ambulantes".

Appendix V. PRO Questionnaire: Belgium

Université catholique de Louvain
Unité de Réadaptation et de Médecine Physique

INSTRUCTIONS FOR THE ACTIVLIM QUESTIONNAIRE

The ACTIVLIM questionnaire

The ACTIVLIM questionnaire was developed as a measure of activity limitations in children and adults with **neuromuscular disorders** (Vandervelde et al, Neuromuscul Disord, 2007). Activity limitations are defined as difficulties a patient may have in executing activities of daily living. The questionnaire includes 22 items that are daily activities. Among these 22 items, 4 are specifically designed for child evaluation, 4 for adult evaluation, and the remaining 14 items are common to all patients. ACTIVLIM was built either on the perception of the parents of the affected children or on the perception of the adult patients themselves. This perception concerns the difficulty in performing each activity of the questionnaire. The 22 items of ACTIVLIM defined a valid, reliable and reproducible scale. ACTIVLIM was originally developed using the Rasch measurement model. It allows to convert ordinal scores into linear measures located on a unidimensional scale.

Evaluation

*For a **child** evaluation (between 6 and 15 years-old):*
The **parents** fill in the questionnaire by estimating their child's difficulty or ease in performing each activity.

*For an **adult** evaluation (more than 16 years-old):*
The **patient** fills in himself the questionnaire by estimating their own difficulty or ease in performing each activity.

The activities should be done:

- **Without technical or human help** (even if the patient actually uses help in daily life)
- Irrespective the limb(s) actually used to achieve the activity
- Whatever the strategy used (any compensation is allowed)

Three responses are presented. These assess the perception of the difficulty/ease depending on whether the activity is "impossible", "difficult" or "easy". Activities not attempted in the last 3 months are not scored and entered as missing responses (to tick the question mark).

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium.
www.rehab-scales.org

Université catholique de Louvain
Unité de Réadaptation et de Médecine Physique

So, for any activity, the four potential answers are:

- **Impossible:** The patient is unable to perform the activity without using any other help**.**
- **Difficult:** The patient is able to perform the activity without any help but experiences some difficulty.
- **Easy:** The patient is able to perform the activity without any help and experiences no difficulty.
- **Question mark:** The patient cannot estimate the difficulty of the activity because he has never done the activity.

Watch out!! If the activity was never attempted because it is impossible, then it must be scored "impossible" rather than "question mark".

Activities order

The activities of the ACTIVLIM questionnaire are presented in a random order to avoid any systematic effect. Ten different random orders of presentation are used. The rater must select the next one of the 10 orders for each new assessment, no matter which patient is tested.

Package content

- 1 instruction sheet.
- Testing forms of ACTIVLIM in 10 random orders (1 sheet for each)

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium.
www.rehab-scales.org

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

	How difficult are the following activities?	Impossible	Difficult	Easy	?
1	Putting on a T-shirt				
2	Washing one's upper body				
3	Dressing one's lower body				
4	Taking a shower				
5	Sitting on the toilet				
6	Taking a bath				
7	Walking dowstairs				
8	Stepping out of a bath tub				
9	Opening a door				
10	Walking outdoors on level ground				
11	Washing one's face				
12	Hanging up a jacket on a hatstand				
13	Wiping one's upper body				
14	Walking upstairs				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Carrying a heavy load	A				
16	Getting into a car	A				
17	Standing for a long time (± 10 min)	A				
18	Walking more than 1 kilometre	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Closing a door	C				
20	Hopping on one foot	C				
21	Putting on a backpack	C				
22	Running	C				

Order 1

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

How difficult are the following activities?		Impossible	Difficult	Easy	?
1	Stepping out of a bath tub				
2	Hanging up a jacket on a hatstand				
3	Wiping one's upper body				
4	Taking a shower				
5	Putting on a T-shirt				
6	Dressing one's lower body				
7	Sitting on the toilet				
8	Walking upstairs				
9	Walking outdoors on level ground				
10	Washing one's face				
11	Walking dowstairs				
12	Taking a bath				
13	Opening a door				
14	Washing one's upper body				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Standing for a long time (± 10 min)	A				
16	Walking more than 1 kilometre	A				
17	Getting into a car	A				
18	Carrying a heavy load	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Running	C				
20	Closing a door	C				
21	Putting on a backpack	C				
22	Hopping on one foot	C				

Order 2

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

	How difficult are the following activities?	Impossible	Difficult	Easy	?
1	Hanging up a jacket on a hatstand				
2	Opening a door				
3	Wiping one's upper body				
4	Dressing one's lower body				
5	Stepping out of a bath tub				
6	Taking a shower				
7	Washing one's upper body				
8	Walking upstairs				
9	Sitting on the toilet				
10	Taking a bath				
11	Putting on a T-shirt				
12	Washing one's face				
13	Walking outdoors on level ground				
14	Walking dowstairs				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Getting into a car	A				
16	Carrying a heavy load	A				
17	Walking more than 1 kilometre	A				
18	Standing for a long time (± 10 min)	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Hopping on one foot	C				
20	Closing a door	C				
21	Putting on a backpack	C				
22	Running	C				

Order 3

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

	How difficult are the following activities?	Impossible	Difficult	Easy	?
1	Wiping one's upper body				
2	Stepping out of a bath tub				
3	Walking dowstairs				
4	Opening a door				
5	Putting on a T-shirt				
6	Sitting on the toilet				
7	Washing one's upper body				
8	Taking a bath				
9	Taking a shower				
10	Dressing one's lower body				
11	Walking upstairs				
12	Walking outdoors on level ground				
13	Washing one's face				
14	Hanging up a jacket on a hatstand				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Carrying a heavy load	A				
16	Getting into a car	A				
17	Walking more than 1 kilometre	A				
18	Standing for a long time (± 10 min)	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Running	C				
20	Closing a door	C				
21	Putting on a backpack	C				
22	Hopping on one foot	C				

Order 4

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

	How difficult are the following activities?	Impossible	Difficult	Easy	?
1	Sitting on the toilet				
2	Dressing one's lower body				
3	Stepping out of a bath tub				
4	Taking a shower				
5	Walking upstairs				
6	Taking a bath				
7	Hanging up a jacket on a hatstand				
8	Walking outdoors on level ground				
9	Washing one's face				
10	Walking dowstairs				
11	Putting on a T-shirt				
12	Opening a door				
13	Washing one's upper body				
14	Wiping one's upper body				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Walking more than 1 kilometre	A				
16	Carrying a heavy load	A				
17	Getting into a car	A				
18	Standing for a long time (± 10 min)	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Hopping on one foot	C				
20	Running	C				
21	Putting on a backpack	C				
22	Closing a door	C				

Order 5

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

	How difficult are the following activities?	Impossible	Difficult	Easy	?
1	Putting on a T-shirt				
2	Walking dowstairs				
3	Taking a shower				
4	Sitting on the toilet				
5	Stepping out of a bath tub				
6	Wiping one's upper body				
7	Washing one's upper body				
8	Washing one's face				
9	Opening a door				
10	Dressing one's lower body				
11	Hanging up a jacket on a hatstand				
12	Walking outdoors on level ground				
13	Taking a bath				
14	Walking upstairs				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Standing for a long time (± 10 min)	A				
16	Carrying a heavy load	A				
17	Walking more than 1 kilometre	A				
18	Getting into a car	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Hopping on one foot	C				
20	Putting on a backpack	C				
21	Closing a door	C				
22	Running	C				

Order 6

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

How difficult are the following activities?		Impossible	Difficult	Easy	?
1	Wiping one's upper body				
2	Taking a bath				
3	Washing one's upper body				
4	Washing one's face				
5	Dressing one's lower body				
6	Putting on a T-shirt				
7	Sitting on the toilet				
8	Walking outdoors on level ground				
9	Walking dowstairs				
10	Opening a door				
11	Hanging up a jacket on a hatstand				
12	Walking upstairs				
13	Stepping out of a bath tub				
14	Taking a shower				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Getting into a car	A				
16	Walking more than 1 kilometre	A				
17	Carrying a heavy load	A				
18	Standing for a long time (± 10 min)	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Hopping on one foot	C				
20	Putting on a backpack	C				
21	Running	C				
22	Closing a door	C				

Order 7

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

	How difficult are the following activities?	Impossible	Difficult	Easy	?
1	Wiping one's upper body				
2	Sitting on the toilet				
3	Taking a bath				
4	Taking a shower				
5	Walking dowstairs				
6	Walking outdoors on level ground				
7	Walking upstairs				
8	Putting on a T-shirt				
9	Opening a door				
10	Washing one's upper body				
11	Hanging up a jacket on a hatstand				
12	Dressing one's lower body				
13	Washing one's face				
14	Stepping out of a bath tub				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Getting into a car	A				
16	Carrying a heavy load	A				
17	Walking more than 1 kilometre	A				
18	Standing for a long time (± 10 min)	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Closing a door	C				
20	Putting on a backpack	C				
21	Hopping on one foot	C				
22	Running	C				

Order 8

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

	How difficult are the following activities?	Impossible	Difficult	Easy	?
1	Hanging up a jacket on a hatstand				
2	Stepping out of a bath tub				
3	Walking upstairs				
4	Sitting on the toilet				
5	Taking a bath				
6	Walking outdoors on level ground				
7	Taking a shower				
8	Walking dowstairs				
9	Wiping one's upper body				
10	Washing one's upper body				
11	Washing one's face				
12	Putting on a T-shirt				
13	Opening a door				
14	Dressing one's lower body				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Getting into a car	A				
16	Carrying a heavy load	A				
17	Walking more than 1 kilometre	A				
18	Standing for a long time (± 10 min)	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Hopping on one foot	C				
20	Running	C				
21	Closing a door	C				
22	Putting on a backpack	C				

Order 9

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

Appendix E (2) - Statistical Analysis Plan Addendum

Non-interventional registry-based Study
Protocol: EUPAS50476

A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs).

This addendum supplements the Statistical Analysis Plan (SAP), which was last updated on 26 April 2023. The study protocol was developed in absence of data access; therefore, the SAP refinement during the implementation process was inevitable. The list of SAP changes – analyses and definitions refinements are provided below.

SAP section	SAP original description where available	SAP refinement or new addition

<table>
<tr>
<td>5.1 Eligibility criteria</td>
<td>The primary study population will include all SMA patients entered in each of the registries selected for the study between registry entry date and 30 November 2022</td>
<td>(Refinement) The primary study population will include all SMA patients entered in each of the registries selected for the study from registry entry date till the end of data availability.
<table>
<tr><th>Registry</th><th>Start date of data collection</th><th>End date of data availability</th></tr>
<tr><td>Belgium</td><td>January 2018</td><td>December 2021</td></tr>
<tr><td>Czech Republic and Slovakia</td><td>May 2011</td><td>May 2023</td></tr>
<tr><td>Germany and Austria</td><td>April 2008</td><td>May 2023</td></tr>
<tr><td>Spain</td><td>February 2015</td><td>April 2023</td></tr>
<tr><td>United Kingdom and Ireland</td><td>December 2007</td><td>May 2023</td></tr>
<tr><td>Sweden</td><td>October 2010</td><td>April 2023</td></tr>
</table>
</td>
</tr>
<tr>
<td>8.3.2. Exposure Definition</td>
<td></td>
<td>(New) Treatment discontinuation (except Zolgensma): a patient is counted as discontinued if they have a stop date or a text discontinuation reason.</td>
</tr>
<tr>
<td>8.6 Functional status at symptom onset</td>
<td></td>
<td>(New) If there isn't an exact match of the functional status date with date of symptom onset, the best-known functional status/motor milestone within +/- 3 months of symptom onset date is used.</td>
</tr>
<tr>
<td>8.7 Achieved motor status at symptom onset</td>
<td></td>
<td>(New) If there isn't an exact match of the achieved motor status date and date of symptom onset, the best-known functional status/motor milestone within +/- 3 months of symptom onset date is used.</td>
</tr>
<tr>
<td>8.8.1 Calendar period</td>
<td>The following time periods will be used.
● Before 2011
● 2011 - 2013
● 2014 - 2016
● 2017
● 2018</td>
<td>(Refinement) The following time periods will be used.
● Before 2011
● 2011 - 2013
● 2014 - 2016
● 2017
● 2018
● 2019</td>
</tr>
</table>

	• 2019 • 2020 • 2021 • 2022	• 2020 • 2021 • 2022 • 2023 (New addition)
9.5.2 Diagnosis date		(New) Indicators at genetic report date will use records closest to the genetic report date within three-month deviation and earliest.
9.5.3 Registry entry	We will derive this from an earliest longitudinal date stamps or timestamps variable, based on the earliest date we observe for a patient.	(Refinement) The date of Registry entry is defined as the earliest longitudinal datestamp or timestamp after the registry start date with assumptions of no historical or retrospective data entry. Any datestamps or timestamps before the registry start date will be removed. This is with assumption that the dates before the registry start date were added as historical data at the registries.
9.6 ICD codes	Other relevant comorbidities: • Osteoporosis • Fractures • Pulmonary infections • Sleep apnea • Pneumothorax • Atrial or ventricular defect • Diabetes • Vertebral fracture • Non-vertebral fractures • Bronchopulmonary infections • Gastrostomy	(Refinement) Amongst other relevant comorbidities list, Bronchopulmonary infections were merged with pulmonary infections as confirmed by Prof. Laurent Servais that there are no differences between them. Other relevant comorbidities: • Osteoporosis • Fractures • Pulmonary infections (including Bronchopulmonary infections) • Sleep apnea • Pneumothorax • Atrial or ventricular defect • Diabetes • Vertebral fracture • Non-vertebral fractures • Gastrostomy
9.6 ICD codes	For indicator 2.95, causes of death, ICD-10 codes will be reported at the four-digit ICD-10 code level (labelled) and all codes above that hierarchically.	(Refinement) For indicator 2.80, causes of death, ICD-10 codes will be reported at the four-digit ICD-10 code level (labelled) and all codes above that hierarchically.
10.2 Reporting statistics	To preserve patient confidentiality, cells with a number of patients or events below five will be	(Refinement) To preserve patient confidentiality when counts are below 5, the values are replaced with '*' for tables and graphs. This is applied to counts, means and medians. Values with 0 are reported as '-' in table outputs.

	merged with another relevant category.	
Table 5: Indicators for the SMA natural history and disease progression analysis	2.17: Age at first acquisition of any of the motor ability episodes (mean, sd)	(Refinement) 2.17: Age at first acquisition of the best motor ability episodes (mean, sd)
Table 5: Indicators for the SMA natural history and disease progression analysis	2.18: Age at first loss of any of the motor ability episodes (mean, sd)	(Refinement) 2.18: Age at first loss of the best of the motor ability episodes (mean, sd)
Table 5: Indicators for the SMA natural history and disease progression analysis	2.70: Bronchopulmonary infections reported in cause of hospitalisation or as a comorbidity (n, %)	(Refinement) 2.70: Pulmonary infections reported in cause of hospitalisation or as a comorbidity (n, %)
10.4.1 PROs		(New) For contractual reasons in the UK and Ireland Registry, PROMs data associated with patients receiving Risdiplam and Nusinersen are not allowed to share with third parties. PROMs data only with Zolgensma is available to share.
Table 6: Description of SMA healthcare management over time	3.07: Pneumococcal vaccination at least every 5 years (n, %)	(Refinement) 3.07: Pneumococcal vaccination at least once every 5 years (n, %)

Table 8: Diagnostic tests and their implications

(New)

Diagnostic test	What is the test investigating?	Alternative course of action
Check for autocorrelation via an autocorrelation plot	Investigating as to whether autocorrelation is present in the residuals of the time series. Autocorrelation will be deemed present if a statistically significant (at 5% level) is present in the plot. However, if the autocorrelation is mild, we may be able to ignore it.	Fit an alternative model such as an INGARCH(p, q) model. This will be possible for Poisson and Negative Binomial models, but not ZIP models.

Appendix F - ITS Analysis Report

Non-interventional registry-based Study
Protocol: EUPAS50476

A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs).

Exploratory Analysis (Version 4)

Jumping Rivers | support@jumpingrivers.com

Aims, scope & methods

The aim of this exploratory analysis is to analyse the numbers of patients in the available data, who either died (Death), or were placed onto full time ventilation, which includes invasive and non-invasive, (Ventilation) before and after the availability of disease modifying therapies (DMTs). We also consider the composite outcome; that is, the numbers of patients who either died or were placed onto full time ventilation (Composite). We may refer to any of the three outcomes as "events". We will model the three outcomes independently. Joint modelling is beyond the scope of this analysis.

The main statistical approach in this analysis is using interrupted time series (ITS) to see if the underlying patterns in the numbers of events per quarter change after the introduction of DMT. In this analysis, we use quarterly event counts as this strikes a good balance between two competing objectives:

1. ensuring that the number of events per quarter is not almost always zero
2. providing a sufficiently large samples size pre- and post- DMT introduction to have sufficient power to estimate model coefficients. For an ITS analysis, it is recommended that *at least* 8 data points are available pre and post intervention.

Data for the analysis

Although the registries have records of data before the foundation of the registry, this data is sparse. To ensure that the data is reliable, we only consider data after the quarter 2008-07. This quarter is the first quarter after the start date of the first registry (`2007-12`) for which the number of patients is non-zero (see Table 4). The start dates for the registries are: 2018-01-01 (BE), 2011-05-01 (CZ), 2008-04-01 (DE), 2015-02-01, 2010-10-01 (SE) and 2007-12-01 (UK).

We therefore do not consider any event that occurred prior to 2008-07-01. The end date for the analysis is NA. All dates are in the format `year-month-day`. All the counts for a quarterly totals of the three outcomes. The population of interest is all patients with SMA types 1 or 2.

DMTs

The DMTs we consider in this analysis are Spinraza and Zolgensma. Evrysdi is not considered, as it was not available until 2021-03-26. this would not give us the required number of quarters (8) to estimate post-DMT regression coefficients. The interruption

points are given in Table 1, and correspond to the start first quarter *after* the date of issue of marketing authorisation valid throughout the European Union.

Models

Our baseline model will be a Poisson GLM with log-link function. This is the simplest appropriate model for an ITS analysis with count data. The formulation for this model is

where Y_t is the number of observed events in quarter t, β_i are unknown regression coefficients to be inferred, and $I(t \geq t')$ is an indicator function returning the value 1 when $t \geq t'$ and 0 otherwise. In our case, t' will be the intervention point corresponding to the introduction of either Spinraza or Zolgensma.

More advanced models considered are:

- Negative Binomial GLM
- Poisson GLM with zero inflation
- INGARCH(1, 1) with quarter, DMT intervention and a corresponding interaction term as covariates.

Our philosophy will be to adopt the simplest possible model unless there is a compelling reason to favour another model. Higher order INGARCH models will not be considered as the sample size is small relative to the model complexity. Compelling reasons to choose a more complex model are:

- Graphical or numerical diagnostics indicating that the Poisson GLM is inadequate
- Model fit — measured by AIC — favours a more complex model.
- For the more complex model to be chosen, it must also pass the relevant graphical and numerical diagnostic checks.

Table 1: Interruptions dates for Spinraza and Zolgensma. These are the first day of the quarters following the Marketing Authorisation for each DMT.

DMT	Quarter
Spinraza	2017-07-01
Zolgensma	2020-07-01

Initial analysis

Prior to any statistical modelling, we plot the data (Figure 1) and make the following observations:

- Prior to 2012-01-01, only one death is recorded across all registries. This will be a difficult aspect of the data to model.
- The number of recorded deaths has steadily increased over time.

- The number of patients receiving full time ventilation for the first time was increasing until about 2017, where the numbers start to decrease. This coincides with the introduction of Spinraza.
- For the composite outcome, numbers are quite small pre 2012 and then start to rise until about 2015 where numbers become fairly stable.
- For each quarter, the number of events is typically quite small. The largest number of events per quarter is 5 which occurs on 2017-01-01.

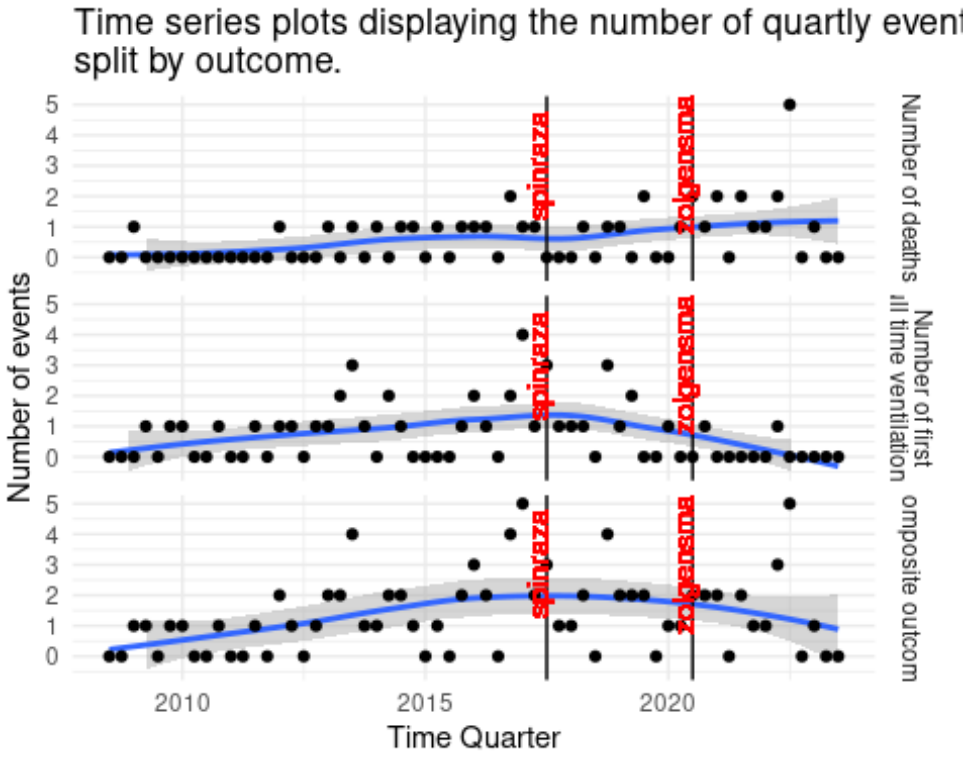


Figure 1: Time series of patients who have died, started full time ventilation for the first time and the composite outcome (top-bottom). Vertical lines are superimpose at the start of the quarter where each DMT became available. Solid blue like is a loess curve, with corresponding grey 95% confidence interval for the mean number of events per quarter.

Diagnostics for the Poisson GLM model.

Residual plots

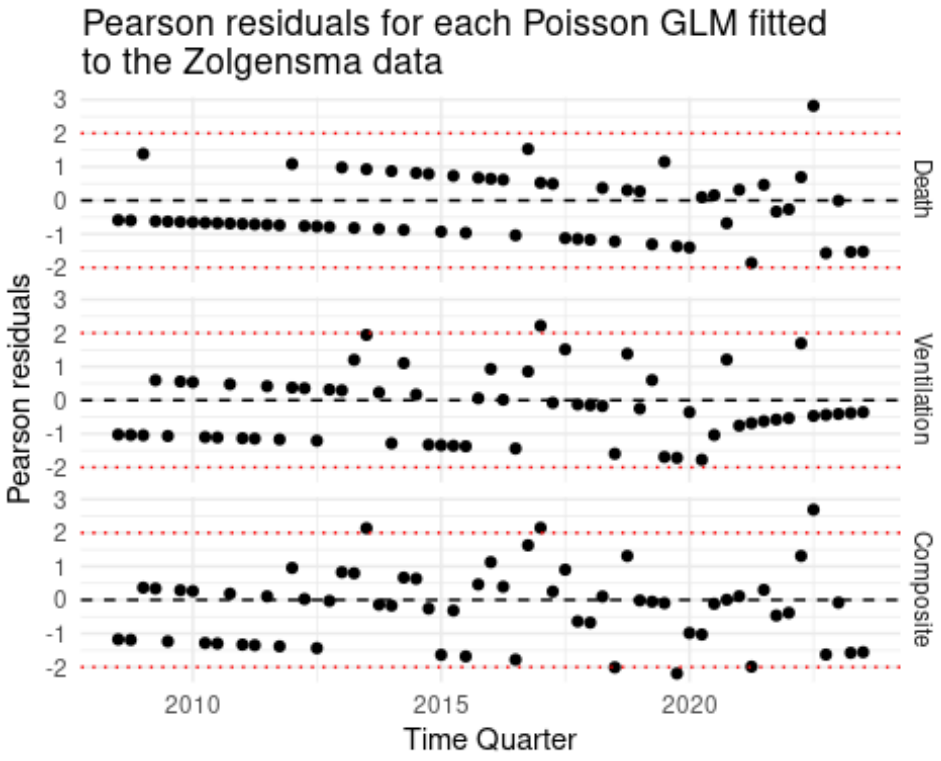


Figure 2: Pearson residual plots for each outcome with the Zolgensma interruption point. Central dashed black line indicates 0 with the dotted red lines being at $\pm$ *2.*

For the Deaths outcome in Figure 2, there may be some autocorrelation in the residuals - around 2016, the residuals form two stripes. However, this may just be a symptom of low numbers of deaths. This will be investigated more formally with autocorrelation plots (this diagnostic will be applied to all models). We see that 2% of Pearson residuals are outside $\pm$ 2. This is slightly less than the 5% we would expect. This could be due to zero inflation, which we will investigate soon.

The other residual plots for the Zolgensma interruption points show no serious issues. There is little reason to suspect autocorrelation in the residual structure. For the Ventilation outcome, 2% of Pearson residuals are outside of the $\pm$ 2 limits, and for the Composite outcome we have 8% are outside of $\pm$ 2. This is slightly above what we expect, but not a major cause for concern.

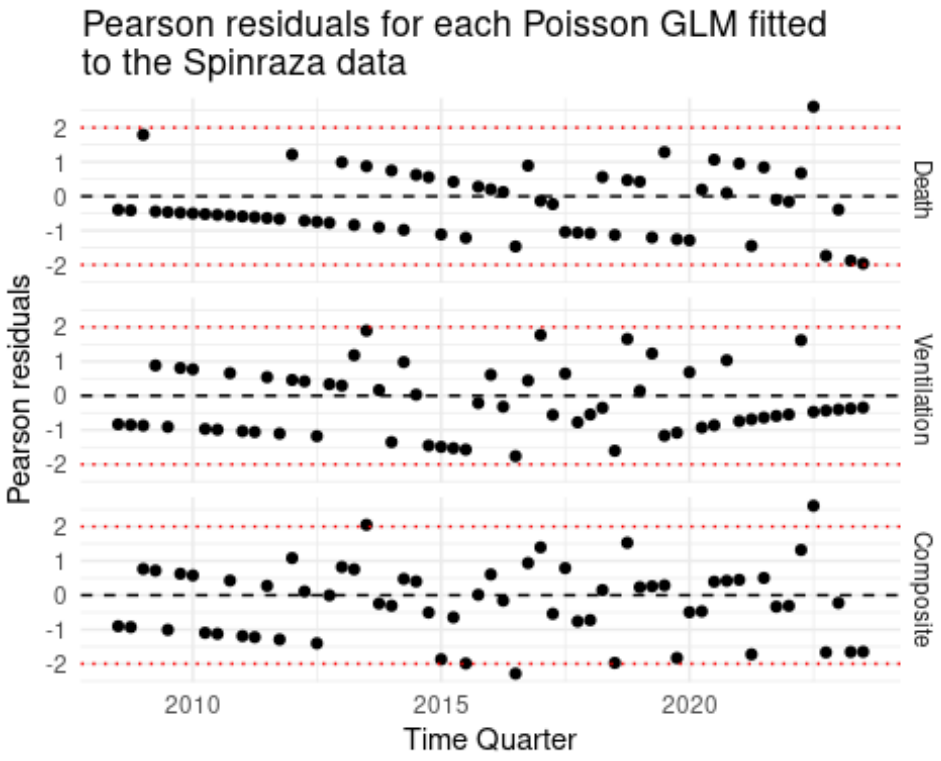


Figure 3: Pearson residual plots for each outcome with the Spinraza interruption point. Central dashed black line indicates 0 with the dotted red lines being at $\pm$ *2.*

Because the observed values are the same for each outcome, regardless of DMT, the residual plots for the same outcomes are similar with the two different interruption periods.

For the Deaths outcome in Figure 3, there may be some autocorrelation in the residuals, again, this may actually be a case of zero inflation. We see that 2% of Pearson residuals are outside $\pm$ 2. This is slightly less than the 5% we would expect, but still close. This could be due to zero inflation, which we will investigate soon.

As above, the residual plots corresponding to Ventilation and Composite for Spinraza show no serious issues, but the respective proportion of Pearson residuals outside $\pm$ 2 are 2% and 8% . There is perhaps a case of the estimated variance being slightly too big, however, many residuals are close to these limits which suggests there is not a serious mismatch between the model and data.

Dispersion tests

Outcome	DMT	Dispersion estimate	p-value
Death	Zolgensma	0.85	0.45
Ventilation	Zolgensma	0.94	0.66
Composite	Zolgensma	1.07	0.72

Outcome	DMT	Dispersion estimate	p-value
Death	Spinraza	0.84	0.34
Ventilation	Spinraza	0.84	0.20
Composite	Spinraza	0.92	0.68

In this case, the estimated dispersion parameters are all close to 1, with p-values comfortably above 0. 05. This indicates that there is little evidence to doubt the Poisson assumption that $mean = variance$. Because the dispersion estimates are all < 1, it is not possible to fit a negative binomial model, which is based on the assumption that the dispersion parameter is ≥ 1.

Zero inflation

We will fit ZIP (zero inflated Poisson) models to each time series. One issue with the ZIP model is the number of parameters. This model is a mixture of a Poisson model and a logistic regression:

where π_t the the mixing proportion, and modelled by a logistic regression with linear predictor and λ_t is the linear predictor for the Poisson aspect of the model, thus has the same form as the linear prediction for a standard Poisson GLM. The logistic regression is used to "inflate" the number of zeros we would expect to see under a Poisson model.

To check for zero inflation, we will use AIC to measure if the zero inflated models are a better fit to the data than the standard Poisson GLMs. Recall that a *lower* AIC indicates a more appropriate model.

Outcome	DMT	AIC (zeroinfl)	AIC (GLM)
Death	spinraza	121.26	120.64
Ventilation	spinraza	135.57	128.48
Composite	spinraza	182.25	179.04
Death	zolgensma	125.40	121.64
Ventilation	zolgensma	141.74	134.23
Composite	zolgensma	188.15	184.78

For all cases, we see that the AIC is lower for the simpler GLMs than the zero inflated variants. For this reason, we do not favour the more complex model in any case and retain the Poisson GLMs.

Residuals Autocorrelation

The next assumption to investigate is autocorrelation in the residuals. Since the data are time series, it is natural to expect autocorrelation in the residuals.

To investigate whether or not autocorrelation is a potential problem, we will first construct autocorrelation plots. We will superimpose cut-off bands on the plots which indicate plausible values for the autocorrelation at lag k under the assumption that the residuals are independent. The bands indicate an acceptance region where approximately 95% of points should lie, under the null hypothesis that residuals are independent. These are approximate bands, with width given by $\frac{4}{\sqrt{n-k}}$ where n is the series length and k is the lag. The bands are known to be on the conservative side (higher than intended type 2 error rate) and should be used as a guide or rule of thumb rather than a hard cut off. We are however performing multiple tests, and we do not correct for multiple testing in these plots.

Figure 4: Autocorrelation plots for the Spinraza models. Grey bars indicate the value of the autocorrelation at a given lag; pink band represents approximate 95% acceptance region.

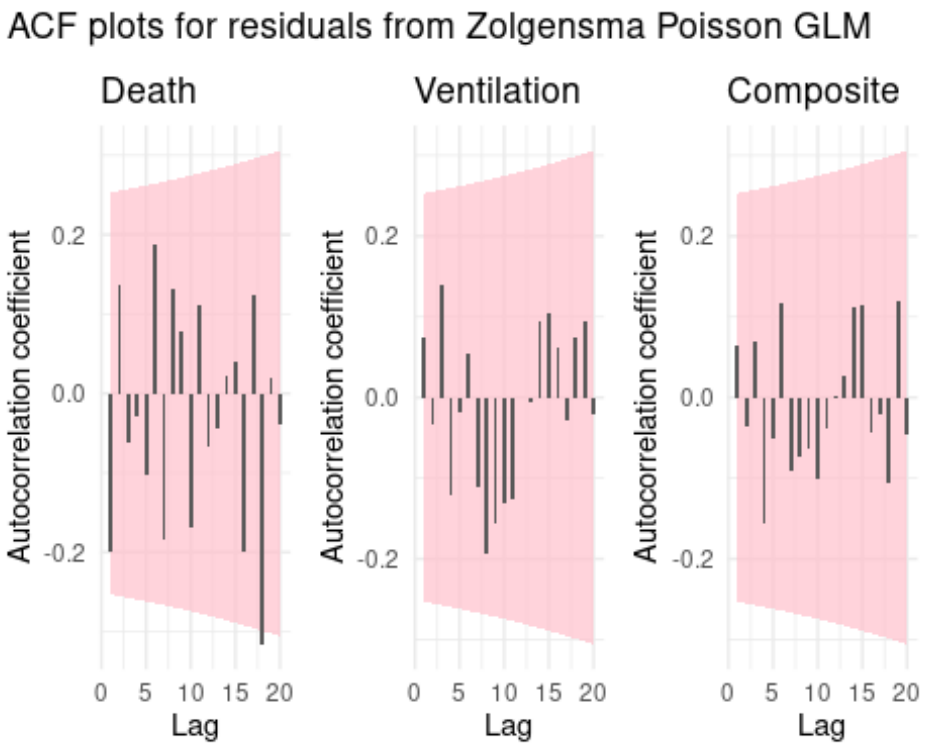


Figure 5: Autocorrelation plots for the Zolgensma models. Grey bars indicate the value of the autocorrelation at a given lag; pink band represents approximate 95% acceptance region.

INGARCH(1, 1) models

A more formal approach to investigating for dependence amongst the standardised residuals would be to git an INGARCH model. The formulation for the particular INGARCH(1, 1) model we use is where α_i and β_1 are coefficients to be inferred, t represents the quarter, and η_i are unknown regression coefficients to be inferred, and D_t is the history of the time series up to time t.

To investigate if there is any improvement offered by the INGARCH(1, 1) model we will use similar diagnostics to before. Namely, plot Pearson residuals against quarter, and construct autocorrelation plots.

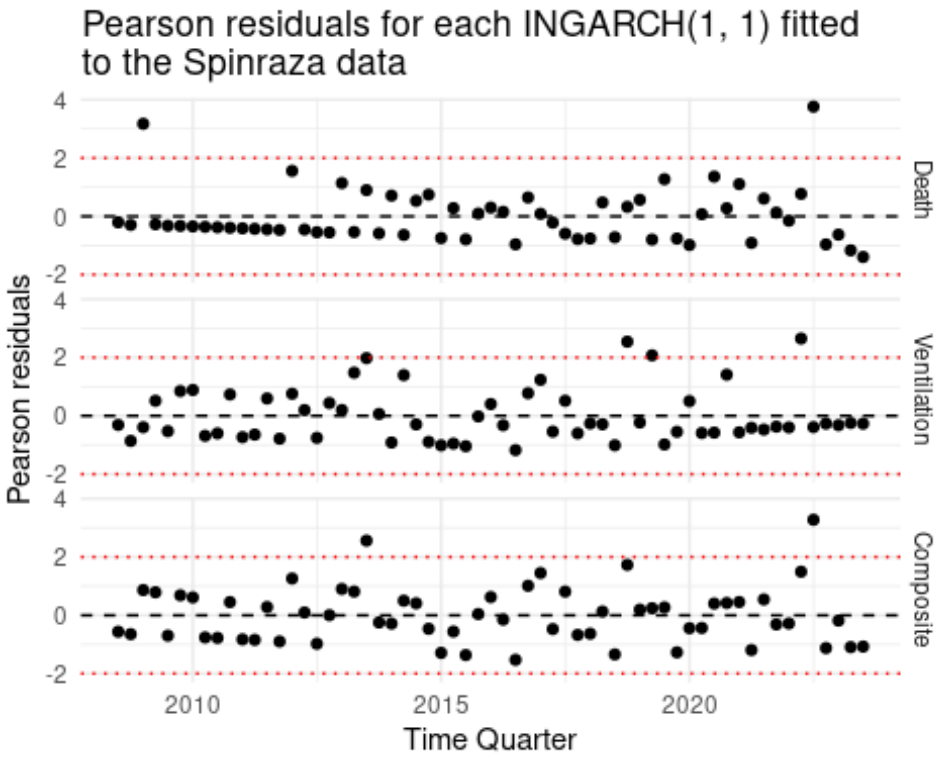


Figure 6: Standardised residuals for spinrazaINGARCH(1, 1) models.

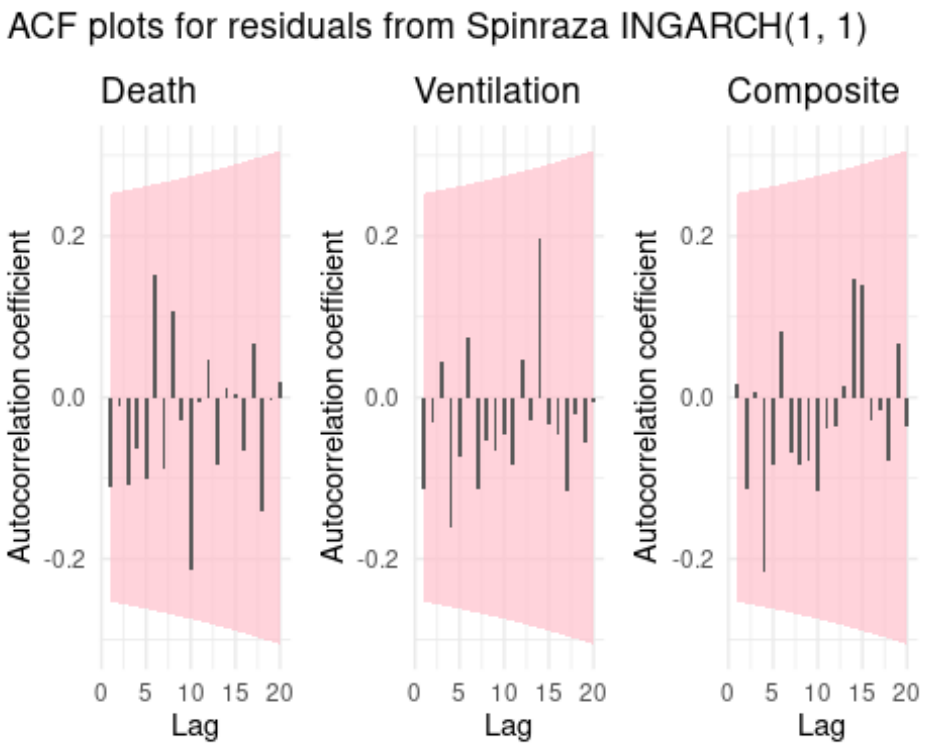


Figure 7: Autocorrelation plots for the Spinraza INGARCH(1, 1) models. Grey bars indicate the value of the autocorrelation at a given lag; pink band represents approximate 95% acceptance region.

The Pearson residual plots for the Spinraza models (Figure 6) all show at least one standardised residual greater than 3 in modulus. The number of residuals greater than 3 in modulus is, 2 for the deaths data, 0 for ventilations and 1 for the composite outcome. For a sample of size 61 we would not expect any to be this large. The autocorrelation do not provide any evidence to suggest the model is inadequate (Figure 7). The autocorrelation coefficients are small and comfortably within the acceptance bands. However, because of the extreme outliers, the INGARCH(1, 1) models will not receive any further consideration for the Spinraza analysis.

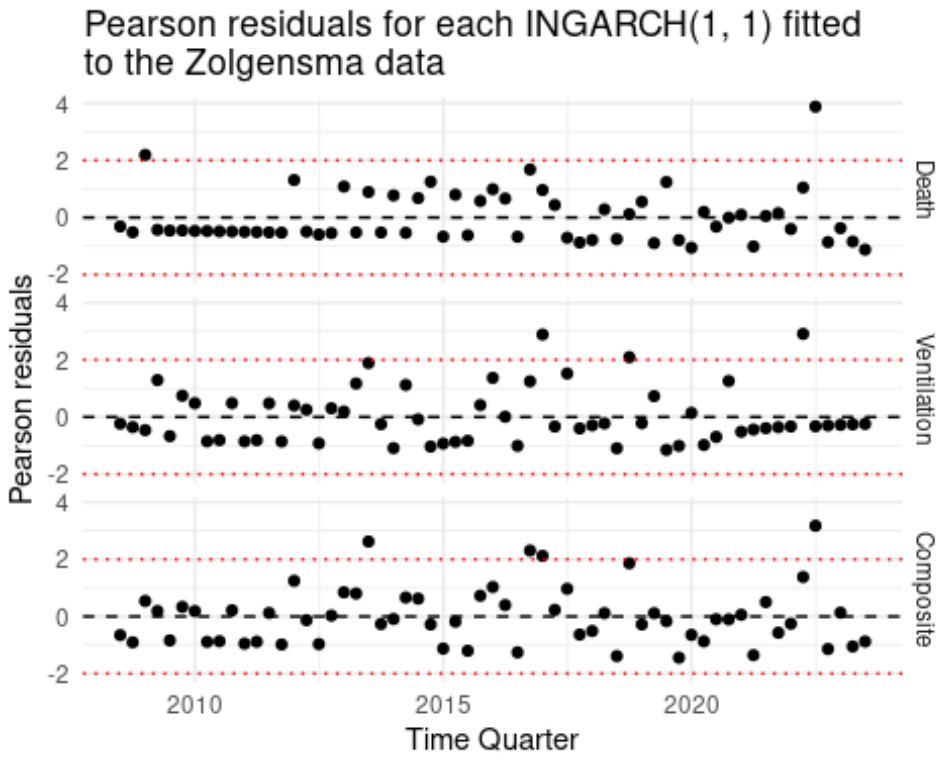


Figure 8: Standardised residuals for Zolgensma INGARCH(1, 1) models.

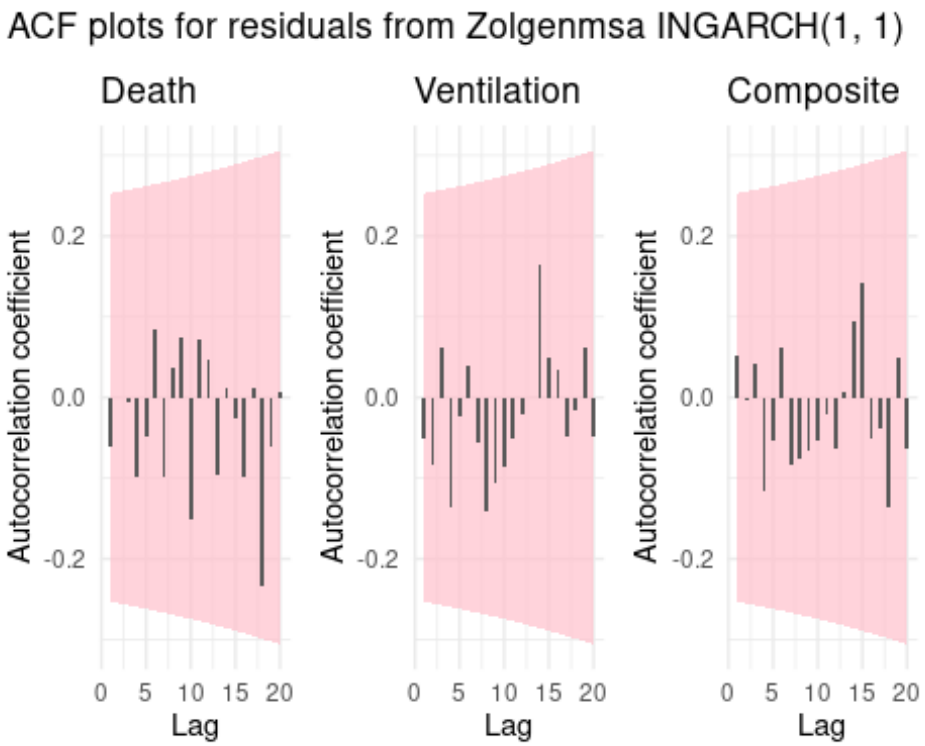


Figure 9: Autocorrelation plots for the zolgensma INGARCH(0, 1) models. Grey bars indicate the value of the autocorrelation at a given lag; pink band represents approximate 95% acceptance region.

In general, the Pearson residuals resulting from fitting an INGARCH(1, 1) model to the Zolgensma data, look fine. The exception being the Deaths data, which has one very large standardised residual; see Figure 8. The autocorrelation plots do not suggest any serious data-model conflict (Figure 9). The autocorrelation coefficients are small and comfortably within the acceptance bands. The INGARCH(1, 1) model will not be considered any further for the Deaths data, but will will retain the INGARCH(1, 1) model as a candidate model for only:

- Ventilation with Zolgensma interruption
- Composite with Zolgensma interruption

Best AIC for each dataset

Table 2: Chosen models for each data set, with their corresponding AIC.

Outcome	DMT	Model	AIC
Death	Zolgensma	GLM	121.6417
Ventilation	Zolgensma	GLM	134.2267
Composite	Zolgensma	GLM	184.7807

Outcome	DMT	Model	AIC
Death	Spinraza	GLM	120.6437
Ventilation	Spinraza	GLM	128.4808
Composite	Spinraza	GLM	179.0384

In all cases but one, we see in Table 2, using AIC for model selection leads to the simple GLM being the most appropriate model. We saw that there was no evidence to suggest the data were over-dispersed, nor that the data were zero inflated. An AIC table for all fitted models is available in the appendix, in particular, see Table 6.

Limitations, results & conclusions

Limitations

One limitation of the analysis is the occurrence of Covid 19. Covid 19 was first present in Europe in early 2020; this is close to the availability of Zolgensma, and after the introduction of Spinraza. This causes problems for multiple reasons, which include:

1. It is well known that Covid 19 may lead to a patient's death, or a requirement for full-time ventilator use, especially for those with pre-existing health conditions.
2. Due to the additional strain on medical professionals, keeping registry data up to date may not have been a priority, especially early on in the pandemic.
3. A decrease in the number of SMA type 1 & 2 patients receiving full time ventilation may be due to the lack of ventilators available.

Accounting for Covid 19 is not possible. This is because the introduction of DMTs has a large overlap with the emergence of Covid 19 across Europe. The available data is not able to distinguish the effects of Covid 19 from DMT. Another complication is that data for this analysis are aggregated across different registries and therefore countries; different countries took different approaches to managing Covid 19, accounting for this in our model is not feasible.

Another limitation of the analysis is not correcting for multiple testing. All p-values have been provided, thus post-hoc methods such as a Bonferroni correction can be applied. A small number p-values in Table 3 has p-values close to $\alpha = 0.05$, so this likely will not cause any drastic changes to conclusions.

Results

Having fit various models for each DMT-outcome combination, we have concluded that the simple GLM models are the most appropriate models. We will now present model summaries in the following order:

1. Fitted model formulations (with coefficients given to 2 significant figures)
2. Table of model coefficients with standard errors, p values and 95% CIs

3. Plots of the data with fitted mean functions superimposed, as well as superimposed 80% and 95% prediction intervals.

1. Fitted model formulations

Recall that all models are of the form $Y_t \sim Poisson(\lambda_t)$. For this reason, we will write out only the linear predictor — the formula for $log\lambda_t$ — for each model. Models will be indicated by the form DMT-outcome

Spinraza-death

$$log\lambda_t = -15 + 0.00088t + (4.9 - 0.00034t)I(t \geq t')$$

Spinraza-ventilation

$$log\lambda_t = -8.2 + 0.0005t + (38 - 0.0022t)I(t \geq t')$$

Spinraza-composite

$$log\lambda_t = -9.7 + 0.00062t + (14 - 0.00084t)I(t \geq t')$$

Zolgensma-death

$$log\lambda_t = -7.5 + 0.0004t + (20 - 0.0011t)I(t \geq t')$$

Zolgensma-ventilation

$$log\lambda_t = -4.2 + 0.00025t + (34 - 0.0019t)I(t \geq t')$$

Zolgensma-composite

$$log\lambda_t = -4.6 + 0.0003t + (19 - 0.001t)I(t \geq t')$$

2. Model coeffcients

Table 3: Table showing the pre-interruption coefficients and the change in the coefficient post-interruption for the slope and intercept for the chosen models.

DMT	Outcome	Term	Pre/Post DMT	Estimate	95% CI	p value
Spinraza	Death	Intercept	Pre	-1.5e+01	(-27, -5.2)	0.00540
Spinraza	Death	Intercept	Post	4.9e+00	(-11, 21)	0.55000
Spinraza	Death	Slope	Pre	8.8e-04	(0.00028, 0.0016)	0.00750
Spinraza	Death	Slope	Post	-3.4e-04	(-0.0013, 0.00056)	0.46000
Spinraza	Ventilation	Intercept	Pre	-8.2e+00	(-15, -1.8)	0.01500

DMT	Outcome	Term	Pre/Post DMT	Estimate	95% CI	p value
Spinraza	Ventilation	Intercept	Post	3.8e+01	(19, 59)	0.00016
Spinraza	Ventilation	Slope	Pre	5.0e-04	(1e-04, 0.00093)	0.01600
Spinraza	Ventilation	Slope	Post	-2.2e-03	(-0.0034, -0.0011)	0.00014
Spinraza	Composite	Intercept	Pre	-9.7e+00	(-16, -4.3)	0.00065
Spinraza	Composite	Intercept	Post	1.4e+01	(3.7, 25)	0.00810
Spinraza	Composite	Slope	Pre	6.2e-04	(0.00029, 0.00098)	0.00040
Spinraza	Composite	Slope	Post	-8.4e-04	(-0.0014, -0.00025)	0.00550
Zolgensma	Death	Intercept	Pre	-7.5e+00	(-14, -1.6)	0.01700
Zolgensma	Death	Intercept	Post	2.0e+01	(-7.2, 48)	0.15000
Zolgensma	Death	Slope	Pre	4.0e-04	(4.9e-05, 0.00078)	0.03100
Zolgensma	Death	Slope	Post	-1.1e-03	(-0.0026, 0.00039)	0.16000
Zolgensma	Ventilation	Intercept	Pre	-4.2e+00	(-8.4, -0.16)	0.04700
Zolgensma	Ventilation	Intercept	Post	3.4e+01	(-46, 140)	0.43000
Zolgensma	Ventilation	Slope	Pre	2.5e-04	(2.6e-06, 5e-04)	0.05100
Zolgensma	Ventilation	Slope	Post	-1.9e-03	(-0.0075, 0.0023)	0.40000
Zolgensma	Composite	Intercept	Pre	-4.6e+00	(-8.1, -1.3)	0.00810
Zolgensma	Composite	Intercept	Post	1.9e+01	(-6.2, 46)	0.14000
Zolgensma	Composite	Slope	Pre	3.0e-04	(9.5e-05, 5e-04)	0.00440
Zolgensma	Composite	Slope	Post	-1.0e-03	(-0.0025, 0.00029)	0.13000

A summary of the column in Table 3 is as follows:

- DMT indicates which DMT the interruption point corresponds to; Outcome indicates the response variable (Deaths, Ventilations, Composite)
- Term indicates the parameter of the statistical model (intercept, slope)
- Pre/Post DMT indicates whether the term corresponds to before or after the interruption point
- Estimate is the point estimate for the parameter
- 95% CI is an approximate 95% confidence interval for the parameter
- p value is the p value under the null that the parameter is zero.

3. Plots of fitted models

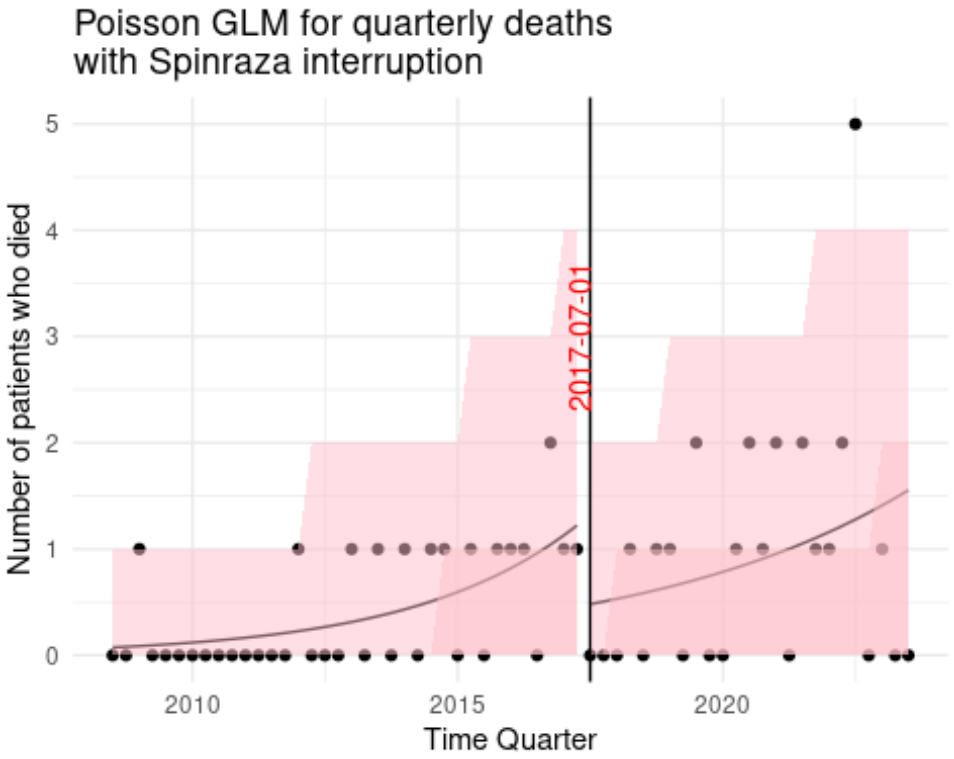


Figure 10: Fitted model with 80% and 95% prediction intervals superimposed for the quarterly deaths and Spinraza interruption.

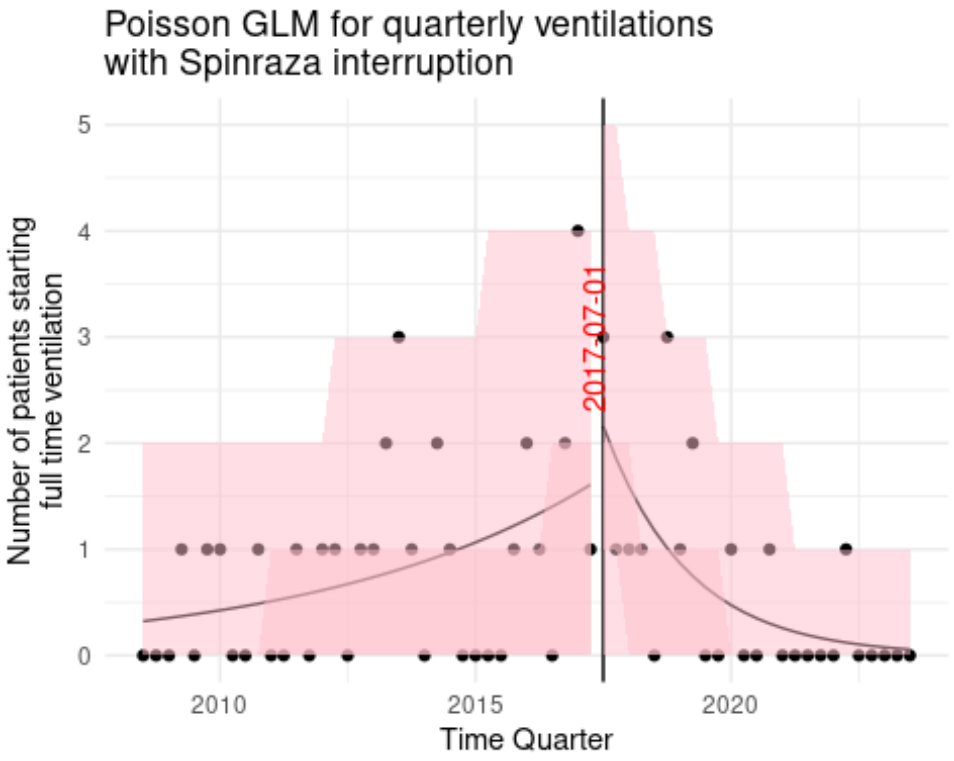


Figure 11: Fitted model with 80% and 95% prediction intervals superimposed for the quarterly first time ventilation episode and Spinraza interruption.

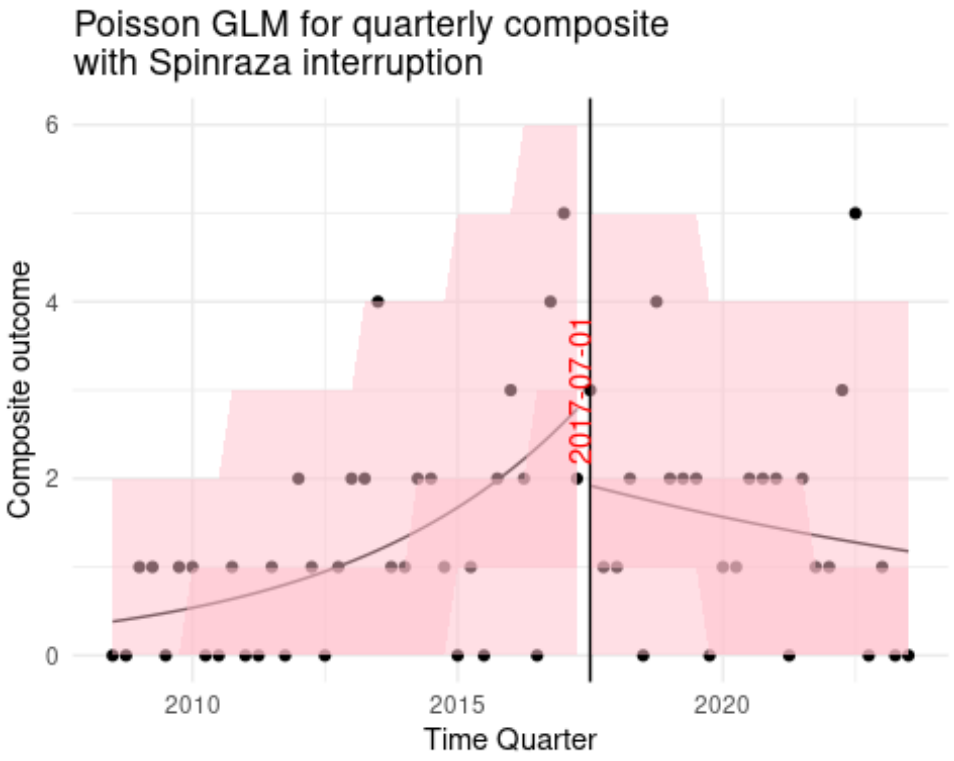


Figure 12: Fitted model with 80% and 95% prediction intervals superimposed for the quarterly composite outcome and Spinraza interruption.

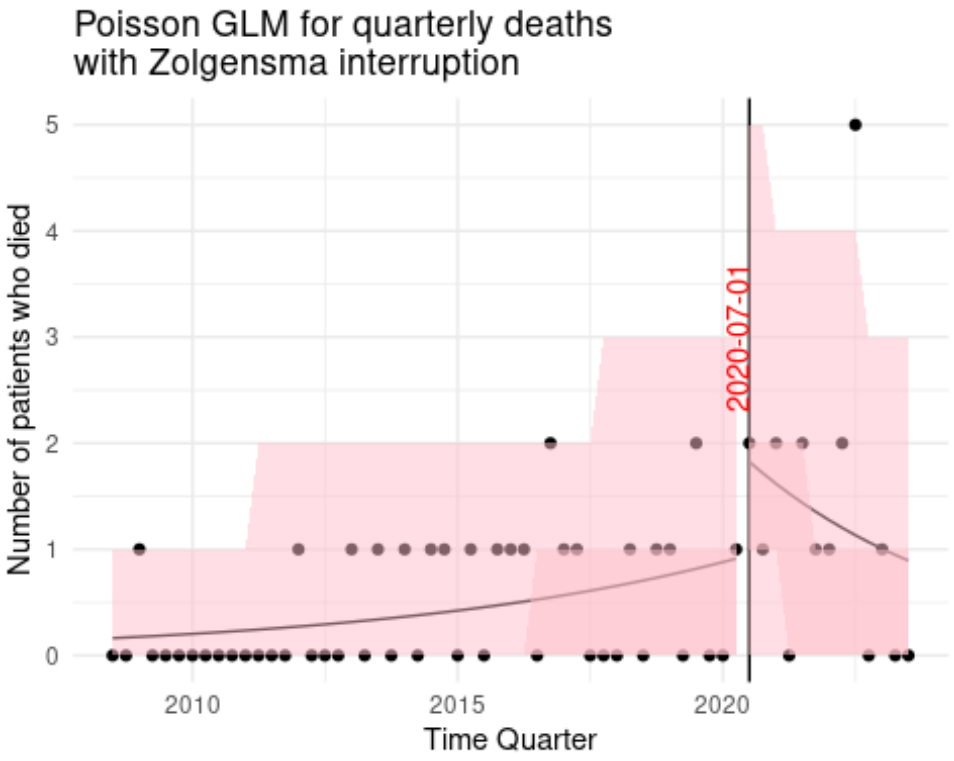


Figure 13: Fitted model with 80% and 95% prediction intervals superimposed for the quarterly deaths and Zolgensma interruption.

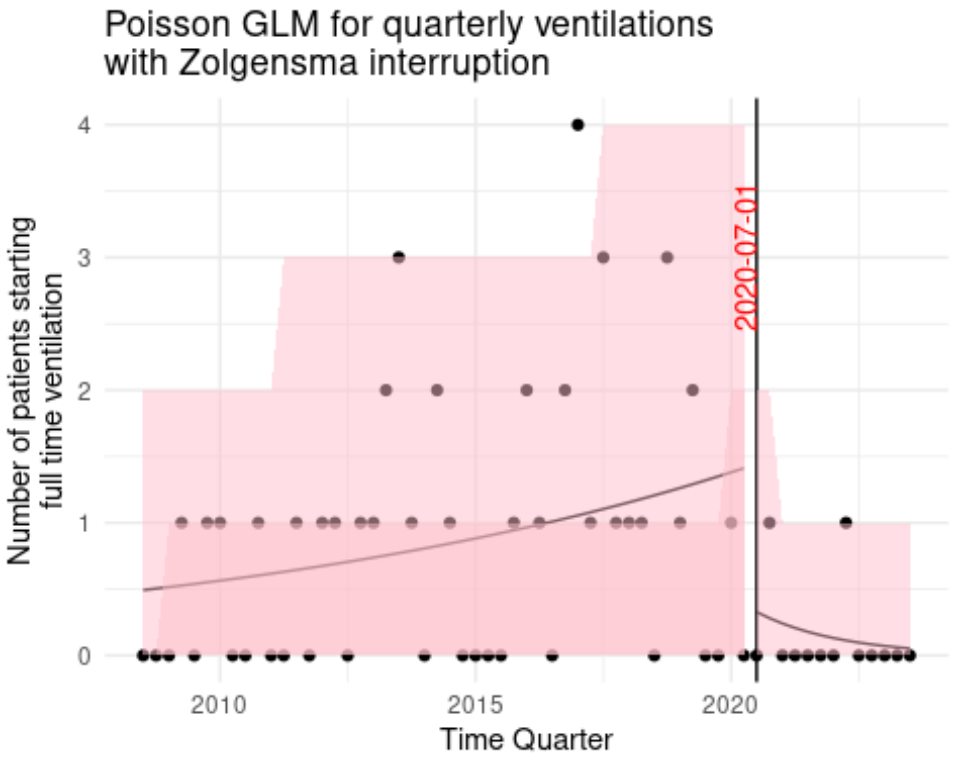


Figure 14: Fitted model with 80% and 95% prediction intervals superimposed for the quarterly ventilations and Zolgensma interruption.

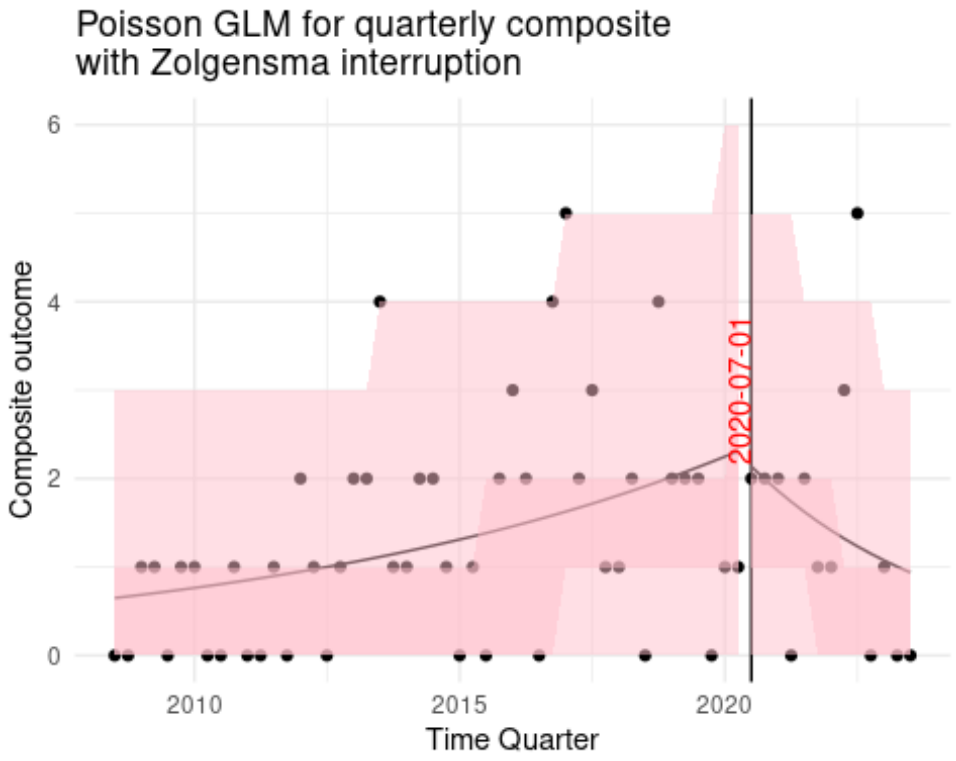


Figure 15: Fitted model with 80% and 95% prediction intervals superimposed for the quarterly composite outcome and Zolgensma interruption.

Conclusions

After the introduction of Spinraza, we observed a statistically significant (at the 5% level) change in the numbers of patients first receiving full time ventilation, and we also saw a statistically significant change in the composite outcome. Observing Figure 11 and Figure 12, and observing the coefficients in Table 3, indicates that this change is a *reduction* in both of these quarterly counts. No other changes can be deemed significant at the 5% level, thus there is no evidence to suggest that after the introduction of Spinraza (i.e. after 2017-07-01), that the number of types 1 & 2 SMA patients who die per quarter has changed. Likewise, none of the coefficients corresponding to Zolgensma can be deemed significant, thus we cannot say that there has been a change in quarterly number of patients who die, start full time ventilation or the composite outcome after 2020-07-01.

All graphs show that prior to the introduction of DMT, that the numbers of all cases were increasing. With the exception of the Deaths and Ventilation outcome for the Zolgensma interruption, the slope parameter for each model pre-DMT is significant at the 5% level. This, in part, will be due to the fact that over time more registries have started to collect data, rather than a higher proportion of patients contributing to each of the possible outcome.

Appendix

Number of patients by quarter

Table 4: Number of patients in the registry for each quarter, from 2008-07 to 2023-07. This data is visually represented in Figure 16.

Quarter	Number of patients across all registries
2008-07-01	5
2008-10-01	25
2009-01-01	30
2009-04-01	32
2009-07-01	42
2009-10-01	49
2010-01-01	57
2010-04-01	67
2010-07-01	75
2010-10-01	81
2011-01-01	87
2011-04-01	100
2011-07-01	117
2011-10-01	137
2012-01-01	156
2012-04-01	217
2012-07-01	253
2012-10-01	275
2013-01-01	295
2013-04-01	340
2013-07-01	360
2013-10-01	369
2014-01-01	394
2014-04-01	469
2014-07-01	509
2014-10-01	552
2015-01-01	592
2015-04-01	626
2015-07-01	639
2015-10-01	671

Quarter	Number of patients across all registries
2016-01-01	740
2016-04-01	760
2016-07-01	783
2016-10-01	821
2017-01-01	872
2017-04-01	906
2017-07-01	941
2017-10-01	981
2018-01-01	1062
2018-04-01	1209
2018-07-01	1295
2018-10-01	1392
2019-01-01	1443
2019-04-01	1491
2019-07-01	1522
2019-10-01	1564
2020-01-01	1615
2020-04-01	1647
2020-07-01	1680
2020-10-01	1710
2021-01-01	1730
2021-04-01	1750
2021-07-01	1772
2021-10-01	1793
2022-01-01	1804
2022-04-01	1823
2022-07-01	1786
2022-10-01	1789
2023-01-01	1616
2023-04-01	1609
2023-07-01	1560

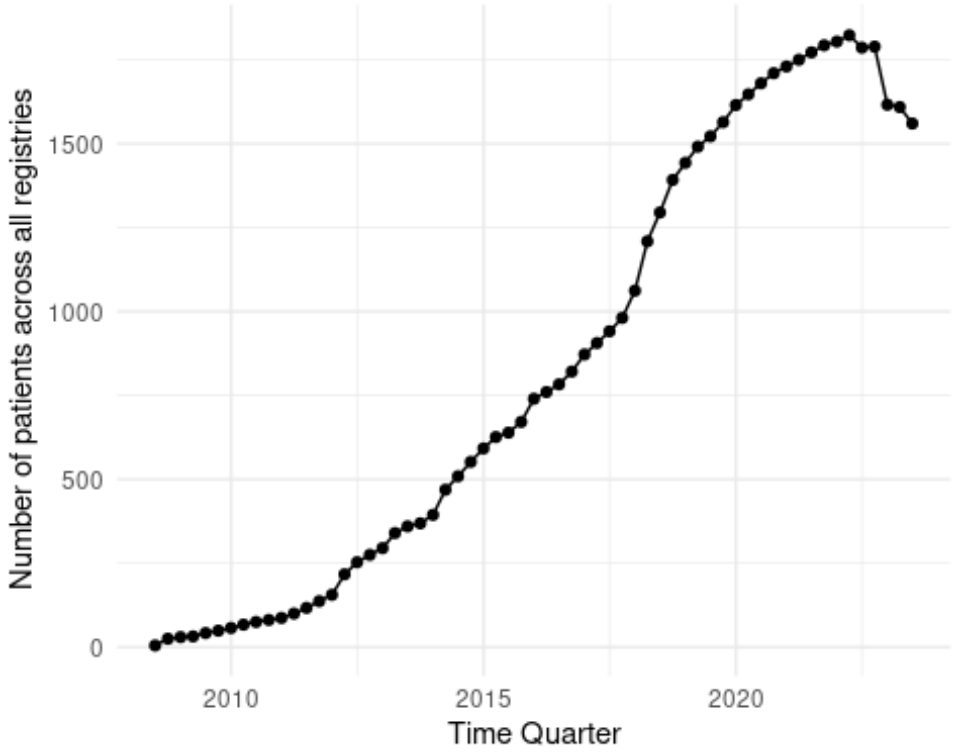


Figure 16: Number of patients in the registry for each quarter,from 2008-07 to 2023-07.

Data used for modelling

Table 5: Data used for modelling.

Quarter	Deaths	Ventilation	Composite
2008-07-01	0	0	0
2008-10-01	0	0	0
2009-01-01	1	0	1
2009-04-01	0	1	1
2009-07-01	0	0	0
2009-10-01	0	1	1
2010-01-01	0	1	1
2010-04-01	0	0	0
2010-07-01	0	0	0
2010-10-01	0	1	1
2011-01-01	0	0	0
2011-04-01	0	0	0
2011-07-01	0	1	1

Quarter	Deaths	Ventilation	Composite
2011-10-01	0	0	0
2012-01-01	1	1	2
2012-04-01	0	1	1
2012-07-01	0	0	0
2012-10-01	0	1	1
2013-01-01	1	1	2
2013-04-01	0	2	2
2013-07-01	1	3	4
2013-10-01	0	1	1
2014-01-01	1	0	1
2014-04-01	0	2	2
2014-07-01	1	1	2
2014-10-01	1	0	1
2015-01-01	0	0	0
2015-04-01	1	0	1
2015-07-01	0	0	0
2015-10-01	1	1	2
2016-01-01	1	2	3
2016-04-01	1	1	2
2016-07-01	0	0	0
2016-10-01	2	2	4
2017-01-01	1	4	5
2017-04-01	1	1	2
2017-07-01	0	3	3
2017-10-01	0	1	1
2018-01-01	0	1	1
2018-04-01	1	1	2
2018-07-01	0	0	0
2018-10-01	1	3	4
2019-01-01	1	1	2
2019-04-01	0	2	2
2019-07-01	2	0	2
2019-10-01	0	0	0
2020-01-01	0	1	1
2020-04-01	1	0	1

Quarter	Deaths	Ventilation	Composite
2020-07-01	2	0	2
2020-10-01	1	1	2
2021-01-01	2	0	2
2021-04-01	0	0	0
2021-07-01	2	0	2
2021-10-01	1	0	1
2022-01-01	1	0	1
2022-04-01	2	1	3
2022-07-01	5	0	5
2022-10-01	0	0	0
2023-01-01	1	0	1
2023-04-01	0	0	0
2023-07-01	0	0	0

AIC for all possible models

Table 6: AIC for all fitted models.

Outcome	DMT	AIC	Model
Ventilation	Zolgensma	136.8654	INGARCH
Composite	Zolgensma	187.9090	INGARCH
Death	Spinraza	123.5039	INGARCH
Ventilation	Spinraza	130.3246	INGARCH
Composite	Spinraza	183.0060	INGARCH
Death	Zolgensma	125.3958	ZEROINFL
Ventilation	Zolgensma	141.7434	ZEROINFL
Composite	Zolgensma	188.1515	ZEROINFL
Death	Spinraza	121.2603	ZEROINFL
Ventilation	Spinraza	135.5652	ZEROINFL
Composite	Spinraza	182.2529	ZEROINFL
Death	Zolgensma	121.6417	GLM
Ventilation	Zolgensma	134.2267	GLM
Composite	Zolgensma	184.7807	GLM
Death	Spinraza	120.6437	GLM
Ventilation	Spinraza	128.4808	GLM
Composite	Spinraza	179.0384	GLM
Ventilation	Zolgensma	136.8654	INGARCH
Composite	Zolgensma	187.9090	INGARCH

Outcome	DMT	AIC	Model
Death	Spinraza	121.2603	ZEROINF
Ventilation	Spinraza	135.5652	ZEROINF
Composite	Spinraza	182.2529	ZEROINF
Death	Zolgensma	125.3958	ZEROINF
Ventilation	Zolgensma	141.7434	ZEROINF
Composite	Zolgensma	188.1515	ZEROINF
Death	Zolgensma	121.6417	GLM
Ventilation	Zolgensma	134.2267	GLM
Composite	Zolgensma	184.7807	GLM
Death	Spinraza	120.6437	GLM
Ventilation	Spinraza	128.4808	GLM
Composite	Spinraza	179.0384	GLM