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EMA-funded registry-based study on spinal muscular atrophy disease (SMA)

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Committee for Advanced Therapies

An agency of the European Union

Background

- Currently 3 medicinal products authorised for the treatment of SMA
  - Zolgensma (onasemnogene abeparvovec)
  - Spinraza (nusinersen)
  - Evrysdi (risdiplam)

- As diagnosis and treatments are changing quickly, we need to better understand
  - The natural history and progression of SMA disease
  - Its standards of diagnosis and clinical care
  - The impact of the disease modifying therapies

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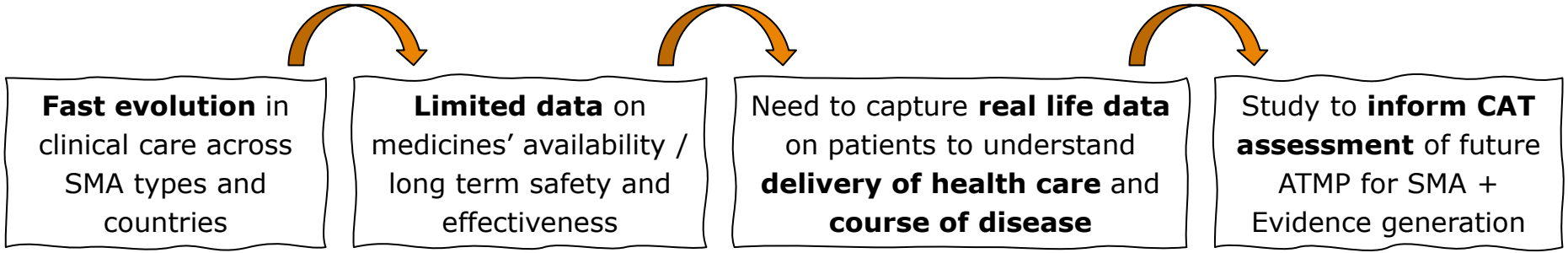
Rationale for this study

- 2022 CAT workplan activities on Real World Data (RWD) in regulatory decision making:
  - **Investigate patients' course of disease and standards of care** delivery over time in an ATMP relevant disease entity based on real world data from EU registries
  - **Develop research questions** and **contribute to an EMA-funded study** in an ATMP relevant disease entity to explore scientific and operational aspects
- SMA registry data in the 3 medicines' dossier + post authorisation registry-based studies



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EMA-funded study – Objectives

1. **To describe existing patient registries that collect data on SMA in the EEA**
   a) General overview of registries in the field
   b) Detailed overview on registries characteristics
   c) Registries interoperability
2. **To understand how to collaborate with registries on registry-based studies**
   a) Registries' overall experience in collaborating with 3rd parties on registry-based studies (i.e. non-for-profit organisations/academia, industry/CRO and regulators)
   b) Description of the administrative process for collaboration
   c) Description of operational aspects
   d) Description of governance aspects

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EMA-funded study – Objectives

3. **To assess registries suitability to take part in the EMA funded registry-based study on SMA: Feasibility analysis**

   a) Assessment of suitability of the identified registries

   b) Mapping of data elements of registries identified as suitable to identify possible overlaps, gaps and interoperability

4. **To develop the study protocol to analyse SMA natural history and its clinical management**

   a) Understand how patients are diagnosed and whether this has changed over time

   b) Understand the disease and its progression by generating evidence on patients' characteristics at baseline and throughout its course

   c) Understand how patients are treated and whether this has changed over time considering all available treatment options

   d) Comparability of patients' characteristics between clinical trials study population and registries population

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Main registry study objectives

To describe **SMA patients' characteristics at baseline** and throughout **course of disease**, as well as **clinical management and its evolution** over time across the multiple disease phenotypes and genotypes in at least **5 European countries**

- Secondary objective: Learn about how we can work with registries to improve evidence generation
- Study design: **Secondary** use of **retrospective** data routinely collected in SMA registries

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Procedural steps

- EMA funded study → EMA procurement rules → Strict timelines for review of deliverables (15 calendar days!)
- Not a formal regulatory procedure → No formal endorsement of deliverables by CAT
- BUT, we need to ensure the study meets CAT's needs → CAT subgroup on RWE
- February 2022: Procurement procedure starts
- Two tenders received and evaluated by EMA staff and CAT subgroup according to tendering criteria
- April 2022: contract signed with research organisation (Aetion). Collaboration with TREAT-NMD

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Study protocol – aim & objectives

- Submitted by Aetion to EMA on 17th November 2022, discussion with CAT members and accepted by EMA
- **Aim proposed by Aetion**: A registry-based cohort study of SMA disease to describe the natural history of SMA, the evolution of SMA care management considering the new disease modifying therapies (DMTs) **and assess the safety and effectiveness of these DMTs**
- **Revision requested** A registry-based cohort study of SMA disease to describe the natural history of SMA, the evolution of SMA care management and **disease progression** considering the new DMTs.
  - In addition, as a secondary objective Aetion is also requested to highlight in the final study report the study challenges and lessons learned from performing the study within the registries.

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Day 2, Session 1

Use case highlighting opportunities and challenges of registries for regulatory decision-making

Seung Lee
TREAT-NMD
(United Kingdom)

- Project Manager, TREAT-NMD

- In charge of the SMA natural history study with EMA and Aetion

Neil Bennett
TREAT-NMD
(United Kingdom)

- TREAT-NMD Global Registries Manager

- Oversees registry enquiries and data projects being undertaken by the registry network

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SCIENCE MEDICINES HEALTH

TREAT-NMD
Neuromuscular Network

AETION®

EMA workshop on patient registries

Spinal Muscular Atrophy use case

February 13, 2024

Research question & study objectives - Study design

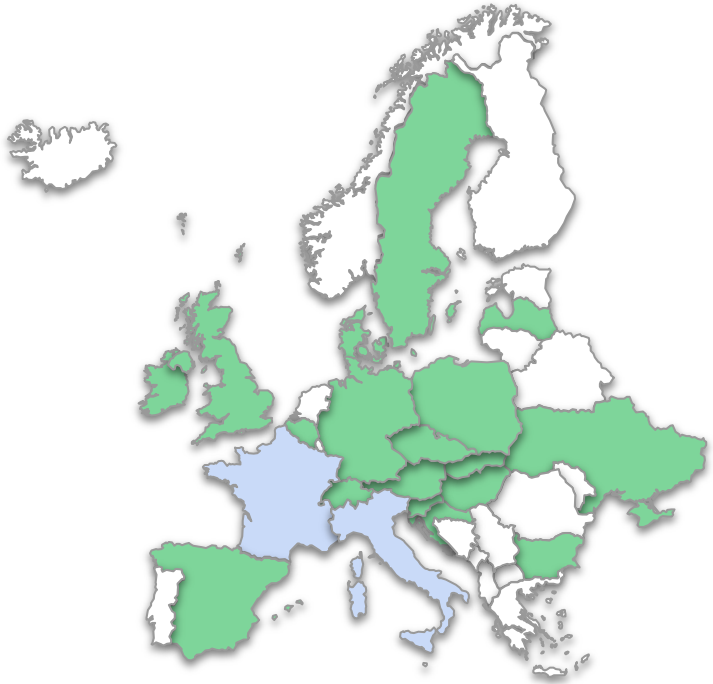
Research question: Investigate SMA patients' course of disease, evolution of standard of care delivery over time, and use, effectiveness and safety of Disease-Modifying Therapies (DMTs: Spinraza, Zolgensma, Evrysdi), in multiple European countries, using data routinely collected by existing SMA registries.

Objectives:

- **Preliminary objective:** Assess the registry specificities in terms of SMA population capture.
- **Objective 1:** Describe, by SMA type, the natural history of SMA (the disease and its progression), including patients characteristics, disease progression based on motor function assessment as well as respiratory, nutritional and skeletal deformities, post-diagnostic outcomes and Serious Adverse Events (SAEs) of interest.
- **Objective 2:** Describe, by SMA type, the evolution of diagnosis methods and of medicinal and non-medicinal treatment over time, including the DMTs use patterns.

Study design: A non-interventional retrospective cohort study of SMA patients using 6 European registries federated in the TREAT-NMD network.

Countries contacted for feasibility assessment



+Turkey and Georgia

- **Across the Treat-NMD network**, all active registries within the EMEA region were contacted for **pre-feasibility assessment - 17 registries**:

  Belgium, Bulgaria, Croatia, Poland, Denmark, Hungary, Latvia, Slovenia, Turkey, Georgia, Ukraine, Spain, Switzerland, UK & Ireland, Czech Republic & Slovakia, Germany & Austria, Sweden

- **Outside the TREAT-NMD network:** France and Italy registries were contacted

Identification of fit-for-purpose registries for the SMA study

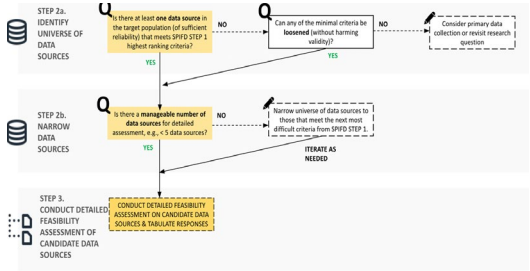
(1) Study concept -> operationalize minimal criteria and rank data

Research question:				
Row	**Design element**	**Minimal criteria for valid capture**	**Operational definition**	**Rank for uniqueness or importance**
1	Study population (inclusion and exclusion criteria)			
2	Treatment group			
3	Comparator group			
4	Primary outcome(s) (definition & ascertainment)			
5	Key secondary outcome(s) (definition & ascertainment			
6	Length and frequency of follow-up			
7	Confounding variable 1			
. . . N	. . . Confounding variable N			

SPACE Step 3

Feasibility questionnaire with a medical leader in SMA to define key variables needed (age, type of SMA, medications, disease characteristics, disease outcomes, …)

(2) Identify and narrow down registries options



Pre-feasibility: Contact of European SMA registries identified through TREAT-NMD network. Initial pre-feasibility questionnaire sent out to all EU registries **.**

Feasibility : Preselected registries received the feasibility questionnaire.

(3) Conduct feasibility assessment *

Row	Design element	Requested information	Data source 1	Data source 2	Data source 3	Data source 4
1	Study population (Inclusion/ Exclusion criteria)	• Availability of needed data types for each I/E • Cohort size				
2	Treatment group	• Availability of needed data types • Number of newly treated				
3	Comparator group	• Availability of needed data types • Number in comparator				
4	Primary outcome(s) (definition & ascertainment)	• Availability of needed data types • Risk of outcome in comparator				
5	Key secondary outcome(s) (definition & ascertainment)	• Availability of needed data types • Risk of outcome in comparator				
6	Length and frequency of follow-up	• Min, max, median follow-up time • Data lag time				
7	Confounding variable 1	• Availability of needed data types				
. . . N	. . . Confounding variable N	• Availability of needed data types				

Registry quantitative and qualitative assessment:

- Qualitative: administrative information, quality requirements (SOP, data cleaning, audit…)
- Quantitative : completeness of variables

Design Element	Data Source A	Data Source B	Data Source C	Data Source D
Database size	5	4	2	2
Lab results	5	3	2	5
Microbiology data	4	5	5	1
Covariates	4	4	4	4
Procedural endpoints	5	5	5	5
Clinical endpoints	4	4	4	4
Contracting time	low	low	medium	high

Guidelines used for questionnaire construction:

- EMA Guideline on registry-based studies (2021)
- EUnetHTA - REQueST tool (2019)
- FAIR Guiding Principles (Wilkinson et al, 2016)

***SPIFD**: Structured process for identifying fit-for-purpose data (Gatto et al., 2022)

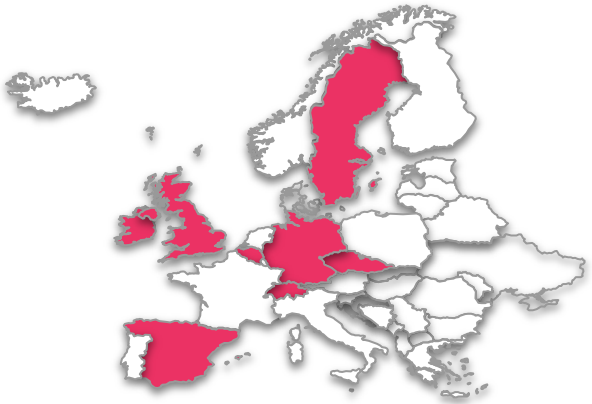
Ranking of registries and recommendations for the SMA study

Data elements	Germany & Austria (p)	Spain (p)	UK & Ireland (p)	Belgium	Sweden	Switzerland	Czech Republic & Slovakia	Bulgaria	Georgia✦	Latvia
Recommended for the study	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	No	No	No
Patient characteristics										
Demographics	5	5	5	5	5	5	5	5	1	1
Height and Weight	3		2	4	4	3	4	3	1	1
SMA characteristics	3	5	2	4	3	4	4	3	5	3
Genetic testing methods	1		1	4	4		1	3	5	3
Motor ability status	2	4	1	2	5	4	4	3	4	3
Comorbidities	2	1	2	5	5	2	4	1	2	1
DMT and Therapies										
DMTs information	2	3	2	5	5	3	3	5	2	1
Non-medicinal product therapies and aid	4	5	4		4	4	3		1	3
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	4	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
Other information										
SAEs				1	1	2	1	1	1	1
PROs		1	1	4	1					3

Ranking	Legend
5	Nearly all patients/items with a value recorded (95-100%)
4	Majority of patients/items with a value recorded (75%-95%)
3	More than half of patients/items with a value recorded (50-75%)
2	Less than half of patients/items with a value recorded (25-50%)
1	Very few patients/items with a value recorded (<25%)
	Data not collected or value recorded(%) is unknown

Countries contacted for feasibility assessment and final country selection

+Turkey and Georgia



- **Across** the Treat-NMD network, all active registries within the EEA region were contacted for **pre-feasibility assessment (17 registries):**
  Belgium, Bulgaria, Croatia, Poland, Denmark, Hungary, Latvia, Slovenia, Turkey, Georgia, Ukraine, Spain, Switzerland, UK & Ireland, Czech Republic & Slovakia, Germany & Austria, Sweden
- **Outside the TREAT-NMD network:** France and Italy registries were contacted

Registries selected after feasibility assessment (7 registries):

Belgium, Spain, Switzerland*, UK & Ireland, Czech Republic & Slovakia, Germany & Austria, Sweden

** Switzerland was finally not included in the study due to lag time in contracting process and data sharing.*

Selected data sources and study period

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

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.

	Registry start date	End date of data availability	Number of patients
Belgium	January 2018	December 2021	**256**
Czech Republic and Slovakia	May 2011	May 2023	**348**
Sweden	October 2010	April 2023	**175**
Germany and Austria	April 2008	May 2023	**697**
Spain	February 2015	April 2023	**319**
United Kingdom and Ireland	December 2007	May 2023	**393**

Distribution of 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)
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)
Sex - female / male (%)	48.4 / 51.6	48.3 / 51.7	48.6 / 51.4
DMTs; n (%)			
at least one DMT	1341* (61.3)	1321* (100)	NA
Spinraza	1003 (45.8)	1003 (75.9)	NA
Zolgensma	101 (4.6)	101 (7.6)	NA
Evrysdi	403 (18.5)	403 (30.5)	NA
Patients lost to follow up n (%)	650 (29.7)	176 (13.1)	474 (55.9)

*20 patients have been excluded from TREATED group as DMT intake start date was not available

2188 patients overall (ALL):

- **779 patients from 3 clinician-based registries** (Belgium, Czech Republic & Slovakia and Sweden,)
- **1409 patients from 3 patient-based registries** (Germany & Austria, Spain, UK & Ireland)

1321 TREATED and 847 NEVER TREATED:

- The proportion of never treated was higher than that of treated patients in Germany & Austria (44.9% vs 22.9%) and UK & Ireland (25.7% vs 12.9%)

SMA types:

- SMA 2 (41.8%), SMA 3 (35.6%) and SMA 1 (19.7%); similarly in treated and never treated

51.6% male and **48.4% female**

DMTs

- **1341 (61.3%) patients have been treated with at least one DMT**
- Among treated group, 75.9% treated at least once with Spinraza

Overall, 29.7% of patients were **lost to follow-up; 55.9% among never treated patients**

Key results / Objective 1

Natural history and disease progression - NEVER TREATED (N=847) and TREATED (N=1321)

In SMA type 1, 2 and 3, the improvements on best functional status observed once patients are under treatment suggest positive effects of DMT on disease progression.

In SMA 1 TREATED patients (N=276):

- **Best Motor function:** 101 patients (36.6%) achieved "sitter" and 33 (12%) "walker" status.
- **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 SMA 2 TREATED patients (N=540)

- **Best Motor function**: 329 patients (60.9%) achieved "sitter" and 133 (24.6%) "walker" status and only 5.9% remaining "non-sitters".
- **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 SMA 3 TREATED patients (N=476)

- **Best Motor function:** 418 patients (87.8%) achieved "walker" and only 1.5% remaining "non-sitters" status.
- **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".

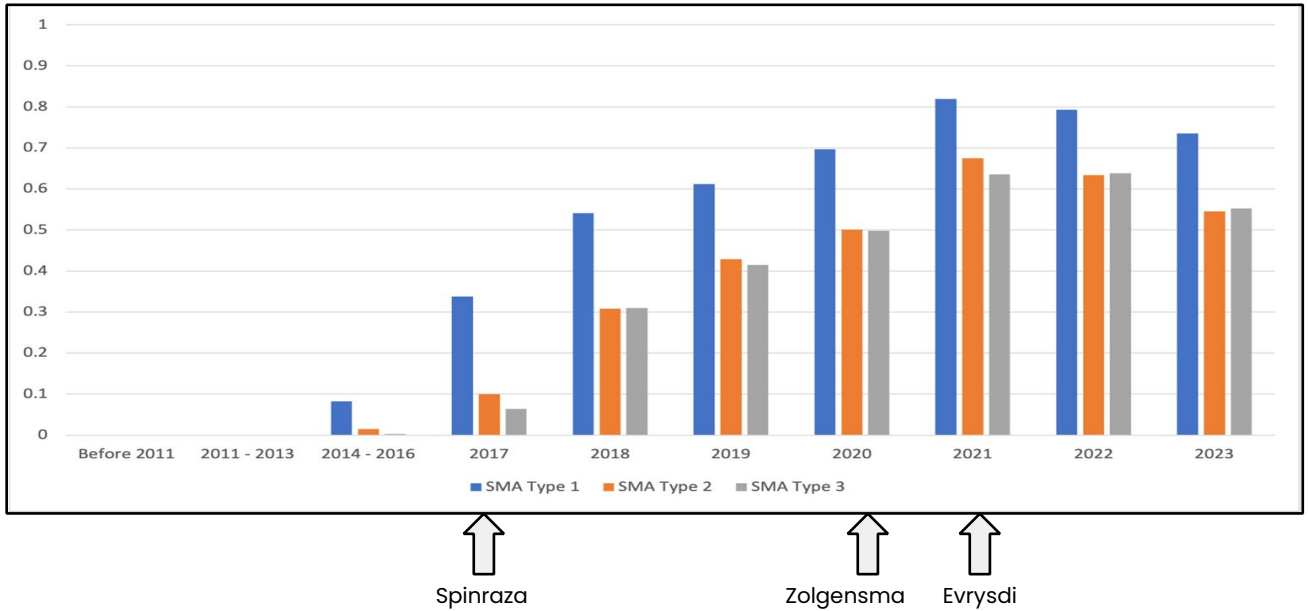
Key results / Objective 2

Evolution of healthcare management - ALL (N=2188)

We observe **an evolution of <u>medicinal treatments</u> over time**:

- **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.
- Overall, **1321 patients (60.4%) received at least one DMT**: 1003 patients (75.9%) were treated with Spinraza, 403 (30.5%) with Evrysdi and 101 (7.6%) with Zolgensma.

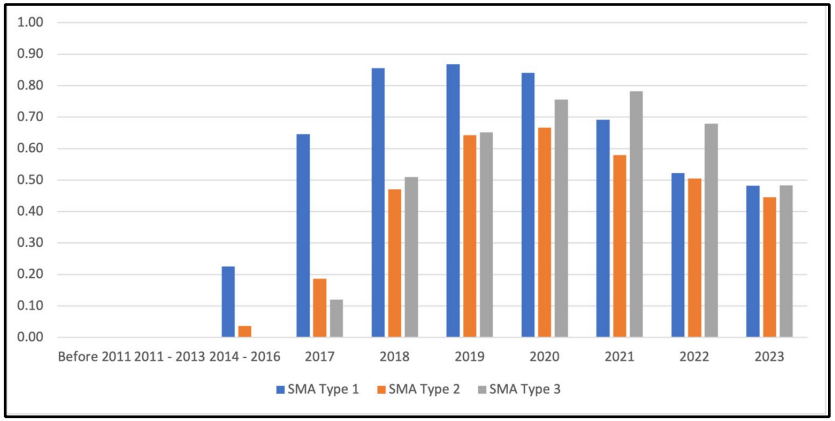
Proportion of patients treated with at least one DMT over time in SMA 1, SMA 2 and SMA 3



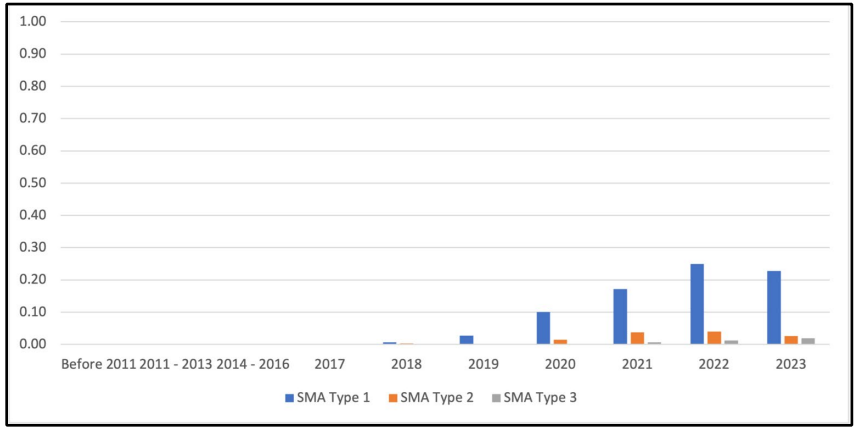
Key results / Objective 2

Evolution of healthcare management

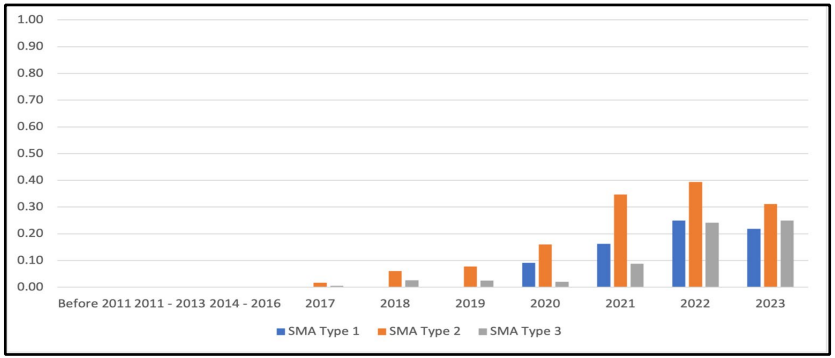
Proportion of patients with Spinraza intake over time in SMA 1, SMA 2 and SMA 3



Proportion of patients with Zolgensam intake over time in SMA 1, SMA 2 and SMA 3



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



- Spinraza was the most used therapy
- Spinraza and Zolgensma usage was often reported among patients with SMA type 1, whereas, a higher percentage of patients with SMA type 2 were treated with Evrysdi.

- 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%).

Conclusion

- The results were globally **consistent with existing studies** evaluating the 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.**

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

Limitations

Quality and completeness of the registry data (assessment in two phases):

- Initial recommendation at **feasibility phase** based on good completeness of records for all data elements, as well as for administrative information and quality requirements
- **Once data were analysed, we observed that the extent of missing data was important for many variables and was notable among never treated patients (e.g., functional status).** In never treated patients, it may suggest a less regular and accurate follow up and/or an under report of data in such patients, alongside the fact that 55.9% of those untreated were lost to follow-up.

AESI and deaths are underreported in such registries

Covid-19 concomitant context (impacting deaths and ventilation reports and completeness of data)

Heterogeneity and sample size across registries:

- Pooling all registries with some heterogeneities may have introduced imbalances and different weights in the descriptive statistics that may have impacted artifactually the percentages and estimates.

Further research projects might include **robust comparative designs** studying the DMTs effectiveness on some key pre-defined motor functions; starting by a pilot in a few voluntary registries to assess accurately the required data.

Lessons learned (=> ideas for improvement)

Use of multiple registries in rare disease provided complementary information and increased sample size.

EMA Guideline on registry-based studies and the SPIFD approach helped in guiding and structuring the assessment of registries' suitability for use in regulatory context.

- ➔ At the feasibility phase, further quantitative counting and higher granularity in defining the required data should be considered in the future.

Contribution from registries and study timelines to be improved

- ➔ Early dialogue with registries beyond a specific study should be promoted (what value can bring the contribution to Regulatory research for registries? e.g. France and Italy refused)
- ➔ Registries to be much more involved when developing the study concept and protocol

Underreporting of serious AE and deaths observed in all registries. Missing data concerning AEs is indicative of the fact that SMA registries have not been originally developed for routine data collection, and consequently, monitoring of safety of medicines

- ➔ Better efforts to collect and report AEs is needed, otherwise can not be used for safety purposes

Linkage availability

- ➔ Linkage of such SMA registries with other data sources available at a country level (e.g., EHR, Claims, PV, deaths,…) should also be considered in a larger vision of possible usages and benefits (i.e., early clinical research, clinical development, regulatory, HTA and Payers decisions).

Lessons learned (=> ideas for improvement)

Systematic data quality assurance processes and **understanding data missingness are important**:

- ➔ Further quality assurance processes and governance have been put in place to ensure further development and structure of individual registries.

Logistical challenges with accessing registries and providing statistical analyses can be addressed:

- ➔ Some registries had timeline issues and delays in delivering the data due to ethical approval and contracting challenges.
  - ◆ Early engagement with Registries
- ➔ Underestimated burden of 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)
  - ◆ Common dictionary and data model facilitate and expedite analyses (e.g. analytics and statistical library)

All these different elements suggest a common dictionary (e.g., common minimal SMA data model, common definition for the collection of key criteria and/or clinical judgement) for SMA Registries across Europe.

Lessons learned (=> ideas for improvement)

UNLOCKING THE POTENTIAL OF REGISTRIES FOR REGULATORY DECISION MAKING: LESSONS LEARNT FROM THE SMA REGISTRY STUDY

Joint HMA/EMA multi-stakeholder workshop on Patient Registries, 12-13th Feb 2024

Mencía de Lemus
Patient Representative at the Committee for Advanced Therapies, EMA

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Lesson learnt (I): It is important to find the best way for the regulator to relate to registries

Registries harbor valuable information…

… but time and effort need to be invested to unlock it for regulatory decisions

Early and direct relationship with registry holders is highly recommended:

- To understand the nature of the registry holder
- To understand the objetives of the registry
- To assess the FFP of the registries for regulatory needs.

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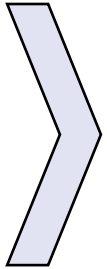
Lesson Learnt (II): the planning phase is large and evolving

- Scanning phase
- Definition of the objectives (after scanning)
- Drafting the ToR
- Establishing the research question
- Designing the study Protocol



Involve registries, patient organisations and HCPs

Different registries may address different questions: big registries- small, patient reported- clinician reported: **good assessment and a harmonised data model can be very useful, and avoid different interpretations.**

The iterative nature of a registry study must be acknowledged: as data is analysed, research questions are revisited and new ways to analyse data come forward.

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Lesson Learnt (III): Long-term relationship with registries must be established.

Registries will probably need to adapt:

- To capture the evolution of a disease with new DMTs (mid and LT) .
- To collect data on AEs
- To offer the opportunity to compare between treatments (if no head to head trials)

Information from registries will be needed throughout the assessment procedure and after the marketing decision has been taken: TIME

A continued dialogue with patients and experts will establish if a certain aspect of the evolution of the disease is meaningful to patients or relevant from a clinical point of view.

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Lesson Learnt (IV): PROMs must be specifically addressed

Patient-reported registries have shown to have comparable quality than clinician-reported registries.

Patient Relevant Outcome Measures must be assessed in the prelir phases and incorporated specifically into the study Protocol.

PROMs can provide complementary information to the clinical data.

.. However, specific attention must be given to them, or they will risk to be underused or incorrectly interpreted.

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Lesson Learnt (V): Registries need support

- Many registries lack of education on regulatory needs.
- Support to regulatory needs require effort and resources.
- Adaptation to regulatory needs require even more effort and resources.

Accompaniment, training and resourcing of registers should be carefully considered

Registry-holders must be reassured on the **correct use of their data**: should have always the capacity to input and correct.

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