SMA Expanded Dataset

Final Report (Year 4)

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Executive Summary

This is the concluding report provided to the project sponsor Biogen, which summarises the results, key highlights and learning gained from a four-year study into the adoption of an expanded dataset for Spinal Muscular Atrophy (SMA) by the TREAT-NMD global affiliated registry network.

32 SMA registries participated in this project with 28 registries (88%) now reporting that their data collection forms, or IT platforms comply with the expanded core dataset. We have recognised that adoption of the dataset has been both complex and challenging for many registries, regardless of size or resource-capacity, and time to adopt has been longer than was first anticipated. Despite this, most registries have acknowledged the real benefit of collecting clearly defined, well-structured standardised data and enjoy being part of a global collaborative network.

The dataset will continue to be reviewed to ensure it remains feasible for collection, responsive to changes in therapies and our increasing knowledge of disease progression. We are mindful however, that dataset updates can have a significant impact on the work of registries and there is a time-lag between the publication of a new dataset and when the registry network starts to collect it. The work undertaken on this project has been instrumental in helping to inform and pave the way for the development of other TREAT-NMD datasets namely DMD & LGMD, with FSHD and COL6 to follow.

There are two recent highlights to share: -

- ***PMS Study*** – a key aim of the project was to be able to utilise this dataset to support Post-Marketing Surveillance (PMS) studies. This provides valuable evidence for regulators and payers regarding the effectiveness of treatments and patient outcomes, and we can report that in 2023 TREAT-NMD is actively supporting two PMS studies.
- ***Data Completeness Study*** - for the first time we've been able to assess the quality and completeness of de-identified patient records for a sub-set of registries. This provides a new level of confidence on what's being collected and identifies potential areas for support/training.

Beyond this project, there are several challenges which still need to be addressed:

- Is the 'one size fits all' model for data collection a feasible approach in the long term
- Quantity V's Quality of data - large volume may impact data quality
- How can we realise the potential of advanced registries whilst not excluding smaller ones?
- How to ensure continued engagement from registries, clinicians, and patients so that data collection is beneficial to all involved?

To conclude, registries and the global registry network are increasingly recognised as having a hugely important role in collecting patient data outside the clinical setting. This project has demonstrated the very real power of global data collection by a strong community network, providing a single point of access to answer key research questions to drive improved outcomes for patients.

1. Background

The purpose of this project has been to implement an expanded core dataset for SMA across the TREAT-NMD Global Registry Network. In the past, global data collection used a core dataset designed to support clinical trial feasibility and recruitment studies.

In 2017, TREAT-NMD identified a need to expand the dataset in response to the changing needs from the SMA community. The therapy landscape had evolved rapidly with the emergence of three disease modifying therapies (DMT's) and there was a growing requirement from both regulators and payers to fully understand the efficacy of expensive treatments and the impact on the natural history and disease progression of SMA. There was also an emerging focus from regulators on the use of registry data to support post marketing surveillance studies and so TREAT-NMD, supported by Biogen, set up a project to address this.

A multi-stakeholder workshop was held to build consensus on a dataset to be collected by the TREAT-NMD global network of registries. This project was supported by Biogen, with the approved therapy Nusinersen (Spinraza), however it was agreed that a disease-specific, not drug-specific, approach would be followed when reviewing the dataset.

Due to the increase in number of data items between version 0 and version 1, it was decided to undertake a Pilot Study which would provide real-world feedback on the feasibility of the proposed expanded dataset. A total of 10 registries took part in this exercise and the results from the pilot study highlighted that across our diverse range of registries, adoption of an expanded dataset was often difficult, time-consuming and largely depended on how well-resourced the registry was.

The pilot study recommended a phased-approach for the roll-out of the dataset and this was outlined in the 3-year project plan (Aug 2018). In each year, a sub-group of registries would be invited to participate with the project team providing support, training and guidance on data collection.

The table below is a high-level overview of the various stages of the project.

2007	TREAT-NMD established as a European Neuro-Muscular Disease registry network
2014	Version 0 dataset introduced
2017	TREAT-NMD initiates project to review and expand the core dataset for SMA registries
2018	Version 1 dataset introduced
2018	Pilot Study - sub-group of 10 registries pilot the V1 dataset to test practically and feasibility with collection
2019	Dataset Revision – feedback from pilot registries and the wider stakeholder community ~ 700 suggestions received and analysed
2019	Expanded Dataset Implementation Project – commence 3-year project to support adoption of the dataset across the TREAT-NMD registry network
2020	Version 2 dataset launched
2022	Approval for one year extension to the project
2023	Close of project t closure

Table 1 – Project Timeline

2. SMA Dataset Overview

It is useful to recap on the development of the TREAT-NMD SMA dataset to understand the journey and how far we have come in a relatively short period of time.

2014 Version 0 (V0) – ***26*** basic data items collected to support clinical trial recruitment.

2018 Version 1 (V1) – dataset expanded to ***167*** data items and introduced new classification of mandatory and highly encouraged data items.

2020 Version 2 (V2) – dataset revised resulting in the introduction of a highly structured and detailed dataset with ***154*** data items.

2023 28 registries report SMA data collection complies with the core (V2) dataset

2.1 Summary of changes between dataset Version 1 > Version 2

Whilst there was minimal change to data items between V1 & V2, there were considerable improvements made to the definitions and structure. The key changes resulted in the following:

- Dataset converted to machine-readable format
- Response options standardised and clarifie
- Data model and data types properly defined and labelled
- Stable and unique identifier assigned to each data item
- A single source file (JSON) for the dataset containing all relevant information for each data item (descriptions, definitions, response options, applicability, implementation notes, conditional logic, suggested wording for data collection forms, and example data representations)

In summary, the SMA Core Dataset V2 is a well-structured, clearly defined dataset supported by a publicly available on-line technical specification tool, adaptable to any registry type and optimised for FAIR (Findable, Accessible, Interoperable, Reusable) data standards. Whilst detailed enough to support standardised data collection, the dataset also allows enough flexibility to be applicable to any registry, country, or software environment. The TREAT-NMD core dataset is deemed to be a minimum dataset, allowing registries freedom to collect additional items of local interest or relevance.

3. Project Deliverables (Years 1-4)

The deliverables as detailed in the research contract are summarised in Table 2.

Initially established as a 3-year project (05-2019 to 05-2022), progress was adversely affected by the COVID pandemic with several registries reporting re-direction of resources to support internal healthcare systems. The project team requested a one-year extension to allow them to continue supporting existing registries and to engage with new registries in the network. An extension was approved for a 4th year with a revised end date of May 2023.

	Deliverable	Due	Completion date
Year 1 (2019/20)	D1: Dataset Manual	M6 (Nov 2019)	13-12-2019
	D2: Year 1 workshop for dataset implementation support/harmonisation	M6 (Nov 2019)	13-12-2019
	D3: Financial bursaries available for year 1 registries not receiving direct Biogen funding	M6 (Nov 2019)	23-12-2019
	D4: Establishment of formalised annual review process and mechanism for stakeholder input	M8 (Jan 2020)	13-12-2019
	D5: Outcome measure toolkit (as defined in Appendix 1)	M12 (May 2020)	15-05-2020
	D6: Year 1 Project Report	M12 (May 2020)	31-07-2020 (extension)
Year 2 (2020/21)	D7: Financial bursaries available for year 2 registries not receiving direct Biogen funding	M13 (June 2020)	30-06-2021
	D8: Year 2 workshop for dataset implementation support/harmonisation	M16 (Sept 2020)	27-10-2020
	D9: Year 2 Project Report	M24 (May 2021)	02-07-2021 (extension)
Year 3 (2021 / 22)	D10: Financial bursaries available for year 3 registries not receiving direct Biogen funding	M25 (June 2021)	30-06-2021
	D11 Year 3 workshop for dataset implementation support / harmonisation	M28 (Sept 2021)	20-05-2021
	D12 Interim Report	M36 (May 2022)	01-07-2022 (extension)
Year 4 (2022/23)	D13 Final Project Report	M48 (May 2023)	24-04-2023
	D14* Year 4 Dataset Workshop	*not specified in the contract extension	07-12-2022
	D15* Year 4 Dataset Workshop report	*not specified in the contract extension	15—01-2023

Table 2 – Project Deliverables

4. Year 4 updates

4.1 Registry Summary

10 registries were invited to participate in Year 4 (May 2022 - Feb 2023) with two registries joining those being Turkey (LUKAM) and Mexico. These registries progressed swiftly and have been able to demonstrate adoption of the core dataset and received bursary support.

The rate of new registries joining the project reduced over time, but this was anticipated with the more well-established registries choosing to engage in the early stages of the project. Other than the 2 registries who joined in Y4, we've been unable to offer financial support to additional registries as bursaries were ring-fenced to existing registries who were mid-way through dataset adoption. Table 3 below summarises on-going contact with registries interested in adopting the core dataset. Further

discussions will be taken forward by the TREAT-NMD Global Registries team who continue to grow the SMA network.

South Korea	Registry member since May 2021 but moving to a new platform for data collection and trialling adoption of TNMD DMD patient data and then adopting SMA.
Argentina (ANMDR)	Registry interested in joining but has struggled with TGDOC membership process and GRP adoption as not available in Spanish. Look to simplifying membership process. The cost of adapting their current IT platform exceeds the financial support available.
ALAME	Association of Latin American Alliance working as a South American network to support patient data collection where in-country registry doesn't exist (e.g Venezuela).
Pakistan	In discussions re TGDOC membership. 124 SMA patients (104 genetically confirmed)
China CGDR	Recent contact with registry following 3 years of no response
China NMD	Continue to follow up with registry.
Hong Kong	Recent TGDOC membership (Jan 2023) and starting discussions on core dataset collection but not part of project as bursary funding already allocated
Japan	SMART consortium is moving to the Rare Disease Data Registry of Japan. Will apply for RGDOC membership once system stabilizes.

Table 3 – Target registries for 2023/4+

4.2 Curator Workshop (D14)

The final workshop was held on 7th December 2022, Vancouver and preceded the TREAT-NMD conference and Annual Curators Meeting. This was the first in-person workshop since Leiden in 2019 and 24 registrations were received. 19 delegates attended the workshop with several curators unable to travel due to visa restrictions. The focus of this final workshop was to provide an overview of the key highlights from the 2022 curator survey report, discuss key challenges and decide on future priorities.. The following topics were the subject of group work:

- Group A – What are the key research questions the SMA community want answers to?
- Group B – How can the global SMA registry network work better together?
- Group C – Working with industry/regulators - share experience of what's worked well / not so well
- Group D – Sharing best practice on patient recruitment strategies and how to make registries more patient centric.

The **Year 4 Workshop Report** can be viewed on the TREAT-NMD website and was circulated to Biogen and all participating SMA curators in January 2023.

5. Results of 2023 Annual Curator Survey

5.1 Registry Summary

All 37 SMA registries in the TREAT-NMD global network were invited to participate in this project, with 32 registries (86%) participating. The remaining curators were either non-responsive or indicated that adoption was not possible for them in the short /medium term.

The final survey was issued in February 2023 with 28 of 32 registries responding. 2 registries did not complete the survey, one registry is no longer collecting SMA patient data and one registry was not issued survey as a result of joining the project at a late stage.

Figure 1 highlights the growth in patient numbers since 2019 with a 38% increase reported between Y1-Y4. This increase reflects the growing attention on the collection of rare patient data and confirms the need to standardise data collection. The majority of the participating registries have less 250 patients with 5 registries having between 500 - 1000 patients.

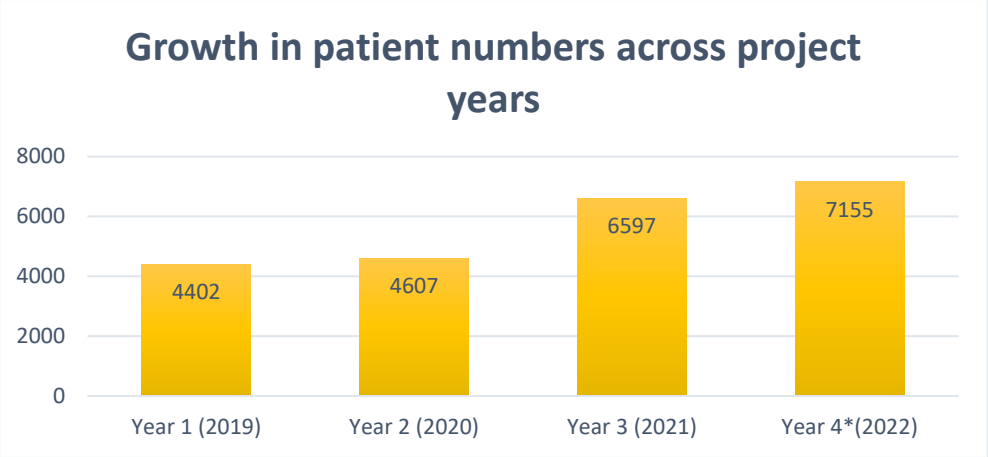


Figure 1. Increase in patient numbers across the project year (including last known patient numbers from Serbia, Egypt NMD and India)*

Table 4 reflects the year in which registries joined the project, details which version of the dataset they report to be using and whether they have adopted the GRP as their input platform. We are very encouraged by the fact that all registries have expanded their data collection activities and now collect either V1 or V2 of the SMA dataset. Of these, 88% (n=28) indicate they have the capacity to collect the core dataset (V2) via their IT platforms or patient data collection forms.

Registry	Project Participation Year	Version of dataset being used	Global Registry Platform (GRP) user
1. Australia	**Pilot (n= 10)**	Version 2	
2. Belgium		Version 2	
3. Canada		Version 1	
4. Egypt (NMD registry)		Version 2	
5. Germany (Munich)		Version 2	
6. India		Version 1	
7. New Zealand		Version 2	
8. Slovenia		Version 2	✓
9. UK & Ireland		Version 2	
10. Ukraine		Version 1	

11. Czech Republic/ Slovakia	**Year 1 (n=8)**	Version 2	
12. Hungary		Version 2	✓
13. Latvia		Version 2	✓
14. Poland		Version 2	
15. Serbia		Version 2	
16. Spain		Version 2	
17. Switzerland		Version 2	
18. Turkey (KUKAS)		Version 2	
19. Armenia	**Year 2 (n=8)**	Version 2	
20. Bulgaria		Version 2	✓
21. Colombia		Version 2	
22. Croatia		Version 2	✓
23. Egypt (PED-NMD)		Version 2	
24. Georgia		Version 2	
25. Malaysia		Version 2	
26. Sweden		Version 2	
27. China (SMA)	**Year 3 (n=4)**	Version 1	
28. Iran		Version 2	
29. Lebanon		Version 2	✓
30. South Africa		Version 2	✓
31. Turkey (LUKAM)[1]	**Year 4 (n=2)**	Version 2	
32. Mexico		Version 2	✓

Table 4 – Year of registry engagement & dataset version collected [1]Turkey (LUKAM) – initially agreed to participate in Year 3, but delays meant it was not able to complete the curator survey in 2022. This registry has been re-classified as a Year 4 registry.

4 registries still collect V1 and have not progressed to V2 for a variety of reasons: national programme review underway, conflict situation, additional funding, or lack of resources. This is an improved picture from 2022 when 1 registry was collecting V0 & 6 registries were collecting V1.

5.2 Motor Outcome Measures (OM) /Patient Reported Outcome Measures (PROMs)

The collection of at least one validated motor OM is a mandatory requirement for clinician-reported registries. However, 25% of registries report that they rarely or never collect a validated motor outcome measure. The reported frequency of motor outcome measure collection is shown in figure 2 below.

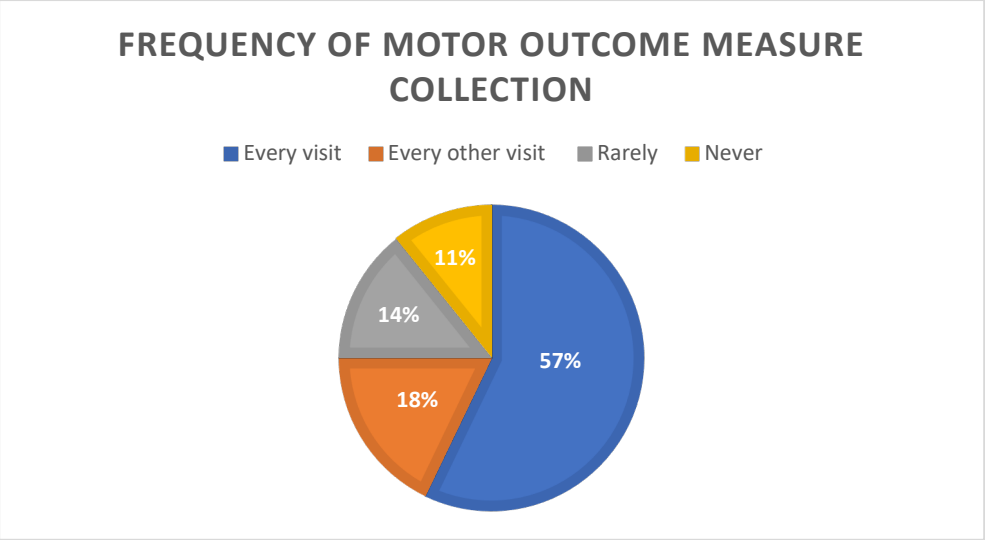


Figure 2. Reported frequency of motor outcome measure collection

Over the course of this project, it has become apparent that many registries still struggle with the collection of these items primarily due to a lack of in-country physiotherapy provision or training. This is problematic, as the standardised collection of motor outcome measures, is essential if we are to properly evaluate and establish the efficacy of available treatments and their impact on patients' lives.

The SMA OM Library was developed as a quick reference tool for registries in the network to support independent decision-making and implementation of the most appropriate OMs for their patients. Whilst TREAT-NMD recognise it's not feasible to mandate which OM's should be collected by registries, the list of 'recommended' OM is becoming more defined as global consensus on the most appropriate OM to use in this population grows.

A key theme from the December 2022 workshop was the ability to share best practise amongst curators. To assist with the consensus-building process around motor OM, registries were asked to define under what conditions they would use each OM from a list of the most collected collected motor measures informed by the Y3 annual survey. Figure 3 below shows the top four most collected motor outcome measures and the conditions under which registries report that they would use them.

Figure 3. Most commonly collected motor OM and populations in which they would be used.

In addition to the collection of one validated motor OM, the items '*patient global impression of severity*' (GIS) and '*patient global impression of improvement*' (GII) are mandatory for both clinician and patient reported registries. It is also highly encouraged (but not mandatory) that registries collect at least one additional patient reported outcome measure (PROM). 9 registries report they weren't collecting 'GIS' and a further 6 registries reported they weren't collecting 'GII'

Curators have informed us that they've noticed a decrease in patient engagement when asked these questions. There are concerns surrounding the use of this measure, particularly in cases where this may be used to inform the decision to renew / stop treatment and so patients are becoming reluctant to answer. 10 registries reported no collection of PROM data, and this was largely due to either disparities in national standards or lack of knowledge on the most useful scales to implement.

The most commonly collected PROMs are shown in figure 4 below.

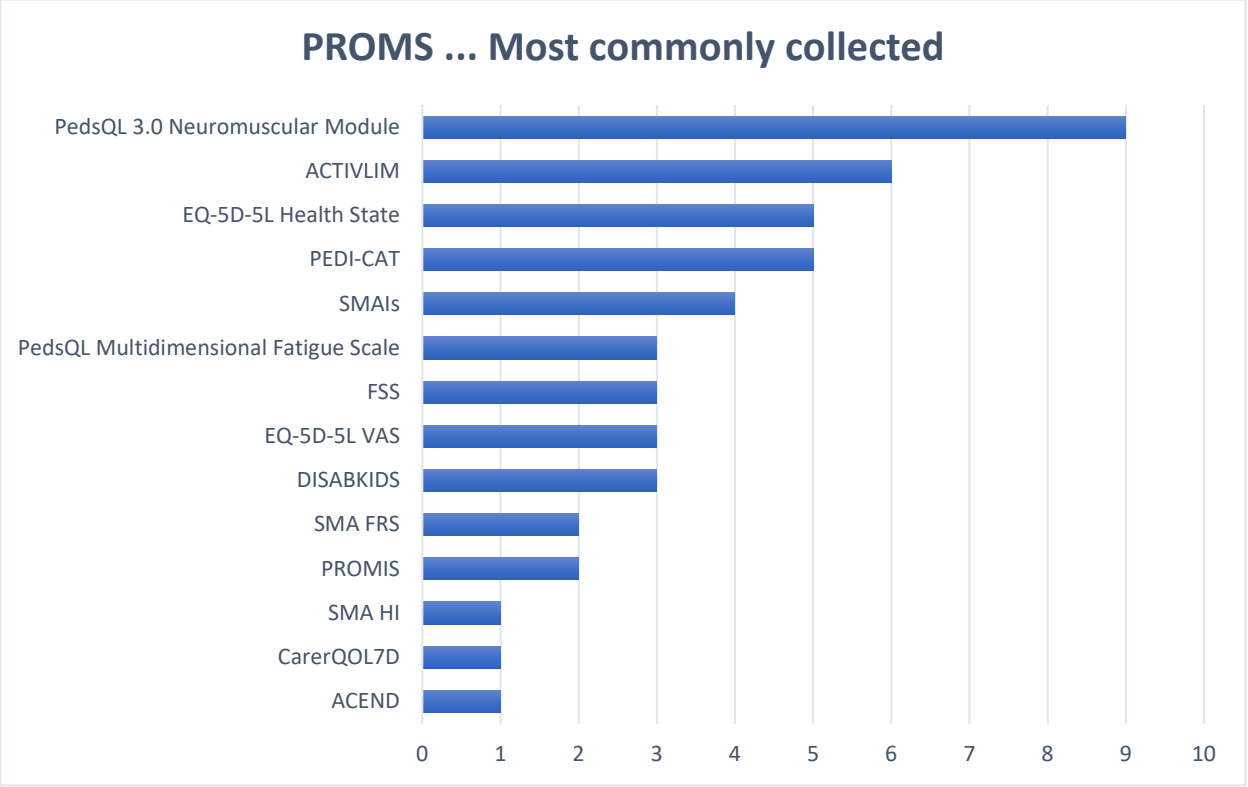


Figure 4. Most commonly collected PROMs reported by registries.

5.3 Disease Modifying Therapies (DMT)

Of the 28 registries who responded to the survey, only three registries reported having no in-country access to any of the three treatment therapies. This is an improved position from 2022, when 5 countries reported no access to any DMT and 13 registries reporting some level of access to all 3 DMTs. The results from the survey are summarised below in figure 5.

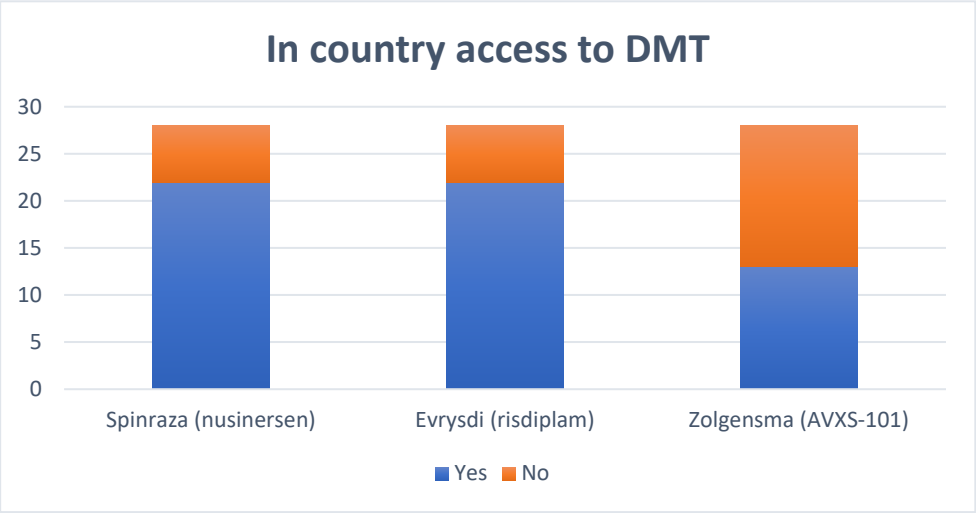


Figure 5. Access to DMT's. Data presented from a curator survey (Feb 2023) and reflects what PI's/curators have reported regarding therapy access in their own country. Access is defined as any DMT available irrespective of reimbursement restrictions or route of access.

5.4 New-Born Screening (NBS)

New-born screening for SMA is becoming more widespread with many countries now implementing SMA testing into their NBS programmes. Evidence shows that the earlier the diagnosis and intervention, the better the patient outcome and work is underway to establish the 'golden window' for treatment. As part of the final survey, curators were asked to indicate if NBS was available in their country, either routinely or as part of a pilot project. It's interesting to note that at the start of our project (2019) NBS was not routine and in the space of 4 years, 50% registries report that this is either available or in pilot phase. The results are shown in figure 6 below.

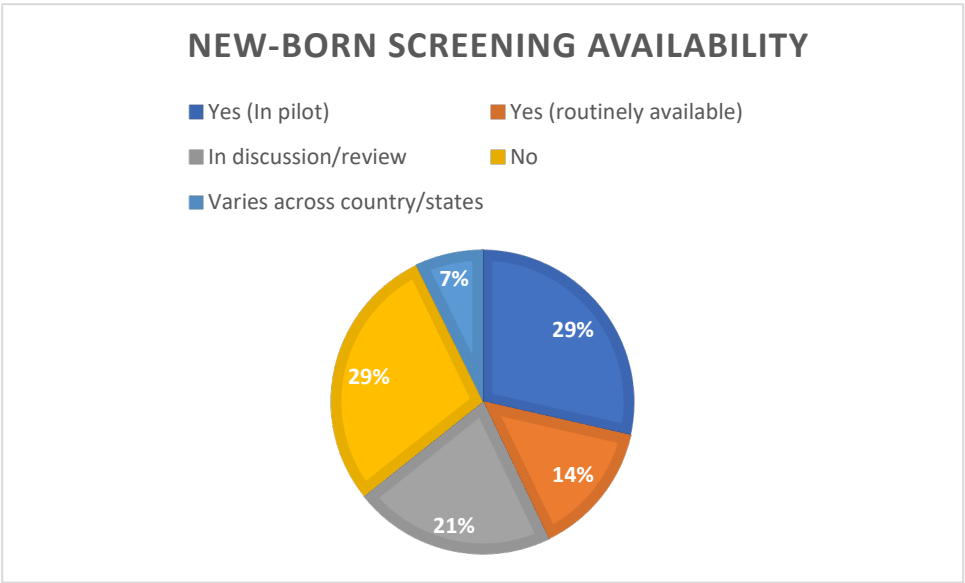


Figure 6. Availability of New-born screening reported by registries.

5.5 Bursary Payments

The bursary payment is paid to recognise the additional effort and costs borne by registries when increasing data collection and to alleviate some of this burden. This was paid in two parts: Part A (€4,000) when a registry commits to participating in the project and Part B (€4,000), when a registry can demonstrate compliance. The extension of the contract for an additional year has allowed us to process 15 additional payments which otherwise would not have been paid had the contract terminated as originally intended in May 2022.

Project Year	Part A Paid	Part B Paid	Total payments
Pilot registries (2 registries given special consideration	2	1	€12,000
Year 1	4	3	€28,000
Year 2	6	3	€36,000
Year 3	3	0	€12,000
Year 4	5	10	€56,000
	20	**1 7**	**€144,000**

Table 5 – Number of bursary payments processed in 2022/3

Whilst the financial support is welcomed by registries, it does not compensate for the true cost of implementation. Registries were asked to give an estimate of total cost considering staffing, IT upgrades and training. The table below reflects what they report the actual costs to be.

	Software	Staff Time	Training	PM/Comms	Other*	Totals
Registry 1	3,500	2,000	1,000	500	2,000	**9,000**
Registry 2	3,000	2,000	1,000	3,000	0	**9,000**
Registry 3	3,000	3,000	1,000	3,000	0	**10,000**
Registry 4	2,000	6,000	1,000	400	1,000	**10,400**
Registry 5	3,710	3,000	100	500	0	**7,310**
Registry 6	83,540	0	0	0	0	**83,540**
Registry 7	8,000	15,300	0	4,200	2,030	**29,530**
Registry 8	1,500	13,000	3,000	1,500	1,000	**20,000**
Registry 9	0	4,000	0	400	0	**4,400**
Registry 10	500	6,000	1,000	500	2,500	**10,500**
Registry 11	10,000	2,500	0	500	0	**13,000**
Registry 12	3,000	2,000	1,000	1,000	1,000	**8,000**
Registry 13	1,000	7,000	0	2,000	2,000	**12,000**
Registry 14	100	1,000	1,000	500	0	**2,600**
Registry 15	7,000	4,000	0	3,500	5,300	**19,800**
Registry 16	0	2,000	2,000	0	0	**4,000**
Registry 17	40,000	0	0	0	0	**40,000**
Registry 18	0	1,800	0	600	6,500	**8,900**
Registry 19	1,800	5,700	750	1,000	250	**9,500**
Registry 20	0	5,000	1,000	1,000	8,000	**15,000**

Table 6. The anticipated true cost of dataset implementation.

(**Other* -** includes such costs as motor testing equipment, Accounting Services, Data Protection Delegate/Advisor & telephone, printing & postal costs sending registry documentation, database

storage, publishing leaflets on SMA for neurologists, genetic testing & counselling, toys to keep SMA babies entertained in clinic)

6. Data Completeness Study

In previous years, the annual report has detailed information on data compliance which was self-reported by the registries. We are pleased to report that for the first time, a ***Data Completeness Study*** has been undertaken with a sub-group of registries (n=7) agreeing to export de-identified patient level data for analysis. We can now report with confidence which items are **actually** being collected and can share these results**.** The registries taking part are Global Registry Platform (GRP) users and agreed to export data so that quality checks could be undertaken to establish accuracy of record-keeping and identify % level of record completeness.

De-identified patient data was uploaded to the secure TREAT-NMD Central Data Warehouse (CDW) in March 2023, and this is a progressive move forward in assessing data quality and robustness.

The results as shown in Figure 7 indicate the range of data completeness across the participating registries (A-G) with an average overall completeness across the range of data items of ***82%.*** The n number represents the total number of answered questions (across all patients and visits)/total number of questions.

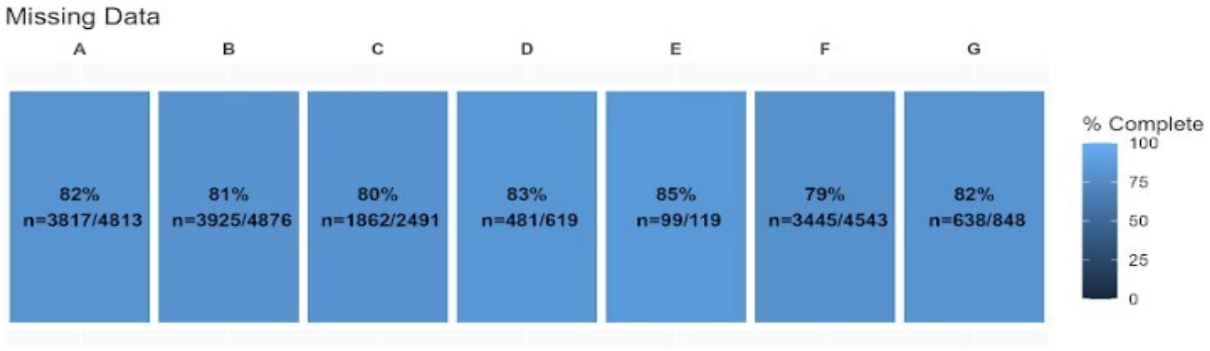


Figure 7: Data completeness by registry

We are encouraged by the level of data completeness given registries are relatively new to using the platform. There is however room for improvement, and we can now identify which data items/groups are most frequently not collected and provide tailored support to bridge any gaps in understanding or better understand reasons for missing data items. There was some commonality across registries of items not collected (Appendix 2) with the most lack of completeness being in relation to patient reported outcome measures (PROMS) and the PPRL (privacy preserving record linkage).

As the platform is designed around the SMA core dataset, and pre-populated with all the conditional logic and variables, we had anticipated a relatively high level of record completeness. This may not be true for all registries, especially those with less well developed IT systems and where there may be a greater degree of incompleteness depending on local interpretation/understanding of the dataset.

Verifying that registries are collecting high quality standardised data is vitally important and TREAT-NMD will be performing a similar study across a wider sample of registries in the future. This will ensure the core dataset are 'fit for purpose' and are able to reliably support PMS studies and answer key research questions.

Figure 8 below depicts a more detailed breakdown of completeness by categories / data groups. The n number represents the total number of answered questions (across all patients and visits)/total number of questions in each section. The full Data Completeness Report is available to view in Appendix 2.

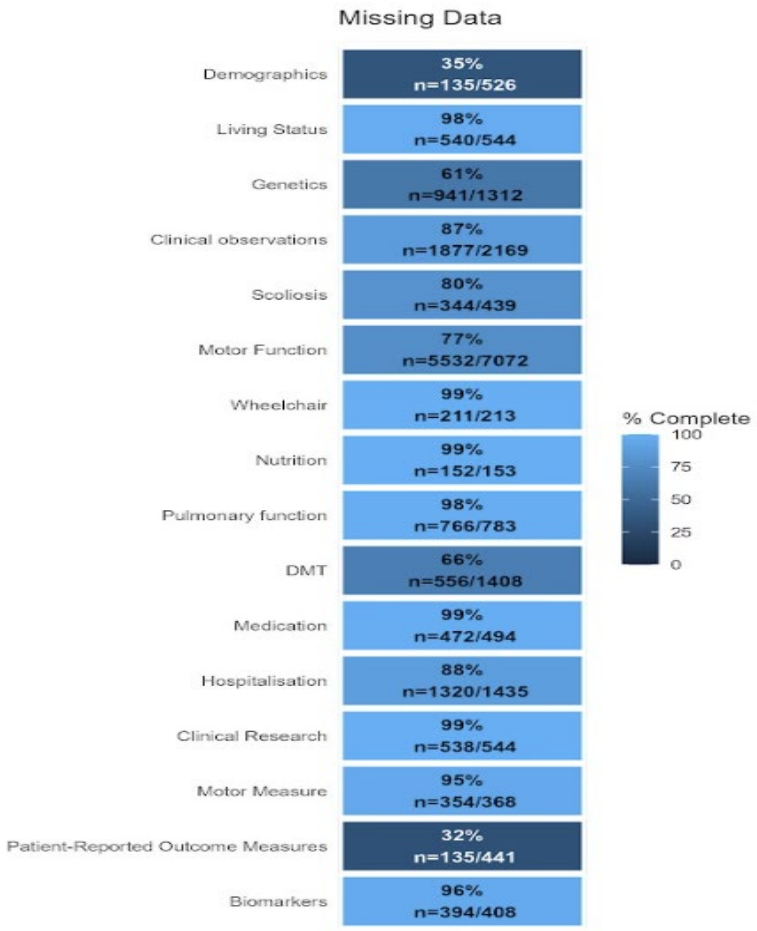


Figure 8: Overall data completeness split by Item grouping

We would like to express our thanks to those registries who took part in this data sharing exercise. The results of this will be fed back to individual registries.

7. Deliverables Update

7.1 Global Registries Platform (GRP)

In July 2021, a free-to-use cloud-based platform was introduced by TREAT-NMD and is pre-populated with the core datasets for SMA, DMD & LGMD. To date, 8 SMA registries have adopted this as their primary means of data collection, and the speed of adoption is on average 6 months from introduction through to implementation. This is significantly quicker than for registries where IT systems need to be updated or built from scratch. Whilst feedback from adoption of the platform is generally positive, there are some challenges to adoption:

1) Platform is available in English only - the costs of translating the platform into other languages has been assessed and is very costly.
2) Only the 'core' data items are specified and should a registry wish to collect additional items they need to maintain a separate database (name, GP information, contact details etc).
3) No bulk upload facility for migration of existing records into the GRP is currently available. This means registries need to re-enter patient history which can be time consuming, particularly so for large registries.
4) Slow performance issues were reported however these have been rectified.
5) Standard reports are available for use by registries, but further work is required to expand the number of reports available to registries so that they can self-report on patient data.

TREAT-NMD will continue to manage and make improvements to the GRP to enhance user experience and address feedback.

7.2 Outcome Measures (OM) Library

In response to registry comments that physiotherapy support was not widely available, the OM library was developed in Year 2. This is as a useful aide to support physiotherapists with the range of outcome measures and PROMS available with appropriate links and guidance as to when they should be applied. This document is available on the TREAT-NMD website and the intention is to further develop this to provide support for other disease areas.

OPEN-TACT is an e-learning physiotherapy resource, created by Anna Mayhew with support from MDUK. The training resources are designed by a panel of expert physiotherapists for the benefit of specialist neuromuscular and community-based physiotherapists. The primary aims of OPEN-TACT are:

- To provide the latest information and learning resources for the physiotherapists on the current landscape of assessments in neuromuscular disease for conditions.
- To provide an interactive space for physiotherapists to learn and share information on assessing and managing neuromuscular conditions.
- To upskill physiotherapists in how to conduct assessments and deliver the necessary standards of care for people with rare neuromuscular conditions.
- To be the go-to learning tool for physiotherapists teaching physiotherapists how to accurately carry out assessments with a view to reducing variability and working towards achieving consensus.

It has been recognised, that this e-learning resource could provide a valuable resource to registries, particularly those who report difficulties in the provision of physiotherapy training. With TREAT-NMD's success in running neuromuscular education initiatives on a global scale, TREAT-NMD is well-placed to build upon the excellent work initiated by Anna Mayhew and MDUK.

TREAT-NMD is currently seeking funding to support the work of the expansion of OPEN-TACT which will include:

- The creation of a suite of interactive e-learning modules
- The integration of knowledge checkpoints and testing to track and monitor learner experience and impact
- The accreditation of all modules for Continuing Medical Education (CME)

7.3 Dataset Revision Process

The Revision Process was published in Year 2 and defines how TREAT-NMD will manage updates to the dataset. The process categorises updates into three categorises Major, Minor & Fix and details version semantics and numbering. There is no change to the published Revision Process, however TREAT-NMD will establish a Change Review Board comprising a range of key stakeholders. The Change Board's role will be to review dataset feedback received and consider additions or deletion to data items and make recommendations.

As a result of the EMA/Aetion study, several potential changes to current data items have been identified for future inclusion. These include diagnosis date, registry entry date, start/stop date for clinician trial participation. As we become more involved in PMS studies, there will be a continuous review process of what we collect and in how we collect it. It is worth highlighting that updates will be kept to a minimum where possible, given the significant workload and impact on registries.

8. Communications & Support

8.1 SMA Roundtable Event

In November 2021, Biogen held a meeting with nominated registries, academics, and key opinion leaders to discuss key research questions, sharing of experiences and data harmonization. The meeting was well-received and suggested to become a regular meeting with representation from other industry partners and TREAT-NMD acting as an independent facilitator. Agreement in principle has been obtained from Biogen, Roche and Novartis to support this event (s) and work to define and agree specific research questionnow is being undertaken to. It is hoped that first meeting with registries will take place in Q3 2023.

8.2 Future Registry Networking events

At the December workshop, registries agreed that they would like to see more regular opportunities for networking to discuss specific issues or challenges and sharing of best practice. It was felt that an annual meeting was insufficient, and it was agreed that a quarterly SMA event should be held which would focus on a specific theme so that curators attend if relevant to them. TREAT-NMD are preparing a schedule of meetings and discussion topics that will be shared with the network.

8.3 Publications, Abstract & Posters

Abstracts & Posters

The work on the expanded dataset has resulted in several abstract and posters presented at various conferences as specified below:

- **Scientific European Congress SMA Europe's 3rd International Scientific Congress on Spinal Muscular Atrophy Oct 2022: "**TREAT-NMD Core Dataset for SMA – An important tool for Post Marketing Surveillance" (Appendix 4)
- C**ure SMA June 2023 June 2023**- Real-world data outcomes by the TREAT-NMD Spinal Muscular Atrophy Registries Network to support post-marketing surveillance (Appendix 5)

Joint Core Dataset publication

A publication from the SMA dataset expansion was planned, however following discussion it was decided that it would be more impactful if the publication discussed the collective approach used for dataset expansion for the TREAT core datasets SMA, DMD & LGMD. Unfortunately, this work has been delayed due to demands on individuals working on other projects, however regular meetings are now taking place to progress this and the aim is to submit a first draft for review to TGDOC in mid-May. Once appropriate reviews are complete, it is hoped that we can submit to the Orphanet Journal of Rare Disease.

8.4 SMA Subgroup Leads (SGL)

The SMA Dataset Expansion Project has been well supported over the past 4 years by Victoria Hodgkinson (Executive Director of CNMD registry) & Miriam Rodrigues (Neurogenetic Research Lead, New Zealand). We would like to formally acknowledge and thank them both for their excellent support and commitment during the project and support of the wider curator network in general. Miriam has recently taken up a new role as incoming Chair for TGDOC and we now delighted to welcome Marlene Jagut (Curator and Scientist) from the Belgium Registry to the role of sub-group lead.

We also welcome Maria Isabel Acevedo (Columbia), who along with Mencia de Lemus will act as patient representatives. The role of the SGL and patient representative are important roles in representing the different voices in the community to ensure a truly collaborative approach is maintained.

9. Key Learning Outcomes

As this project concludes, we can reflect on the past 4 years to assess the key learnings and identify what's worked well, what we would do differently and identify next steps. This project has helped us to inform and improve on future dataset expansions for other rare neuromuscular diseases.

9.1 Dataset Size

The current dataset consists of 154 data items (117 mandatory, 37 non-mandatory). There is a growing swell of opinion that collection is too onerous, costly in terms of time in clinic and is proving difficult to retain engagement with clinicians and patients. It is reported that collection of new patient data can take between 2-3 hours for new patients and 1hr for follow-up visits.

In the Y4 survey, curators were asked to review the dataset and to highlight items which they think should be changed:

- reclassified from mandatory → non-mandatory
- reclassified non-mandatory → mandatory
- removed entirely

The results of this exercise flagged some common views on a number of data items such as removal of 'affected family member side' and 'affected family member sex'. This information will feed into the next dataset revision process.

The dataset is being used to undertake patient-led studies (one natural history study and one post-authorisation safety study) and our initial experience is that the dataset is capable of supporting these projects. Whilst some requests for data items beyond the dataset have been received, there are generally insignificant and will be included in future reviews.

Registry feedback has flagged a potential relationship between the quantity of data collected and the quality of that data. The concern is whether the large size of the dataset size may negatively impact on the quality and so this needs monitoring to ensure what's being collected is both valuable and usable.

Learning #1 Consider alternative approaches with regards to dataset collection. This might, for example, involve a more tiered approach to datasets within the network which could see registries collecting a smaller 'core' dataset with a strong focus on data quality. There could then be optional modules/ data groups (Respiratory, Comorbidities etc) for those registries who have the resources and capacity to collect the additional items.

It has also been proposed that we have different datasets for different patient types and treatment availability (paediatric treated/paediatric non-treated, adult treated/adult non-treated). These are options for consideration in the next full dataset review.

9.2 Time to Adopt

TGDOC membership requires registries to collect the latest version of the dataset within 12 months of publication. From experience, it takes considerably longer to adopt than first anticipated with many registries taking more than 24 moths to implement. This was particularly challenging for pilot registries who were part-way through introducing V1 when V2 was published.

The reasons attributed to slower adoption include the need to gain ethical approval, resource constraints and expensive IT costs related to system updates. It should also be recognised that registries also involved in initiatives outside of TREAT-NMD which impact on resource time.

Learning #2. Whilst the dataset needs to be responsive to changes in the therapy landscape and for tracking the natural history of SMA, changes need to be carefully managed to minimise disruption and impact on the registry community. Depending on the size of the change, it is important to recognise that there may be a considerable lag between dataset publication and data collection by the registry network.

9.3 Costs of Adoption & Data Collection

The bursary funding of €8,000 provided valuable assistance to registries expanding data collection activities and was a key driver of registry engagement. Whilst acknowledging this support, registries reported that the true cost of implementation was much higher than what was offered and has resulted in the registries shouldering much of the cost burden themselves. This can be a major barrier for registries who are less well-resourced especially when extensive IT updates are required.

One NMD registry (part of a national healthcare system and tied into a national IT provider) has reported that system updates have taken more than 2 years to implement at a cost of €70k with annual maintenance fees of €6,500.

Learning #3 - Registries recognise the importance of collecting patient data in a detailed and standardised way conforming to a globally defined dataset. However, we need to recognise that the true cost of data collection should not fall disproportionately on registries who often struggle with funding. To improve data quality and increase the amount of data being collected, the wider community need to identify ways that adequately reimburse registries and their curators to ensure their continued existence and long-term sustainability.

9.4 Future Dataset Revision

In Year 1, the dataset was revised **V1→V2**. This was a significant change and resulted in a highly structured and detailed dataset which included conditional logic for the first time along with an on-line data specification. An extensive consultation process took place with key stakeholders invited to comment on the proposals and it resulted in 700 items of feedback to analyse. This was an extremely onerous for the Project Team to manage and took some time to assess responses and decide on the final dataset.

Learning #4 Future dataset revisions should be developed in collaboration with key stakeholders from across the community represented by patient organisations, clinicians, regulators, pharma and academics, however the number involved should be limited to a smaller, more manageable working group. It is likely that future revisions will result from smaller stakeholder meetings such as the one that was recently held for DMD in Amsterdam (Feb 2023).

9.5 Training and Support

Many registries report that, while the defined structure of the dataset supports collection of high quality real-world evidence, starting to collect **episodic** and **longitudinal data** can be particularly challenging.

The project team delivered both in-person and virtual training via workshops, monthly drop-in session and 1-2-1 sessions with individual registries to support knowledge and understanding. This support has been invaluable and it is doubtful that registries would have gained the level of knowledge required to implement the dataset without project assistance.

Results from the Y4 survey show that work is needed to improve understanding of specific data items (i) PPRL (privacy preserving record linkage) - tool which creates a unique patient identifier generated from 6 static data items enabling allows records to be de-duplicated across registries. (ii) Episodic data collection which collects start, stop and on-going dates to build history of such items as mobility status.

Learning Outcome # 5 – To improve SMA data quality on a global level, dedicated support in terms of personnel and resources is required to provide training and ongoing guidance. Opportunities for networking should be continued to form closer links between TREAT-NMD and registries, and amongst the registry community.

9.6 PROMS (Patient Reported Outcome Measures)

One of the least commonly collected items in the dataset are PROMS, for reasons which are not clear. It may be influenced by the positioning of PROMS data at the end of the dataset which may result in them being omitted, especially in the context of limited time available in clinic. Since Regulators and Payers are increasingly interested in patients' quality of life and how this is impacted follows treatment, it will be important to understand barriers to collection and promote the collection of these data items.

Learning Outcome #6

Consider working with registries, patient organisations and KOL's to develop recommended PROM's to promote global standardisation of patient assessment. This might involve the UK SMA registry which recently launched a short video promoting the collection of PROMS and shared this with the registry community as an example of good working practice and engagement.

10. Conclusion

During Year 4 the key highlights are as follows

- Significant increase in registry adoption of the expanded core dataset with 88 % (n=28) registries now reporting collection of the core dataset compared to 80% in Year 3. ✓
- 17 Part B bursary payments processed as registries shared their data collection forms / IT platforms to demonstrate compliance with V2 dataset. ✓
- 2 new registries (LUKAM, Mexico) joined the TREAT-NMD SMA network ✓
- Data Completeness Study - this is a major move forward as we are now able to assess the level of record completeness and undertake qualitative checks. This will allow us to provide additional training and support registries in a targeted way. ✓
- Delivery of an in-person workshop in December ✓

The project has highlighted the importance and benefits of registry networks, with Registries reporting they value being part of a global effort working towards standardised data collection and being part of a network of curators sharing information, discussing challenges and best practice.

Deployment of the dataset has been a challenging and complex task for registries irrespective of their size or resource capacity. Some valuable curator feedback was received from our recent survey and can be seen in Appendix 3.

We are now entering a new era of utilising data being collected to support studies into SMA natural history, therapies and their effectiveness, and other areas that are important to patients and stakeholders. It is vital that we continue our effort to provide data that is standardised, of good quality, and meets the needs of regulators, payers and researchers.

As this project concludes, we can report to having successfully delivered on our original objective of implementing an expanded dataset across the global registry network. That being said, we must not remain complacent and additional work remains to be carried out in the following key areas.

- On-going dataset refinements to ensure responsiveness to the needs of stakeholders
- Improve Outcome Measure and PROMS collection so that the patient voice becomes a primary focus

- Continue our work to understand and improve the quality of data
- Support registry curators to ensure long term sustainability of the network and continued engagement

The registry network will continue to respond to data requests from across the SMA field. However, one of the key priorities within the network is that the data being collected should be used to maximise impact for patient care and quality of life. To deliver this aim and drive forwards SMA research, TREAT-NMD aims to establish a collaborative, pan-SMA consortium that will allow stakeholders to identify research questions that could have the widest impact and could be addressed using registry data. We aim to establish this group in 2023

11. Acknowledgements

We'd like to recognise the huge effort undertaken by all those involved working towards improving data collection activities and appreciate the commitment and support which has been demonstrated.

The project team and TGDOC chairs would like to express their thanks and appreciation to Biogen for funding this important initiative and for their continued on-going support of the work of TREAT-NMD.

We would also like to take this opportunity to thank Jo Bullivant (Project Manager) and Joanna Das (Project Co-ordinator) in recognition of the work in the early years of this project to determine the expanded core dataset, development of the Outcome Measures library and support initial implementation across the registry network. The expert advice provided by Marcel Heidemann (IT data expert) in developing the online data specification and continued support has been invaluable. It has truly been a global team effort to achieve and implement the SMA expanded dataset.

Reference

Copies of the previous annual project reports (Year 1, 2, 3) can be accessed on the TREAT-NMD website along with the online specification V2 SMA core dataset

Appendix 1 - Annual Curator Survey (PDF)

63FD1AC3.pdf

Appendix 2 – Data Completeness Report

SMA Data Completeness

Registry Participation

Number of registries = 7

Number of patient entries = 136

Number of unique patients = 97

Methods and Analysis Rationale

Demographics

DOB[1]
Sex[1]
Country of Residence[1]
Is family member affected?
Affected family member relation[2]
Affected family member sex[2]
Affected family member side[2]

[1] Data are automatically removed during the PPRL de-identification process if using TREAT-NMD GRP. This should therefore always be marked as missing.

[2] Fields only open when "Is family member affected?" is marked as YES. If this field is not filled in, it is marked as missing.

Living Status

Alive[1]
Date of death
Cause of death code
Cause of death classification

[1] If "Alive" is marked as YES, then remaining fields will be marked as not needed, and are NOT marked as missing values.

Genetics

Genetic Confirmation
Screening
Genetic report date
SMN1 variant
SMN1 variant HGVs
SMN1 testing method
SMN2 copy number
SMN2 copy number testing method
SMN2 variant c859GtoC
SMN2 variant c859GtoC testing method

Clinical Observations

Symptom Onset
Symptom Onset Date
SMA Type
Clinician Global Impression of Severity
Clinician Global Impression of Improvement
Height[1]
Weight
Head Circumference
Shoulder Contractures
Elbow Contractures
Wrist Contractures
Finger Contractures
Hip Contractures
Knee Contractures
Ankle Contractures
Jaw Contractures

[1] "Height" field is marked with a decimal, a height measurement method and a date stamp. If one of these data items is missing, this is counted as incomplete and thus missing.

Scoliosis

Scoliosis Diagnosis
Scoliosis Surgery performed[1]
Scoliosis Surgery Date[2]
Cobb Angle[2]
Cobb Angle Date[2]

[1] If "Scoliosis Diagnosis" is marked as NO, "scoliosis surgery performed" will be marked as not needed and is NOT marked as missing. If "scoliosis diagnosis" is marked as YES, "scoliosis surgery performed" is required. If this field is not filled in, it is marked as missing.

[2] If "Scoliosis Diagnosis" is marked as NO, these fields are not available. If "scoliosis diagnosis" is marked as YES, unanswered fields are marked as missing.

Motor Function

Motor Ability
Motor Ability Status
Motor ability observed in clinic[1]
Motor Ability Episode[2]

[1] If "Motor ability status" is marked as NEVER, then "Motor ability observed in clinic" will be marked as not needed and is NOT marked as missing. Multiple motor abilities can be entered at each timepoint.

[2] If "Motor Ability Episode" has a date entered in either the START or STOP field, then it is NOT counted as missing.

Wheelchair

Wheelchair Usage
Wheelchair Usage Frequency[1]

[1] "Wheelchair usage frequency" is only available if "wheelchair usage" is marked as something other than NEVER.

Nutrition

Feeding tube Usage
Feeding tube Usage type[1]

[1] "Feeding tube usage type" is only available if "feeding tube usage" is not marked NEVER.

Pulmonary Function

Invasive ventilation usage
Invasive ventilation duration[1]
Non-invasive ventilation usage
Non-invasive ventilation duration[1]
Airway clearance assistance
Pulmonary function test performed
Pulmonary function test date[2]
Forced vital capacity volume[2]
Forced vital capacity percentage[2]
Peak cough flow[2]

[1] "Invasive ventilation duration" and "Non-invasive ventilation duration" fields are only available if "invasive ventilation usage" and "non-invasive ventilation usage" are marked as something other than NEVER.

[2] "Pulmonary function test date", "FVC volume", "FVC percentage" and "Peak Cough Flow" are only available if "pulmonary function test performed" field is marked YES.

Disease Modifying Therapy

DMT Received[1]
DMT
DMT status
DMT single administration date
DMT stopping reason
DMT dosage value
DMT dosage unit
DMT administration route
DMT administration intervals
DMT administration schedule deviation
DMT administration schedule deviation reason
DMT corticosteroid administration duration
DMT corticosteroid drug

[1] If "DMT Received" is NO, then all following fields will be marked as not needed.

Medication

Allopathic drug usage[1]
Allopathic drug[2]
Rehabilitative interventions[2]

[1]"Allopathic drug usage" (yes/no) was not asked at all visits.

[2]Multiple inputs can be entered at one time.

Hospitalisation

Hospitalisation Occurred
Hospitalisation admission date[1]
Hospitalisation type[1]
Hospitalisation nights[1]
Hospitalisation acute reason code[1]
Hospitalisation acute reason classification[1]
Hospitalisation planned reason[1]
Hospitalisation SAE[1]
Hospitalisation SAE DMT[1,3]
Comorbidities diagnosed[2]
Comorbidities code[2]
Comorbidities classification[2]
Comorbidity SAE[2]
Comorbidity SAE DMT[2,3]

[1] If "Hospitalisation Occurred" is marked as NO, then the remaining hospitalisation fields are marked as not needed and are NOT counted as missing data.
[2] If "Comorbidities diagnosed" is marked as NO, then the remaining comorbidity fields are not presented as options.
[3] If "Hospitalisation SAE" or "Comorbidity SAE" are missing, or marked as yes, these fields are presented as options.

Clinical Research

Clinical trial participation
Clinical trial[1]
Other registry participation
Other registry[2]

[1] If "clinical trial participation" is NEVER, then "clinical trial will be marked as not needed and is NOT counted as missing data.
[2] If "Other registry participation" is NO, then "Other registry" will be marked as not needed and is NOT counted as missing data.

Motor Measures

Motor measure
Motor measure score

Patient-Reported Outcome Measures

Patient global impression of severity
Patient global impression of Improvement
Patient-reported outcome measure
Patient-reported outcome measure score

Biomarkers

CMAP performed
DEXA performed
Muscle imaging performed

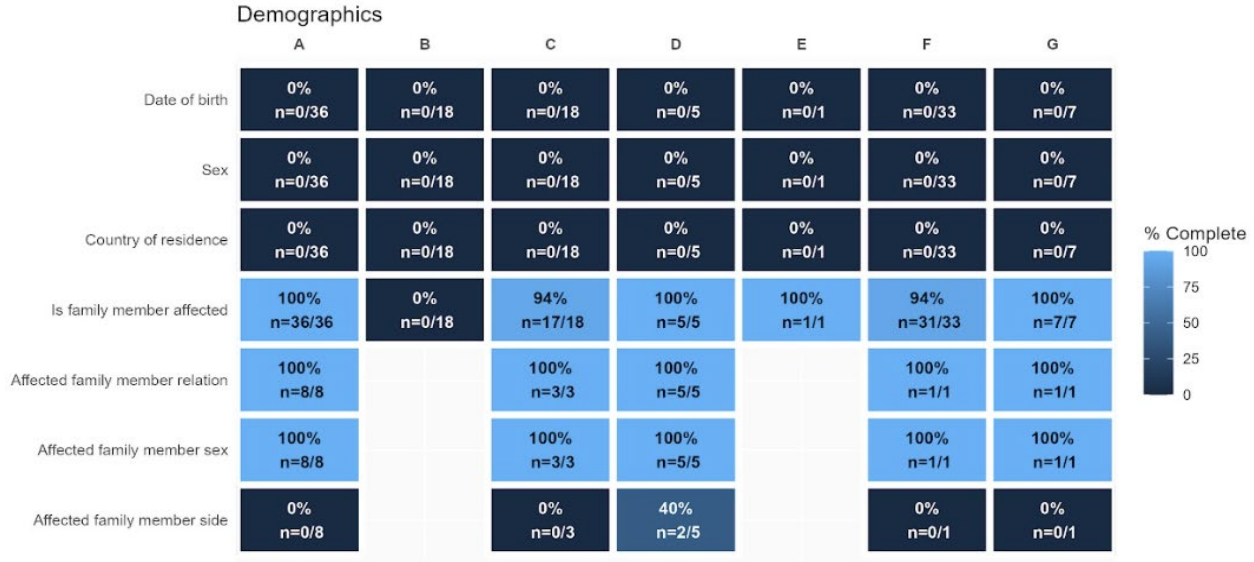
Results

Percentage of answered data overall are presented below:

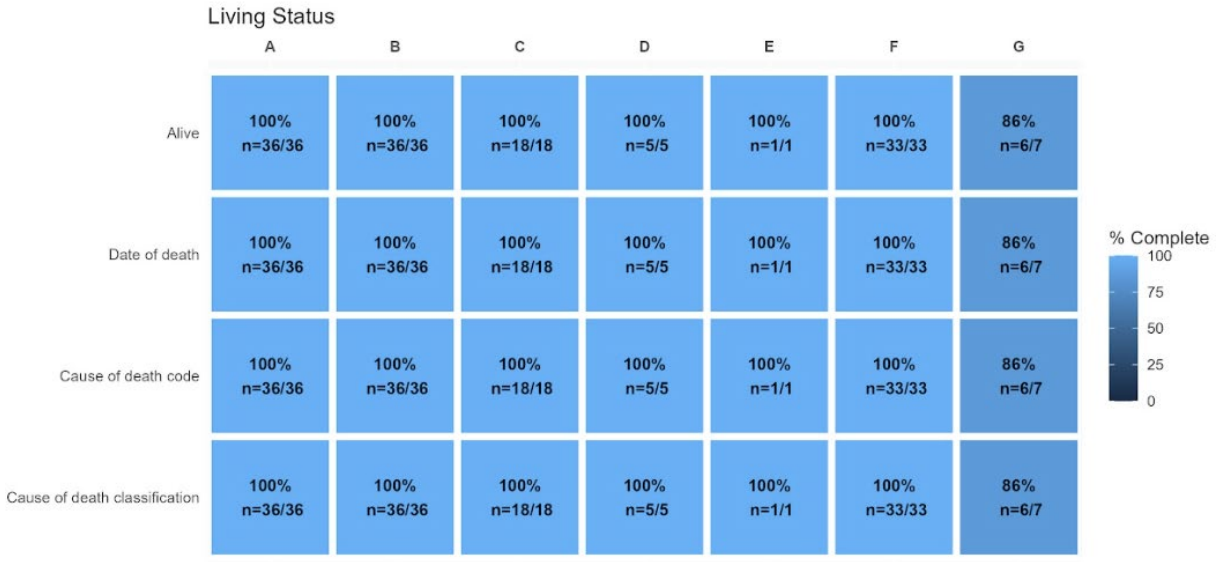
N = total number of **answered** questions (across all patients and visits) in this section / total number of (across all patients and visits) questions in this section.

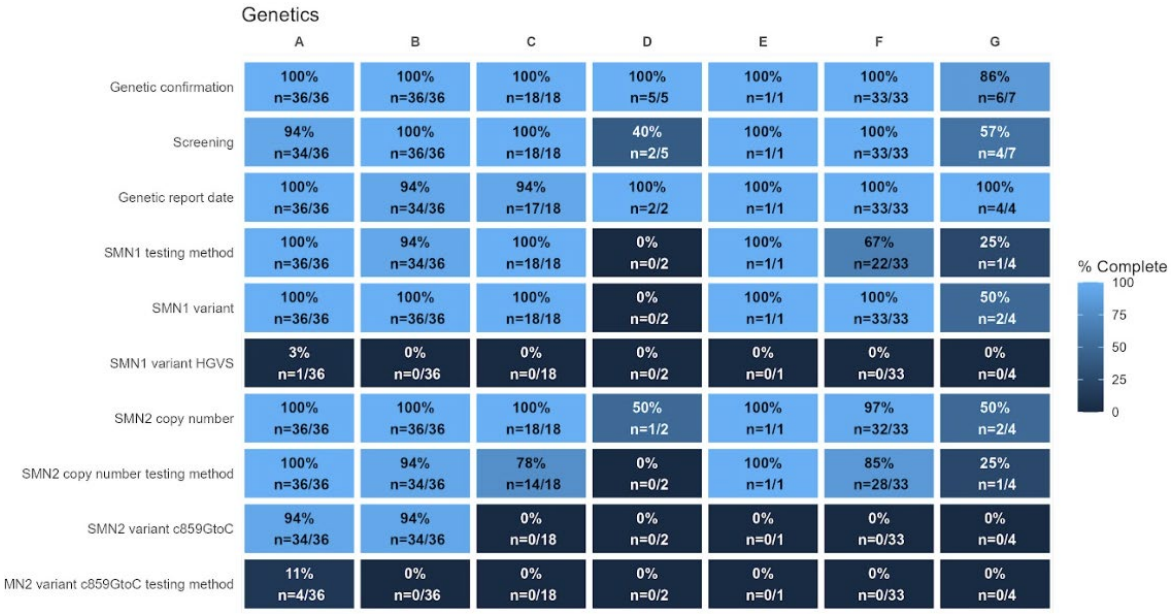
Percentage of answered data broken down by section are presented below:

N = total number of **answered** questions / total times this question was presented.

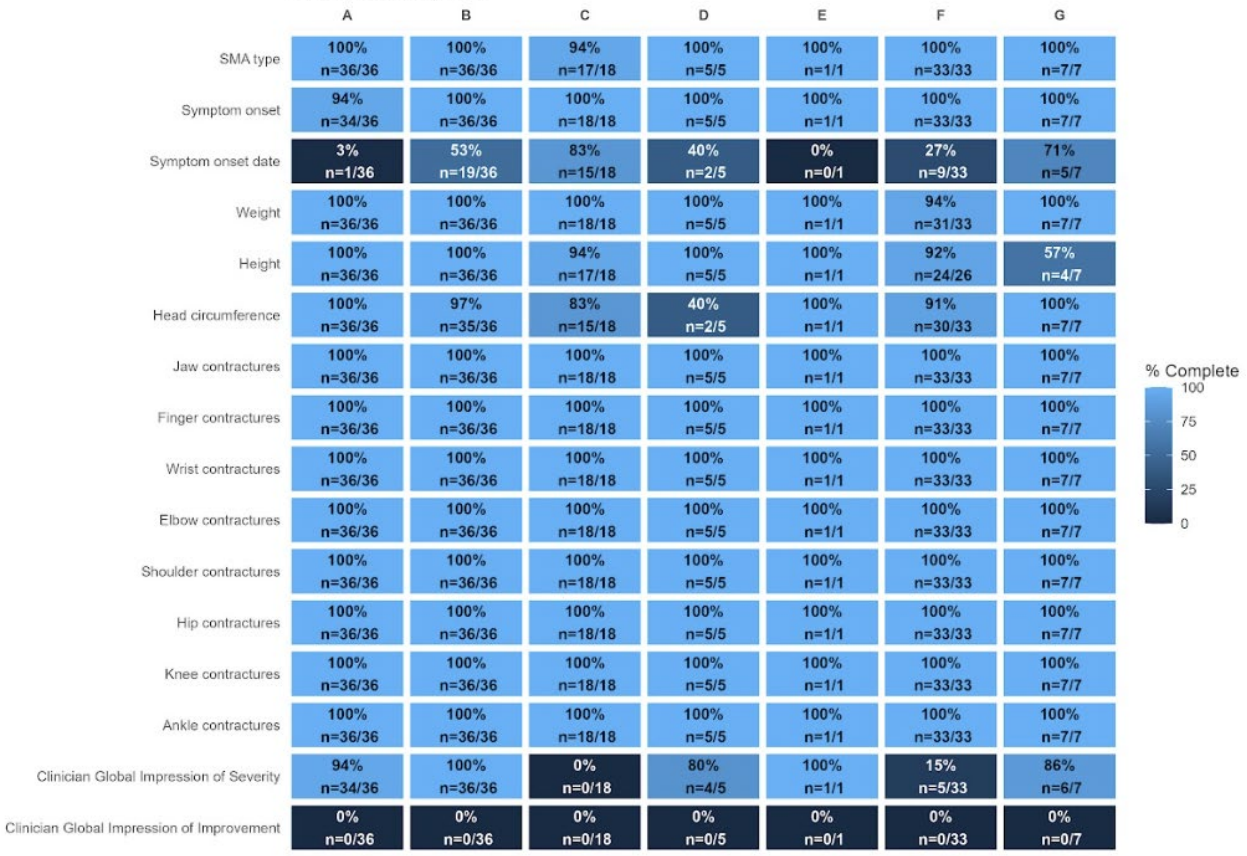


*PPRL tool automatically removes DOB, sex, and country of residence information.

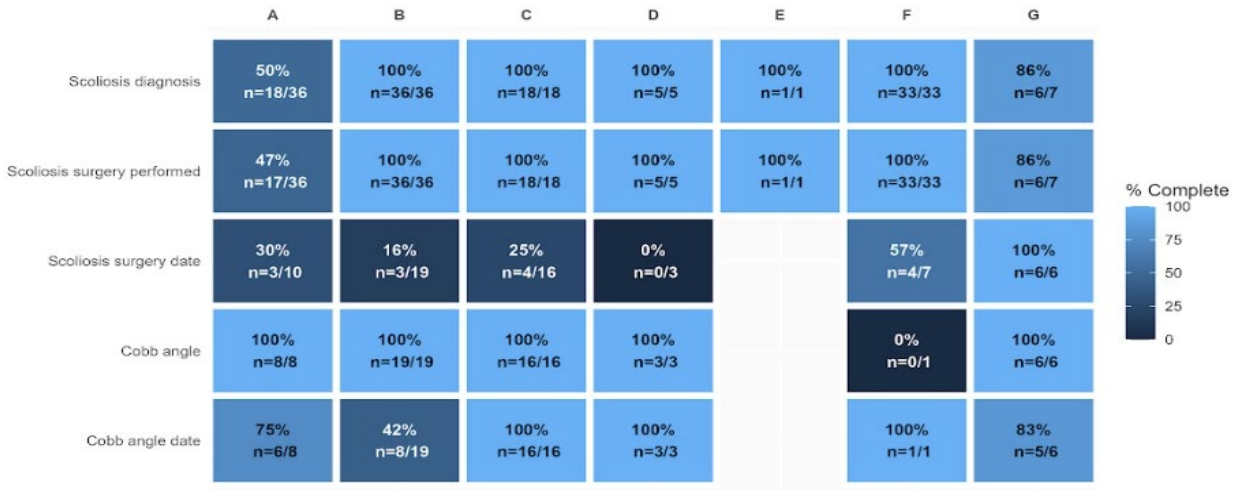


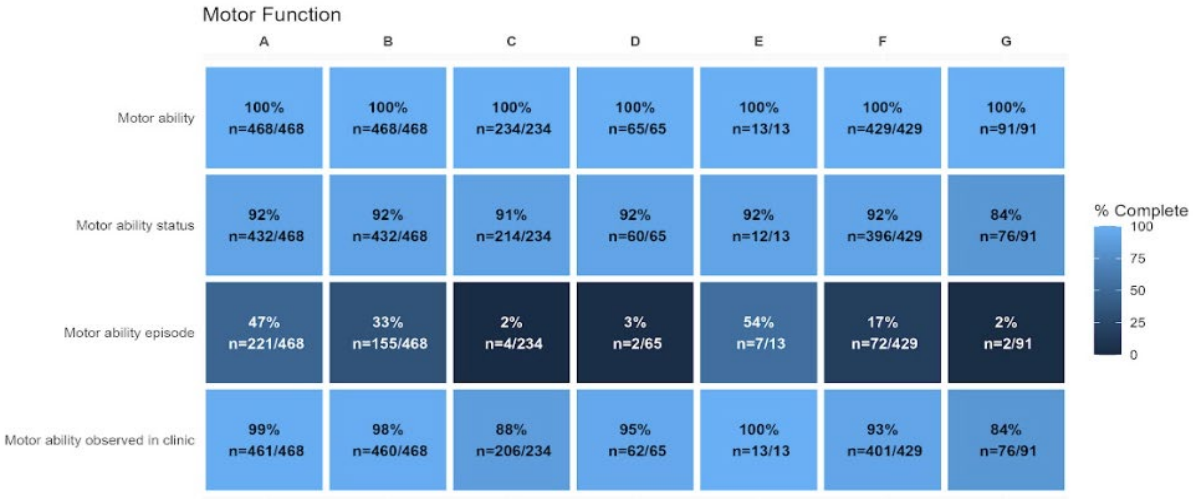


Clinical Observations



Scoliosis




Motor Function
A
B
C
D
E
F
G
Motor ability
100% n=468/468
100% n=468/468
100% n=234/234
100% n=65/65
100% n=13/13
100% n=429/429
100% n=91/91
Motor ability status
92% n=432/468
92% n=432/468
91% n=214/234
92% n=60/65
92% n=12/13
92% n=396/429
84% n=76/91
Motor ability episode
47% n=221/468
33% n=155/468
2% n=4/234
3% n=2/65
54% n=7/13
17% n=72/429
2% n=2/91
Motor ability observed in clinic
99% n=461/468
98% n=460/468
88% n=206/234
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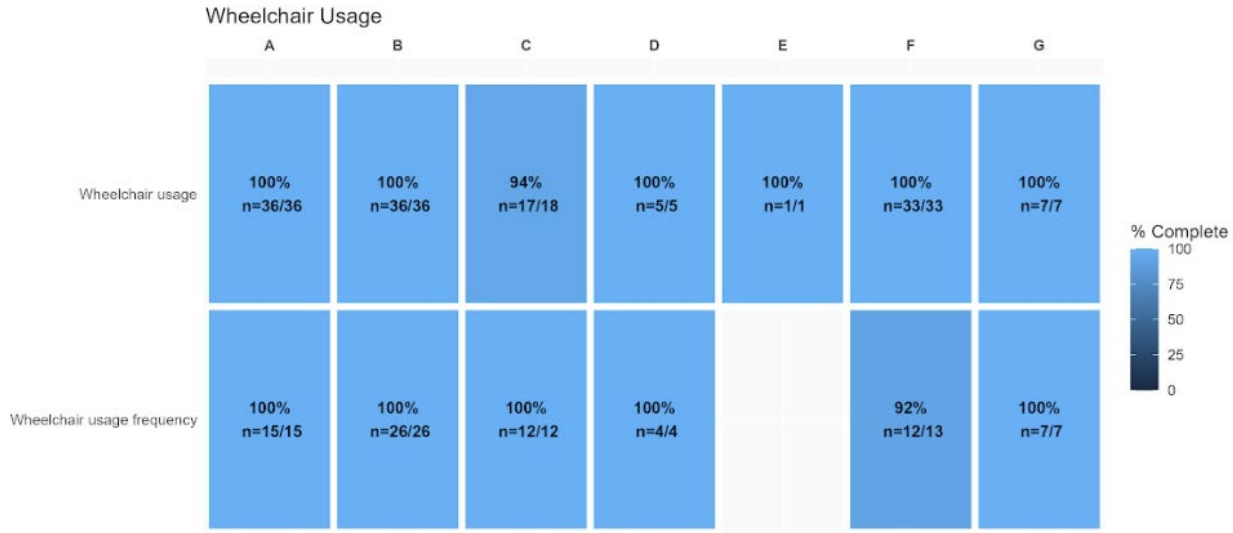
84% n=76/91
% Complete
100
75
50
25
0


Wheelchair Usage
A
B
C
D
E
F
G
Wheelchair usage
100% n=36/36
100% n=36/36
94% n=17/18
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
Wheelchair usage frequency
100% n=15/15
100% n=26/26
100% n=12/12
100% n=4/4
92% n=12/13
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% Complete
100
75
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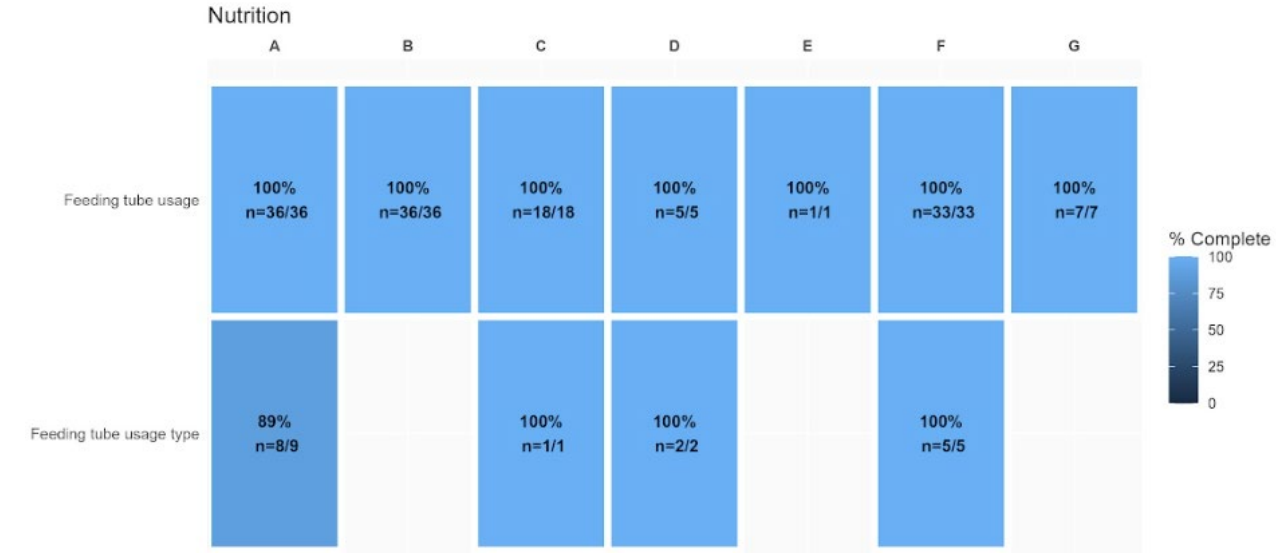
Nutrition
A
B
C
D
E
F
G
Feeding tube usage
100% n=36/36
100% n=36/36
100% n=18/18
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
Feeding tube usage type
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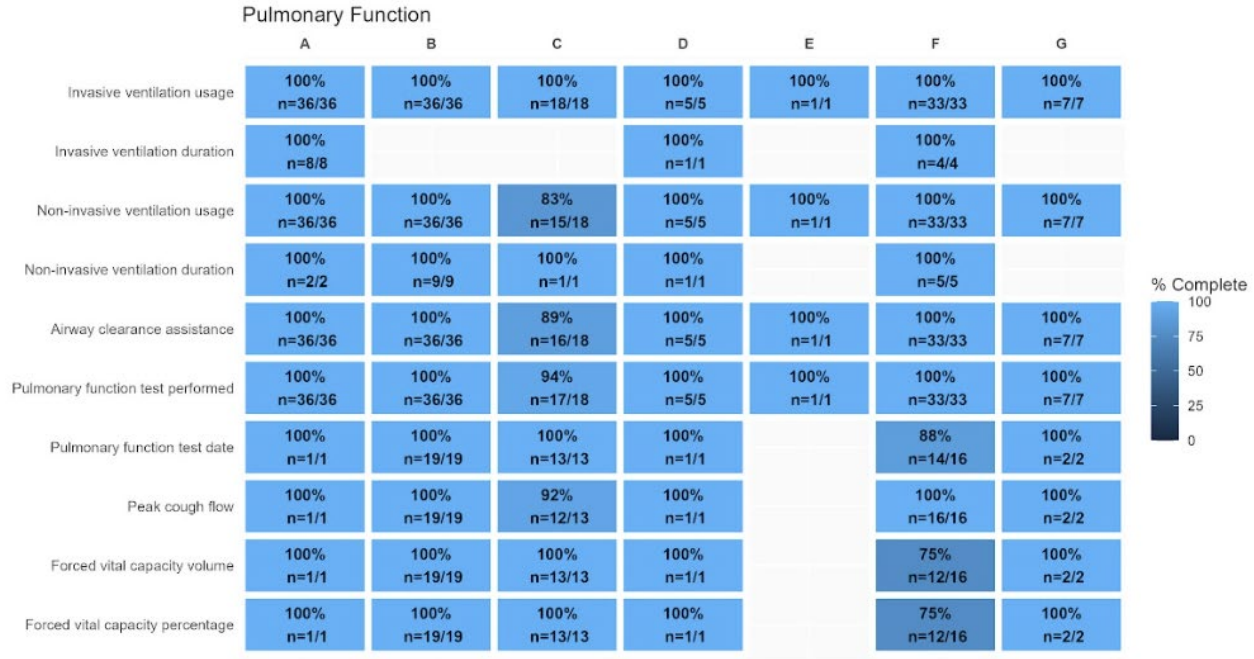
100% n=2/2
100% n=5/5
% Complete
100
75
50
25
0


Pulmonary Function
A
B
C
D
E
F
G
Invasive ventilation usage
100% n=36/36
100% n=36/36
100% n=18/18
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
Invasive ventilation duration
100% n=8/8
100% n=1/1
100% n=4/4
Non-invasive ventilation usage
100% n=36/36
100% n=36/36
83% n=15/18
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
Non-invasive ventilation duration
100% n=2/2
100% n=9/9
100% n=1/1
100% n=1/1
100% n=5/5
Airway clearance assistance
100% n=36/36
100% n=36/36
89% n=16/18
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
Pulmonary function test performed
100% n=36/36
100% n=36/36
94% n=17/18
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
Pulmonary function test date
100% n=1/1
100% n=19/19
100% n=13/13
100% n=1/1
88% n=14/16
100% n=2/2
Peak cough flow
100% n=1/1
100% n=19/19
92% n=12/13
100% n=1/1
100% n=16/16
100% n=2/2
Forced vital capacity volume
100% n=1/1
100% n=19/19
100% n=13/13
100% n=1/1
75% n=12/16
100% n=2/2
Forced vital capacity percentage
100% n=1/1
100% n=19/19
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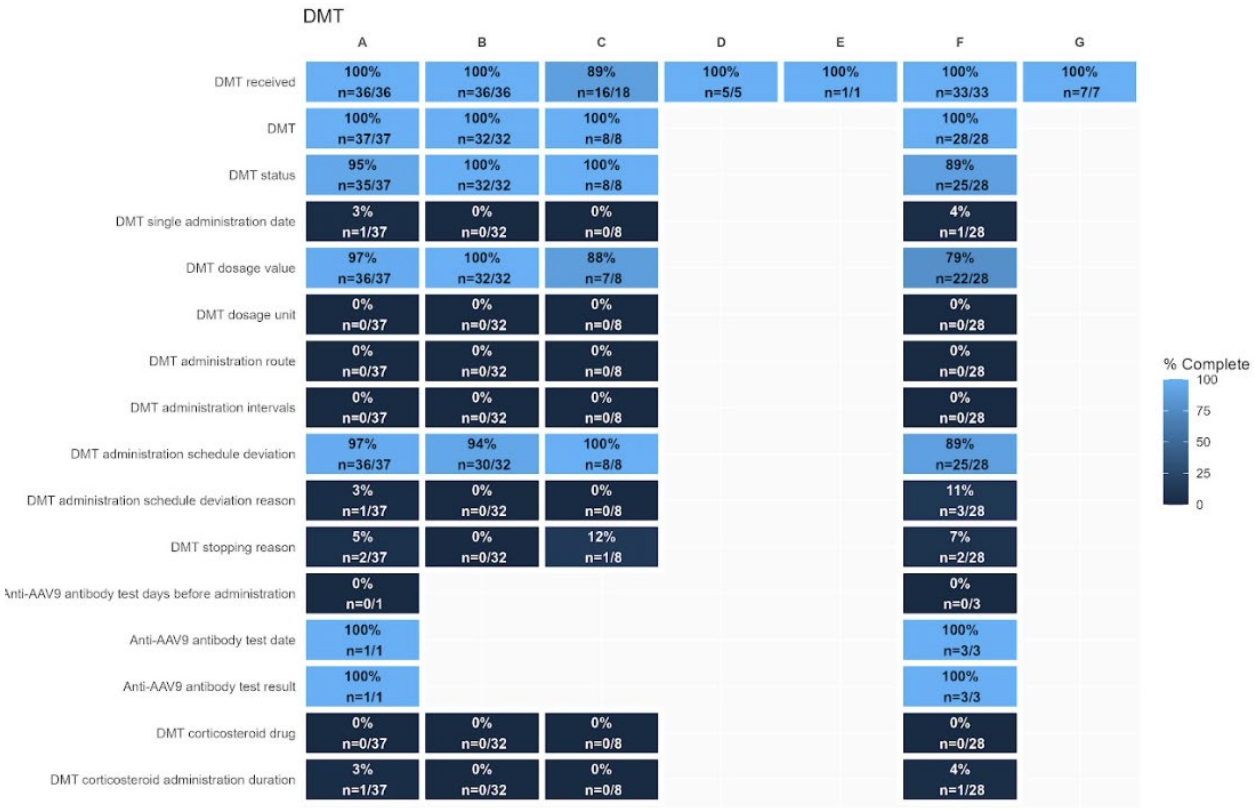
100% n=2/2
% Complete
100
75
50
25
0


DMT
A
B
C
D
E
F
G
DMT received
100% n=36/36
100% n=36/36
89% n=16/18
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
DMT
100% n=37/37
100% n=32/32
100% n=8/8
100% n=28/28
DMT status
95% n=35/37
100% n=32/32
100% n=8/8
89% n=25/28
DMT single administration date
3% n=1/37
0% n=0/32
0% n=0/8
4% n=1/28
DMT dosage value
97% n=36/37
100% n=32/32
88% n=7/8
79% n=22/28
DMT dosage unit
0% n=0/37
0% n=0/32
0% n=0/8
0% n=0/28
DMT administration route
0% n=0/37
0% n=0/32
0% n=0/8
0% n=0/28
DMT administration intervals
0% n=0/37
0% n=0/32
0% n=0/8
0% n=0/28
DMT administration schedule deviation
97% n=36/37
94% n=30/32
100% n=8/8
89% n=25/28
DMT administration schedule deviation reason
3% n=1/37
0% n=0/32
0% n=0/8
11% n=3/28
DMT stopping reason
5% n=2/37
0% n=0/32
12% n=1/8
7% n=2/28
nti-AAV9 antibody test days before administration
0% n=0/1
0% n=0/3
Anti-AAV9 antibody test date
100% n=1/1
100% n=3/3
Anti-AAV9 antibody test result
100% n=1/1
100% n=3/3
DMT corticosteroid drug
0% n=0/37
0% n=0/32
0% n=0/8
0% n=0/28
DMT corticosteroid administration duration
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4% n=1/28
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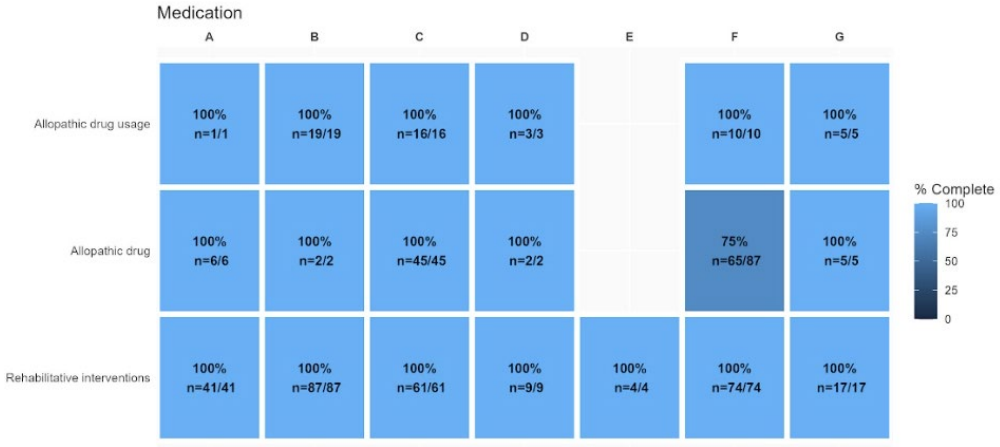
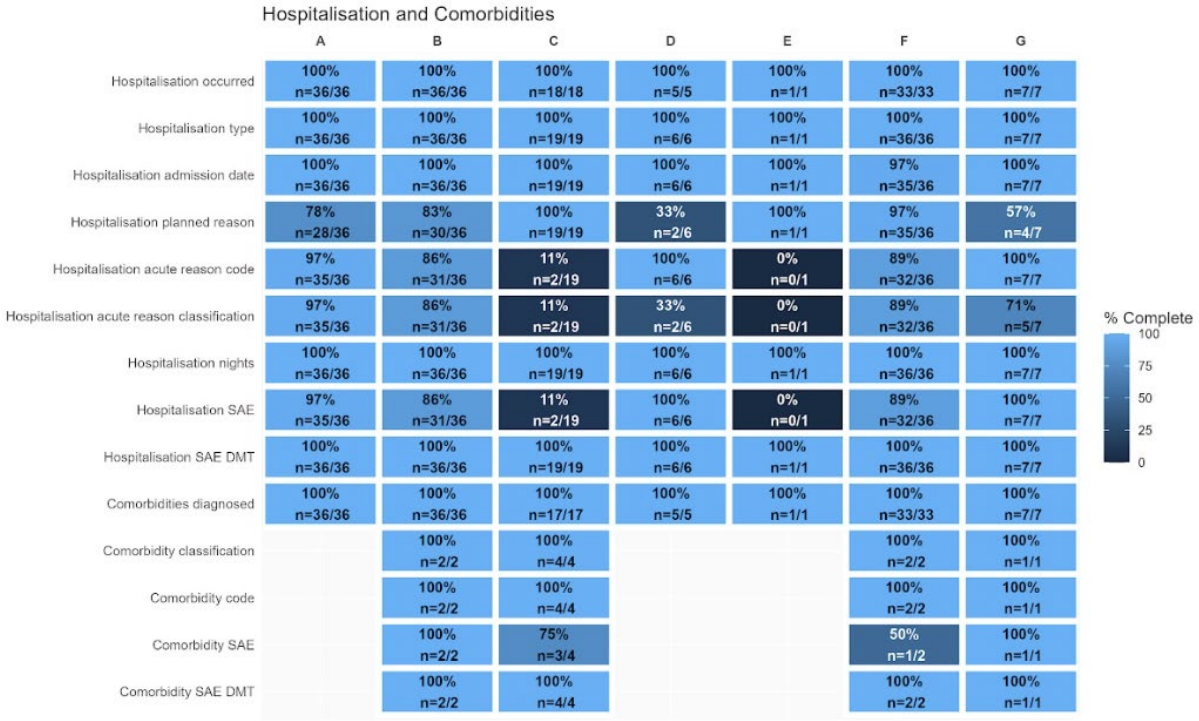
100
75
50
25
0


Medication
A
B
C
D
E
F
G
Allopathic drug usage
100% n=1/1
100% n=19/19
100% n=16/16
100% n=3/3
100% n=10/10
100% n=5/5
Allopathic drug
100% n=6/6
100% n=2/2
100% n=45/45
100% n=2/2
75% n=65/87
100% n=5/5
Rehabilitative interventions
100% n=41/41
100% n=87/87
100% n=61/61
100% n=9/9
100% n=4/4
100% n=74/74
100% n=17/17
% Complete
100
75
50
25
0


Hospitalisation and Comorbidities
A
B
C
D
E
F
G
Hospitalisation occurred
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100% n=36/36
100% n=18/18
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
Hospitalisation type
100% n=36/36
100% n=36/36
100% n=19/19
100% n=6/6
100% n=1/1
100% n=36/36
100% n=7/7
Hospitalisation admission date
100% n=36/36
100% n=36/36
100% n=19/19
100% n=6/6
100% n=1/1
97% n=35/36
100% n=7/7
Hospitalisation planned reason
78% n=28/36
83% n=30/36
100% n=19/19
33% n=2/6
100% n=1/1
97% n=35/36
57% n=4/7
Hospitalisation acute reason code
97% n=35/36
86% n=31/36
11% n=2/19
100% n=6/6
0% n=0/1
89% n=32/36
100% n=7/7
Hospitalisation acute reason classification
97% n=35/36
86% n=31/36
11% n=2/19
33% n=2/6
0% n=0/1
89% n=32/36
71% n=5/7
Hospitalisation nights
100% n=36/36
100% n=36/36
100% n=19/19
100% n=6/6
100% n=1/1
100% n=36/36
100% n=7/7
Hospitalisation SAE
97% n=35/36
86% n=31/36
11% n=2/19
100% n=6/6
0% n=0/1
89% n=32/36
100% n=7/7
Hospitalisation SAE DMT
100% n=36/36
100% n=36/36
100% n=19/19
100% n=6/6
100% n=1/1
100% n=36/36
100% n=7/7
Comorbidities diagnosed
100% n=36/36
100% n=36/36
100% n=17/17
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
Comorbidity classification
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100% n=2/2
100% n=1/1
Comorbidity code
100% n=2/2
100% n=4/4
100% n=2/2
100% n=1/1
Comorbidity SAE
100% n=2/2
75% n=3/4
50% n=1/2
100% n=1/1
Comorbidity SAE DMT
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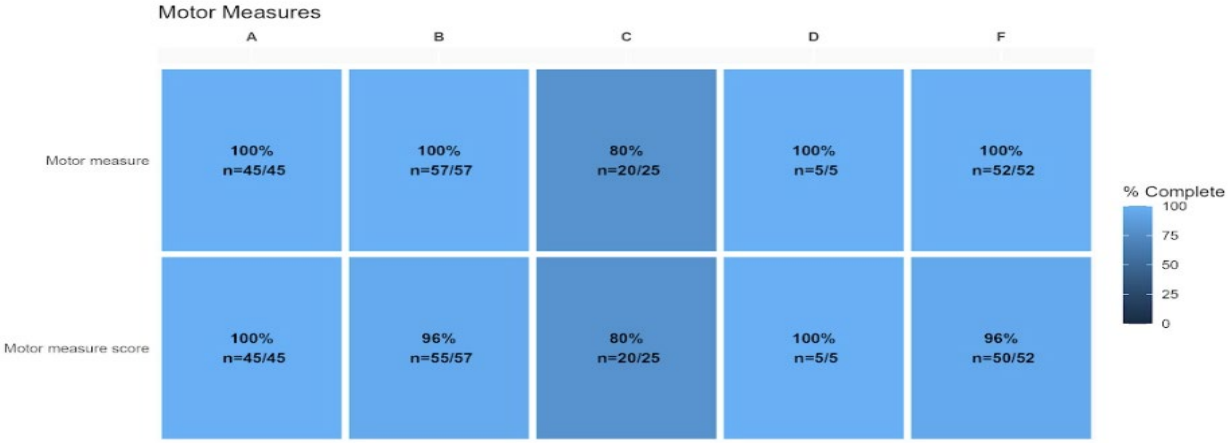
100% n=4/4
100% n=2/2
100% n=1/1
% Complete
100
75
50
25
0


Motor Measures
A
B
C
D
F
Motor measure
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100% n=57/57
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100% n=5/5
100% n=52/52
Motor measure score
100% n=45/45
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80% n=20/25
100% n=5/5
96% n=50/52
% Complete
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50
25
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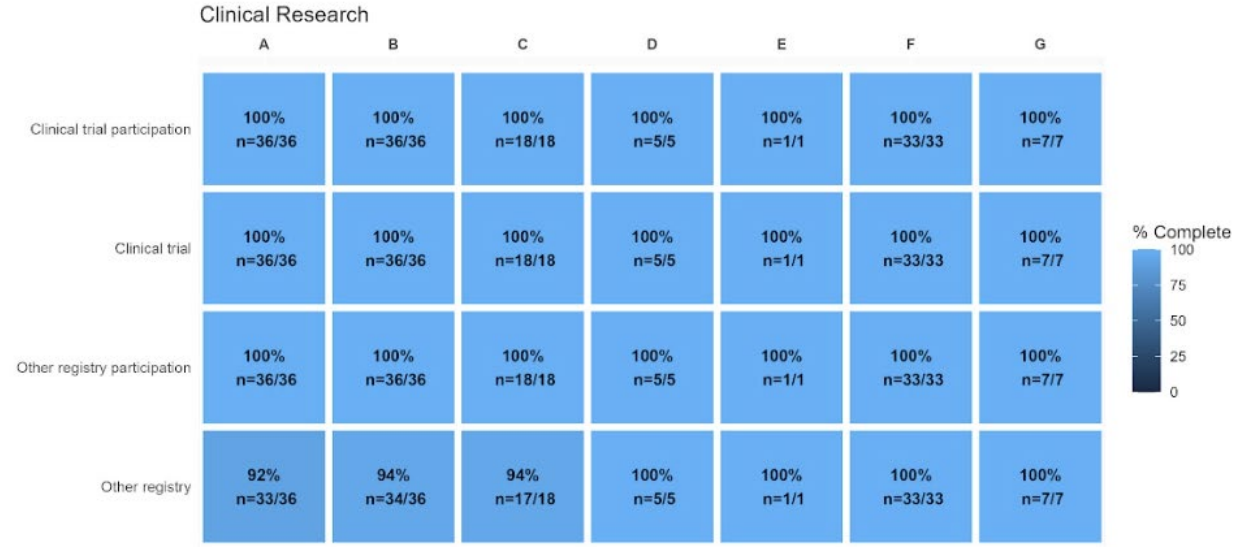
Clinical Research
A
B
C
D
E
F
G
Clinical trial participation
Clinical trial
Other registry participation
Other registry
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100% n=36/36
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100% n=1/1
100% n=33/33
100% n=7/7
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100% n=5/5
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100% n=33/33
100% n=7/7
92% n=33/36
94% n=34/36
94% n=17/18
100% n=5/5
100% n=1/1
100% n=33/33
100% n=7/7
% Complete
100
75
50
25
0


Patient-Reported Outcome Measures
A
B
C
D
E
F
G
Patient-reported outcome measure
Patient-reported outcome measure score
Patient Global Impression of Improvement
Patient Global Impression of Severity
0% n=0/36
72% n=26/36
39% n=7/18
0% n=0/5
0% n=0/1
0% n=0/33
0% n=0/7
54% n=14/26
100% n=7/7
56% n=20/36
8% n=3/36
0% n=0/18
40% n=2/5
100% n=1/1
45% n=15/33
14% n=1/7
3% n=1/36
53% n=19/36
33% n=6/18
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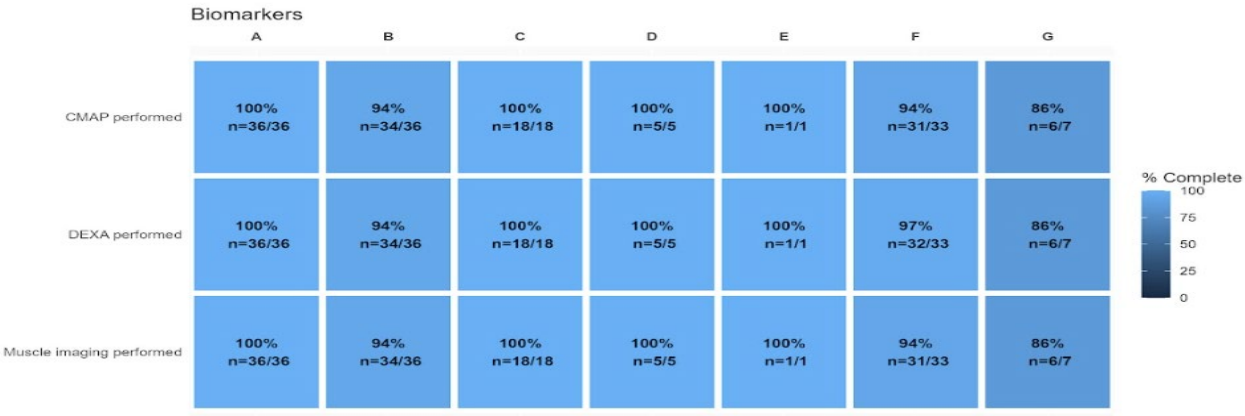
71% n=5/7
% Complete
100
75
50
25
0


Biomarkers
A
B
C
D
E
F
G
CMAP performed
DEXA performed
Muscle imaging performed
100% n=36/36
94% n=34/36
100% n=18/18
100% n=5/5
100% n=1/1
94% n=31/33
86% n=6/7
100% n=36/36
94% n=34/36
100% n=18/18
100% n=5/5
100% n=1/1
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86% n=6/7
100% n=36/36
94% n=34/36
100% n=18/18
100% n=5/5
100% n=1/1
94% n=31/33
86% n=6/7
% Complete
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0

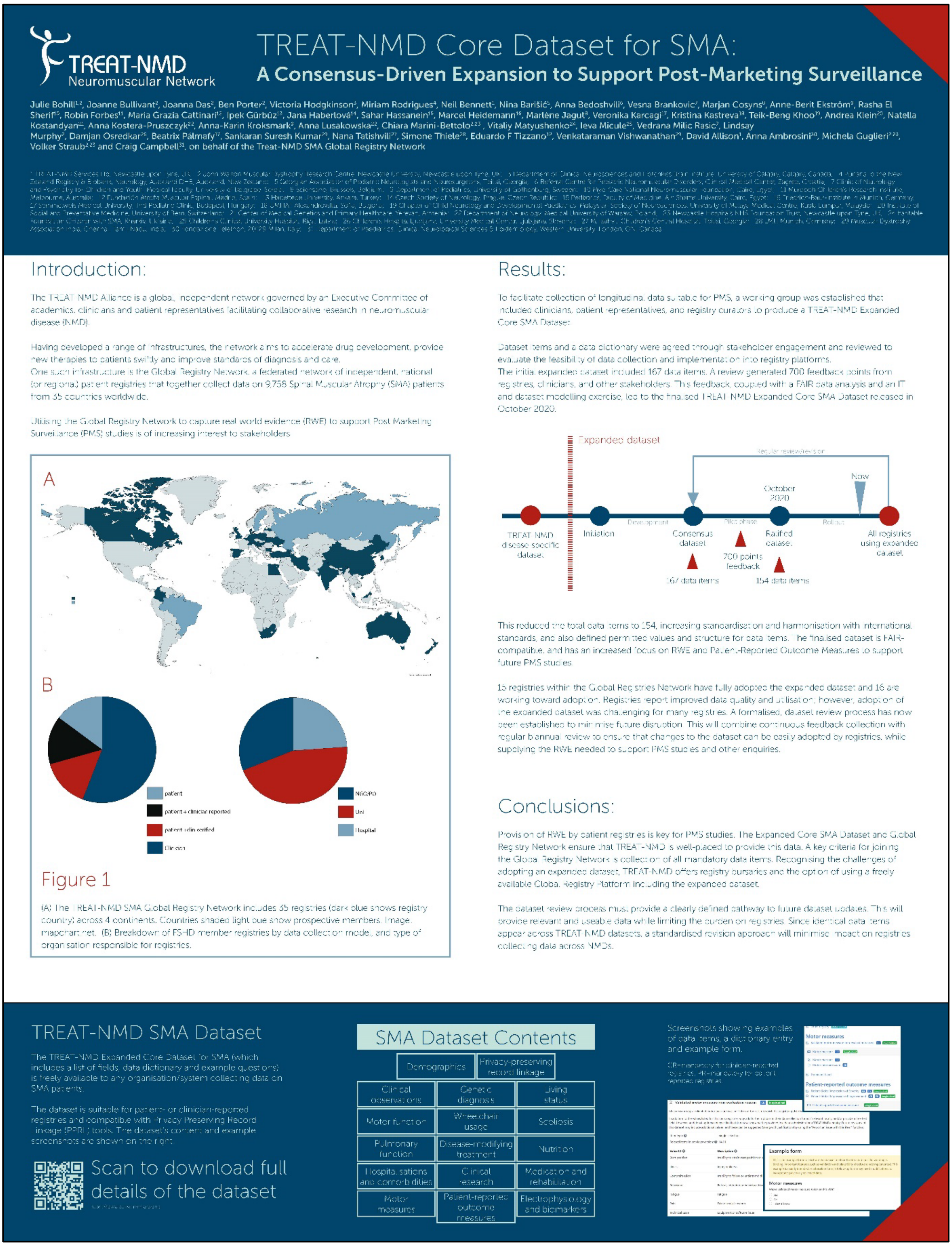
Appendix 3 – Registry Testimonials

Question 1 : In your experience so far, what are the <u>advantages</u> of the expanded dataset?
"Government and pharma already asking for Registry data to support reimbursement". "It changed mainly the use of the data. Before we were more focused on epidemiology and natural history. The new dataset opened new objectives such as efficacy and post marketing surveillance. Our experts agree that despite the workload of entering the data, it is a really good dataset giving us amazing opportunities to answer regulators but also scientific questions … " "Systematic and comprehensive approach to our patients" "It provides opportunity to capture, store, manage and analyse our patient profiles, as well as their comorbidities, complications and treatment success very precisely". "It contains every aspect of patient's disease course, anything any research project could possibly have an interest to investigate" "Helps in tracking specific patients' requirements and identify health problems, helps in lobbying activity to secure needed treatment for patients, creates a worldwide communication network, helps in advocating for improving specific care. "Provides clarity on the variable that we are collecting and enables global data analysis with a more homogenous dataset. keeping up with progress made in SMA treatment with DMT'". "Facilitates a very thorough follow-up for patients with SMA". "International exposure, working with others in a similar situation, contributing to global networks and research" "provides more comprehensive information about the natural course of the disease. It also helps to reveal to what extent the patients benefiting from the current treatment options and their side effects" Detailed information was obtained from patients. Patient expectations increased which is sometimes a disadvantage. The communication with TREAT NMD increased and provided bursaries by TREAT NMD which made us strong for sustainability Getting clearer picture of SMA both paediatric and adult. Engagement with patient population has been rewarding. Parents say they reflect on positive changes in their child when we do the updates which they may not have otherwise done (we update every 6 months). Parents say it also reminds them of things they need to discuss with their clinicians. It has been good to help advocate with and for adult patients for treatment access. Very excited to have been a part of this.

Q2: In your experience so far, what are the main issues with the expanded dataset?
Difficulty in finding suitable time for patients to have 30 minutes to go through data questions. We phone patient, add the data and verify with clinicians. Time that takes is the main issue for us. Providing all necessary data is very time-consuming work, and it is not always possible to give precise answers when other specialists are not completely familiar with NMD patients and their problems. The filling of all the data takes much time .. physicians are not referring patients to be registered. Lack of data verification specifically the genetic part, no dedicated staff, it is based on a voluntary work by one person, families not interested in being registered because they are not aware about its role and importance Striking a balance between collecting too much and too little. We must omit many of the optional variables as they are not routinely collected. High level of commitment is required from the participating centres because the data collection can be time consuming. expanded dataset is too long … this issue is difficult for all sides (clinicians, babies, and families) Persuading members of the importance of giving consent and being added to the registry. Reaching members that do not have adequate access to the internet and devices". On-going staff training is necessary to ensure good quality registry

Q3**. Any other suggestions regarding improvements you'd like to see?**
Persuade members of the importance of giving consent and being added to the registry. Reaching members that do not have adequate access to the internet and devices". We suggest a query form that will be simplified (not more than one page of questions needed) The questionnaire should be designed for clinicians to use routinely for all patients visiting neurologist Please do not change again too soon! … dataset collection is impossible without the development of clinical care. As soon as clinical care of our paediatric patients advanced to the international standard level, the implementation of dataset required more staff time due to bigger amount of data. The bursary scheme supported this. conduct a training for the following Patient-reported outcome measures, our families and AHP are not familiar with these scales, Add items for swallowing, Positioning and postures problems. Sharing experiences meetings helps to understand others' perspective. … have a subset of paediatric treated/not treated and adults treated/not treated would be a great way forward

Appendix 4 - Cure SMA June 2022- Real-world data outcomes by the TREAT-NMD Spinal Muscular Atrophy Network



Appendix 5 - Scientific European Congress on Spinal Muscular Atrophy Oct 2022: "TREAT-NMD Core Dataset for SMA – An important tool for post Marketing Surveillance"

TREAT-NMD Neuromuscular Network

TREAT-NMD Core Dataset for SMA: An Important Tool for Post-Marketing Surveillance

John Walton Muscular Dystrophy Research Centre · Newcastle University · NHS · The Newcastle upon Tyne Hospitals NHS Foundation Trust

Jess Pago[1], Julie Bohill[1], Victoria Hodgkinson[1], Miriam Rodrigues[1], Neil Bennett[1], Nina Barišić[2], Anna Bedoshvili[3], Vesna Brankovic[4], Marjan Cosyns[5], Anne-Berit Ekström[6], Rasha El Sherif[7], Robin Forbes[8], Maria Grazia Cattinari[9], Ipek Gurbüz[10], Jana Haberlová[11], Sahar Hassanein[12], Marcel Heidemann[13], Marlène Jagut[14], Veronika Karcagi[15], Kristina Kastreva[16], Telk-Beng Khoo[17], Andrea Klein[18], Natella Kostandyan[19], Anna Kostera-Pruszczyk[20], Anna-Karin Kroksmark[21], Anna Lusakowska[22], Chiara Marini-Bettolo[23], Vitaliy Matyushenko[24], Ieva Micule[25], Vedrana Milic Rasic[26], Lindsay Murphy[27], Damjan Osredkar[28], Beatrix Palmafy[29], Sankaran Suresh Kumar[30], Nana Tatishvili[31], Simone Thiele[32], Eduardo F Tizzano[33], Venkataraman Vishwanathan[34], David Allison[1], Anna Ambrosini[1], Michela Guglieri[1,35], Volker Straub[1,35] and Craig Campbell[1], on behalf of the Treat-NMD SMA Global Registry Network

1 TREAT-NMD Services Ltd, Newcastle upon Tyne, UK; 2 John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK; 3 Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary, Calgary, Canada; 4 Pūnaha Io the New Zealand Registry & Biobank, Neurology, Auckland DHB, Auckland, New Zealand; 5 Georgian Association of Pediatric Neurologists and Neurosurgeons, Tbilisi, Georgia; 6 Referral Centre for Pediatric Neuromuscular Disorders, Clinical Medical Center, Zagreb, Croatia; 7 Clinic of Neurology and Psychiatry for Children and Youth, Medical Faculty, University of Belgrade, Serbia; 8 Sciensano, Brussels, Belgium; 9 Department of Pediatrics, University of Gothenburg, Sweden; 10 Myo-Care National Neuromuscular Foundation, Cairo, Egypt; 11 Murdoch Children's Research Institute, Melbourne, Australia; 12 Fundación Atrofia Muscular Espinal, Madrid, Spain; 13 Hacettepe University, Ankara, Turkey; 14 Czech Society of Neurology, Prague, Czech Republic; 15 Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt; 16 Friedrich-Baur-Institute in Munich, Germany; 17 Semmelweis Medical University, Ind Pediatric Clinic, Budapest, Hungary; 18 UNIMAT Alexandrovska, Sofia, Bulgaria; 19 Chapter of Child Neurology and Developmental Paediatrics, Malaysian Society of Neurosciences, University of Malaya Medical Centre, Kuala Lumpur, Malaysia; 20 Institute of Social and Preventive Medicine, University of Bern, Switzerland; 21 Center of Medical Genetics and Primary Healthcare, Yerevan, Armenia; 22 Department of Neurology, Medical University of Warsaw, Poland; 23 Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; 24 Nastasie Foundation Children with SMA, Kharkiv, Ukraine; 25 Children's Clinical University Hospital, Riga, Latvia; 26 Children's Hospital Ljubljana, University Medical Center, Ljubljana, Slovenia; 27 St. Jarvis Children's Central Hospital, Tbilisi, Georgia; 28 LMU Munich, Germany; 29 Muscular Dystrophy Association India, Chennai, Tamil Nadu, India; 30 Fondazione Telethon, 20129 Milan, Italy; 31 Department of Paediatrics, Clinical Neurological Sciences & Epidemiology, Western University, London, ON, Canada

Project Background:

Registries are considered an effective, feasible and cost-effective tool in tracking the natural history of neuromuscular diseases. TREAT-NMD helps to co-ordinate a global network of neuromuscular patient registries, including SMA, governed by the TREAT-NMD Global Data systems Oversight Committee (TGDOC). Due to the rapidly emerging SMA treatment landscape, TREAT-NMD expanded its SMA Core Dataset in September 2018 (v1) via extensive consultation with multiple stakeholders. Following user feedback from 10 pilot registries, the dataset was revised in October 2020 (v2) and resulted in a comprehensive dataset that is compliant with FAIR data principles and, when implemented, can support post-marketing surveillance (PMS). The Expanded Dataset project is now entering its fourth year and this poster will present an up-to-date overview of the progress made and demonstrate the impact of the expanded dataset and illustrate its potential use in PMS.

Collaborative Dataset Development:

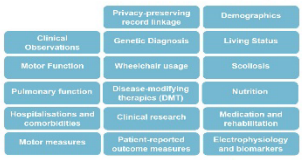
Workshops and a pilot study were held between May 2017 and June 2018 involving clinicians, physiotherapists, registry curators, patient representatives, industry representatives, and other stakeholders from across the world. Consensus building using either Delphi-style or MoSCoW methodology led to the release of an expanded SMA Core Dataset (v1) in September 2018.

Informed by the pilot project, a 3 year phased implementation project began in May 2019 to support the remaining TGDOC SMA Registries in implementing the expanded SMA Core Dataset (v1). The dataset was further revised in 2020 to respond to the needs of the SMA community and promote global harmonisation across relevant initiatives. This was done through 2 rounds of extensive and inclusive consultation with a wide range of stakeholders including patient advocacy groups, industry, regulators and payers, registry curators and owners, healthcare professionals and other academic groups and registry initiatives. Over 700 individual items of feedback were received for consideration and version 2 of the SMA Core Dataset was published in October 2020.

Dataset version comparison:

Item type	V1 (Sept 2018)	V2 (Oct 2020)
Mandatory Clinician reported	113	117
Mandatory Patient reported	92	91
Non-Mandatory	50	37
Total Items	167	154

TREAT-NMD SMA Core Dataset item groupings:

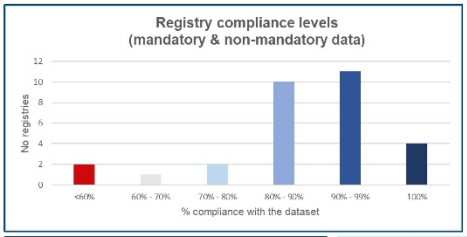


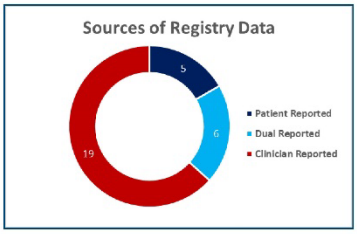
4402 Patients from 18 Registries in 2019…

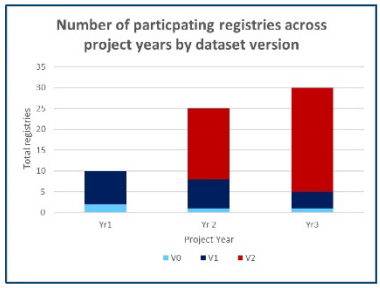
To 6492 Patients from 30 Registries in 2022

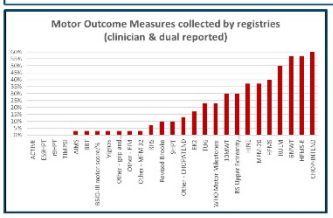
Scan to download full details of the dataset

Expanded Dataset Implementation:

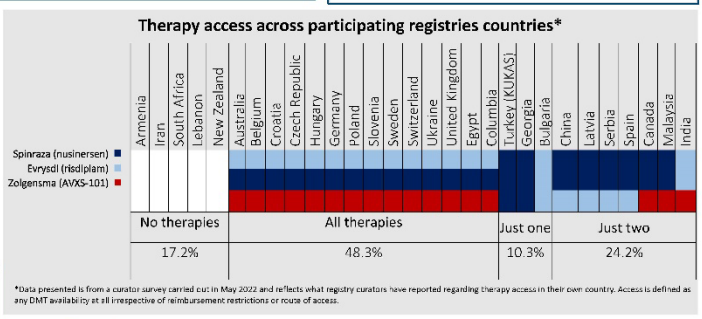




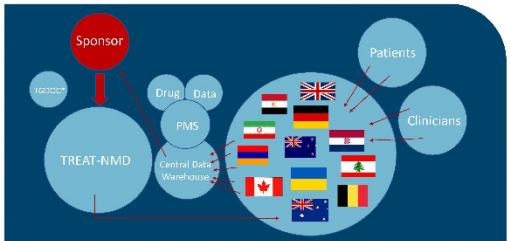




Scan to download the SMA Outcome Measures Library



*Data presented is from a curator survey carried out in May 2022 and reflects what registry curators have reported regarding therapy access in their own country. Access is defined as any DMT availability at all irrespective of reimbursement restrictions or route of access.



In 2021, TREAT-NMD conducted an initial registry enquiry that demonstrated the potential use of PMS data. In addition, TREAT-NMD are currently supporting an industry sponsored registry study to provide PMS data to the European Medicines Agency. The diagram above shows the enquiry process at the patient level whereby TREAT-NMD contracts individual registries and provide data reports to the sponsor from all global registries. *TREAT-NMD Global Data systems Oversight Committee

Conclusions:

With SMA therapies now available, the TREAT-NMD SMA Core Dataset aims to facilitate the availability of real-world data from registries to support PMS. Participating registries report an improvement in data quality and utilisation, and have noted an increase in demand for their data, from pharmaceutical companies, regulators and payers. They also report an ability to provide better evidence to lobby nationally for therapy access and reimbursement. The continued collection of high quality data by registries holds the key to successful PMS.

Acknowledgments:
The project wants to recognise the support and involvement of registries globally who have risen to the challenge of extensive data collection and to Biogen who have funded this project.