Workshop Report:

Developing recommendations for expanding the Core Dataset of SMA Registries

8-9 May 2017

Amsterdam, Netherlands

Disclosure and conflict of interest statement

This workshop was supported by Biogen, a pharmaceutical company with a recently approved therapy for spinal muscular atrophy (SMA).

This report was prepared by members of the TREAT-NMD secretariat; Jo Bullivant and Becca Leary, employees of Newcastle University in the UK, with review and input from the workshop planning committee.

The workshop planning committee comprised the TGDOC Chairs and support from TREAT-NMD Secretariat:

- Nathalie Goemans
- Craig Campbell
- Hugh Dawkins
- Rebecca Leary
- Jo Bullivant

With input from Biogen employees:

- Sue Hall
- Sarah Clark
- Cynthia Jones

The purpose of this report is to provide an overview of the meeting's discussions and resulting recommendations. It does not necessarily represent the full perspectives of any individual attendees, Biogen, or TREAT-NMD.

Contents

1. EXECUTIVE SUMMARY

TREAT-NMD identified a need to review and alter the data items collected within the core dataset of the TREAT-NMD global SMA registry. This is to inform the understanding of the natural history of SMA, provide context to understand the safety and effectiveness of new treatments, and to potentially support post marketing surveillance (PMS) for a new treatment for SMA, nusinersen; however it is acknowledged that updating the core dataset with PMS in mind may also offer solutions for future therapies through a disease-specific rather than drug-specific registry approach.

The purpose of this workshop was to update stakeholders on the current SMA landscape, and coordinate a global approach to the dataset expansion by gathering input, building consensus on the main issues, and producing a set of recommendations and next steps for collecting additional items.

Key findings:

1. The purpose of expanding the core dataset of the TREAT-NMD SMA registries should be "to collect robust longitudinal data that (a) captures natural history, (b) measures the effectiveness of interventions and (c) informs standards of care for patients"

2. It was acknowledged that he recommendations produced must make provision for the varied resources, funding and capacity across the different registries. A tiered approach is one potential solution to this requirement.

3. A total of 38 data items across 9 different categories are recommended for consideration for inclusion in the revised core dataset. It is not proposed that all 38 items are included. The data items within each category are ranked in order of priority/preference and have been assessed against a matrix of feasibility measures (administrative, information technology (IT). data capture, and regulatory issues).

4. Data is already being collected from some patients taking nusinersen, and there appears to be a strong appetite from the SMA community for immediate direction and guidance on how to go about this. Despite some areas of disagreement, the workshop also resulted in a strong level of consensus about which are the most desirable data items to consider adding to the core dataset.

5. It is important to consult widely, consider upcoming regulatory changes, ensure appropriate training and IT infrastructures are available, and coincide timings with other key developments such as standards of care. However, it is also important that a 'first draft' version is compiled as a matter of urgency, so that registries with patients already taking nusinersen can start implementing straight away if they are able.

6. The existing core dataset remains important for many stakeholders, and will continue to be highly valued.

7. It is proposed that:
    a. The recommended (prioritised and feasibility-assessed) list of items should be reviewed by stakeholders who were not present at the workshop, including registries that did not participate in the TREAT NMD audit, especially those led by patient advocacy organizations.
    b. The report recommendations are developed into a short term plan for urgent implementation, and medium / long term plans for discussion at the next TGDOC meeting in November 2017.
    c. In order to progress this, a smaller core working group should be formed, who can meet more frequently face to face.

d. A small number of registries are identified as a pilot group (short-term) for the first draft of the updated dataset.

2. ABOUT THE WORKSHOP

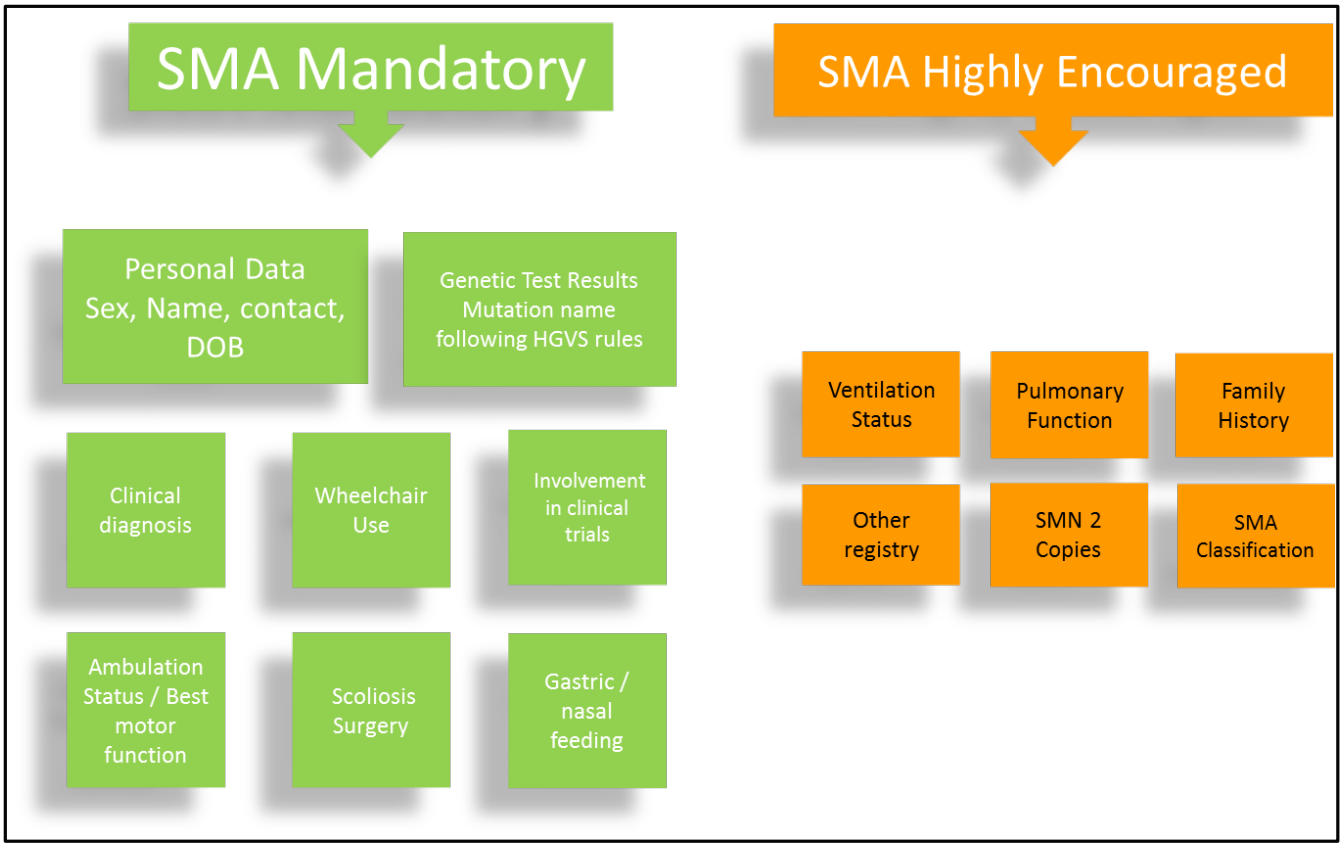
2a. Context and background

Spinal Muscular Atrophy (SMA) is a rare, genetically inherited neuromuscular condition, of which there are several distinct types.

Biogen is a pharmaceutical company with a treatment for spinal muscular atrophy (SMA) (nusinersen), which has been approved by the Food and Drug Administration (FDA) for use in the US and is currently being reviewed by the European Medicines Agency (EMA) for approval in Europe. On the 21st April 2017 the Committee for Medicinal Products for Human Use (CHMP) of the EMA adopted a positive opinion recommending the granting of a marketing authorization for SPINRAZA® (nusinersen) to treat patients with (SMA). Following the workshop the drug was approved by the EMA on 1st June.

There is an existing worldwide network of SMA patient registries affiliated to and coordinated by the TREAT-NMD Neuromuscular Network, and there is an existing core data set collected by these registries, made up of mandatory and highly encouraged data items.

Figure 1: Current set of mandatory and highly encouraged data items



TREAT-NMD identified a need to revisit and extend this core data set, in order to:

- Improve the quality and quantity of natural history / longitudinal SMA data.

- Provide context for understanding safety and effectiveness of nusinersen
- Provide data to support the post-marketing surveillance (PMS) of nusinersen and other future therapies.

The intention of this workshop was:

- To gather input from key stakeholders in the SMA community
- To build consensus around which data items are appropriate to be added
- To highlight practical factors to be taken into consideration.

The intention was not to make any final decisions; rather to produce a collective set of well-thought-out suggestions for consideration by the TGDOC Chairs.

This workshop built upon a similar workshop held in Sydney, Australia in July 2016, from which a full report is also available upon request.

2b. Methodology and pre-work

The workshop was delivered with the support of an external, impartial, freelance facilitator sourced by the TREAT-NMD secretariat.

It was designed around the principles of the Delphi method, which "*entails a group of experts who anonymously reply to questionnaires and subsequently receive feedback in the form of a statistical representation of the "group response," after which the process repeats itself. The goal is to reduce the range of responses and arrive at something closer to expert consensus.*" (https://www.rand.org/topics/delphi-method.html)

The TREAT-NMD Executive Committee produced a list of 47 potential data items based on outcomes that had been used in clinical trials or other natural history studies of SMA. These items were sorted into 9 suggested categories, to be considered for inclusion in the core data set. In advance of the workshop, stakeholders were asked the following question for each category:

"How important is it for the following measures to be added to the SMA Registries data set?"

Each category also allowed for additional data items to be added that were not in the original suggestions

Figure 2 below shows the 47 potential items included in the pre-work survey

Figure 2: Potential data items sent to stakeholders for pre-work survey

Motor measures in infantile onset SMA 1. Hammersmith Infant Neurological Exam (HINE) 2. WHO Gross Motor Milestones 3. CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders)	**Motor measures in later onset SMA** 1. 6-minute walk test 2. HFMSE (Hammersmith Functional Motor Scale – Expanded) 3. ULM (Upper Limb Module) 4. Myometry (grip strength +/- other muscle groups)	**Electrophysiology and biomarkers** 1. CMAP (Compound Muscle Action Potential) 2. MUNE (Motor Unit Number Estimation) 3. EIM (Electrical Impedance Myography) 4. SMN Levels in Cerebral Spinal Fluid 5. MRI or other imaging
Patient-reported outcome measures (PROMS) 1. PedsQL (Pediatric Quality of Life Inventory - HRQOL measure with generic and NM scales) 2. ACEND (Assessment of Caregiver Experience of NMD) 3. CGI (Clinical Global Impressions scale - severity of illness) 4. PedsQL (Pediatric Quality of Life Inventory) Fatigue Scale 5. Overall visual analogue scale for wellness 6. Employment or school functioning scale 7. Pain scale 8. Socio-economic status (i.e. income, parental education)	**Medical outcomes** 1. Pulmonary function measures 2. Time to ventilation 3. Time to Bi-PAP 4. Time to death 5. Time to loss of ambulation 6. Time to feeding tube required 7. Degree of scoliosis / time to scoliosis surgery	**Other aspects of SMA** 1. Medications 2. Co-morbidities 3. Contractures 4. Complementary and alternative treatments 5. Therapy interventions (occupational therapy, physical therapy, range of motion, splinting, etc.) 6. Clinic attendance (level of clinical care?) 7. Hospitalizations (number / reasons) 8. Growth parameters 9. Cognitive status
Diagnostic aspects 1. Age at diagnosis 2. Method of diagnosis 3. Newborn screening	**Treatment factors** 1. Compliance 2. Adverse events 3. Dose 4. Specific monitoring (i.e. Liver Function Tests) 5. Treatment efficacy 6. Reason to stop treatment 7. Nusinersen levels in cerebral spinal fluid	**Demographics** 1. Cultural / racial background

2b. Methodology and pre-work (continued)

Respondents were then asked to either rank the items in order of importance, or score them as Essential / Nice to have / Not necessary. There was the opportunity to provide comment and suggest additional items against each category, which were then incorporated into the workshop for discussion. A full copy of the pre-work survey is available in Appendix A, and a full list of additional items suggested by survey respondents is available in Appendix B.

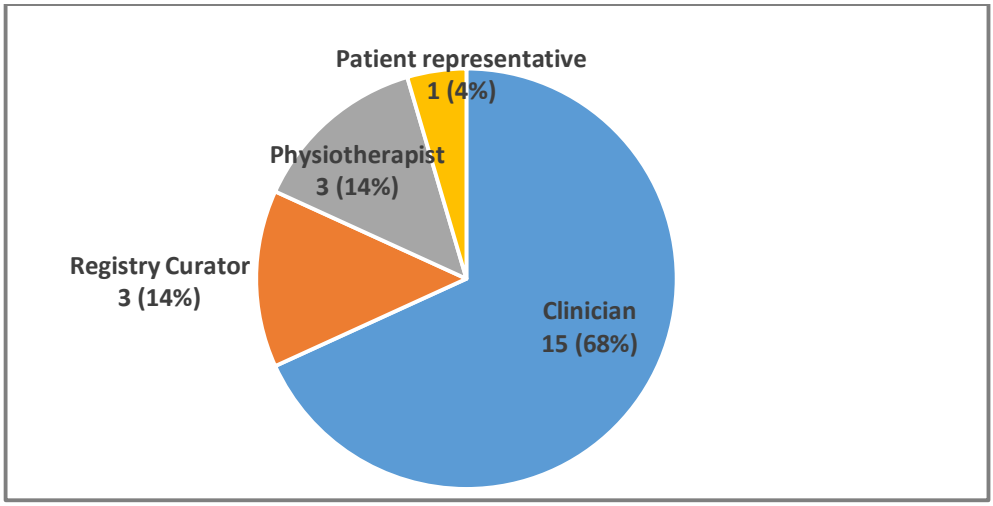
Responses were gathered anonymously via an online survey, which was sent to a wider group of stakeholders than just those able to attend the workshop (see figure 3).

Figure 3: Workshop stakeholders:

Stakeholders (◊= invited to complete pre-work, ⌂= attended workshop, * = participated in some sessions via Skype)			
Name	**Stakeholder Group**	**Name**	**Stakeholder Group**
Adrien Bretagne ⌂	Biogen	Eugenio Mercuri ◊*	Clinician
Jo Bullivant ⌂	TREAT-NMD Secretariat	Jacqueline Montes ◊⌂	Physiotherapist
Craig Campbell ◊⌂	Clinician / TGDOC VC	Robert Muni-Lofra ◊⌂	Physiotherapist
Sarah Clark ⌂	Biogen	Francesco Muntoni ◊	Clinician
Hugh Dawkins ◊⌂	TGDOC Past Chair	Maryam Oskoui ◊	Clinician
Michelle Farrar ◊	Clinician	Marie-Christine Ouillade ◊⌂	Patient Representative
Richard Finkel ◊	Clinician	Sandra Reyna ⌂	Biogen
Nathalie Goemans ◊⌂	Clinician / TGDOC Chair	Agata Robertson ◊⌂	Registry Curator
Sue Hall ⌂	Biogen	Miriam Rodrigues ◊⌂	Registry Curator / Patient Representative
Tim Hood ⌂	TREAT-NMD Secretariat	Monique Ryan ◊	Clinician
Cynthia Jones ⌂	Biogen	Thomas Sejersen ◊	Clinician
Jan Kirschner ◊⌂	Clinician	Laurent Servais ◊	Clinician
Anna Kostera-Pruszczyk ◊⌂	Clinician	Anita Simonds ◊	Clinician
Becca Leary ⌂	TREAT-NMD Secretariat	Craig Smith ⌂	Facilitator
Hanns Lochmuller ◊	Clinician	Volker Straub ◊	Clinician
Oscar Henry Mayer ◊	Clinician	Kathy Swoboda ◊⌂	Clinician
Elena Mazzone ◊⌂	Physiotherapist	Ludo Van der Pol ◊	Registry Curator

Of the 25 stakeholders who were invited to complete the pre-work survey, 22 (88%) started it (see figure 4 below) and 20 (80%) completed it.

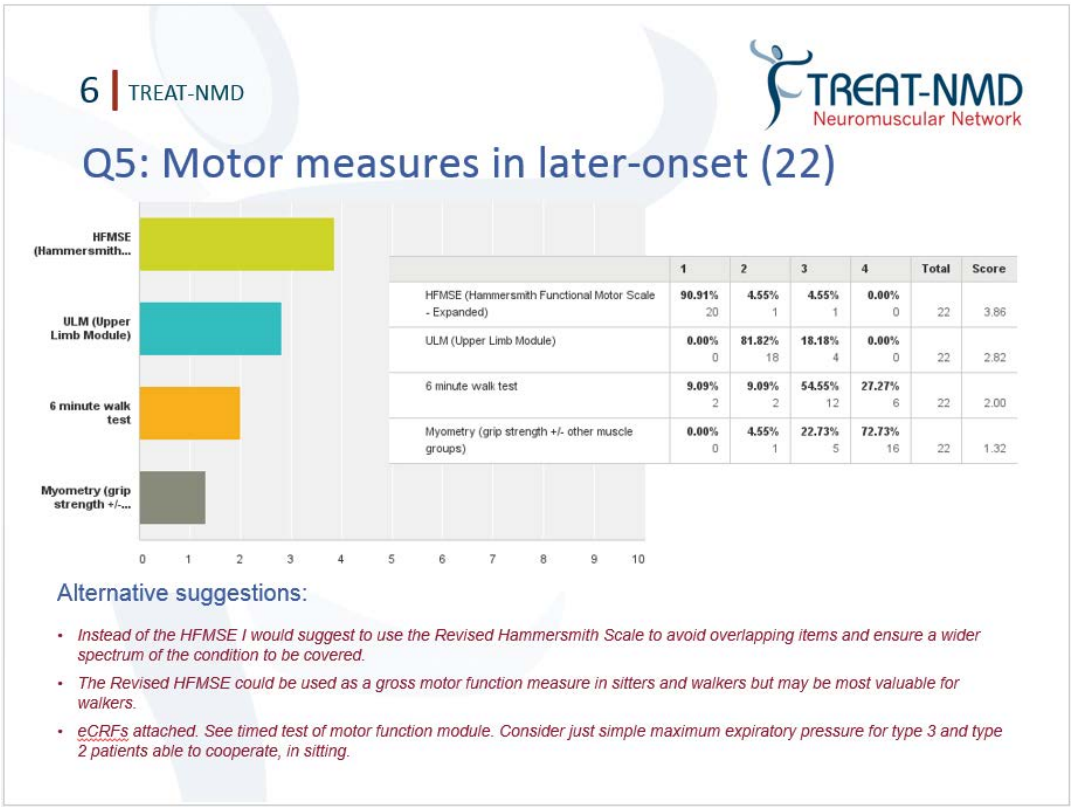
Figure 4: Pre-work survey respondents



2b. Methodology and pre-work (continued)

The results of the pre-work survey were then presented at the start of the workshop and used as a basis for discussion, debate and decision-making. Some samples of the results slides are included below, and the full results presentation is available in Appendix C.

Figure 5: Sample of results presentation slides



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Comments on Motor measures in later onset

- *Myometry is more precise but take time and equipment. 6 minutes walk not usable for most SMA patients*
- *Depends if ambulant or non ambulant*
- *Myometry could be a good strength specific assessment if the right muscle groups and protocol was described but difficult to read if not accompanied with functional assessments such as ULM or HFMSE (or RHS)*
- *The revised version of the ULM called RULM that has been used in CS4 should be considered*
- *I feel that patient reported outcome measurements and quality of life (quality of function) are under appreciated and underutilized*
- *It wouldn't be possible to complete this type/ level of information in purely patient self reported registries*
- *HFMSE and ULMs are clinically meaningful and applicable to spectrum of severity*
- *HFMSE and ULM offer complementary information. However both need a trained PT to complete.*
- *The main outcome measure should be chosen based on function. All walkers should get the 6MWT, non-walkers HFMSE and RULM.*
- *1) HFMSE. Advantage covering large spectrum of functions and severities. 2) ULM. Upper limb function very important in later-onset SMA, well measured ULM. 3) 6 MWT. Restricted to fairly well ambulant individuals. 4. Myometry. Not "functional" scale.*
- *I really hate 6 minute walk and think it is inappropriate for most children - can work reasonably well in still ambulatory teens and adults, but 2 minute may well be sufficient. Prefer a 2 minute walk construct or timed tests of motor function. I think myometry is really not helpful except in type 3 adults or older children as currently practiced. I think PFT measures need to be considered further.*

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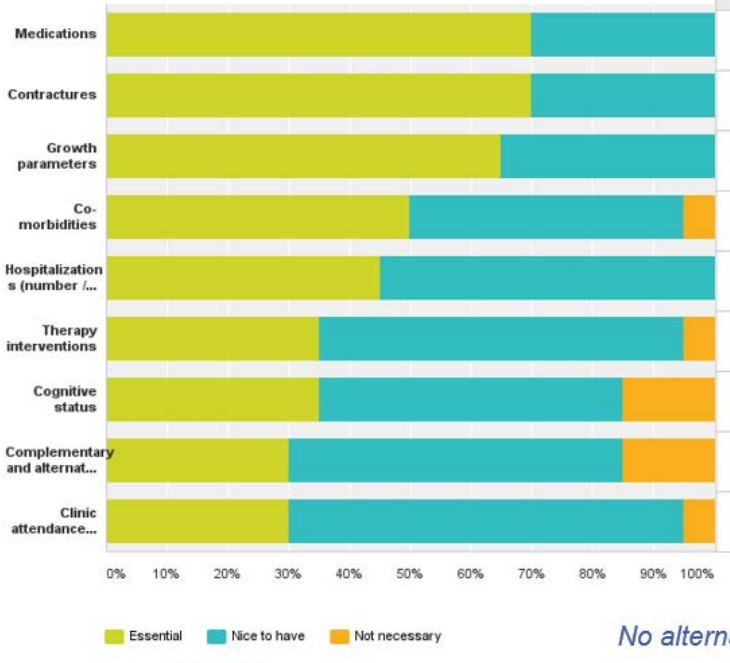
Q20: Other aspects (20)



	Essential	Nice to have	Not necessary	Total
Medications	70.00% 14	30.00% 6	0.00% 0	20
Contractures	70.00% 14	30.00% 6	0.00% 0	20
Growth parameters	65.00% 13	35.00% 7	0.00% 0	20
Co-morbidities	50.00% 10	45.00% 9	5.00% 1	20
Hospitalizations (number /...	45.00% 9	55.00% 11	0.00% 0	20
Therapy interventions	35.00% 7	60.00% 12	5.00% 1	20
Cognitive status	35.00% 7	50.00% 10	15.00% 3	20
Complementary and alternat...	30.00% 6	55.00% 11	15.00% 3	20
Clinic attendance...	30.00% 6	65.00% 13	5.00% 1	20

No alternative measures suggested

2c. Workshop agenda and structure

Following the pre-work results, the workshop was structured with the intention of ensuring that:

- Every participant had opportunity to provide their opinion where they wished
- Participants had opportunity to change their preferences or opinions after listening to input from other stakeholders
- Participants from different stakeholder groups had the opportunity to work with and learn from each other.

The independent facilitator outlined clear 'ground rules' at the start of the workshop, which set the scene for open, collaborative and inclusive discussions.

For most discussion tasks, participants were divided into groups with (wherever possible) equal representation from the different stakeholder groups:

- Clinicians
- Physiotherapists
- Registry curators and/or patient representatives
- Biogen representatives

The agenda was intended to be flexible to respond to the course and pace of discussions. Figure 6 below reflects the original plan and, in blue, the changes that were made throughout in response to the needs of the group:

Figure 6: Flexible agenda; planned versus actual structure of workshop (changes tracked)

Monday 8th May		
09:00-11:00	Welcome, introductions, setting the scene	Facilitator, TREAT-NMD EC, Biogen
11:15-11:45	PMS: lessons learnt in Duchenne Muscular Dystrophy	Anne Oyewole
11:45- 12:30	Presentation and review of pre-work survey results	Craig Campbell, Jo Bullivant
~~13:15-15:15~~ 13:15-17:00	Group work: discussion and re-ranking of data items in each bucket	Facilitator
~~15:35- 17:00~~	~~Group work: practical considerations of extending the data set~~ (moved to day 2)	~~Facilitator~~
17:00- 17:30	Review of the day	Facilitator

Tuesday 9th May		
08:30- 10:30	~~Issues and troubleshooting~~ Group work: practical considerations of extending the data set	Facilitator
10:45- 11:30	Data standards, quality assurance, regulatory compliance	Biogen
11:30- 12:45	Consensus agreement and next steps	Facilitator

3. WORKSHOP DISCUSSIONS

The workshop activities and strategies were designed to highlight areas of consensus, resolve areas of disagreement, and narrow down the selection of data items proposed for consideration. Biogen did not participate actively in the small group discussions:

4a. Ranking exercise *(Monday 8th May)*

- Participants were split into 4 groups comprising an even distribution of stakeholder representatives (clinicians, physiotherapists and curators/patient representatives)
- 4 discussion 'stations' were set up, each focussed on 2 or 3 of the categories of data items.
- Each station had a facilitator (from the TREAT-NMD secretariat) who stayed at that station to record the main discussion points, areas of consensus, and areas of disagreement.
- Each group spent 25 minutes at each station, sorting the items (on post-it notes) in each category into priority order and providing further context or clarity if needed.

For these discussions, participants were asked to concentrate purely on the appropriateness and desirability of the data to be collected; temporarily suspending any considerations of funding, resources, IT system or other logistics of adding the data items or collecting the data.

The suggestions from each group in each category were then displayed on the wall and areas of consensus were confirmed. Further discussions helped to reach a wider group consensus on any areas of differing opinions.

This resulted in some items being discounted entirely, some items being narrowed down and given more detail/specificity, and some newly suggested items being prioritised over original items proposed.

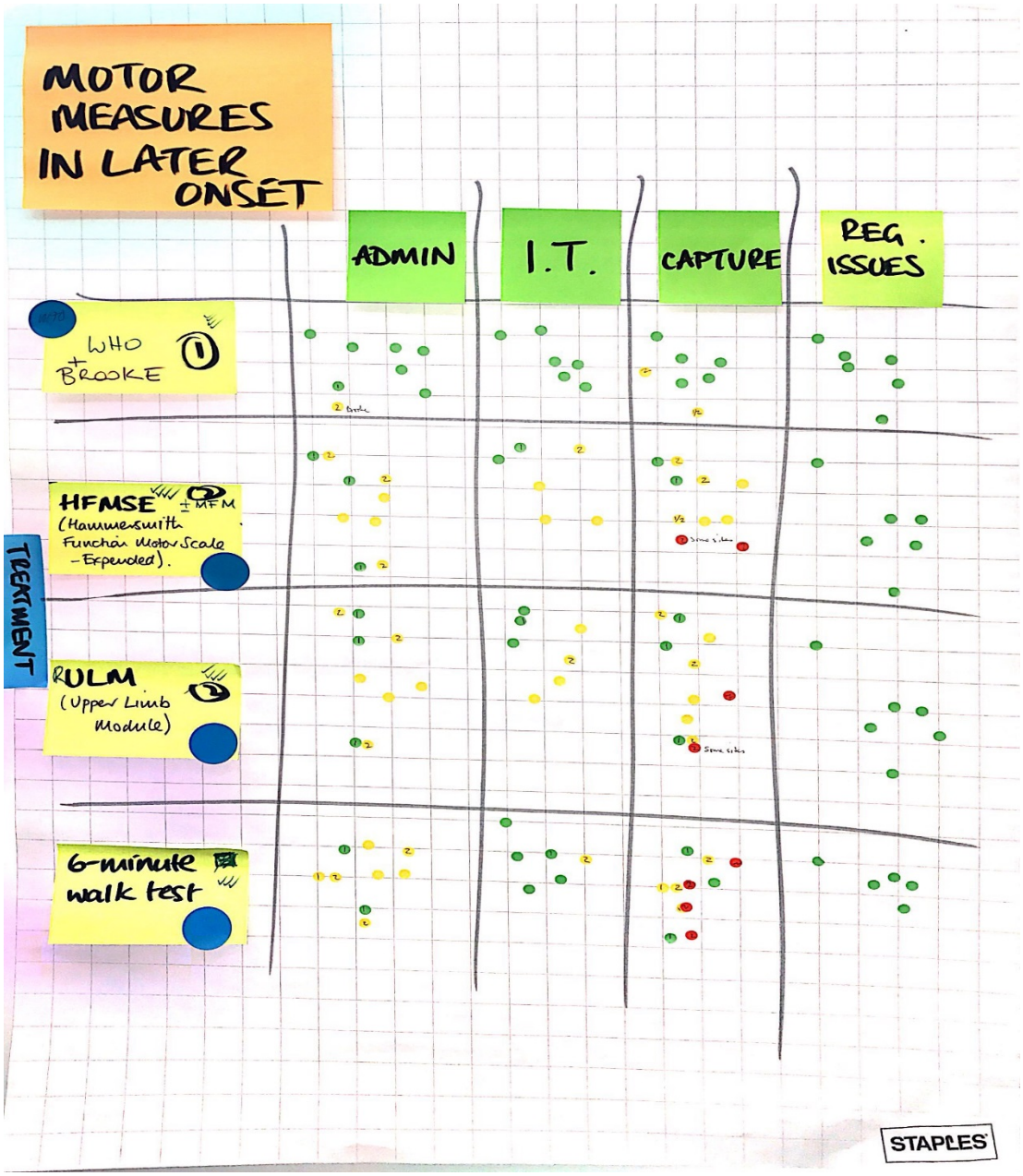
4b. Feasibility considerations *(Tuesday 9th May)*

Participants moved around the room in pairs, assessing the practicalities and logistics of collecting the data items proposed in each category. Each data item was assessed against the following logistical considerations; admin, I.T., data capture and regulatory issues

Participants assigned a red, yellow, or green dot to each data item to indicate how easy they thought that item would be to add to the core data set, in the context of each logistical consideration.

Figure 7 below shows an example of a completed feasibility matrix. The full set of images is available in Appendix D.

Figure 7: Example of a completed feasibility matrix:



Key:

- Green dot =
- Yellow dot =
- Red dot =
- Larger blue dot = Items seen as (immediate-term) priority by Biogen
- Large pink dot = important items where further work is necessary.

4c. The Biogen perspective *(Tuesday 9th May)*

After the workshop participants had reached general consensus on the priority order within categories, and after the feasibility assessment was completed, Biogen representative Cynthia Jones allocated large blue

dots to the data items that Biogen would currently view as high priority for collection in the short term and pink dots to the data items viewed as important items where further work (and time) is necessary.

Blue dots:		**Pink dots:**
WHO and Brooke	Hammersmith	Electrophysiology
HMFSE	Hospitalisations	CMAP
RULM	Co-morbidities	All PROMS
6 MWT	Therapy interventions	Pulmonary Function Measures
HINE	Physical Assessment	Reason to stop treatment
CHOP-INTEND	Ventilation	Family History
Disease modifying drug	Scoliosis	
Dose	Bulbar function	
Adverse events	SMN2 copy number	
Age of diagnosis	Age of symptom onset	

4. PRESENTATIONS – With links

4a. Current landscape of TREAT-NMD SMA Registries

4c. Lessons learned from post marketing surveillance in Duchenne Muscular Dystrophy (DMD)

4d. Results of the pre-work survey

4d. Data standards, quality, accuracy and regulatory compliance (Biogen)

5. CONCLUSIONS AND NEXT STEPS

5a. Conclusions

It was agreed that significant positive progress had been made during the workshop, and the outcome was overall consensus on a categorised list of 38 items for consideration for inclusion into the Global SMA Registry core dataset; prioritised and assessed against a feasibility matrix. Again it is important to note that the intention is not to add this number of data items, but to provide the TGDOC Chairs with considered recommendations to inform their decision-making.

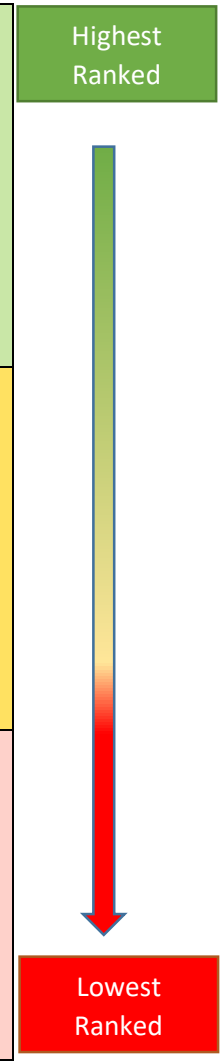
It is also important to acknowledge that although an overall consensus was reached, there were areas of strongly differing opinion and inevitable disagreement. It is to the credit of every participant that different opinions were discussed in an open and receptive environment, and participants were not adverse to changing their standpoint after hearing other perspectives, or making compromises in search of a solution to suit all parts of the wider community. Nevertheless, the group also acknowledges that no solution is perfect for everyone, and there is much work still to do to develop these recommendations into a realistic and implementable plan.

To support this achievement, facilitation from a suitably qualified, impartial, independent, external person is highly recommended for future similar workshops.

Figure 8 below shows the final list of prioritised data items in each category. It is important however to view this alongside the feasibility-assessed matrices in Appendix D. With the understanding that nusinersen was pending EC decision at the time of the meeting (now granted), consensus elements were urgently requested to inform clinician data collection to be implemented at patient visits. This led to the agreement for a small group to pilot implementation.

Figure 8: Prioritised data items recommended for consideration for inclusion in the core dataset

Motor measures in infantile onset SMA 1. HINE Section 2 only, with SMA-specific training 2. WHO Gross Motor Milestones 3. CHOP-INTEND 4. Hammersmith Functional Motor Scale	**Motor measures in later onset SMA** 1. WHO and BROOKE 2. HFMSE (Hammersmith Functional Motor Scale – Expanded) 3. RULM (Upper Limb Module) 4. 6-minute walk test	**SMA-specific drug treatment** 1. Disease modifying drug ** 2. Compliance: a. Dose b. Frequency c. Route 3. Adverse events (related to route administration only) 4. Reason to stop treatment
Diagnostics 1. Age at diagnosis via genetic test** 2. SMN2 copy number * 3. Age of onset of symptoms**	**Medical history** 1. Hospitalisations 2. Co-morbidities 3. Therapy interventions 4. Medications (other meds not related to disease modification)**	**Physical assessment** 1. Physical assessment 2. Pulmonary function measures* 3. Ventilation (Y/N, IV/NIV)* 4. Bulbar function 5. Scoliosis (Y/N, Severity, Surgery)* 6. Highest and current motor function achieved* 7. Cognition 8. Fatigue
Demographics 1. GUID / PPRL 2. Date of death** 3. Sibling / Family* 4. Ethnicity: cultural / racial background**	**Patient-reported outcome measures (PROMS)** 5. Overall visual analogue scale for wellness 6. PedsQL (Pediatric Quality of Life Inventory - HRQOL measure with generic and NM scales) 7. PEDICAT or equivalent (SMA FRS) 8. PedsQL Fatigue Scale 9. ACEND (Assessment of Caregiver Experience of NMD)	**Electrophysiology and biomarkers** 1. CMAP (Compound Muscle Action Potential) 2. DEXA (whole body and spine): training must promote consistency in collection



*already in core dataset **ranked as easy to include

5b. Next steps

It is now proposed that:

- This report, and in particular the recommended (prioritised and feasibility-assessed) list of items for consideration are reviewed by stakeholders who were not present at the workshop, especially those with patient-entered data.

- The report recommendations are developed into a short term plan for urgent implementation, and medium / long term plans for discussion at the next TGDOC meeting in November 2017.

- In order to progress this, a smaller core working group should be formed, who can meet more frequently face to face.

- A small number of registries are identified as a pilot group for the implementation of the first draft of the updated dataset in the immediate future.

5c. Further reflection

Discussions since the workshop have also resulted in the following reflection for consideration:

The existing core data set consists of mandatory and highly encouraged data items. In order to extend this model a tiered approach could be adopted, with tier 1 requiring the lowest number of data items (e.g. suitable for patient-entered registries), and the higher tiers being more suitable for specialist neuromuscular centres with lots of resource and clinician-entered registries. For example:

1. Patient driven registries: core items with patient reporting, PROMS

2. Clinic driven registries, without access to additional resources such as physio and biomarkers

3. Clinic driven registries with enhanced resources. Could collect all items

A tiered structure would also provide direction and guidance for registries seeking to expand, or improve the quality of their data.

Two possible ways of implementing a tiered structure have been discussed:

1. Add a limited number of items to the mandatory dataset for all registries. Then, within the highly encouraged (HE) dataset, introduce tiers to reflect different levels of resource and capacity:

Registry type	Mandatory items	HE Tier 2 items	HE Tier 3 items
Tier 1	✓		
Tier 2	✓	✓	
Tier 3	✓	✓	✓

2. Introduce tiers across both datasets (mandatory and highly encouraged), so that a higher tier registry would have a larger set of mandatory data items than a lower tier registry.

Registry type	Mandatory items	HE items
Tier 1	Core	Core
Tier 2	Core + 2	Core + 4
Tier 3	Core + 4	Core + 8

Appendices

A -Survey Responses

B- Alternative Responses

C – Survey results

D - Flipcharts