LGMD Dataset Project
Pilot Feasibility Study
Project Feedback Review

Working Group Output Document – Meeting 6

Version 1

Document Control Sheet

Document Preparation Information

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Change History

Date	Change Description	Version	Approved By
04/10/21	Initial structure & re-drafting – JMcK	V0.1	John McKenna
07/10/21	Updates to section 2 & 3	V0.1	John McKenna
10/10/21	Updates to section 4	V0.1	John McKenna
13/10/21	Updates to sections 4,5 &6	V0.1	John McKenna
14/10/21	Updates to section 1	V0.1	John McKenna
15/10/21	Updates to all sections	V0.1	John McKenna
18/10/21	Updates based on feedback from SS all sections	V0.2	John Mckenna
21/10/21	Confirmation of feedback from SS	V0.3	John Mckenna

Contents

1 Executive Summary

Limb Girdle Muscular Dystrophies (LGMDs) are a heterogeneous group of genetic muscle diseases causing permanent and irreversible disability. There are currently no specific LGMD treatments and limited consensus of understanding on differential diagnosis, best practice management and standards of care.

The current LGMD registry landscape is fragmented with limited communication between registries or with TREAT-NMD. Previously no generally accepted mandatory core dataset existed for registries to collect. Therapeutic developments in LGMDs, the potential need for clinical trial development and the need for post market surveillance, require collaboration and consensus on a core data set for LGMD registries.

It is expected that the availability of a universal core data set will encourage the collection of appropriate, harmonized and reproducible data which can be reliably used for the analysis of natural history data to support clinical trial design and improve patient recruitment to trials. Treat-NMD is ideally placed to drive the development of a unified LGMD Core Dataset & believes the LGMD community are now at a point to meet and share their views and ideas.

To deliver the required dataset a series of 6 workshops & meetings with LGMD stakeholders and Key Opinion Leaders (KOLs), was arranged, with the aim of agreeing & developing a core data set for LGMD registries to use. More information on the meetings can be found in section 2

Following and during the period the meetings were held a pilot feasibility study evaluation exercise was conducted with 20 participants from 10 registries. More information on the pilot feasibility study can be found in appendix 1. Meeting 6 was held on 30th September 2021 to review feedback received from participants, agree any changes required to the study version of the dataset and agree the definitive version (V1.0) of LGMD Core dataset.

As was noted in the presentation during the meeting:

- The TREAT-NMD LGMD Core dataset was designed to collect data for all types of LGMD.
- Registries are free to collect any other data to complement the dataset.
- TREAT-NMD Datasets are defined to standardize and homogenised the data collected across registries TGDOC enquiries.
- Future approach: Extended LGMD Core dataset to collect specificities of LGMD subtypes.

During the course of meeting 6 the objective was achieved. 3 changes were proposed and agreed, these are:

1. Removal of the Creatine Kinase data item
2. Removal of the Creatine Kinase date data item
3. Addition of verification to the genetic confirmation data item in the response options

    From:

    a. Yes
    b. No

    To:

    a. Yes - confirmation only
    b. Yes, confirmation and verified
    c. No

Note that registries are free to continue collecting the CK data and CK data items independently if they feel it useful and appropriate to do so, however they are no longer part of the core dataset.

The changes noted above have been communicated to the Global Registries Platform (GRP) team to update the LGMD module in the application & the project's web developer for the appropriate amendments to be made to the Dataset. This is prior to their final approval and adoption as the official TREAT-NMD Core LGMD dataset version 1 and publication on the company's website.

The projects immediate next steps are:

- Seek approval from the Chairs of TGDOC for the approval of the finalised v1 of the dataset
- Engage with LGMD registries to assess their intentions regarding adopting the dataset, either into their existing platform or via the GRP
- Commence the immediate roll out of v1 of the LGMD dataset with registries who are able and willing to progress
- Confirm that the appropriate changes to the LGMD module in the GRP have been actioned

2 Introduction and Background

Limb Girdle Muscular Dystrophies (LGMDs) are a heterogeneous group of genetic muscle diseases characterized by progressive weakness and wasting of the shoulder and pelvic girdle muscles, leading to permanent and irreversible disability. There are currently no specific treatments available for these conditions and there is limited consensus of understanding on differential diagnosis, best practice management and standards of care.

The current LGMD registry landscape is fragmented. There are multiple small, subtype registries that do not routinely communicate with each other or with professional organizations such as TREAT-NMD. In addition, there was previously no generally accepted mandatory core dataset that multiple registries have agreed to collect. The acceleration of therapeutic development in LGMDs, the potential need for clinical trial development and ultimately the need for post market surveillance, require collaboration and consensus on a core data set for LGMD registries.

It is believed that the creation of a universal core data set at this point will lead to more appropriate, harmonized and reproducible data. This can be reliably used for the analysis of natural history data to support clinical trial design and improve patient recruitment to trials. Treat-NMD, through its network of registries, stakeholders and partners, is ideally placed to drive forward the development of a unified consensus on an LGMD Core Dataset, by working with Key opinion leaders, ensuring stakeholder collaboration, and encouraging partnership engagement. TREAT-NMD believes the LGMD community are now at a suitable point to meet and share their views and ideas.

A series of 6 workshops & meetings with LGMD stakeholders and Key Opinion Leaders (KOLs), was arranged, with the aim of agreeing & developing a core data set for LGMD registries to use:

Meeting 1. Define the objectives of LGMD registries
A report on Meeting 1 is available *here*

Meeting 2. Define the LGMD Core Dataset
A report on Meeting 2 is available *here*

Meeting 3. Assess the feasibility of the LGMD Core Dataset
A report on Meeting 3 is available *here*

Meeting 4 . Discuss selected data items
A report on Meeting 4 is available *here*

Meeting 5 . Presentation of LGMD Dataset v0.1
This meeting presented an overview of the pilot feasibility study dataset (v0.1) to the full working group & selected pharma companies

Following the previous 5 meetings, meeting 6 was held on 30th September 2021 and sought to review feedback received from participants in the recently completed pilot feasibility study evaluation exercise in order to agree and approve the definitive version (V1.0) of LGMD Core dataset. That objective was achieved in the meeting.

The agreed changes have been communicated to the Global Registries Platform (GRP) team to update the LGMD module in the application & the project's developer for the appropriate amendments to be made to the LGMD Dataset prior to its final approval and publication on the TREAT-NMD website.

3 Disclosures and Conflicts of Interest

This meeting was part of the TREAT-NMD Limb Girdle Muscular Dystrophy (LGMD) Core Dataset project. This report has been written by John Mckenna, Project Manager of the DMD & LGMD Core Dataset projects and employee of the TREAT-NMD Services Limited. This document has been reviewed by the project's previous project Manager, Sonia Segovia, Principal Investigator, the TREAT-NMD LGMD Advisory Board and the TGDOC (TREAT NMD Global Data systems Oversight Committee) Chairs.

Principal investigator

- Michela Guglieri (Newcastle University-John Walton Muscular Centre)

Advisory board

- Jordi Díaz Manera (Newcastle University-John Walton Muscular Centre)
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- Maggie Walter (Munich University)
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- Elena Pegonaron (University of Pafova)
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- Anna Mayhew (Newcastle University-Jonh Walton Muscular Center)
- Edmar Zantoneli (Sao Paolo, Brazil)
- John Vissing (Rigshopitalet, Copenhagen)
- Laura Rufibach (Jain Foundation)
- Jennifer Levy (Coalition to cure Calpain 3)

TGDOC Chairs

- Craig Campbell
- Anna Ambrosini
- Michela Guglieri

This report provides the overall conclusions and outputs of collaborative discussions which took place during the 6th Workshop meeting among the LGMD Working Group. The report does not represent the independent views of individual attendees, project funders or TREAT-NMD.

4 LGMD Dataset Project - Context & Background

Pilot feasibility study test

The pilot feasibility study test phase focused on understanding the capacity and capability of the selected registries to implement the Core dataset. Registries volunteered to participate in the pilot feasibility study (and were asked to conduct an assessment on:

a. The feasibility (ease of) implementing the LGMD Core Dataset
and
b. If rated as difficult, provide information as to why the item would be difficult to collect
c. Compare LGMD Core Dataset with the dataset currently collected by the registry (Gap analysis).

The project team worked with the Pilot feasibility study group registries to identify the challenges in collecting the LGMD Dataset and understand the difficulties in preparation for the roll out phase.

4.1 Aims of Workshop Meeting 6

The aims of the 6th workshop meeting were to:

- Review the pilot feasibility study feasibility assessment results from the 20 surveys received
- Allow an opportunity for participants to share any testimonials about the dataset or the pilot feasibility study
- Discuss general or specific items before deciding on their inclusion in the final dataset
- Draw conclusions, agree next steps and allocate actions

The objective of meeting 6 was to review and approve the definitive version (V1.0) of LGMD Core dataset and this document describes the process by which that was achieved.

A copy of the slides used in the meeting can be found in appendix 5

4.2 Agenda

The 6th Workshop Meeting agenda was structured to take place in one session, with a focus on the consensus building process on key items with the whole WG. A facilitator was not used on this occasion :

Time	Topic area	Person
13:00	Welcome and introduction	Michela Guglieri and Sonia Segovia
13:15	Results of the feasibility assessment	Sonia Segovia
13:30	Testimonials (feedback from participants)	Various participants
13:45	Break	
14:00	Discussion 1. General topics 2. Specific items & voting	All
14:50	Conclusions and next steps	Michela Guglieri John Mckenna

4.3 Participants

Chairs/Organizers	
Michela Guglieri	Principal Investigator-Newcastle University
Sonia Segovia	Project Manager
Anna Ambrosini	TGDOC, Chair elect
Advisory board	
John Vissing	Copenhagen Neuromuscular Centre, Denmark
Meredith James	Newcastle University, United Kingdom
Jordi Díaz-Manera	Newcastle University, United Kingdom
Clinical experts and registry curators	
Robin Forbes	Australian Neuromuscular Disease Registry, Australia
Lindsay Alfano	Nationwide Children Hospital, United States
Rasha el Sharif	Egyptian Neuromuscular registry, Egypt
Marlene Jagut	Belgium Neuromuscular Disease Registry
Tanya Stojkovic	Pitié-Salpêtrièr Hospital, neuromuscular reference center , Paris, France
Erik Niks	Neurology department LUMC, Leiden
Miriam Rodrigues	New Zealand Neuromuscular Disease Registry (Punaha Io Neurogenetic Research Bank)
Simone Thiele	Friedrich-Baur-Institute in Munich
Marcel Heidemann	Friedrich-Baur-Institute in Munich
Patients' representatives	
Lindsay Murphy	Global FKRP Registry
Carles Sanchez	Muscular diversity Project
Sarah Foye	CMDIR, Titin Family Advocate - LGMD2J
Stefania Pedroni	LGMD Registry- Unione Italiana Lotta alla Distrofia Muscolare Italy
Sarah Sirah Emmons	Jain Foundation
Jennifer Levy	Cure Calpain 3
Jessica Furlan	Conquistando Escalones
Beatrice Vola	Gruppo Familiare Beta-Sarcoglicanopatie Onlus *
TREAT-NMD secretariat	
John McKenna	Project Manager TREAT-NMD
Janet Wilkins	Project Co-ordinator TREAT-NMD
Caroline Ogden	Project Manager TREAT-NMD
Susan Cardiff	Data Systems Support Officer TREAT-NMD
Lynsey Surtees	Admin & Project Support Assistant TREAT-NMD

**Additional attendee who is not a member of the WG, feasibility study registries or task force.*

4.4 Methodology

As in previous meetings Zoom video conferencing was used to organise a virtual and interactive session. The discussion was divided into two main topics: Discussion of the feedback received and voting on individual items for which Zoom polls were used.

The session was recorded. Participants were asked to turn off their camera if they prefer not to be recorded.
Participants were asked to ensure their microphone was muted unless they were speaking and to write any comments in the "chat function" whilst presentations were being delivered. Participants were also asked to
raise their "virtual hand" to ask questions during any curated question sessions in the meeting.

4.4.1 Items for Discussion – Feedback Surveys

Ahead of the meeting the feedback received from participants during the evaluation exercise was analysed and categorised. The feedback, gathered via an online survey, asked participants four questions on each data item:

Question 1: Please tell us how easy or difficult it is for you to **collect** this information?
Question 2: If you answered **difficult or very difficult** to any of the dataset items in the above question, please complete any additional support required to collect this information in your registry.
Question 3: Please tell us how easy or difficult it would be to **input** this information into the registry? (Manually enter the information)?
Question 4: If you answered **difficult or very difficult** to any of the dataset items in the above question, please complete any additional support required to collect this information in your registry.

Participants rated each data item in the proposed dataset against a number of criteria. Users chose one of six options ranging from Very Easy to Very Difficult. Details of the questions and related information are shown below:

Question 1:
*Please tell us how easy or difficult it is for you to **collect** this information?*
Options 1:
Very Easy, Easy, Moderate, Difficult, Very Difficult, Not Applicable
Option Descriptions 1:
Very Easy (I can get this information very easily with no extra effort required)- Easy (I can easily get this information with little extra effort)- Moderate (I can get this information but extra time and effort may be needed)- Difficult (The information is difficult for me to collect and will take a lot more time and effort)- Very Difficult (This information is not available or would take a huge amount of time to collect)
User Guidance 1 (patient registries only):
For this question, think about whether this is information is easy to collect as you know this information or have this in your own records. It maybe that you can get this information but it would require extra effort to contact a clinician for the information, then this should be rated as moderate/difficult. If you don't know the information or is not available the item should be rated as very difficult. It maybe that you do not understand the information, which is required, then it would be very difficult for you to collect and would require a lot of effort to get this information. You should rate each item according to the time and effort that will be required to understand them. Taking in consideration the above, please reflect this in your ratings below.

Question 2:
*If you answered **difficult or very difficult** to any of the dataset items in the above question, please complete any additional support required to collect this information in your registry.*
Options 2:
Technical support, Human resources, Finances, Training in the Dataset Specification, Other, if other, please specify (free text)
User Guidance 2:
N/A

Question 3:
*Please tell us how easy or difficult it would be to **input** this information into the registry? (Manually enter the information)?*
Options 3:
Very Easy, Easy, Moderate, Difficult, Very Difficult, Not Applicable
Option Descriptions 1:
Very Easy (I can get this information very easily with no extra effort required)- Easy (I can easily get this information with little extra effort)- Moderate (I can get this information but extra time and effort may be needed)- Difficult (The information is difficult for me to collect and will take a lot more time and effort)- Very Difficult (This information is not available or would take a huge amount of time to collect)
User Guidance 3: (patient registries only):
For this question think about whether this information is very easy to understand and can be entered easily. It maybe that you have this information but would take you more time to enter as it is more difficult to understand or you just don't have the time capacity to enter this information. Taking into account the above, please reflect this in your ratings below.

Question 4:
*If you answered **difficult or very difficult** to any of the dataset items in the above question, please complete any additional support required to collect this information in your registry.*
Options 4:
Technical support, Human resources, Finances, Training in the Dataset Specification, Other, if other, please specify (free text)
User Guidance 4:
N/A

4.4.2 Summary of Pilot feasibility study Evaluation Feedback

Once the surveys had been completed the results were analysed and each data item was colour coded as either Red, Amber or Green using the following criteria:

- Green: Data item was already being collected by registries with no issues OR is a new item but which registries did not identify any issues in collecting
- Amber: Data item was identified as new by at least one registry and expected to require some additional effort to collect
- Red: Data item was identified as new by multiple registries and was expected to be challenging to collect

Applying this colour coding to the feedback identified the following within the data items:

Colour	Items	%
Green	44	55%
Amber*	12	15%
Red	24	30%
Total	**80**	**100%**

* Of the12 Amber rated items only 4 were agreed to be valid. This is because the other 8 are mandatory for clinically reported registries but the feedback received was from patients reported registries who would not be expected to collect the data items.

4.4.3 Discussion and voting

The RAG ratings were shown to the attendees on the call (See appendix 5). It was proposed at this point that those items coded as green should be accepted as agreed for inclusion in version 1 of the dataset. As no objections were raised to this proposal it was agreed.

It was further discussed and agreed that the Red items would be prioritised for discussion and voting. Also, that Amber rated items would be discussed and voted on, if time allowed (the meeting was limited to 2 hours)

Each of the Red items were considered in turn and various participants gave their views as to the best course of action to take and why. Some participants submitted comments via the chat and these were read out to the attendees by either the Project Manager or Principal Investigator.

Once the discussions concluded a Zoom poll was launched by the Project Coordinator and participants were encouraged to vote on the following options for each item:

- Keep the item as it currently is in the dataset
- Change the classification of an item from clinician reported to patient reported or vice versa
- Remove the item from the dataset

4.5 Results & findings

The following results were noted from the Zoom polls:

LGMD Data Item	Majority voted for
Date of Death	Keep in the dataset unchanged
Genetic Confirmation	Keep in the dataset unchanged
Symptoms onset	Keep in the dataset unchanged
Muscle Biopsy	Keep in the dataset unchanged
Muscle Biopsy date	Keep in the dataset unchanged
Muscle MRI	Keep in the dataset unchanged
CK level*	Removed from the dataset
CK date*	Removed from the dataset
PROM**	Unchanged
PROM Score**	Unchanged
Initial Signs	Keep in the dataset unchanged
Initial Signs date	Keep in the dataset unchanged
Initial Phenotype	Keep in the dataset unchanged
Pulmonary test date	Keep in the dataset unchanged
FVC volume/%	Keep in the dataset unchanged
FVC %	Keep in the dataset unchanged
peak cough flow	Keep in the dataset unchanged
Spirometry position	Keep in the dataset unchanged
Cardiac imaging	Keep in the dataset unchanged
Cardiac imaging date	Keep in the dataset unchanged
Cardiac imaging type	Keep in the dataset unchanged
Left VEF	Keep in the dataset unchanged
Fractional shortening	Keep in the dataset unchanged
Electromyography	Keep in the dataset unchanged

*It was decided earlier in the project process that only mandatory items would be included in the core dataset. Therefore, these items have been removed from version 1 of the LGMD dataset. Registries are free to continue collecting this data if they feel it useful and appropriate to do so.

Following a group discussion, it was proposed to add verification to the genetic confirmation data item in the response options . This changed the item as below

From:

a. Yes
b. No

To

c. Yes - confirmation only
d. Yes, confirmation and verified
e. No

**The PROM and PROM Score data items were voted on but no overall majority was achieved for any course of action and so the items remain unchanged and are mandatory to collect for both patient and clinically reported registries.

5 Conclusions & Next steps.

The LGMD Core Dataset development has completed the first phase of a broader project that includes three phases.

1. LGMD Core Dataset development
2. Roll out of the LGMD Core Dataset
3. Expansion of the LGMD Core Dataset

The TREAT-NMD LGMD Core dataset was designed to collect data for all types of LGMD.
Registries are free to collect any other data to complement the dataset.

TREAT-NMD Datasets are defined to standardize and homogenised the data collected across registries – TGDOC enquiries.

Future approach: Extended LGMD Core dataset to collect specificities of LGMD subtypes.

During the course of meeting 6 the objective was achieved. Only 3 changes were proposed and agreed, these being the removal of the Creatine Kinase & Creatine Kinase date data items from the core dataset and the addition of verification to the Genetic Confirmation noted earlier. Registries are of course free to continue collecting Creatine Kinase data independently if they feel it useful and appropriate to do so, however the items are no longer part of the core dataset.

As a result of meeting 6 and the first phase of this project, the Working group has reached an agreement on the items that are to be included in version 1 of the LGMD Core Dataset.

The second phase is expected to start in January 2022 with the objective of rolling out the LGMD Core Dataset among all the TREAT-NMD registries that are collecting LGMD data.

The Projects Next Steps are listed below:

- Seek approval from the Chairs of TGDOC for the approval of the finalised v1 of the dataset
- Engage with LGMD registries to assess their intentions regarding adopting the dataset, either into their existing platform or via the GRP
- Commence the immediate roll out of v1 of the LGMD dataset with registries who are able and willing to progress
- Confirm that the appropriate changes to the GRP & Dataset Specification have been actioned
- Investigate a gap analysis and an expansion phase with the inclusion of the dataset in the registries.

6 Acknowledgements to Funders

We would like to thank the funders of this project for their invaluable contribution. Our current funders are Sarepta Therapeutics. We continue to seek additional funding for this project and for future projects, required to further develop LGMD datasets and registry data collection capability in 2020/2021.

7 Appendices

7.1 Appendix 1: LGMD Pilot feasibility study Summary Document:

Link here

7.2 Appendix 2: Working Group Participants list:

Link here

7.3 Appendix 3: Link to the TREAT-NMD LGMD Core Dataset v1:

Link here

7.4 Appendix 4: Data Items Reviewed:

Link here

7.5 Appendix 5: LGMD Dataset Presentation:

Link here