Improving Standards of Care and Translational Research in Spinal Muscular Atrophy (SMA) – Functional Scales

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Background: Recent discoveries and advances in Spinal Muscular Atrophy (SMA) have led to the development of potential therapeutic treatments; consequently there is a need for a robust clinical and research network poised for designing valid outcome measures for clinical trials, and to collect longitudinal data. SMA REACH And Clinical Hub UK (SMA REACH UK) is a two year study funded by a grant from The SMA Trust to GOSH Children’s Charity. SMA REACH UK is a new initiative, in collaboration with the existing UK SMA Patient Registry and the SMA Research network, to establish the first national clinical and research network to determine national agreement on clinical and physiotherapy assessment and standards of care for patients with Spinal Muscular Atrophy in the UK. This project is being led by the Dubowitz Neuromuscular Centre at University College London in collaboration with the MRC Neuromuscular Centre in London and Newcastle, and Newcastle University.

Aim: To ensure that functional scales are robust and clinically meaningful for clinical trials in Spinal Muscle Atrophy.

Methods:
Physicians and physiotherapists from London, Newcastle, Rome and USA were invited to the 1st SMA REACH UK International Workshop in December 2013 to discuss currently reported functional scales in patients with type 2 & 3 SMA –

- Hammersmith Functional Motor Scale Expanded (HFMSEx) – This scale tests motor function of patients with SMA. The original 20 item Hammersmith Functional Motor Scale was expanded to include 13 additional adapted items from the Gross Motor Function Measure to improve sensitivity for the higher functioning ambulant population.
- Upper Limb Module for SMA (ULM for SMA) – This consists of 9 items that test proximal and distal motor function of the arm in patients with SMA.
- Performance of the Upper Limb Module for DMD (PUL for DMD) – This was designed to test upper limb function in patients with Duchenne Muscular Dystrophy. It consists of 21 items testing shoulder, elbow and distal upper limb performance reflecting functional tasks.
- 6 Minute Walk Test (6MWT) – This is a measure of functional exercise capacity and in SMA it is used as a measure of endurance/fitness. It is able to identify functional deterioration in the ambulant population and distinguishes between type 3a and 3b SMA. It involves walking up and down a 25 metre track without aids or orthotics at least twice in 6 minutes. Lap splits, minute splits and total distance are recorded, in addition to any rests and falls.
- North Star Ambulatory Assessment for SMA (NSAA for SMA) – The NSAA was originally developed to assess ambulant individuals with Duchenne Muscular Dystrophy, but has been modified for use in ambulant individuals with type 3 SMA. It tests ambulatory function with 17 items including walking, stepping on and off a box, jumping and running.

Results:
HFMSEx: This was revised - new items were added, some items were combined and re-scored. All items remained. This resulted in an exploratory HFMS for patients with type 2 and 3 SMA. This scale was piloted from December 2013 to January 2014 and the refinement informed further changes. This scale has undergone several revisions with the latest version dated 30.01.2014, see figure 1.

The Exploratory HFMSEx is being prospectively piloted alongside the original HFMSEx and the NSAA in London, Newcastle and Rome. It is likely that following the pilot this scale will be revised as a result of further evaluation and analysis.

ULM for SMA & PUL: Following a pilot of the ULM for SMA and PUL in 50 patients (July 2013 – December 2013) across all three sites the ULM was refined. It now consists of 18 items - 9 core and 9 extra (06.02.2014). This version is being piloted and compared against the mobility of the dominant hand (3 finger pinch, key and paper grip).

The ULM for SMA and Exploratory HFMSEx are being trialled in patients with type 2 & 3 SMA in London, Newcastle and Rome.

Table 1: Current Outcome Measures Used in Spinal Muscular Atrophy

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>SMA</th>
<th>ULM</th>
<th>NSAA</th>
<th>POPO</th>
<th>PUL</th>
<th>6MWT</th>
<th>HFMSEx</th>
<th>HFMSEx</th>
<th>SMA REACH UK</th>
<th>REACH Database</th>
<th>Further Work Required</th>
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<tbody>
<tr>
<td>SMA 2</td>
<td>16</td>
<td>9</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SMA 3</td>
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<td></td>
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<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anticipated</td>
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References:

Table 2: Current Participant Numbers in Pilot of Functional Scales & SMA REACH UK Recruitment

<table>
<thead>
<tr>
<th>Exploratory HFMSEx</th>
<th>ULM for SMA</th>
<th>SMA REACH UK - London</th>
<th>SMA REACH UK - Newcastle</th>
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<tbody>
<tr>
<td>SMA 2</td>
<td>16</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>SMA 3</td>
<td>12</td>
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</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>18</td>
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Figure 1: Current Working Version of Exploratory Hammersmith Functional Motor Scale Expanded

Conclusion:
Preliminary work has commenced to develop robust functional scales in type 2 & 3 SMA, further work is required regarding type 1. It is too early to draw conclusions, more data is required for rigorous assessment using the Rasch Measurement Model.

The current Exploratory HFMSEx requires further work in order to prevent –
- Ceiling effect in type 3’s
- Floor effect for weaker type 2’s
- Consideration of a scale that transitions through type 1, 2 & 3
- Age-appropriateness of the scale throughout lifetime

SMA REACH UK will provide clinicians and researchers with a rich resource of information on a large cohort of SMA patients, thereby facilitating translational research in preparation to design National and International clinical trials.

Once the SMA REACH UK database, assessment tools and functional measures arefinalised UK sites with a history of successful SMA enrolment will be invited to participate andcollect high quality longitudinal data.

This work will be an invaluable tool for centres likely to be involved in upcoming SMA multicentre randomised clinical trials in SMA type 1, 2 & 3.