Functional outcome measures for type 2 and 3 Spinal Muscular Atrophy

Jacqueline Montes – SMA Clinical Research Center
Columbia University, New York, USA

Anna Mayhew – John Walton Muscular Dystrophy Research Centre, Newcastle, UK
Physiotherapists
11th November 2016
Disclosures

Jacqueline Montes
• Receives support from NIH, Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD) K01HD084690-01A1
• Consultant for IONIS pharmaceuticals
• Advisory boards for Biogen and Roche Pharmaceuticals

Anna Mayhew
• Consultancy for IONIS, Roche, PTC, Summit, BMS – training clinical evaluators and preparing manuals for functional assessments
• Advisory boards for Summit and Roche Pharmaceuticals
A measure of performance that relates to an individuals’ function in everyday life carries more meaning and relevance than a measure that quantitates strength.
Functional Scales - Experience


E. Mercuri, A. Mayhew, F. Muntoni, S. Messina, V. Straub, G.J. Van Ommen, T. Voit, E. Bertini, K. Bushby, On behalf of the TREAT-NMD Neuromuscular Network

Table 2
Summary of respondents' opinions on advantages and disadvantages for each assessment

<table>
<thead>
<tr>
<th>Measure</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFMS</td>
<td>Quick/easy</td>
<td>Ceiling effect</td>
</tr>
<tr>
<td>M-HFMS</td>
<td>As HFMS</td>
<td>As HFMS</td>
</tr>
<tr>
<td>MFM</td>
<td>Generic</td>
<td>Too non-specific</td>
</tr>
<tr>
<td>GMFM</td>
<td>Good sensitivity</td>
<td>Too long, can fatigue neuromuscular patients easily</td>
</tr>
<tr>
<td>HAMA</td>
<td>Quick</td>
<td>Rolling over-represented within scales</td>
</tr>
<tr>
<td>NSAA</td>
<td>Quick</td>
<td>Ceiling effect for more able patients</td>
</tr>
<tr>
<td>EK</td>
<td>Quick</td>
<td>Only relevant to ambulant patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of Studies - as of 2008

- MFM: Development and validation Studies, Reliability Studies, Natural history data, Clinical trials
- HFMS/HFME: Development and validation Studies, Reliability Studies
- GMFM: Development and validation Studies, Reliability Studies
- ULM/RULM: Development and validation Studies, Reliability Studies
- 6MWT: Development and validation Studies, Reliability Studies
Moving in the right direction– work to be done

- Complimented on proactive approach, organisation and teamwork
- Type II – non-ambulant: Important to demonstrate internal consistency, clinical meaning and responder profiles for the functional scales. Secondary measures trending in the same direction will be important
- Type III (ambulant): 6MWT seems reasonable but the clinical meaning of improvement needs to be carefully described. Secondary measures need to be further refined.

Moving in the right direction– work to be done
Motor Function Measure – Generic scale

• Ambulatory and non-ambulatory children and adults aged 6 - 62 years, and for all levels of severity of the disease (Vuillerot 2010, 2012, 2013)
• MFM32 is suitable for children older than 6 years
• Modified version (MFM20) has been validated for children under 6 years of age (de Lattre 2013)
• Longitudinal data is available in a small sample of SMA type 2 and 3 patients demonstrating slow deterioration over follow-up greater than 6 months (Vuillerot 2013)
• Used in a recent clinical trial to detect change (Clinicaltrials.gov NCT02628743)
• Issues - Administration time, potential gaps in items between the non-ambulant and ambulant phenotypes with a possible ceiling effect for stronger non-ambulant patients (Cano 2014)
Disease specific scales

• Majority of the available natural history studies have been using disease specific assessments
• Designed to target the functionally relevant problems common to SMA patients and are less likely to include items not appropriate to the disease phenotype
• Reduces the burden to individuals where fatigue is a major issue (Piepers 2008, Iannaccone 1997, Montes 2010, 2013).
The Hammersmith Functional Motor Scale for Children with Spinal Muscular Atrophy: a Scale to Test Ability and Monitor Progress in Children with Limited Ambulation

Marion Main, Harvey Kairon, Eugenio Mercuri, Francesco Muntoni

Dept of Physiotherapy, Hammersmith Hospital, Du Cane Road, London W12 OHS, UK
Dept of Paediatrics, Dubowitz Neuromuscular Centre, Hammersmith Hospital, Imperial College
Du Cane Road, London W12 OHS, UK
Dept of Paediatric Neurology, Catholic University, 02100 Rome, Italy

Received 17 April 2002; received in revised form 6 August 2002; accepted 16 April 2003

20 items ordered according to frequency distribution and the number of patients being able to achieve them.

Hierarchical organization of items permits characterization of patients across the spectrum of type 2 patients from those who are just able to sit to those who are able to stand with and without support.

The aims of the scale were to:

(i) Evaluate and illustrate the motor ability of children with SMA with limited ambulation;
(ii) monitor the progression of function;
(iii) provide a tool for an accurate classification of SMA and in particular to allow a graded scale that takes into account the significant clinical variability of children with this disorder.
Hammersmith Functional Motor Scale Expanded (HFMSE)

- HFMSE adds 13 clinically relevant items from the GMFM to include ambulant SMA and eliminate a ceiling effect
- Detailed manual with operational definitions and training videos
- Minimal patient burden requiring only standard equipment and taking less than 15 minutes on average
Hammersmith Functional Motor Scale Expanded

Type I
Type II SMA
Type III SMA

HFMSE

Squat/Jump
Standing
Transitions/Kneeling
Sitting
Rolling
Transitions/Crawling
Standing
Transitions/Kneeling
Squat/Jump
Stairs

HFMSE ITEMS

Sitting without support
Hands and knees crawling
Standing with support
Walking with assistance
Standing alone
Walking alone

World Health Organization

Motor Milestones
Correlation of HFMS with MFM20

Hammersmith Functional Motor Scale and Motor Function Measure-20 in non ambulant SMA patients

E. Mazzone a, R. De Sanctis a, L. Fanelli a, F. Bianco a, M. Main b, M. van den Hauwe c, M. Ash b, R. de Vries d, J. Fagoaga Mata e, K. Schaefer f, A. D’Amico g, G. Colia g, C. Palermo a, M. Scoto b, A. Mayhew h, M. Eagle h, L. Servais i, M. Vigo e, A. Febrer e, R. Korinthenberg f, M. Jeukens d, M. de Viesser d, A. Totoescu i, T. Voit i, K. Bushby h, F. Muntoni b, N. Goemans c, E. Bertini g, M. Pane a, E. Mereunia a, a

Fig. 2. Correlation of the HFMS and MFM20 baseline scores.
HFMS assists with sensitivity of MFM in non-ambulant population

MFM assists with floor of HFMS – distal dimension
Assessment of arm function has been specifically designed as an add on module (Mazzone 2011).

The ULM is intended to capture performance of activities of daily living not typically included in measures of gross motor function.

9-item scale can be reliably performed in children - 10 minutes to complete.

Used in a multicentric setting and in clinical trials (Darras, WMS, 2016).
Assessing upper limb function in nonambulant SMA patients: Development of a new module

Elena Mazzone\textsuperscript{a,1}, Flaviana Bianco\textsuperscript{a,1}, Diego Martinelli\textsuperscript{a}, Allan M. Glanzman\textsuperscript{b}, Sonia Messina\textsuperscript{a,c}, Roberto De Sanctis\textsuperscript{a}, Marion Main\textsuperscript{d}, Michelle Eagle\textsuperscript{e}, Julaine Florence\textsuperscript{f}, Kristin Krosschell\textsuperscript{g}, Gessica Vasco\textsuperscript{a}, Marco Pelliccioni\textsuperscript{a}, Marilena Lombardo\textsuperscript{a}, Marika Pane\textsuperscript{a}, Richard Finkel\textsuperscript{h}, Francesco Muntoni\textsuperscript{d}, Enrico Bertini\textsuperscript{i}, Eugenio Mercuri\textsuperscript{a,*}

- ULM can detect changes in the weaker SMA patients
- Used to expand the range HMFSE
Suitability of Functional Scales

- Longitudinal natural history data
- Reliability
- Validity
- Clinically meaningfulness
- Used in previous clinical trials
- Clinical utility
Scale requirements

<table>
<thead>
<tr>
<th>Conceptual framework fits SMA</th>
<th>✔</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suitability for multicentric studies</td>
<td>✔</td>
</tr>
<tr>
<td>Reliability</td>
<td>✔</td>
</tr>
<tr>
<td>Validation with other measures</td>
<td></td>
</tr>
<tr>
<td>Natural history data</td>
<td></td>
</tr>
<tr>
<td>Responsiveness to treatment</td>
<td></td>
</tr>
<tr>
<td>Clinical meaningfulness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method studies (description, validation, reliability etc)</th>
<th>Hammersmith Functional Motor Scale</th>
<th>Motor Function Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main et al, 2003</td>
<td>Main et al, 2003</td>
<td>Berard et al, 2005</td>
</tr>
</tbody>
</table>
## Scale requirements

<table>
<thead>
<tr>
<th>Conceptual framework fits</th>
<th>Hammersmith Functional Motor Scale</th>
<th>Motor Function Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA</td>
<td><strong>Correlation</strong></td>
<td><strong>UL measures</strong></td>
</tr>
<tr>
<td>Reliability</td>
<td>Quality of life (De Oliviera et al, 2011)</td>
<td></td>
</tr>
<tr>
<td>Correlation with other measures</td>
<td>MFM (Mazzone et al, 2013)</td>
<td>UL measures (Werlauff et al, 2014)</td>
</tr>
<tr>
<td>Natural history data</td>
<td>6MWT (Montes et al, 2010; Dunaway Young et al, 2016)</td>
<td>HFMSE (Mazzone et al, 2014)</td>
</tr>
<tr>
<td>Responsiveness to treatment</td>
<td>ULM (Mazzone et al, 2012)</td>
<td></td>
</tr>
<tr>
<td>Clinical meaningfulness</td>
<td>Timed Up and Go (Dunaway et al, 2013)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DXA scans (Sproule et al, 2010)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMAP (Lewell et al, 2010)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SMN2 copy number (Tiziano, 2007)</td>
<td></td>
</tr>
</tbody>
</table>
### Conceptual framework fits SMA
- Suitability for multicentric studies
- Reliability
- Correlation with other measures
- Natural history data
- Responsiveness to treatment
- Clinical meaningfulness

### HFMS etc

<table>
<thead>
<tr>
<th>Drug</th>
<th>HFMS etc</th>
<th>Pz</th>
<th>MFM</th>
<th>Pz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valproic acid</strong></td>
<td></td>
<td></td>
<td><strong>Trophos</strong></td>
<td></td>
</tr>
<tr>
<td>Swoboda et al, 2009 (SA)</td>
<td>42</td>
<td>61</td>
<td>(Clinicaltrials.gov NCT02628743)</td>
<td></td>
</tr>
<tr>
<td>Swoboda et al, 2010 (RPCT)</td>
<td></td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darbar et al, 2011 (OA)</td>
<td></td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kissell et al, 2011 (OA)</td>
<td></td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kissell et al, 2014 (RPCT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Albuterol/Salbutamol</strong></td>
<td></td>
<td>23</td>
<td><strong>Riluzole</strong></td>
<td></td>
</tr>
<tr>
<td>Tiziano et al, 2013 (RPCT)</td>
<td></td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydroxyurea</strong></td>
<td></td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al, 2010 (OA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phenylbutyrate</strong></td>
<td></td>
<td>10</td>
<td></td>
<td>107</td>
</tr>
<tr>
<td>Mercuri et al, 2004 (OA)</td>
<td></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercuri et al, 2007 (RPCT)</td>
<td></td>
<td>107</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nusinersen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiriboga et al, 2016 (OA)</td>
<td></td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Olesoxime</strong> (Clinicaltrials.gov NCT02628743)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4-Aminopyridine</strong> (Clinicaltrials.gov NCT01645787)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Natural history data

<table>
<thead>
<tr>
<th>HFMS etc</th>
<th>Pz</th>
<th>MFM</th>
<th>Pz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natural history data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Longitudinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercuri et al, 2007</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kauffman et al, 2012</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kauffamn et al, 2013</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazzone et al, 2013</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazzone et al, 2014</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercuri et al. 2016</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vuillerot et al 2013</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazzone et al, 2014</td>
<td>74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Methods
Data from children with SMA Type 1, 2, and 3 were available for HMFS/E, MFM, GMFM, NSAA, EK, CHOP, TIMP

Results
Each scale had good reliability but several issues impacting scale validity, including the extent that items defined clinically meaningful constructs and how well each scale measured performance across the SMA spectrum.

Conclusions
The utility of each SMA scale could be improved by establishing clear definitions of what is measured, reconsidering items that misfit and items whose response categories have reversed thresholds, and adding new items at the extremes of scale ranges.
Revised Upper Limb Module (RULM)

Mazzone et al – 2016

Type I SMA

Type II SMA

Type III SMA
Revised Hammersmith Scale (RHS)

SMA Type & Current Ambulatory Status $p < 0.001$

Current Functional WHO Motor Milestones $p < 0.001$

- Improving psychometric measurement properties of the HFMSE additional items from NSAA, and the WHO Motor Milestones
- International development: $n = 138$ SMA 2 & 3, Longitudinal changes under investigation

Type I

Type II SMA

Type III SMA

RHS
Test-retest reliability at 1 month was excellent for all participants (n = 18)
ICC: 0.984; 95% CI: 0.959–0.994

Convergent validity

Mean velocity walked during the 1st and 6th minute were significantly different (p = 0.0003)
Six minute walk test (6MWT)

- Reliable and valid functional assessment in patients with SMA (Dunaway Young 2016)
- Capture fatigue (Montes 2011, 2013)
- Fatigue was demonstrated by a 17% decrease in gait velocity from the first minute to the last during the 6MWT (Montes 2010). Not observed in patients with other neuromuscular conditions and weakness (Montes 2013)
- Longitudinal experience of the 6MWT in SMA has been reported (Mazzone 2013)
Efforts underway to capture fatigue in non-ambulant individuals

Endurance Shuttle Nine Hole Peg Test

Endurance Shuttle Box and Block Test

Endurance Shuttle Ride Test

Endurance Shuttle Walk Test

Courtesy of Bart Bartels, Utrecht, Netherlands
Under current development

- Timed Up and Go (TUG) - Quick, meaningful, and applied objective measure of balance, gait speed, and functional mobility, has been applied to ambulatory SMA patients (Dunaway 2014)

- Composite score – ULM, HFMSE, 6MWT (Montes 2015)
Patient Reported Outcome Measures in SMA - exploratory

- Limited disease specific PROMs
- Pediatric Evaluation of Disability Inventory
- Computerised Adapative Test
- PEDICAT applied modern psychometrics to this scale to review its use in SMA (Pasternak 2016)
  - Measure mobility and daily activity skills in children
- ACTIVLIM – Generic PROM for NMD (Sebiyo Batcho 2016)
Functional scales relate to everyday life

Type I
Type II SMA
Type III SMA

- 6MWT
- RULM
- HFMS(E)
- MFM
- ULM