Dr Anna Mayhew, Dr Michelle Eagle, Physiotherapists, Newcastle Muscle Team

Outcome measures in non-ambulatory patients
<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Griffiths locomotor</th>
<th>Bayley III Gross Motor</th>
<th>North Star Amb. Ass. (NSAA)</th>
<th>Timed Function Tests</th>
<th>6MWT</th>
<th>Strength MMT</th>
<th>Strength Quant.</th>
<th>Pulmonary Function Tests</th>
<th>Perf Upper Limb (PUL)</th>
<th>PROs - PODCI</th>
<th>PROs - PROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical subgroups</td>
<td>0-8 years</td>
<td>1-42 mo.</td>
<td>3.5 years until non-amb</td>
<td>4 years until non-amb</td>
<td>5 years until non-amb</td>
<td>4 years to grade 2-</td>
<td>LE: 5-12</td>
<td>UE: 5-20+ years</td>
<td>7 – 20+ years</td>
<td>7 – 20+ years</td>
<td>3 – 21 years</td>
</tr>
<tr>
<td>Supports mechanism of action</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
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<td>✔️</td>
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</tr>
<tr>
<td>Conceptual framework fits DMD</td>
<td>✔️</td>
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</tr>
<tr>
<td>Validation with other measures</td>
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<tr>
<td>Normative ranges</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Ongoing natural history Studies</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Multicenter studies</td>
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<td>✔️</td>
</tr>
<tr>
<td>Responsiveness to treatment</td>
<td>?</td>
<td>?</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Clinical meaningfulness</td>
<td>?</td>
<td>?</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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</tr>
</tbody>
</table>
Clinical Endpoints with Validation and Existing Longitudinal

Griffiths
Bayley III

Northstar Ambulatory Assessment (NSAA)
Timed Function Tests

6MWT
Strength: Manual muscle testing
Strength: Quant. Lower limb
Strength: Quant. Upper limb (proximal and distal)

Pulmonary Function Testing
EK scale, Performance of Upper Limb Scale (PUL)

Patient Reported Outcomes (PROs): PCOSI, PROM
Outcome measures in non-ambulant DMD

Known measures
• Spirometry (FVC, mouth pressures)
• Egen Klassifikation

New measures in development
• Performance of Upper Limb
• PROM for Upper Limb
• Additional measures – covered later

• Conceptual Framework for DMD
• Data Driven
• Validation/Reliability/Sensitivity
• Correlation to other outcome measures
• Longitudinal
• Multicentric
• Ongoing natural history studies
• Normative ranges
• Proven responsiveness to treatment
• Clinically meaningful
Spirometry (FVC)

• Well documented
• Shown in previous presentations correlating with other outcome measures
  ▪ FVC predicts survival and requirement for ventilation
  ▪ Higher peak FVC reached at an older age correlates positively with better outcomes
• More appropriate in older children and adults as can be unreliable in younger children
The EK scale was developed by Birgit Steffensen for use in non-ambulant patients with DMD and SMA. It asks clinically meaningful questions about “own functioning” of individuals. It has been very well validated and published (Steffensen). Used in natural history and intervention studies. Over the last two years an international team have worked to improve the sensitivity of the scale (EK2) including Rasch analysis.

- Feeding
- Use of arms
- Turning in bed
- Cough
- Speech
- Transfers
A critical review of functional assessment tools for upper limbs in Duchenne muscular dystrophy

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1 Department of Paediatric Neurology, Catholic University, Rome, Italy. 2 Dubowitz Neuromuscular Centre, Institute of Child Health, London. 3 Institute of Genetic Medicine, Newcastle Upon Tyne, UK.

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*The first two authors contributed equally to the study.

Requirement for new outcome measures

Review of current rating scales showed need for something better
What is the driving force for upper limb measurement?

- Imminent natural history studies require an upper limb assessment tool
- To measure the disease process in boys and adults who have lost ambulation
  - The non-ambulatory stage may last longer than the ambulatory phase and needs to be recognised
- To have a tool that could be used in patients who may lose ambulation during a trial ensuring long term evaluation across disease stages
AIMS:
1. To devise a scale capable of documenting change in motor performance of the upper limb over time including both ambulant and non-ambulant subjects (ClinRO)
2. Develop a related PROM for Upper Limb

To be relevant and meaningful for the patient the assessment must reflect the patient’s function in the perspective of daily living (Fowler 1982)

Underlying definition of function are components of strength and range of movement so that in weak patients a small change in any component can have a disproportionate effect on function

Therefore scales must work alone or in combination to provide a “total” picture of the patient and his performance

(Hyde 2001)
ClinRO – A road map

i. Hypothesise conceptual framework

ii. Adjust conceptual framework and draft instrument

iii. Confirm conceptual framework and assess other measurement properties

iv. Collect, analyse and interpret data

v. Modify instrument
Workshop report

International workshop on assessment of upper limb function in Duchenne Muscular Dystrophy
Rome, 15–16 February 2012

Eugenio Mercuri\textsuperscript{a,b,*}, Craig McDonald\textsuperscript{c,1}, Anna Mayhew\textsuperscript{d,1}, Julaine Florence\textsuperscript{e,1}, Elena Mazzone\textsuperscript{a,1}, Flaviana Bianco\textsuperscript{a,1}, Valerie Decostre\textsuperscript{f,1}, Laurent Servais\textsuperscript{f,1}, Valeria Ricotti\textsuperscript{b,1}, Nathalie Goemans\textsuperscript{g,1}, Elizabeth Vroom\textsuperscript{h,1}

\textsuperscript{1} On behalf of the DMD Upper Limb Function working group.

DMD Upper Limb Function working group: Maria Ash, London, UK, Kate Bushby, UK. Imelda de Groot, NL, Tina Duong, USA, Michelle Eagle, UK, Michela Guglieri, Newcastle, UK, Erik Henricson, USA, Katrijn Klingels, Belgium, Marion Main, UK, Marika Pane, Italy, Marleen Van den Hauwe, Belgium, Fiona Bull, Prosensa, NL; Giles Campion, Prosensa, NL; Filippo Buccella, Parent Project, Italy; Francesca Ceradini, Parent Project, Italy; Fernanda De Angelis, Parent Project, Italy.
Scale construction

Dimensions

High Level: Shoulder Dimension

Mid level: Elbow Dimension

Distal Level: Wrist and Finger Dimension

Conceptual Framework

Motor Performance

Muscle Weakness

Growth

Contractures
### Clinical meaning of current PUL items

<table>
<thead>
<tr>
<th>Activity</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder abduction flexion to and above</td>
<td>Access to cupboards, book shelves, using hair dryer, combing hair</td>
</tr>
<tr>
<td>shoulder height</td>
<td></td>
</tr>
<tr>
<td>Hands to mouth</td>
<td>Self feed</td>
</tr>
<tr>
<td>Hand(s) to table from lap</td>
<td>Independence to reach things on a table from a chair</td>
</tr>
<tr>
<td>Move weight on table</td>
<td>Classroom activities, feeding table use, board games</td>
</tr>
<tr>
<td>Lifting light cans</td>
<td>Reaching across a table to get something</td>
</tr>
<tr>
<td>Lifting heavy cans</td>
<td>Putting things away, getting things out</td>
</tr>
<tr>
<td>Remove lid from container</td>
<td>Can access items in a container</td>
</tr>
<tr>
<td>Tearing paper</td>
<td>Simulates two handed activity like opening letters or crisps</td>
</tr>
<tr>
<td>Tracing path</td>
<td>Simulates writing</td>
</tr>
<tr>
<td>Push on the light</td>
<td>Simulated activities that require application of pressure with fingers</td>
</tr>
<tr>
<td>Supination</td>
<td>e.g. door bell</td>
</tr>
<tr>
<td>Picking up coins</td>
<td>Giving and receiving of money</td>
</tr>
<tr>
<td>Placing finger on number diagram</td>
<td>Handling money</td>
</tr>
<tr>
<td>Finger grip items</td>
<td>Simulating use of a key pad eg text and phone and remote</td>
</tr>
<tr>
<td></td>
<td>Simulates fine motor activities accessing technology that requires</td>
</tr>
<tr>
<td></td>
<td>minimal finger movement</td>
</tr>
</tbody>
</table>
Development of a Performance of Upper Limb (PUL) module for Duchenne muscular dystrophy

Anna Mayhew* PT, Elena Mazzone* PT, Michelle Eagle* PT, Tina Duong PT, Maria Ash PT, Valerie Decostre PT, Marlene Vandenhauwe PT, Julaine Florence PT, Marion Main PT, Flaviana Bianco MD, Erik Henrikson PT, Laurent Servais MD, Giles Campion, Elizabeth Vroom, Valeria Ricotti MD, Natalie Goemans MD, Craig McDonald MD, Eugenio Mercuri MD, on behalf of the PUL working group

*Authors contributed equally

DMCN – in press
Data collected as part of Italian study:

• Longitudinal multi centric study aimed at establishing changes in upper limb function in DMD

• 12 Italian tertiary care centers for neuromuscular disorders

254 Typically developing boys and young adults examined in their schools by six examiners from 3 centers (Rome, Milan, Pisa)

322 DMD patients attending their routine follow up clinics between September 2012 and April 2013.

Reliability analysis conducted in multi-centre study
Separation of children with DMD scores and typically developing children
Good distribution of scores and clear evidence of weakness in ambulant boys.
Patient reported outcome for upper limb in DMD

- Parallel development to PUL
- Questionnaire filled out by boy or family
- Sections relating to:
  - Transfers
  - Food and nutrition
  - Self care
  - Household environment
  - Leisure and communication
Psychometric Evaluation Using Rasch Analysis

- Rasch analysis is a measurement diagnostic tool which enables us to dig deeper into mechanics of scale performance.
- Examines:
  - Clinical cohesiveness, independence and stability of items
  - How response options are performing
- Identifies:
  - Anomalous data which either identifies problem people who misfit the measure or problem items which misfit the construct
- Allows for better understanding of how individuals change over time
Results of Exploratory Rasch analysis

**Cohort description**

- Eighty-eight individuals with DMD - Ambulant = 52, non-ambulant = 49
- Data came from 5 centres
- Age range was 5 – 23 years of age (mean 12.4, SD 3.61)

- Scale shows promising content and cohesiveness of items but needs clarification of some scoring options
- Revised
- Re-tested
<table>
<thead>
<tr>
<th>Conceptual Framework for DMD</th>
<th>PUL</th>
<th>PROM UL</th>
<th>EK</th>
<th>FVC</th>
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<tbody>
<tr>
<td>Data Driven</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Correlation to other outcome measures</td>
<td>In progress</td>
<td>In progress</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Longitudinal</td>
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<td>✓</td>
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<td>✓</td>
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<td>Normative range</td>
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<td>✓</td>
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<tr>
<td>Proven responsiveness to treatment</td>
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<td>In progress</td>
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<tr>
<td>Clinically meaningful</td>
<td>✓</td>
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</table>
Summary

- FVC and association with survival clearly demonstrate its importance
- Upper limb outcome measures are increasingly recognised as valuable and meaningful
- Rapid progress over the last few years has facilitated measurement of the upper limb in both ambulant and non-ambulant boys to enable longitudinal evaluations in clinical trials and natural history studies