Outcome measures in ambulatory boys with DMD
(London, UK 21 June 2013)

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## Decision Framework for Inclusion of Clinical Outcome Measures in Trials

<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 UE:5-20+</td>
<td>7 – 20+ years</td>
<td>7 – 20+ years</td>
<td>3 – 21 years</td>
<td>7 – 20+ years</td>
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<tr>
<td>Supports mechanism of action</td>
<td>✔️</td>
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<td>Conceptual framework fits DMD</td>
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<td>Reliability</td>
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<td>Validation with other measures</td>
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<td>Normative ranges</td>
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<td>Ongoing natural history Studies</td>
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<td>Multicenter studies</td>
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<tr>
<td>Responsiveness to treatment</td>
<td>?</td>
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<td>✔️</td>
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<td>✔️</td>
<td>✔️ or (-)</td>
<td>✔️ or (-)</td>
<td>✔️ if age ≥ 10</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Clinical meaningfulness</td>
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<td>?</td>
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Line 305-307

“There are however several caveats with using the 6MWT as an outcome measure, which mainly pertain to a learning effect, to inter- and intra-personal variability, and to the definition of a clinically relevant differences.

Much new data has been published in 2012 -2013 concerning the 6MWT in DMD
Validation: 6MWT in DMD as a global / integrated measure of systems involved in walking

Gait Pathomechanics / Disease Progression
- 6MWD Correlates w/ Stride length/ Cadence (McDonald 2010)

Skeletal Muscle Strength
- Knee Ext (NM/Kg) (McDonald 2013)

Biomechanical efficiency
- Energy Exp Index (Heart Rate) (McDonald 2013)

Endurance
- 10 min Continuous Step Activity (StepWatch) (McDonald 2013)

Gross motor skills
- North Star (Mazzone 2010, Goemans 2013)
Natural History of the 6MWD (1-2 years)

Most publications 2012-2013
Observed mean change in 6MWD by baseline 6MWD (≥350 meters vs <350 meters from McDonald et al 2013)  
6MWT measures disease progression (no “learning effect”)

Natural History of 6MWT Findings in DMD

Maturational Issues

Variability Issues
6MWT AND other endpoints (TFTs; North Star)

- Steroids
- Genetics/Polymorphisms
- Baseline function

Observational Study
McDonald et al 2010

Ataluren trial N=57
McDonald et al. 2013

6-Test Field Trial Study - TFTs
DMD Natural History: 6MWD plotted by age


Maturational Issues

Variability in disease progression

N=65
Percent Predicted 6MWD to Account for Maturational Influences: Geiger Equation

Age and baseline 6MWD are key factors in predicting change in function over 48 weeks

Placebo Data: Ataluren Trial – 37 sites
Change in % Predicted 6MWD
(Baseline to Week 48)

Natural History Data: Belgium
Change %-predicted 6MWD
(Baseline to Week 52)

Δ - 44 meters (SD 88)
Δ – 7.3%
McDonald et al.
Muscle & Nerve 2013

Δ - 43 meters (SD 90)
Δ – 8.1%
N. Goemans et al.
Neuromuscular Disorders, 2013
EMA guidelines: Is there a “caveat” in terms of definition of clinically relevant differences?

- What is a Clinically Meaningful Change in 6MWD?
  - Statistical Distribution Properties
Table: Estimates of the MCID for 6MWD and other endpoints in DMD based on pretreatment baseline data (McDonald et al. Muscle & Nerve 2013)

<table>
<thead>
<tr>
<th>6MWD</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Correlation</th>
<th>MCID</th>
<th>MCID / Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Error of Measurement Method (baseline SD * √ (1 – r))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline 6MWD, m</td>
<td>174</td>
<td>358</td>
<td>95</td>
<td>0.91</td>
<td>28.5</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1/3 of SD Method (baseline SD * 1/3)</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>MCID</th>
<th>MCID / Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 6MWD, m</td>
<td>174</td>
<td>358</td>
<td>95</td>
<td>31.7</td>
<td>8.9%</td>
</tr>
</tbody>
</table>

TFTs: MCID / Mean 2-3X Greater

Clinical Meaningfulness of 6MWD: Prediction of Milestones
Strong linear relationships exists between % change in 6MWD and % change in 10m run/walk. (McDonald et al Muscle & Nerve. 2013 May 16. doi: 10.1002/mus.23902)

- 10 meter walk/run has a lower re-test reliability compared to 6MWD
- Easily performed in clinic
- Substantial amount of natural history data linking 10m run/walk values to clinically meaningful milestones
Cooperative International Neuromuscular Research Group (CINRG) natural history data indicate changes in 10m run/walk over 1 year predict for future loss of ambulation (McDonald et al. 2013)

10-meter run/walk data in a DMD natural history study (N=177 pts)

- >= 10% decline over 1 year
- Loss of ambulation over 4 years
Responsiveness to Therapy of 6MWD
Observed mean change in 6MWD with Ataluren

Change in 6MWD, mean ± SE (m)

-60 -40 -20 0 20 40

Baseline 6 12 18 24 30 36 42 48

Time (weeks)

Low Dose (N=57)

High Dose (N=60)

Placebo (N=57)

Low-dose vs. Placebo
Refined analysis: $p = 0.0281$
Adjusted $p = 0.0561$

Delta = 31.3 m

-44.1 (±90) m

-12.9 (±71) m
Time to persistent 10% worsening indicated a slower disease progression in the low-dose ataluren group.

Low-dose vs. Placebo
Nominal p = 0.0386

- **Low Dose (N=57)**: 26% progressed
- **High Dose (N=60)**: 44% progressed
- **Placebo (N=57)**: 48% progressed
% Predicted 6MWD in Prosensa Extension Study (PRO 051 X 93 weeks)
Drisapersen (GSK) Demand II (Phase II) (those who stand in < 7 sec)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Week 25</th>
<th>Week 49</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical Benefit</td>
<td>P value</td>
</tr>
<tr>
<td>Drisapersen (Continuous vs. Placebo)</td>
<td>35.09 m</td>
<td>P= 0.014</td>
</tr>
<tr>
<td>Drisapersen (Intermittent vs. Placebo)</td>
<td>3.51 m</td>
<td>P=0.801</td>
</tr>
<tr>
<td>Placebo Δ6MWD</td>
<td>-3.6 m</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Meaningfulness of 6MWD: Prediction of Disease Progression and Loss of Ambulation

Higher baseline function or stabilization of baseline function over the short-term by ≥ 30 meters is almost always associated with slower long-term decline in DMD.
Initial 6MWD and Time to 10% Progression

6MWD as a Predictor of Loss of Ambulation (PTC ataluren trial)

Δ 30 meters from mean 6MWD

Baseline 6MWD predicts weeks to lose of ambulation over 48 weeks with $r = 0.85$ and $R^2 = 0.73$

Ataluren trial:
6MWD < 320 m $\Rightarrow$ 33% lost ambulation over 1 year

Italian series (Mercuri et al. 2013):
6MWD < 320 m $\Rightarrow$ 30% lost ambulation over 2 years
Proportion of boys with DMD losing ambulation over 2 years by baseline 6MWD (30 meter increments) (Mercuri, and colleagues 2013)

Δ 30 meters
Clinical Meaningfulness of 6MWD: Relationship to person-reported outcomes (PROs)
6MWD correlates with PODCI (POSNA) Global Scale Score (adjusted $R^2 = 0.83$)

Fig 2a: 6-Minute Walk Distance vs. PODCI Global Score

- Transfers & Basic Mobility
- Sports / Physical Functioning
- Upper extremity and physical function
- Pain/Comfort

Henricson EK, Abresch RT, Han JJ, Nicorici A, Goude E, DeBie E, McDonald CM. The 6-minute walk test and person-reported outcomes in boys with Duchenne muscular dystrophy and typically developing controls: Longitudinal comparisons and clinically-meaningful changes over one year. Submitted for publication.
6MWD as a Measure of Disease Progression

Higher baseline function or stabilization of baseline function over the short-term by ≥ 30 meters is almost always associated with slower long-term decline in DMD.

Walking Function and Prediction of Loss of Ambulation

30 m ↓ from baseline → 10% worsening over 1 year → Loss of Ambulation (4 yrs)

Log Rank p = 0.0001

% not 10% Worsened

Week of Progression

100 90 80 70 60 50 40 30 20 10 0

< 325 m (n=19)

325 - 410 m (n=19)

≥ 410 m (n=19)

Log-rank P-value < 0.0001
EMA Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy

“Several “caveats” with using the 6MWT:

- **learning effect** → Not over 12 months

- **inter- and intra-personal variability**

- Variability due to disease progression in all measures, mitigated by selection criteria, and use of percent predicted 6MWD

- **definition of a clinically relevant differences**

- 30 Meters matters (MCID; disease progression)
North Star Ambulatory Assessment

- 17 point disease and stage specific rating scale
- Clearly defined Conceptual Framework (Scott 2011)
- Development process outlined in earlier papers (Scott 2011)
- Reliability and validity data published (Mazzone 2009, Mazzone 2010)
### Clinical Meaning of North Star

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 1</td>
<td>Stand</td>
</tr>
<tr>
<td>Item 2</td>
<td>Can't stand to pee, access to high items like elevator buttons, light switches and cupboards</td>
</tr>
<tr>
<td>Item 3</td>
<td>Stand up from chair</td>
</tr>
<tr>
<td>Item 4 &amp; 5</td>
<td>Stand on one leg</td>
</tr>
<tr>
<td>Item 6-9</td>
<td>Climb on and off box step</td>
</tr>
<tr>
<td>Item 10</td>
<td>Get to sitting</td>
</tr>
<tr>
<td>Item 11</td>
<td>Can get up if falls down, can sit on floor with the rest of classmates without needing help to get up</td>
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<tr>
<td>Item 13</td>
<td>Can sit up in bed, can assume a safer position if fall occurs</td>
</tr>
<tr>
<td>Item 14-17</td>
<td>Jump, hop and run</td>
</tr>
<tr>
<td>Item 18</td>
<td>Playing, access to sport, keeping up socially and physically with peers</td>
</tr>
</tbody>
</table>
Baseline NorthStar vs Baseline 6MWD

Italy: (Mazzone et al. 2010)  
$r = 0.675$

Belgium:  
N. Goemans et al. 2013  
Pearson $r = 0.76$

Slope = 5.7/100 Meter  
Correlation: $r = 0.675$
Detecting meaningful change in North Star Ambulatory Assessment in Duchenne Muscular Dystrophy

Anna G. Mayhew\textsuperscript{1}, Stefan J. Cano\textsuperscript{2}, Elaine Scott \textsuperscript{3}, Michelle Eagle\textsuperscript{1}, Kate Bushby\textsuperscript{1}, Adnan Manzur\textsuperscript{4}, Francesco Muntoni\textsuperscript{4} ON BEHALF OF THE NORTH STAR CLINICAL NETWORK FOR PAEDIATRIC NEUROMUSCULAR DISEASE
NSAA scale: Transformation of ordinal level scores into linearised measurements

21 to 11 = loss of ability to stand still

50 to 40 = inability to rise independently from the floor

90 to 80 = can no longer hop.

Minimal Important Difference (MID), calculated as $\frac{1}{2}$ SD demonstrated to be slightly less than 10 points on the transformed NSAA scale.
Responsiveness analysis based on longitudinal data comparison of stable prednisolone regimes daily v intermittent

- NSAA scale (Linearized data): detected a difference in the two steroid regimes (daily versus intermittent steroids). Mean person estimates were higher in the daily prednisolone group.

N=198 boys (total of 805 longitudinal assessments) from sixteen UK Neuromuscular specialist centres.
NSAA in clinical trials – commonly used as a secondary endpoint

- Proensa Natural History
- AFM Natural History
- GSK/Proensa Exon skipping programme – Phase 2/3
- For DMD Phase 3
- PTC – 020 Phase 3
- Eli Lilly – Tadalafil phase 3
- Serepta/AVI exon skipping programme
Conclusions regarding ambulatory measures

• Much new data in 2012-2013 linking the 6MWT to clinically meaningful changes in DMD
• 30 meters = MCID
• 6MWD measures disease progression and predicts loss of ambulation

\[
30 \text{ m} \downarrow \text{from baseline} \rightarrow 10\% \text{ worsening over 1 year} \rightarrow \text{Loss of Ambulation (4 yrs)}
\]

\[
\Delta 30 \text{ meters from baseline associated with a risk of losing ambulation over 2 years}
\]

• Northstar: A DMD disease and stage specific rating scale
• (0-100 Linearised): 10 point change is clinically meaningful