P.2.5

Performance of Upper Limb Scale for use in Duchenne muscular dystrophy – An iterative process to establish its suitability for clinical trials

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Over 300 assessments from both ambulant and non-ambulant individuals with DMD were analysed using RUMM2030 from Italy, UK, Belgium and USA. The age range was from 4 to 25 and data were subdivided according to type and site of mutations.

In 2012 a group of international physiotherapists specializing in neuromuscular assessments devised a ClinRO to assess upper limb performance (PUL) for use in Duchenne muscular dystrophy (DMD). An exploratory Rasch analysis helped establish version one of the PUL although it was recognized at the time further analysis was required in a larger subset to confirm these preliminary findings and potentially remove redundant items. The aim of this study is to repeat the analysis in a larger cohort, again on an international level.

This iterative process of ClinRO development is essential to establish a robust measure. Further work needs to be conducted on reliability and responsiveness to confirm the PUL’s suitability for inclusion in clinical trials.

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P.2.6

Comparison of 6MWD and person-reported functional measures in boys with Duchenne muscular dystrophy aged 4–12 years

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30-m change in walking ability by 6MWT may not always be clinically meaningful from a quality of life perspective. Differing changes in ability may contribute to patient-reported function at differing levels of ability.

We describe correlation between measures, 1-year change in measures, and correlation of 1-year changes between measures for 6MWT, PedsQL and POSNA PODCI in 24 4–12 y.o. ambulatory DMD and 36 typical controls, and determine if minimal clinically-important differences (MCID) of HRQOL measures contribute to different estimates of walking distance change at differing levels of ability.

PedsQL total/physical function and PODCI global, transfer/mobility and sports/physical function demonstrated significant differences between DMD and controls (p < 0.0001). In DMD, 6MWT distance was correlated with PODCI, with the transfer/mobility scale showing the strongest relationship (r = 0.79). In DMD 6MWT distance weakly correlated with PedsQL. In DMD, 6MWT and PODCI global and transfer and mobility demonstrated significant one-year change and exceeded the amount of change representing MCID. In DMD, 6MWT change highly correlated with change in PODCI global and PODCI transfer/mobility scores (r = 0.76 and r = 0.93). PODCI global and PODCI transfer/mobility scales provided the best estimates of 6MWT performance. A “meaningful” 4.5 point change in a low PODCI transfer/mobility score of 30–34.5 was associated with a 5.6 m 6MWT change from 150.3 to 155.9 m. At PODCI levels closer to normative levels changes in 6MWT distance needed to affect a “meaningful” change in PODCI scores were associated with a 6MWT change of almost 46 m.

At lower levels of function, smaller increases 6-min walk distance result in meaningful change in quality of life. At higher levels of function, larger increases may be necessary to achieve the same QoL effect.

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P.2.7

6 min walk test 12 month changes in DMD: Correlation with genotype

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In the last few years a number of therapeutical approaches have become available for patients affected by Duchenne muscular dystrophy (DMD). The majority of the approaches proposed so far are specifically targeting distinct group of mutations, such as stop codon point mutations or groups of deletions as in exon skipping studies. Because of this, the number of patients eligible for these studies is limited to those having specific mutations or groups of mutations. This has raised the question of whether natural history data should be used as controls in studies with few eligible patients and, more specifically, whether individual groups of mutations follow the general natural history of boys of DMD or have distinct profiles of progression of functional impairment.

The aim of this study was to report 12 month longitudinal changes of the 6 min walk test (6MWT) in a large cohort of DMD ambulant patients subdivided according to type and site of mutations.

6MWT was performed in 198 DMD ambulant boys, older than 4 years at baseline and repeated after 12 months. 137 had deletions, 18 had duplications and 43 point mutations. Patients with deletions were further subdivided into subgroups according to whether they had mutations eligible for skipping in different exons, selecting those who were currently or likely to be part of clinical trials, eligible for skipping in different exons, selecting those who were currently or likely to be part of clinical trials, eligible for skipping 44 (n = 18), eligible for skipping 45 (n = 16), eligible for skipping 51 (n = 27), eligible for skipping 53 (n = 28).
Patients with point mutations were also subdivided identifying those with stop codon mutations.

The 6MWD showed 12 months changes between −325 and 175 (mean −10) m.

There was no significant difference between deletions, duplications and point mutations neither at baseline nor in the 12 month changes. When patients were subdivided into different subgroups of deletions according to their eligibility to skip specific exons, there was little difference between the individual subgroups and the patients with the whole cohort. The subgroup eligible for skipping exon 44 however had a trend to perform better at baseline and to show less deterioration than the other subgroups.

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P.2.8

The 6-min walk test and clinical endpoints in Duchenne MD: Reliability, validity, and clinically-important differences

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Introduction: An international clinical trial enrolled 174 ambulatory males ≥5 years old with nonsense mutation Duchenne muscular dystrophy (DMD). Pre-treatment data provide insight into reliability, concurrent validity, and minimal clinically important differences (MCID) of the 6-min walk test (6MWT), and other endpoints. Methods: Eligibility criteria included nonsense-mediated severe dystrophinopathy, males ≥5 years, and ambulatory (defined as ability to walk >75 m on the 6MWT). A total of 174 patients, 70% of whom were treated with corticosteroids, were randomized into three treatment groups for the PTC124-GD-007 Ataluren clinical trial and evaluated initially at screening and baseline visits. The 6 min walk distance (6MWD) was defined as primary endpoint and other secondary and exploratory endpoints included timed function tests (TFTs) (time to stand from supine, time to climb 4 stairs, time to run/walk 10 m, and methods during TFTs), quantitative strength by hand-held myometry (knee extensors, knee flexors, elbow extensors, and elbow flexors), the PedsQL physical functioning scale, and energy expenditure index determined by heart rate measurement during the 6-min walk test. Results: The 6MWT proved feasible and reliable in a multicenter context. Concurrent validity with other endpoints was excellent. The MCID for 6MWD was 28.5 m based on two statistical distribution methods. Discussion: The ratio of MCID to baseline mean is lower for 6MWD than for other endpoints demonstrating the sensitivity of this endpoint. The 6MWD showed an MCID of approximately 30 m — similar to the magnitude of change observed in previous registration trials focused on other clinical populations. The 6MWD is a reliable, valid and clinically meaningful primary endpoint and an optimal primary endpoint for DMD clinical trials that are therapeutically focused on preservation of ambulatory functioning and slowing disease progression.

P.2.9

The 6-min walk test and other endpoints in Duchenne MD: Multi center longitudinal natural history observations over 48 weeks

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Duchenne muscular dystrophy (DMD) subjects ≥5 years with nonsense mutations were followed for 48 weeks in a multicenter, randomized, double-blind, placebo-controlled trial of ataluren. Placebo arm data (N = 57) provide insight into the natural history of the 6-min walk test (6MWT) and other endpoints. Eligibility criteria included nonsense-mediated severe dystrophinopathy, males ≥5 years, and ambulatory (defined as ability to walk >75 m on the 6MWT). A total of 57 males (70% of whom were treated with glucocorticoids) were randomized to orally receive placebo treatment and followed for 48 weeks. Evaluations performed every 6 weeks included the 6-min walk distance (6MWD), timed function tests (TFTs), and quantitative strength using hand-held myometry.

Natural history (placebo treated) data on 57 males over 48 eeks showed decline in mean scores and mean change scores from baseline in 6MWD, increase in time to climb 4 stairs and time to run/walk 10 m, and increase in EEI. Quantitative strength remained fairly stable over 48 weeks. Baseline age (≥7 years), 6MWD, and selected TFT performance, are strong predictors of decline in ambulation (Δ 6MWD) and time to 10% worsening in 6MWD. Baseline 6MWD was also predictive of weeks to loss of ambulation. A baseline 6MWD of <350 m was associated with greater functional decline and loss of ambulation was only seen in those with baseline 6MWD <325 m. Only 1/42 (2.3%) of subjects able to stand from supine lost ambulation.

A 30 m change from mean 6MWD places patients at a level of ambulatory function where they will experience increased risk of disease progression and loss of ambulation. Findings confirm the clinical meaningfulness of the 6MWD—the most accepted primary clinical endpoint in ambulatory DMD trials.

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P.2.10

A shorter timed walking or running test may be sufficient for testing function in Duchenne muscular dystrophy

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Clinical trials involving exon skipping, gene transfer, and small molecule development are currently underway for children with Duchenne muscular dystrophy. These experimental trials typically use timed walking as the primary measure of efficacy due to ease of test administration, ability to quantify distance walked, and a body of literature investigating the reliability and validity of these walking outcomes. However, a test lasting 6-min has inherent difficulties when testing young children in clinical trials. Ambulatory subjects with DMD (5–12 years old; mean = 9.6 ± 2.1 years) completed timed walking tests, strength testing, the North Star Ambulatory Assessment (NSAA), and timed 4 stairs. The 6-min walk test