Outcome measures for Duchenne muscular dystrophy from ambulant to non-ambulant: Implications for clinical trials

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Novel emerging therapies for Duchenne muscular dystrophy (DMD), such as antisense oligomer (AO) mediated exon skipping, have generated the need of understanding the natural history study of the targeted genotype subgroups. Most natural history studies are focused on ambulant subjects; therefore very little data exists on non-ambulant DMD. Specifically targeting skippable deletions, we aim to assess the natural history of DMD through a composite assessment tool capable of capturing disease progression beyond loss of ambulation. With a recruitment target of 80 DMD patients with AO-skippablemutations across 5 centres (i.e. London, Newcastle, Paris, Leiden, and Nijmegen), subjects are assessed every 6 months for 3 years according to an internationally agreed shared protocol, including the 6-minute walk test (6MWT), the North Star Ambulatory Assessment (NSAA), as well as the Performance of Upper Limb (PUL) and the MyoSet (i.e. MyoGrip MyoPinch and MoviPlate). Both ambulant and non-ambulant subjects undergo upper limb evaluation, respiratory function test and quality of life questionnaires. Serum biomarkers, including antidystrophin autoreactive T cells, are also evaluated. To date, 57 DMD subjects have been recruited (London, Newcastle and Paris), aged 5 to 18 years; 33 ambulant and 24 non-ambulant; 49 with 18 month follow-up data. The prevalence of autoreactive T cells is ~16%. Using multilevel modelling, nested within a random effect for centre/site, we describe the decline in motor functional parameters over time. We further investigate the relationship between these different variables, focussing on upper body measures, in relation to NSAA score and the 6MWT. We explore any relationship differences between boys with different skippable deletions. Our study offers a comprehensive up-to-date natural history data across all stages of ambulation for DMD subjects with skippable mutations amenable to AO therapies.