ESTIMATING CLINICALLY MEANINGFUL CHANGE THRESHOLDS IN THE NORTH STAR AMBULATORY ASSESSMENT (NSAA) AND FOUR-STAIR CLIMB (4SC) IN DUCHENNE MUSCULAR DYSTROPHY (DMD)

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Background: Efficacy of DMD treatments for ambulatory boys is assessed by measuring their impact on functional assessments such as the North Star Ambulatory Assessment (NSAA) and the timed four stair climb (4SC) test. Quantifying the level of change in these assessments that is *clinically meaningful* (i.e., reflective of change that is meaningful to patients' functioning in daily life) is important to help inform design and interpretation of DMD clinical trials. In this study, we used three different statistical approaches to estimate clinically meaningful thresholds for change in the NSAA total score and 4SC velocity.

Methods: Patients in this study were boys with DMD receiving care at Cincinnati Children's Hospital and Medical Center who were aged 6-18 years, had at least 6 months of steroid use, and had either 4SC time ≤ 12 seconds or NSAA total score > 12. Estimates of clinically meaningful change were obtained for NSAA total and 4SC velocity (measured in stairs per second) using three well-established approaches: (a) *anchor-based*, using the Functional Motor Scale as the anchor measure, (b) *distribution-based*, using 0.5 standard deviations (SD) of the baseline values, and (c) *standard error of measurement (SEM)*, obtained from statistical models fit to patients' individual outcome trajectories.

Results: Depending on the approach used, the analyses were based on between 156 and 247 patients for NSAA total score, and between 171 and 273 patients for 4SC velocity. For NSAA total score, the estimates of clinically meaningful change were 2.22, 2.96 and 2.24 points for the anchor-based, 0.5 SD and SEM approaches, respectively. The corresponding estimates for 4SC velocity were 0.29, 0.47 and 0.33 stairs/second. Although estimates were generally similar across the three approaches for both NSAA total and 4SC velocity, estimates based on 0.5 SD tended to be slightly higher than the other approaches.

Conclusion: The three approaches utilized here suggest that clinically meaningful thresholds for 48-week change are 2 to 3 points for NSAA total and 0.3 to 0.5 stairs/second for 4SC velocity. Additional research is underway to assess the consistency of these estimates across different natural history studies. Meaningful thresholds such as these can be useful in informing endpoint definitions and sample size requirements, and as reference points when interpreting treatment effects in clinical trials.