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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Quantifying clinically meaningful change in functional assessments such as the NSAA and the timed 4SC test is important to inform design and interpretation of DMD clinical trials. We used three different approaches to estimate clinically meaningful thresholds for change in NSAA total score and 4SC velocity. 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 ≥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 (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 mixed effects models fit to patients' individual trajectories. Depending on the approach, the analyses were based on between 156 and 247 patients for NSAA total, and between 171 and 273 patients for 4SC velocity. For NSAA total, clinically meaningful change estimates 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 approaches for both NSAA total and 4SC velocity, estimates based on 0.5 SD tended to be slightly higher than the other approaches. These approaches 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 sources. These thresholds can be used to inform endpoint definitions, power calculations, and as reference points to contextualize treatment effects.

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