

Can natural history controls be used for functional outcomes in Duchenne muscular dystrophy (DMD) drug trials? Assessing the consistency of 48-week changes in six-minute walk distance (6MWD) between multiple natural history data sources and clinical trial placebo arms.

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Using natural history cohorts (NH) to supplement, or replace, placebo in controlled trials is a high priority for DMD patients and families, and could also render clinical trials more efficient. However, an important concern, which has been noted by regulators, is that comparisons of functional outcomes such as 6MWD between drug trials and NH controls could be biased by differences in patient motivation, supportive care or assessment procedures. To empirically assess this potential for bias we conducted a multi-sponsor, multi-institution, multi-registry collaboration enabled by the Trajectory Analysis Project (cTAP) to compare 48-week changes in 6MWD (Δ 6MWD) between trial placebo arms and NH data sources subjected to equivalent inclusion/exclusion (I/E) criteria. Participating collaborators included UZ Leuven, Fondazione Telethon, CINRG, Imaging DMD, and the PRO-DMD-01 study provided by CureDuchenne (420 NH patients, overall). Five placebo arms yielding a total of 375 patients and employing four sets of I/E criteria were identified: tadalafil phase 3, ataluren phases 2b and 3, drisapersen phase 2 trials (pooled), and drisapersen phase 3. For each set of I/E criteria, Δ 6MWD was compared between placebo and harmonized NH. No statistically significant differences were identified in these comparisons. Numerical differences ranged from -19.4 to 19.5 meters. This lack of evidence of systematic bias is encouraging for use of NH controls in DMD trials. Additional research will continue to leverage the power of the cTAP collaboration and evaluate adjustment for prognostic factors for Δ 6MWD and consistency of additional outcome measures.

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