Suitability of external controls for drug evaluation in Duchenne muscular dystrophy

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Study objective
To evaluate the suitability of real-world data (RWD) and natural history data (NHD) for use as external controls in drug evaluations for patients with ambulatory Duchenne muscular dystrophy (DMD).

What is known and what this paper adds
Augmenting or replacing clinical trials’ placebo arms with RWD/NHD controls could hasten research into therapies for DMD. This investigation’s results provide evidence of no systematic bias between clinical trials and RWD/NHD data sources when equivalent inclusion/exclusion criteria and comparable clinical assessment protocols are applied in clinical trials and RWD/NHD sources.

Participants and setting
These analyses used data from 383 ambulatory patients with DMD who were in the 48-week placebo arms of 6 clinical trials (NCT01865084, NCT00592553, NCT01826487, NCT01153932, NCT01462292, and NCT01254019) and RWD/NHD data from 430 ambulatory patients with DMD enrolled in 5 cohort studies (Universitaire Ziekenhuizen Leuven (UZL), the DMD Italian Group, the Cooperative International Neuromuscular Research Group (CINRG), the ImagingDMD study, and the PRO-DMD-01 study).

Design, size, and duration
Patients in RWD/NHD were subjected to age, steroid duration, and functional inclusion/exclusion criteria from the clinical trials. Mean changes in the 6-minute walking distance (6MWD) over approximately 48 weeks (Δ6MWD) were then compared between RWD/NHD sources and trial placebo arms. Generalized estimating equations with an exchangeable covariance structure were used to estimate standard errors. A total of over 1,200 years of follow-up for 6MWD were included in the analyses from RWD/NHD and placebo arms.

Primary outcome measures
The primary outcome was the 48-week change in 6MWD (Δ6MWD) observed in clinical trial placebo arms, and calculated from approximate 48-week intervals (9–13 weeks) in RWD/NHD.

Main results and the role of chance
Differences in mean Δ6MWD between trial placebo arms and RWD/NHD cohorts ranged from −19.4 meters (i.e., better outcomes in RWD/NHD) to 19.5 meters (i.e., worse outcomes in RWD/NHD). None of the differences observed between trial placebo arms and RWD/NHD cohorts was statistically significant. Among the harmonized RWD/NHD cohorts, means for Δ6MWD were all within 25 m of each other.

Bias, confounding, and other reasons for caution
These analyses depended on the RWD/NHD data sources using equivalent inclusion/exclusion criteria and consistent methods to measure Δ6MWD values. Use of inconsistent measurement methods may undermine the validity of RWD/NHD controls.

Study funding/potential competing interests
This study was funded by various healthcare companies and foundations affiliated with the collaborative Trajectory Analysis Project. Some authors report additional competing interests. Go to Neurology.org/N for full disclosures.

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