COLLABORATIVE
TRAJECTORY
ANALYSIS
PROJECT

Learning from natural history patient data to drive smaller, faster, trials – a case study in Duchenne Muscular Dystrophy (DMD)

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As in many rare disorders, longitudinal heterogeneity in disease progression in patients with DMD leads to in high variance in clinical trials, confounding results and resulting in an unacceptably high rate of statistical failures. Regulators urge drug companies to repeat failed placebo-controlled clinical trials with yet larger studies, while patient advocates champion replacing placebo-controlled trials with single arm studies using natural history (NH) or real world data (RWD) as an external control. For 'precision' drugs in particular, where patient numbers are even smaller, the need to solve the problems arising from heterogeneity in disease progression is paramount.

The collaborative Trajectory Analysis Project (cTAP) is an innovative, multi-stakeholder platform formed in 2015 to find statistical solutions to heterogeneity-driven issues, thereby enabling "smarter" clinical trials that yield clear, unambiguous understanding of the efficacy of a new therapy.

When using NH/RWD as an external control, the potential for bias (between patients in trials vs those under routine care) is real, especially in situations, as in DMD, where clinical outcome measures are somewhat subjective, or when standards of care are evolving rapidly.

Through collaborative studies conducted by cTAP, this presentation will demonstrate that minimum requirements to reassure oneself that the apparent efficacy of a treatment in an externally-controlled trial is 'real' can be met, even in the face of high heterogeneity of disease progression. Thus, we have i) demonstrated that functional progression in NH/RWE is consistent with that seen in placebo, ii) identified prognostic factors that predict trajectory of functional progression, and iii) shown these prognostic factors are consistent across data sources.

Moreover, these tools enable adjustment for any observed imbalances at baseline between drug-treated and placebo arms, and provide the basis for confident matching of patients in a drug treated arm to NH/RWE control.

A similar approach is being used to build evidence to support pan-genotypic controls for precision drugs (studies ongoing).