Development of a Regulatory-Ready Clinical Trial Simulation Tool for Duchenne Muscular Dystrophy.

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Early clinical trials of therapies to treat Duchenne muscular dystrophy were designed based on limited information and limited understanding of clinical endpoints. This led to suboptimal clinical trial protocols that resulted in uncertainty about the effectiveness of therapies. Over time, increasing data have been collected. The Duchenne Regulatory Science Consortium integrated available data into the largest available database of Duchenne clinical data; 1,137 patients and 23,305 observations in the analysis dataset, and nearly 5,000 patients in total. This database is being used to build a clinical trial simulation platform designed to be acceptable to the regulators for optimizing clinical trial design.

D-RSC has modeled the dynamics of change and sources of variability of five endpoints (velocities of time to stand from supine, time to climb 4 stairs, 10 m walk/run time, Northstar Ambulatory Assessment and Forced Vital Capacity and Brooke score). The models consider the effects of steroid treatment, genetic mutation, race, weight, height and baseline function, which for each model accounts for about 50% of the variance in the population. Models also consider trial-related aspects such as dropout, loss of ability and differences between clinical trial and natural history populations.

The final models capture longitudinal changes in the endpoints including both the increase and decline phases. The models will be joined and used in clinical trial simulations to optimize selection of inclusion/exclusion criteria, endpoints and other trial parameters. The planned datasets, models and simulation tool have been reviewed by the US Food and Drug Administration and the European Medicines

Authority and have been accepted into the Fit-for-Purpose and Qualification for Novel Methodologies pathways respectively. The platform will be submitted for potential endorsement by both agencies by mid-2020. The tools will be made publicly available through C-Path's website.