

Development of Clinical Trial Simulation Tool for Duchenne Muscular Dystrophy Through the Duchenne Regulatory Science Consortium

Jane Larkindale¹, Sarah Kim², Karthik Lingueni², Stefan Schmidt², Diane Corey¹, Klaus Romero¹, on behalf of the Duchenne Regulatory Science Consortium (D-RSC) and the CINRG DNHS investigators

¹Critical Path Institute, Tucson, AZ, USA;

Developing clinical trial protocols that give definitive answers as to whether potential new therapies are effective for rare diseases is challenging due to the small population sizes, limitations on availability of natural history data and limited understanding of disease progression. In Duchenne muscular dystrophy (DMD) this has contributed to few trials meeting primary endpoints, and led to questions as to how best to evaluate efficacy of therapeutic candidates. The Duchenne Regulatory Science Consortium (D-RSC) is a public-private-partnership that aims to develop quantitative tools to accelerate drug development and seeks approval of such tools through regulatory pathways at FDA (Food and Drug Administration) and EMA (European Medicines Authority) to confirm utility and value. D-RSC is developing a multivariate model-based clinical trial simulation (CTS) tool, based on longitudinal models of endpoints that span the course of disease (velocity of completion of supine to stand test, 4-stair climb test, and 10-meter walk/run test, NorthStar Ambulatory Assessment, forced vital capacity and Brooke scale). Models include covariates that predict differences in DMD progression such as use of steroids, height, weight, genetics and baseline function. D-RSC has integrated data from 14 independent studies using CDISC standards, the largest DMD clinical database currently available. The final analysis data set after exclusions, excluding missing observations, includes 1139 individuals with a total of 24210 observations of the endpoints from 4 to 34 years of age. The CTS tool that will be developed based on the disease progression models will help drug developers determine optimal clinical study characteristics, including selection of endpoints, inclusion criteria, trial design, size and duration. This will allow development of trial protocols using the lowest number of patients and in the least time possible to reach conclusive decisions on drug efficacy.

