The Duchenne Regulatory Science Consortium (D-RSC) at the Critical Path Institute was set up to develop tools to accelerate therapy development for Duchenne muscular dystrophy (DMD). D-RSC will provide the Duchenne drug development ecosystem with:


- An integrated database bringing together disease natural history data from multiple sources using the standard – available for analysis by the community to the extent permitted by the owners of each dataset. [Currently includes 15 datasets, 7 can be shared]

- Clinical trial simulation tool developed from mathematical models of disease progression of 6 endpoints selected based on use in trials and data availability. Goal is for tools to be endorsed by FDA and EMA and therefore deemed accepted for the defined context of use. [Plans for models have been accepted by both agencies, models have been built]

- Plans for additional tools are under discussion. The Critical Path Institute is a non-profit organization that specializes in forming public-private partnerships to develop drug development tools, and works towards qualification/endorsement of such tools with the regulatory authorities (e.g. FDA, EMA). Each consortium is advised by an FDA liaison to ensure that products of the consortia are suitable for regulatory acceptance.

**Context of Use**

**General Description:** A disease progression model-based clinical trial simulation (CTS) tool designed to optimize clinical trial enrollment and design of studies to investigate efficacy of potential therapies for DMD. Measurements of DMD disease progression will be parameterized in a series of endpoints:

- Velocity of completion of a supine-stand test
- Velocity of completion of 4-stair climb test
- Velocity of completion of 10-meter walk/run test or 30-foot walk/run test
- Forced vital capacity (FVC)
- NorthStar Ambulatory Assessment
- Transition between scores in the Brooke scale.

**Stage of Drug Development for Use:** All clinical efficacy evaluation stages of drug development in DMD, including early efficacy, proof-of-concept, dose-ranging, and registration studies.

**Intended Application:** To help inform, through simulations, trial enrichment strategies, including the selection of inclusion/exclusion criteria, stratification approaches, timing and selection of clinical assessments, trial duration, and sample size for studies evaluating therapeutic candidates for DMD.

**Methods:** D-RSC has developed mixed effects models of the dynamics of change and sources of variability of six clinical endpoints that span the disease course as shown in the flow chart. NSAA model development is shown throughout as an example, although other models are similar.

**Use Cases**

A primary use case is to optimize Phase II trial designs. The platform will aid in the selection of inclusion/exclusion criteria and inform how long and how large a trial is needed to show a proposed drug effect using specific endpoints. This will aid in more quickly reaching an interpretable Phase II readout, which will inform the likelihood of success in larger/larger trials.

Additional use cases include:

- Simulations to inform Phase III trial design
- Optimization of control arms
- Optimization of potential novel trial designs in which multiple endpoints are considered

**Data**

D-RSC’s integrated database consists of 15 datasets from clinical trials, natural history studies, registries and clinical collections. This contains a total of nearly 5,000 patients. 1,137 patients and 23,305 observations are used in the analysis. This is the largest database of clinical data for DMD. Data shown in green can be shared with consortium members.

**Development of the Clinical Trial Simulation Platform**

**Model Structure:** The Chapman-Richards growth function X Sigmoid e sigmoid Model

The base model describes the growth phase where the boys get stronger and the subsequent decline phase where function is lost. Base models similar to this described changes in all endpoints except Brooke score adequately. A different model structure was used for Brooke.

**NSAA Score vs. Age of Assessments**

The graphs below show the change in NSAA in the training and test dataset using the base model.

**Effects of covariates**

The effects of covariates (baseline function, mutation, steroid use, height, weight, race) were assessed. Some of these reduced the variance and improved the model quality.

**Covariate effect on NSAA**

Predicted vs. observed NSAA scores using the NSAA covariate model on a population and individual level show that the models reflect disease progression accurately.