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 muscle drug development ecosystem with:

- A CDISC (Clinical Data Interchange Standards Consortium) standard for Duchenne, which defines the regulatory-acceptable format, structure and terminology used in databases from clinical studies, enabling comparison between datasets. Available at https://www.cirdisc.org/standards/therapeutic-areas/duchenne-muscular-dystrophy/duchenne-muscular-dystrophy-therapeutic-area.
- 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 14 datasets, 7 can be shared]
- Clinical trial simulation tool developed from mathematical models of disease progression for submission to the regulatory authorities as a fit-for-purpose tool—which will be available to the community when qualified; potentially other regulatory-sponsored development tools.

The Critical Path Institute is a non-profit organization that specializes in forming public-private partnerships to develop drug development tools, and work 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 qualification.

**Proposed Context of Use for Platform**

**General Description:** A disease progression model-based CTS tool designed to optimize clinical trial enrichment and design of studies to investigate efficacy of potential therapies for DMD. Measurements of DMD disease progression will be based on changes in a series of endpoints—velocities of completion of the supine-test, 4-stair climb test, 10-meter walk/run test and 30-foot walk/run test, forced vital capacity, North Star Ambulatory Assessment and the transition between scores in the Brooke scale.

**Target Population for Use:** Individuals with DMD 4 years or older (endpoint-dependent) regardless of stage of disease.

**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, the definition of inclusion/exclusion criteria, enrichment strategies, stratification approaches, timing and selection of clinical assessments, trial duration and sample size for studies evaluating therapeutic candidates for DMD.

**Database**

D-RSC has created an integrated database of patient-level data collected in DMD clinical trials.

The database currently contains 14 clinical datasets ([Table 1](#)) that may be made available to the broader community to the extent permitted by the owners of each contributing dataset. Data exceeds HIPAA “Safe Harbor” standards and is mapped to CDISC standards, making it ready for regulatory submissions.

**Plan for Model Development**

**Figure 1. Flow chart describing process of development of clinical trial simulation platform**

- **Describe the progression of DMD over years of age as measured by:**
  - Velocity climb
  - Velocity stand
  - Velocity walk/run
  - NSAA
  - FVC
  - Brooke

- Identify mathematical functions that describe changes over years of age for each of the measures

- Incorporate two levels of random effects:
  - between-individual variability (BV) and residual variability (RV)

- Incorporate additional candidate covariates:
  - Steroids (current, past, never; deflazacort and prednisone), mutation group, age, race, BMI

- Perform simulation-based diagnostics

- Incorporate a third level of random effects: between-study variability (RSV) (data permitting)

- Perform simulation-based diagnostics stratified by relevant covariable

- Perform model validation

- Final multivariate or univariate DMD progression model(s)

- Understanding of the trajectory of DMD progression over years of age and its predictors

**Preliminary Models**

**Figure 3. Example of preliminary models – quadratic functions for velocity of completion of timed functional tasks**

- Stand
- Climb
- Walk/Run

Graphs show that the relationship between the measurement predicted by the quadratic function correspond to actual observations.

**Summary of Covariate Data**

**Table 2. Summary of the data on the selected covariates in the database**

The covariates of interest include age, body mass index (BMI), race, mutation group and steroid use.

**Next Steps**

- Letter of Intent to FDA Fit-for-Purpose pathway was filed February 2019
- Agree on statistical analysis plan w. regulators – June 2019
- Develop models – By 2020
- Regulatory submission and more interactions, 2020
- Consider additional data and variables for modeling – ongoing

**Figure 4. Example of what final simulation tool might look like.**