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:

- 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.
- A clinical trial simulation tool developed from mathematical models of disease progression of 6 endpoints for use in optimizing trial design (size, length, endpoints etc.). 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 and prototype clinical trial simulator have been built]
- Additional tools to help accelerate drug development. [In development: a biomarker to detect liver damage in patients with muscle disease, markers of imaging biomarkers, a protocol for a platform trial].
- 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.cdisc.org/standards/therapeutic-areas/duchenne-muscular-dystrophy/duchenne-muscular-dystrophy-therapeutic-area.

Context of Use for Clinical Trial Simulator

**General Description:** A disease progression model-based clinical trial simulation (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:

- Velocity of completion of supine-stand test
- Velocity of completion of 4-stair climb test
- Forced vital capacity (FVC)
- NorthStar Ambulatory Assessment (NSAA)
- Transition between scores in the Brooke scale.

**Target Population for Use:** Individuals with DMD 4 years of age and 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, 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.

**The Models and Clinical Trial Simulator**

- D-RSC developed mixed effects models of the dynamics of change and sources of variability of six clinical endpoints that span the disease course
- Each model was built in one part of the data and confirmed in reserved data
- Models describe the growth and decline phases of disease
- Models were used as a basis to develop a clinical trial simulator

**Clinical Trial Simulations**

CTS tool allows for visualization by time in study or age groups

**Example:** Simulation of 100 trials, 50 patients/arm, baseline age 6-12yrs, duration 3 years, drug predicted to have 30% effect on maximum FVC achieved.

**Data**

D-RSC’s integrated database consists of 20 datasets from clinical trials, natural history studies, registries and clinical collections. This contains a total of over 5,000 patients. 1,157 patients and 23,055 observations are used in our initial analysis. This is the largest database of clinical data for DMD.

Data shown in white can be shared with consortium members.

**Regulatory Summary and Next Steps**

D-RSC’s models and clinical trial simulations platforms will be complete by the end of 2020

The final tools will be submitted to FDA and EMA for potential endorsement, which means the agencies accept the tools for the specified context of use. Work has been informed by our regulatory partners throughout development:

- Extensive discussion of ongoing projects on monthly calls, which include D-RSC’s liaisons from FDA and EMA as available
- Plans for the CTS tool have been reviewed through FDA's Fit-For-Purpose pathway and EMA's qualification of Novel Methodologies pathways and the proposed plans have been accepted by both agencies, and feedback has been incorporated.
- D-RSC’s models and model code will be made available through our website after endorsement.

**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/longer 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

**Clinical Trial Simulator**

**New Projects**

In addition to the current projects, D-RSC is involved in additional projects to accelerate drug development for DMD:

- Working with Imaging-DMD to help build models describing how to use muscle strength measures (myometry) in trials
- Working with PPMID and the Institute for Advanced Clinical Trials for Children to develop a platform trial protocol for DMD.
- Developing glutamate dehydrogenase as a liver safety biomarker in patients with underlying muscle damage with C-Path’s Predictive Safety Testing Consortium.

D-RSC is considering additional projects:

- Addition of Becker muscular dystrophy data to database
- Disease modeling of performance of upper limb (PUL2.0), data dependent.
- Support for development of new outcome assessments
- Further understanding of how to measure DMD progression across the disease spectrum