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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. D-RSC will provide the Duchenne 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.cdisc.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 9 datasets, 5 can be shared)
- A mathematical model of disease progression for submission to the regulatory authorities as a fit-for-purpose tool – which will be available to the community when qualified
- Investigation into qualification of biomarkers (see poster #846)

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 is suitable for qualification

**Proposed Context of Use for Platform**

"The platform would be used to forecast changes in clinically-meaningful endpoints, which would inform clinical trial protocol development with respect to inclusion criteria, endpoints, as well as the size and length statistical analysis of clinical trials." (Figure 1)

**Modeling Plan**

D-RSC proposes to develop a model-based trial simulation platform, to inform inclusion criteria and endpoints for trials. The platform will be based on longitudinal quantitative descriptions of disease progression coupled with longitudinal models of the varying probability of reaching clinically relevant milestones of disease (Table 2).

This will help choose the right endpoint for a defined set of patients so that a trial might be shorter and give definitive answers.

Forced Vital Capacity (FVC) has been identified as the candidate longitudinal measure for development of the disease progression model

- 7 of the 9 datasets in the D-RSC data platform have longitudinal data on FVC, about 900 patients age 5 to 30, up to 16 visits per patient
- FVC is sensitive to patient growth and maturation as well as DMD disease progression, especially in patients ≥ 5 years old (Figure 2A, from D-RSC data)
- FVC correlates with functional measures such as Brooke scale (Figure 2B, from Meier et al., 2017)

**D-RSC has identified a set of sequential, clinically-relevant, disease milestones that can be derived from the data, suitable for analysis (Table 2). These will be linked to the longitudinal FVC model**

**Table 2. Definitions of Disease Progression Milestones**

**D-RSC will develop a joint disease progression model platform linking time-dependent changes in FVC to time-to-event data for clinically relevant endpoints (Figure 4)**

**Figure 4. Longitudinal FVC-Endpoint Model Schematic**

**Next Steps**

Reviewing and curating the data within the consolidated data platform

Drafting an analysis plan to meet the proposed CoU, detailing the overall approach for development and validation of the clinical trial simulation platform

Drafting Letter of Intent to apply for Qualification/Fit for Purpose pathways at EMA and FDA.

**Value of D-RSC for Drug Development**

- Development of regulatory ready tools to accelerate, enhance and inform trial design – ensure trials inform if a drug works or not using as few patients and as little time as possible.
- Data standards that allow learning as much as possible from every data point, and combine data from multiple studies to learn more.
- Database of clinical data – ready for use in drug development – sharing as permitted by owner
- Public-private partnership structure to support science in precompetitive research.

**References:**
