Duchenne Regulatory Science Consortium – developing tools to accelerate drug development for Duchenne

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Background and Objectives

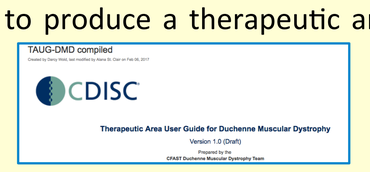
The Duchenne Regulatory Science Consortium (D-RSC) was formed by the Critical Path Institute and Parent Project Muscular Dystrophy to develop tools to accelerate therapy development for Duchenne muscular dystrophy. D-RSC's will provide the Duchenne drug development ecosystem with:

- A CDISC (Clinical Data Interchange Standards Consortium) standard for Duchenne allowing for agreed upon standards and definitions of format, structure and terminology in clinical studies, enabling comparison between datasets, and acceptable to regulatory authorities
- 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
- Use of that data to develop a model based enrichment platform for submission to the regulatory authorities as a fit-for-purpose tool – which will be available to the community when validated
- Qualification and *in vitro* diagnostic status of a novel liver safety biomarker, in collaboration with C-Path's predictive safety testing consortium, PSTC – available for use in clinical trials and care to monitor liver safety

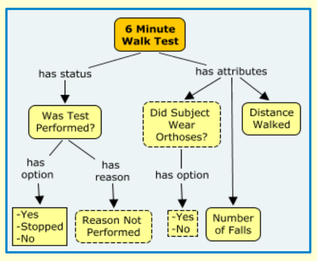
The Critical Path Institute is a non-profit organization that specializes in forming public-private partnerships to develop drug development tools, and work towards qualification/endorsement of such tools with the regulatory authorities (e.g. FDA, EMA). Each consortium is advised by an FDA liaison to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

CDISC Standards

CDISC data standards specify the format, structure and terminology to be used for databases in clinical studies. As of 2017, the FDA requires all data submissions for new clinical trials to be in this format. There is currently no defined CDISC standard for many elements collected in Duchenne trials, so D-RSC has partnered with CFAST (the Coalition for Accelerating Standards and Therapies) to develop such standards and to produce a therapeutic area user guide for Duchenne.



This guide was completed on March 1 2017 and it will be available for public review soon. Please consider reviewing and submitting comments



Example of a CDISC Concept Map: Each concept in a CDISC database is labeled with defined terminology describing the measurement precisely, allowing for comparison and combination of datasets, increasing sample size for analysis.

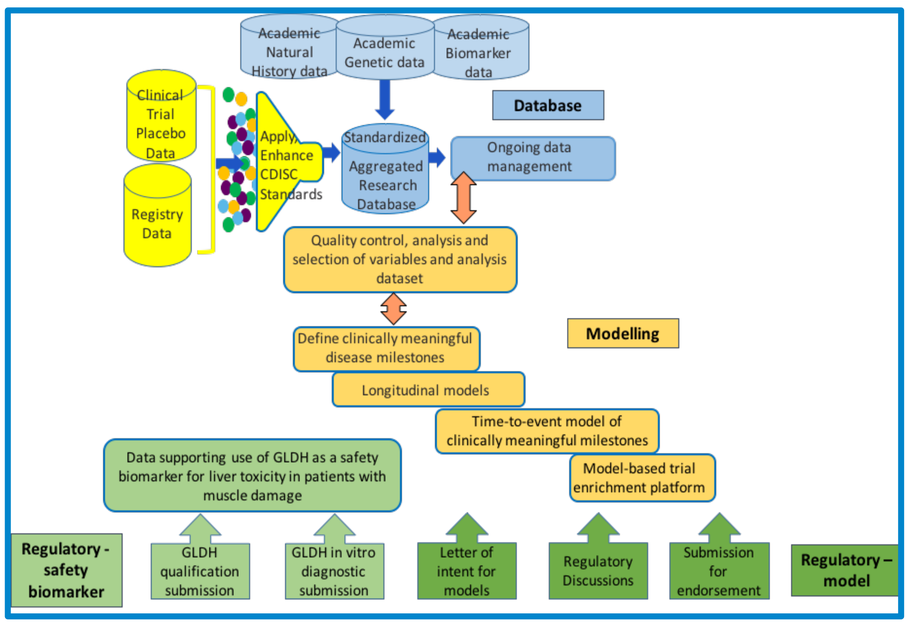
The guide includes genetics and disease assessments including imaging and cardiac, musculoskeletal, and pulmonary function assessments, as well as functional tests.

Regulatory Engagement

D-RSC was built around the concept of developing drug development tools that can be accepted into FDA and EMA regulatory pathways.

We work closely with our FDA liaison throughout development. We will seek:

- Qualification of Glutamate Dehydrogenase (GLDH) as a liver safety biomarker in patients with underlying muscle disease [with PSTC]. EMA and FDA qualification decision expected 2017.
- *In vitro* diagnostic status for a GLDH assay to ensure it is available for use in clinical care and in trials.
- Endorsement of "Fit for Purpose" models: 1) longitudinal quantitative description of disease progression and 2) models of the varying probability of reaching clinically relevant milestones of disease. "Fit for Purpose" is a regulatory convention defining the context in which the model can be used.



Integrated Database

The D-RSC database contains 6 datasets, which have been quality controlled and mapped to CDISC data standards. Additional data is being loaded.

Database	Type of data	Number of patients	Age range	Length of follow up	Types of variables
UC Davis	Natural history	73	2 -31 years	up to 10 years	Functional, respiratory measures, myometry
Santhera	Placebo arm	34	10-18 years	up to 420 days	Respiratory measures, myometry, cardiac
Lily	Placebo arm	115	7-14 years	up to 395 days	Functional, respiratory, cardiac measures
CHOP	Clinical	66	13-33 years	up to 3 years	Respiratory measures
Cincinnati	Clinical	97	7-16 years	up to 5 years	Functional, respiratory, cardiac measures
Duchenne Connect	Patient reported registry	3736	reports 1-115 years	none	Questionnaire

- ✓ Data owners determine level of sharing for their data (just with C-Path, with the consortium or more widely)
- ✓ Full data anonymization that exceeds HIPAA "Safe Harbor"
- ✓ C-Path databases have been used for storing and dissemination of 49,000 subjects' data, over 100 million data points
- ✓ Extensive security measures for online data access & database management
- ✓ Data owner may receive data back in CDISC format

Value of D-RSC for drug development

- *Database of clinical data in CDISC format – ready for use in drug development – sharing as permitted by owner*
- *Publically available CDISC therapeutic area user guide to inform data structure for future projects*
- *Creation of regulatory ready tools to inform clinical trial protocols.*
- *Tools to accelerate, enhance and inform trial design*
- *Public-private partnership structure to support science in the precompetitive space.*

Model-based trial enrichment platform

Discussion of Duchenne natural history has dominated many of the regulatory interactions to date, which have been made more challenging by misunderstandings between stakeholders. Points of inflection in clinical disease course are not clearly defined, and may be defined differently in different datasets, making comparison of data between datasets challenging. While the use of CDISC standard data structures will allow better comparisons between datasets, the community also needs to use the same definitions for clinically relevant disease milestones. We propose to use the definitions below, which can be extracted accurately from our datasets:

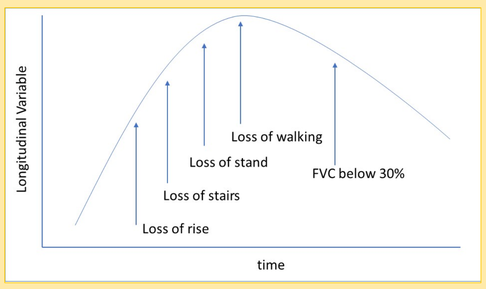
Clinical Milestones

Categorical Endpoint	Definition
Loss of stand from supine	Inability to complete rise from floor (supine up) test in 30s or less.
Loss of ability to jump	Inability to get both feet at the same time, clear the ground simultaneously [NSAA 0]
Loss of ability to hop	Unable to bend knee and raise heel (floor clearance not needed) [NSAA 0 for right or left]
Loss of ability to run	Unable to run with both feet off the ground at the same time [NSAA 1 or 0]
Loss of ability to climb stairs	Inability to complete 4 step climb in less than 120s
Loss of ambulation	Inability to complete 10m walk test in less than 30s.
Loss of standing	Inability to stand still independently, needs support (even minimal) [NSAA 0].
Loss of ability to raise hands above head	Unable to raise hands above head; using straight or bent arms. [Brooke upper- 2]
Loss of ability to touch head	Unable to raise hands above the head, but can raise an 8-oz. glass of water to the mouth (using both hands if necessary) [Brooke upper – 3]
Loss of ability to put hand to mouth	Unable to raise hands to the mouth, but can use the hands to hold a pen or to pick up pennies from a table. [Brooke upper -5]
Recommend initiate nocturnal non-invasive ventilation	FVC<40% *
Recommend ventilator support	FVC<30% *

* - The exact definitions of these milestones are still under discussion

D-RSC proposes to develop a model-based trial enrichment 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.

This will be able to be used to predict which groups of patients might change in which clinically meaningful milestones over a given period of time.



The platform will be based on a model that describes the change in a longitudinal variable over time, and maps onto that model the probability of milestone events occurring.

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