# Accelerating drug development: data sharing and developing quantitative tools through the Duchenne Regulatory Science Consortium (D-RSC).

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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 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.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 #46)

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

## Background

- Although DMD is considered an orphan disease, (prevalence of ~1.4 per 10,000 males ages 5 to 24 years)[4], recent advances in DMD research have provided a robust development pipeline for potential treatments[2]
- While the high interest in DMD drug development is encouraging for patients and caregivers, this presents challenges to the design and execution of clinical trials, given the low prevalence of DMD, the targeting of certain therapies to genetic sub-populations and the reliance on endpoints that can only be measured in patients of narrow age range
- To address these challenges, a better understanding of disease progression in identifiable subpopulations of patients is required, which can help identify endpoints that provide an accurate measure of relevant drug effects in a short trial duration
- Better access to natural history data will allow development of more informed protocols

## Database

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

- All datasets have been quality controlled and mapped to the DMD CDISC data standards
- Full data anonymization that exceeds HIPAA "Safe Harbor"
- The database currently contains 9 clinical datasets (**Table 1**) that may be made available to the broader community to the extent permitted by the owners of each contributing dataset.

**Table 1. Studies Included in Integrated D-RSC Data Platform**
Green datasets can be shared with the community

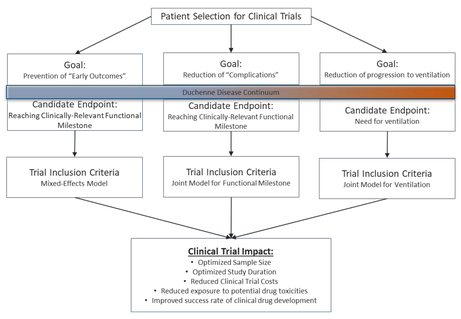
| Database | Type of data | Number of patients | Age range | Length of follow up | Types of variables |
|---|---|---|---|---|---|
| UC Davis | Natural history | 73 | 2 -31 years | up to 10 years | Functional measures, respiratory measures, myometry |
| Lilly | Placebo arm of trial | 115 | 7-14 years | up to 395 days | Functional measures, respiratory measures, cardiac measures |
| CHOP | Clinical | 66 | 13-33 years | up to 3 years | Respiratory measures |
| Leiden | Protein biomarker study | 14 | 5-18 years | up to 5 years | FVC, drug effects, protein biomarkers |
| Duchenne Connect | Patient reported registry | 3736 | reports 1-115 years | none | Questionnaire |
| Santhera | Placebo arm of trial | 34 | 10-18 years | up to 420 days | Respiratory measures, myometry, cardiac |
| Cincinnati | Clinical | 97 | 7-16 years | up to 5 years | Functional measures, respiratory measures, cardiac measures |
| Imaging DMD | Natural history | 100 | 5-18 years | up to 7 years | Functional measures, myometry (limited) |
| CINRG DNHS | Natural history | 440 | 2-30 years | up to 12 years | Functional measures, respiratory measures, myometry |

**References:**
**1) Romitti, P. A. et al. *Pediatrics* 135, 513–521 (2015). 2) Guiraud, S. & Davies, K. E. *Curr. Opin. Pharmacol*. 34, 36–48 (2017). 3) Meier T, et al. *Neuromuscul Disord (*2017)**

## 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 and statistical analysis of clinical trials." **(Figure 1)**

**Figure 1. Application of DMD Model per Proposed Context of Use**




## 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[3])

**Figure 2: Forced Vital Capacity (FVC) changes with age and association with function.**

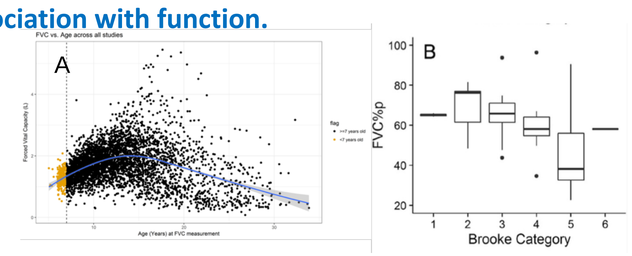
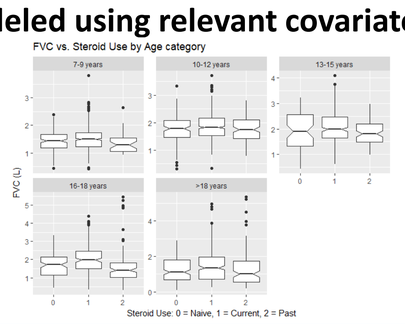



**Figure 3: Preliminary analysis of steroid effect on FVC.**

**FVC variance will be modeled using relevant covariates:**

- Height
- Weight
- Race
- Baseline function
- Steroid use (**Figure 3**)
- Others




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

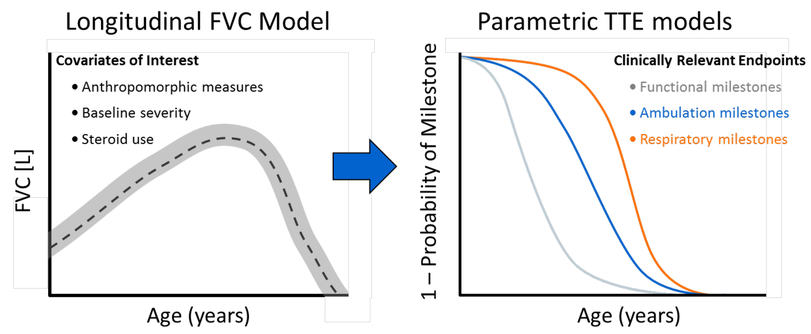
**Table 2. Definitions of Disease Progression Milestones**

| 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 30-foot 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] |
| FVC<50% | FVC<50% |
| FVC<1L | FVC<1L |

## Joint Model Schematic

**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. Joint Longitudinal FVC-Endpoint Model Schematic**




## Next Steps

- Reviewing and curating the relevant 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.

***Additional D-RSC Members -** Academic Collaborators: Yetrib Hathout, Hank Mayer, Heather Gordish-Dressman, Brenda Wong, Ray Hu, Jean Bange , Annemieke Aartsma-Rus, Pietro Spitali , Tina Duong, Eric Henricson, Craig McDonald, Kathleen Rodgers, Sindhu Ramchandren, Advisors: Ted Abresch, Buddy Cassidy (Patient Representative), Nicholas Kozauer, Atul Bhattaram and Veneeta Tandon (FDA/CDER), Tom Cheever (NIH/NIAMS), Glen Nuckols (NIH/NINDS); Parent Project MD: Pat Furlong, Abby Bronson and Liz Habeeb-Louks; Industry Collaborators: Joanne Donovan and Joe Johnston (Catabasis); Patrice Becker and Bryan Due (Mallinckrodt Pharmaceuticals); Doug Chapman, Janice Chin, Camille Vong, Beth Belluscio and Lutz Harnisch (Pfizer); Jodi Wolff and Guenther Metz (Santhera Pharmaceuticals), Chris Mix and Douglas Ingram (Sarepta Therapeutics), Anne Heatherington and Neil Bhattacharya (Summit Therapeutics); Wendy Erler, Mike Panzara and Jennifer Panagoulias (Wave Life Sciences); C-Path staff: Peggy Abbott, Laura Butte, Diane Corey, Richard Liwski, and Robert Stafford;
With special thanks to The Cooperative International Neuromuscular Research Group (CINRG) Investigators from the CINRG DNHS

**Acknowledgments:** The authors acknowledge the support of Parent Project Muscular Dystrophy and member companies