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

Jane Larkindale[1], Klaus Romero[1], Alexander Berg[1], CINRG investigators and members of the Duchenne Regulatory Science Consortium (D-RSC).* [1]*Critical Path Institute (C-Path), Tucson, AZ*

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 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 10 datasets, 6 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
- Other biomarkers and drug development projects in the Duchenne space (e.g. see additional poster)

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

- Clinical trials in Duchenne are challenging due to 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
- A better understanding of how identifiable subpopulations of patients are likely to progress through a series of disease milestones will help identify endpoints that provide an accurate measure of relevant drug effects in smaller trials that take less time to complete.
- 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

The database currently contains 10 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.

Table 1. Studies Included in Integrated D-RSC Data Platform

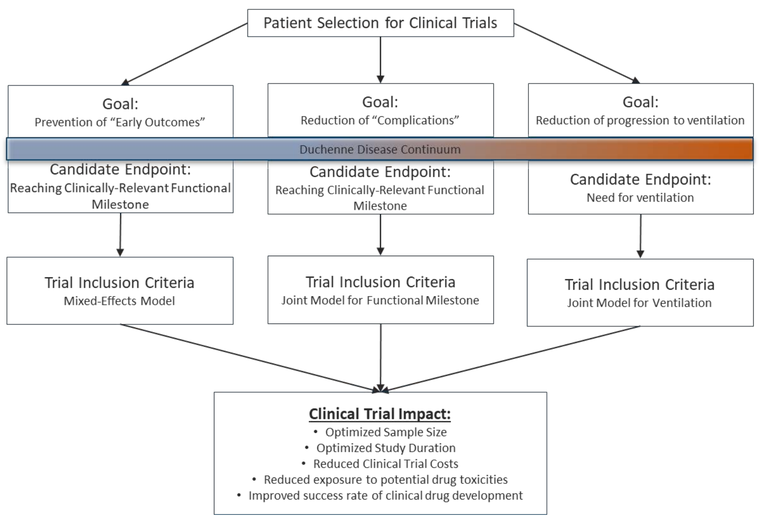
Green datasets can be shared with the community

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
UC Davis 2	Outcome measurement study	24	4-14 years	1 year	Functional measures, limited respiratory measures
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

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 that will be based on longitudinal quantitative descriptions of disease progression coupled with models of the varying probability of reaching clinically relevant milestones of disease across the course of the disease.

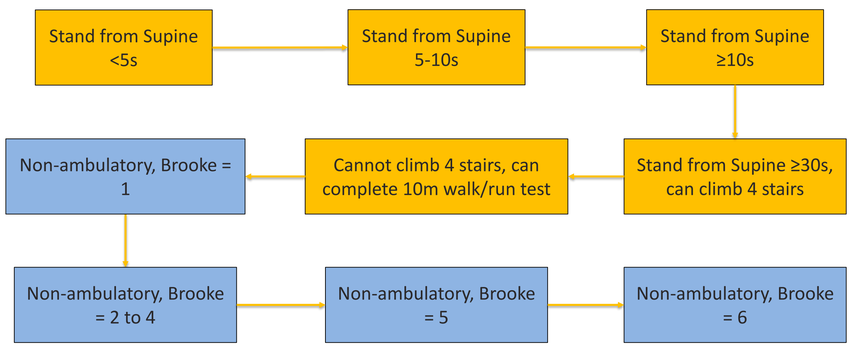
This platform will help pre-select endpoints for defined sets of patients so that a trial might be shorter, use fewer patients, and give definitive answers.

D-RSC plans to develop longitudinal models of:

- Velocity of completion of timed functional tests
  - Stand from supine,
  - 4 stair climb,
  - 10m walk
- Forced vital capacity (FVC)
- These models will be coupled to loss of meaningful function over disease course (Figure 2).
- D-RSC has 3,000-4,000 data points for each of these measures across disease course from multiple studies

Figure 2: Proposed stages of disease progression.

Adapted from McDonald et al., 2017

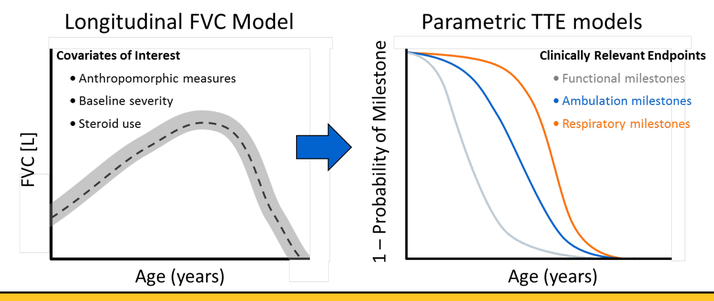


References: **1) Meier T, et al. *Neuromuscul Disord* (2017). 2) McDonald et al., *Lancet* (2017)**

Joint Model Schematic

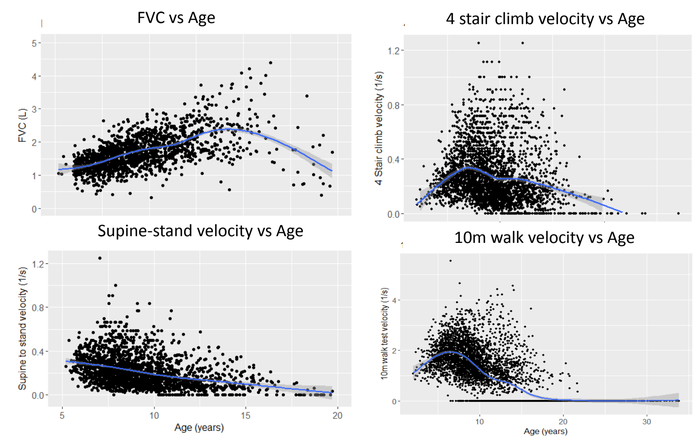
D-RSC will develop a joint disease progression model platform linking time-dependent changes in FVC / velocities to clinically relevant endpoints **(Figure 3)**

Figure 3. Joint Longitudinal FVC-Endpoint Model Schematic



Data Supporting Model Development

Figure 4. Changes in FVC and velocity of functional tests with age



- The 10m walk test, 4 stair climb and stand from supine velocities show similar profiles, expected to relate to early disease milestones.
- FVC tracks with loss of upper body milestones (Brooke score) later in disease (Meier et al., 2017, Figure 5B).

Figure 5: Changes in Brooke score with age and correlations with FVC

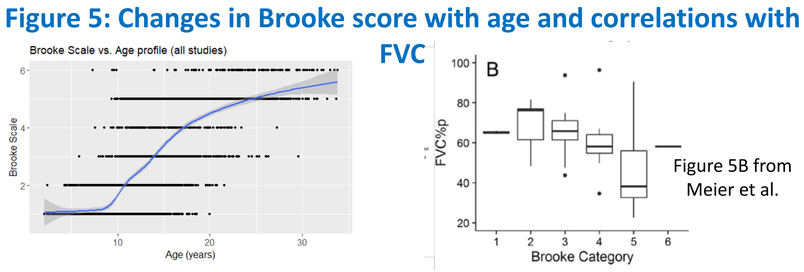
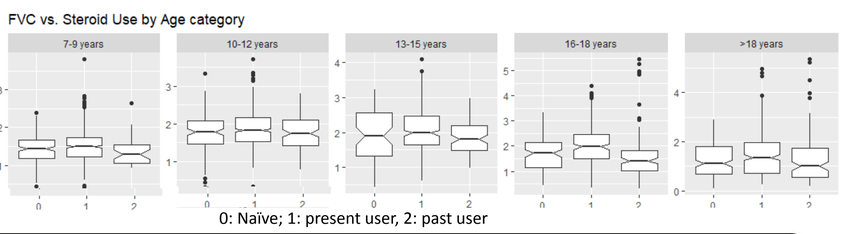


Figure 5B from Meier et al.

Variance for each model will be determined using relevant covariates:

Height - Weight - Race - Baseline function - Steroids

Figure 6: Preliminary analysis of steroid effect on FVC.



Value of D-RSC for drug development

- Development of regulatory ready tools to inform trial design – ensure trials inform if a drug works or not using as few patients and as little time as possible.
- Data standards allow maximal learning from every data point.
- Database of clinical data – ready for use in drug development – sharing as permitted by owner
- Consortium structure allows pre-competitive development of tools for the community.

Next Steps

- Draft Letter of Intent to apply for Qualification/Fit for Purpose pathways at EMA and FDA. – August 2018
- Agree on statistical analysis plan w. regulators- end 2018
- Develop models – By end of 2019
- Regulatory submission and more interactions, 2020

***Additional D-RSC Members** - Academic Collaborators: Yetrib Hathout, Hank Mayer, Heather Gordish-Dressman, Cuxia Tian, Ray Hu, Jean Bange, Annemieke Aartsma-Rus, Pietro Spitali, Brenda Wong, Tina Duong, Eric Henricson, Craig McDonald, Kathleen Rodgers; Advisors: Ted Abresch, Buddy Cassidy (Patient Representative), Teresa Buracchio, Atul Bhattaram and Veneeta Tandon (FDA/CDER), Tom Cheever (NIH/NIAMS), Glen Nuckolls (NIH/NINDS); Parent Project MD: Pat Furlong, Abby Bronson and Liz Habeeb-Louks; Industry Collaborators: Joanne Donovan and Joe Johnston (Catabasis); Patrice Becker, Bryan Due and Laura Stearns (Mallinckrodt Pharmaceuticals); Doug Chapman, Janice Chin, Camille Vong, Beth Belluscio and Lutz Harnisch (Pfizer); Jodi Wolff and Guenther Metz (Santhera Pharmaceuticals), Chris Mix, Ashish Dugar and Navid Khan (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;
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