Development of a regulatory-ready clinical trial simulation tool for Duchenne muscular dystrophy

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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 (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. [Currently includes 20 datasets, 8 can be shared]
- 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 damage, models 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.

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 regulatory acceptance

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
- Velocity of completion of 10-meter walk/run or 30-foot walk/run 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.

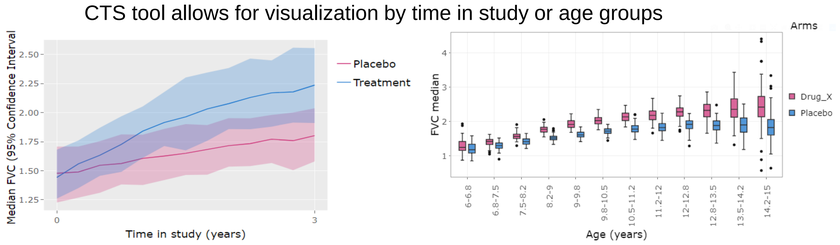
Intended Application: To help inform, through simulations, trial enrichment strategies, including the selection of inclusion/exclusion criteria, stratification approaches, timing and selection of clinical assessments, trial duration, and sample size for studies evaluating therapeutic candidates for DMD.

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 6-12 yrs, 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. 1,137 patients and 23,305 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.

Database	Type of data	No.	Age range	Time	Types of variables
Santhera DMD 1004	Placebo arm of trial	34	10-18 years	up to 420 days	Respiratory measures, myometry, cardiac
Lilly* DMD 1005	Placebo arm of trial	115	7-14 years	up to 395 days	Functional measures, respiratory measures, cardiac measures
PTC -1 DMD 1009	Placebo arm of trial	57	older than 5	48 weeks	Functional measures, myometry, respiratory measures
PTC -2 DMD 1010	Placebo arm of trial	114	7-16 years	48 weeks	Functional measures, myometry, respiratory measures, Northstar
Pfizer – DMD 1014	Placebo arm of trial	40	6-15	49 weeks	Functional measures, MRI/MRS, Respiratory measures, Northstar, PUL, muscle strength,
Biomarin – DMD 1015	Placebo arm of trial	61	5 – loss of ambulation	48 weeks	Functional measures, respiratory measures, cardiac measures
Biomarin – DMD 1016	Placebo arm of trial	18	5 – loss of ambulation	24 weeks	Functional measures, respiratory measures, cardiac measures
Biomarin – DMD 1017	Placebo arm of trial	16	5 – loss of ambulation	24 weeks	Functional measures, respiratory measures, cardiac measures
Biomarin – DMD 1018	Natural History	269	3-18	3 years	Functional measures, respiratory measures, cardiac measures
Summit *– DMD 1012	Clinical trial data	40	5-10	52-56 weeks	Respiratory measures, MRI/MRS measures, functional measures, PODCI, Northstar
PTC – steroid – DMD 1013	Clinical trial data	115	5-14	52 weeks	Functional measures.
CINRG Steroid DMD 1011	Steroid Clinical Trial	64	4- 12 years	608 days	Functional measures, respiratory measures, myometry
CHOP* DMD 1006	Clinical	66	13-33 years	up to 3 years	Respiratory measures
CCHMC DMD 1002	Clinical	97	7-16 years	up to 5 years	Functional measures, respiratory measures, cardiac measures
ImagingDMD DMD 1007	Natural history	100	5-18 years	up to 7 years	Functional measures, myometry
CINRG DNHS DMD 1003	Natural history	440	2-30 years	up to 12 years	Functional measures, respiratory measures, myometry
UC Davis* DMD 1000	Natural history	73	2 -31 years	up to 10 years	Functional measures, respiratory measures, myometry
UC Davis 2* DMD 1000A	Test/re-test data for COA	24	4-14 years	1 year	Functional measures, respiratory measures
LUMC* DMD 1008	Biomarker study	14	5-18 years	Up to 5 years	FVC, drug effects, protein biomarkers
Duchenne Registry* DMD 1001	Patient Reported Registry	3736	Reports 1-115 years	none	Questionnaire

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.

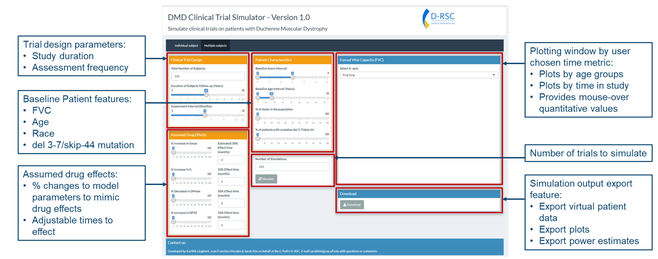
Use Cases

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 imaging (MRI) biomarkers in trials.
- Working with PPMD 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

***Additional D-RSC Members -** Academic Collaborators: Yetrib Hathout, Hank Mayer, Heather Gordish-Dressman, Cuixia Tian, Ray Hu, Jean Bange, Annemieke Aartsma-Rus, Pietro Spitali, Brenda Wong, Tina Duong, Eric Henricson, Craig McDonald, Kathleen Rodgers, Keith Abrams, Michael Crowther, Micki Hill, Sarah Kim, Karthik Lingineni, Stephan Schmidt, Krista Vandenbourne; Advisors: Ted Abresch, Camille Vong, Pavel Balabanov (EMA), Buddy Cassidy (Patient Representative), Teresa Buracchio, Atul Bhattaram and Veneeta Tandon (FDA/CDER), Tom Cheever (NIH/NIAMS); Parent Project MD: Pat Furlong, Abby Bronson; Industry Collaborators: Joanne Donovan and Joe Johnston (Catabasis); Alan Russell, Edgewise Therapeutics, Jacqueline Delfgaauw (Mallinckrodt Pharmaceuticals); Yohei Satou (NS Pharma), Beth Belluscio, Doug Chapman, Lutz Harnisch (Pfizer); Jodi Wolff and Guenther Metz (Santhera Pharmaceuticals); Jon Tinsley (Sarepta Therapeutics); C-Path staff: Klaus Romero, Jackson Burton, Jane Larkindale, Diane Corey, Katherine Rudnitsky, Richard Liwski, and Robert Stafford;

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