Welcome!

Duchenne Muscular Dystrophy Regulatory Science Consortium (D-RSC)

June 23, 2016
D-RSC Team

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• Ann Robbins, Regulatory Consultant
• Ted Abresch, Duchenne Clinical Consultant

Plus scientific experts from consortium members
D-RSC
“Why the need for the D-RSC?”

- Development of drugs for the disease is moving forward rapidly, with 23 interventional clinical trials currently ongoing (clinicaltrials.gov).

- The regulatory authorities (FDA and EMA) are open to considering additional endpoints, biomarkers or other ways to more rapidly test therapeutics for this deadly disease.

D-RSC was formed to develop tools to accelerate therapy development for this urgent unmet medical need, aiming to accelerate and improve trial protocol development and reduce the numbers of patients needed to demonstrate the effect of new therapies.
D-RSC: a new consortium to support collaborative research and regulatory qualification of new drug development tools (DDTs) for Duchenne muscular dystrophy to enable the earliest possible patient access to new treatments.
1. Development of a data sharing platform for Duchenne clinical data

D-RSC will work with consortium members and other organizations to obtain contributions of clinical data. These data will be converted to a common data structure through the use of Clinical Data Interchange Standards Consortium (CDISC) clinical data standards, and then combined to build a pooled database of de-identified patient data that can include current clinical measures, patient-reported outcomes, pathology, imaging, and other biomarkers that describe the disease progression of Duchenne. D-RSC members will have access to this database per the terms and conditions established for each contributed dataset. The integrated database will be an invaluable research tool for current and future D-RSC projects.
2. Development and publication of a CDISC therapeutic area standard for Duchenne muscular dystrophy

During the conversion of data to CDISC standards format to enable pooling of data from multiple sources, C-Path staff will document any gaps in the CDISC clinical data standard as they apply to Duchenne. C-Path will prepare draft supplemental CDISC standards documents and then work with CDISC to publish a new CDISC SDTM therapeutic area standard for Duchenne.

These standards are going to be required for all FDA submissions by 2017
3. Develop a disease progression model for Duchenne muscular dystrophy via application of the consortium shared data

This model is envisioned to quantitatively describe disease progression and capture all relevant sources of variability, with three main purposes:

1) serve as the backbone for the future development of a drug-disease-trial model, which can then be turned into a clinical trial simulation platform;
2) serve as a quantitative clinical trial enrichment platform;
3) inform further biomarker efforts.

This will be developed with FDA/EMA input using combined datasets so that the final tool is in a form that can be endorsed by the regulatory authorities. Development of the tool will occur with input from the consortium members.
Possible Additional Objectives

3. Qualify skeletal muscle MRI imaging (fat fraction) as a prognostic or pharmacodynamic biomarker for Duchenne. D-RSC may partner with the NIH-funded Imaging-DMD consortium to qualify MRI measurements as a biomarker with both FDA and EMA. Discussions are ongoing with Imaging-DMD and the data will let us determine the exact context of use for qualification.

4. Development of additional drug development tools.

The consortium has yet to vote on moving forwards with these additional objectives.
After the initial period....

Additional Projects:

1. Consortium members will be able to use the part of the database that is shared with consortium members for their own analyses.

2. Parts of the database may be shared with all researchers, depending on the requests of the data owner.

3. Consortium members may choose to embark on the development of additional drug development tools, which will require additional funding.
D-RSC Workflow

Legacy Data
Apply, Enhance CDISC Standards
Additional Data
CDISC Standards Development

Standardized Data
Aggregated Research Database

Duchenne CDISC Standard

Ongoing data management
Research and Analysis
Publish Findings, Prepare & Submit Regulatory Documents

Context of use
Letter of support
Regulatory Endorsement/Qualification

Advisory Board
Community Support

### Data Sharing – Key Success Factors

<table>
<thead>
<tr>
<th>Consistent data structure</th>
<th>Utility of data</th>
<th>Data integrity</th>
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<tr>
<td>Everything in its place, a place for everything</td>
<td>Represent data using smallest usable elements of information</td>
<td>Do not alter the meaning of the data</td>
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**CDISC clinical data standards provide this capability**
Nine member companies agreed to share data from 24 Alzheimer’s disease (AD) trials. The data were not in a common format. All data were remapped to the CDISC AD standard and pooled. A new clinical trial simulation tool was created and has been the first model endorsed by the FDA and EMA. Researchers utilizing database to advance research.

- Integrated database
- 24 studies, > 6500 patients
- Database accessed by > 200 qualified researchers in 35 countries
Clinical Trial Simulator for AD

What the tool is:

• A clinical trial simulation tool to help optimize clinical trial design for mild and moderate AD, using ADAS-cog as the primary cognitive endpoint

What it is based on:

• A drug-disease-trial model that describes disease progression, drug effects, dropout rates, placebo effect, and relevant sources of variability

What it is NOT intended for:

• Approve medical products without the actual execution of well conducted trials in real patients
Regulatory conclusions

This model adequately captures relevant information regarding disease progression, drug effects and clinical trial aspects (placebo effect and dropouts)

Clinical Trial Simulations based on this tool allows the objective, prospective and realistic evaluation of the operating characteristics of different trial designs.

FDA fit-for-purpose decision on CAMD CTS tool. 2013
EMA qualification opinion on CAMD CTS tool. 2013
**What Will a Disease Progression Tool do?**

### DISEASE PROGRESSION MODEL

**Understand Natural History:**
- Understand / identify subgroups
- Enrich clinical trials
- Identify modifiers of progression
- Identify responders to treatment

### DISEASE / BIOMARKER MODEL

**Disease/Biomarker Model:**
- Shows how the biomarker changes with disease progression
- Frequently required for qualification of imaging biomarkers

### PLACEBO EFFECT MODEL

**Reduce Size of Placebo Arm of Trials:**
- Understand disease progression
- Accepted historical controls
- Model replaces some placebos in trial, increases power of trial

### DRUG –DISEASE - TRIAL MODEL

**Drug-Disease Model as a Clinical Trial Simulation Tool:**
- Simulate trial to optimize protocol
- Quantitative trial enrichment
- Reduces trial failure rate
- Informs biomarker discovery
Developing a Comprehensive Database (endpoints, covariate data) is a Critical Step for Success

**MODEL CALCULATIONS**

"Garbage In-garbage Out" Paradigm

- **Garbage Data** → **Perfect Model** → **Garbage Results**
- **Perfect Data** → **Garbage Model** → **Garbage Results**

**Experienced CDISC database programmer**

**Experienced DDT qualification process**

- **Database**
- **Model**
- **Qualification**

**Today: Data Inventory Step**

**Experienced modeling team**
Duchenne Disease Progression Model – current view

- Non-linear mixed effects model of relevant continuous measure through disease: Fat fraction (by MRI) in a specific muscle or group of muscles over time; or strength in specific muscle groups; NSAA; FVC

- Develop time to event analysis to predict loss of major clinical milestones.

![Diagram](image)
D-RSC Progress
Timeline

3/16/2015: Research Agreement signed – C-Path and PPMD
5/22/2015: First Member Signed (Santhera)
8/3/2015: Official Launch (3 members signed on)
8/21/2015: First Consortium Meeting
10/26/2015: Fourth Consortium Member Joined
11/1/2015: First Data Contribution
12/1/2015: CDISC Standards Proposal Submitted
2/1/2016: 4 companies, 4 academics, 2 NIH advisors, FDA liaison involved
4/13/2016: First annual meeting,
            3 datasets in house, two additional data sharing agreements
            2 new academic members
5/1/2016: Launch of CDISC and Modeling Workgroups
6/15/2016: Launch of database
D-RSC Initial Objectives

- Development of a data sharing platform for Duchenne clinical data
  
  Three datasets received, two more data agreements signed, additional in the pipeline. Mapping work initiated, Database developed.

- Development and publication of a CDISC therapeutic area standard for Duchenne muscular dystrophy
  
  FDA priority area for 2016 for CDISC standards, Proposal accepted, standards development initiated, project schedule development and approval is next formal CDISC milestone

- Develop a disease progression model for Duchenne muscular dystrophy via application of the consortium shared data
  
  Early meeting with modeling and clinical experts, Nov. 2015, Meeting in April 2016 to launch the project with the wider community
Data Sharing
D-RSC Data Capability & Safeguards

Establish a pooled, standardized, secure database of Duchenne clinical trial control arm data to support D-RSC objectives

- Data access limited to D-RSC members and/or C-Path staff as authorized by D-RSC Leadership Team, and the owner of the data
- Data owners determine the level of sharing for their data contributions
- Full data anonymization that exceeds HIPAA “Safe Harbor” specification
- C-Path Online Data Repository (CODR) platform
  - Extensive security measures for online data access & database management
  - Proven open source database technology
- Leverages existing data sharing and data standards partnerships
  - C-Path consortia expertise
  - CFAST data standards partnership with CDISC and TransCelerate BioPharma Inc.
Consortium Membership
D-RSC Governance and Funding Model

Parent Project Muscular Dystrophy
- Principal funder and sponsor of the consortium
- Negotiates and agrees with Work Plans
- One of the several voices in the scientific direction of the D-RSC
- Is a D-RSC member
- Has one vote and veto in the D-RSC

Critical Path Institute
- Negotiates and agrees with Work Plans
- Manages project
- Performs many aspects with in-house staff
- Coordinates consortium
- Brings valuable expertise & infrastructure
- Has one vote and veto in the D-RSC

**SPONSORED RESEARCH AGREEMENT**

Consortium
- Strategy, priorities & coordination
- Dissemination and end-use of deliverables

**CONSORTIUM AGREEMENT**

"For Profit" Company
- Pays annual fee
- Has one vote

Non-Profit Company
- Pays annual fee
- Has one vote

Academic
- Pays no annual fee
- Contributing data
- Has one vote

Academic
- Pays no annual fee
- Not contributing data
- Has No vote

NIH and FDA Advisors
- Advisors

Deliverables

NIH and FDA
- Advisors
C-Path
C-Path: A Public Private Partnership

- A trusted, non-profit, neutral third party
- Convenes scientific consortia of industry, academia, and government for sharing of data/expertise
  - The best science
  - The broadest experience
  - Active consensus building
  - Shared risk and costs

- Enables iterative FDA/EMA/PMDA participation in developing new methods to assess the safety and efficacy of medical products

- To achieve official regulatory endorsement of novel methodologies and drug development tools
Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
January 2014
Procedural

Twelve global consortia collaborating with 1,300+ scientists and 61 companies

- **Coalition Against Major Diseases**
  Focusing on diseases of the brain

- **Coalition For Accelerating Standards and Therapies**
  Data standards

- **Critical Path for Parkinson’s Consortium**
  Enabling clinical trials in Parkinson's Disease

- **Critical Path to TB Drug Regimens**
  Accelerating the development of TB drug regimens and diagnostics

- **The Duchenne Regulatory Science Consortium**
  Duchenne Muscular Dystrophy

- **International Neonatal Consortium**
  Neonatal clinical trials

- **Multiple Sclerosis Outcome Assessments Consortium**
  Measuring drug effectiveness in MS

- **Polycystic Kidney Disease Outcomes Consortium**
  New imaging biomarkers

- **Patient-Reported Outcome Consortium**
  Assessing treatment benefit

- **Electronic Patient-Reported Outcome Consortium**
  Electronic capture of treatment benefit

- **Predictive Safety Testing Consortium**
  Drug safety

- **Pediatric Trials Consortium**
  Developing effective therapies for children

- ✔ Biomarkers
- ✔ Clinical outcome assessment instruments
- ✔ Clinical trial simulation tools
- ✔ Data standards
- ✔ In vitro tools
C-Path Collaborators

Industry

- AbbVie
- Acorda Therapeutics
- Actelion Pharmaceuticals
- Allergan
- Almac
- Amgen
- AstraZeneca
- Biogen Idec
- Boehringer Ingelheim
- Bracket
- Bristol-Myers Squibb
- Celgene
- Cepheid
- CRF Health
- Daiichi Sanyo
- Edetek
- Eisai
- Eli Lilly and Company
- EMD Serono
- Ephibian
- ERT
- Exco InTouch
- Forest Laboratories, Inc.
- GE Healthcare
- Genentech
- Genzyme
- GlaxoSmithKline
- Hoffmann-La Roche, Inc.
- Horizon Pharma
- ICON
- Ironwood Pharmaceuticals
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Medidata Solutions
- Merck and Co., Inc.
- Meso Scale Discovery
- Millennium: The Takeda Oncology Company
- Mitsubishi Tanabe Pharma Corporation
- Novartis
- Novo Nordisk
- Oracle
- Otsuka Pharmaceutical
- Pfizer
- Pharsight/Certara
- PTC Therapeutics
- PHT
- Sanofi
- Sarepta Therapeutics
- Shire
- Sunovion Pharmaceuticals
- TAG
- Takeda
- Teva Pharmaceuticals
- UCB
- Vertex

Nonprofit Research Organizations

- Alzheimer’s Association
- Alzheimer’s Drug Discovery Foundation
- Alzheimer’s Research UK
- Bill & Melinda Gates Foundation
- CDISC
- Cincinnati Children’s Hospital
- Engelberg Center for Health Care Reform
- EDCTP
- Flinn Foundation
- Foundation for National Institutes of Health
- National MS Society
- Parent Project Muscular Dystrophy
- Parkinson’s UK
- PKD Foundation
- Reagan-Udall Foundation
- Science Foundation Arizona
- SRI International
- Stop TB Partnership
- TB Alliance
- US Against Alzheimer’s

Government and Regulatory Agencies

- Centers for Disease Control and Prevention
- European Medicines Agency
- Innovative Medicines Initiative
- International Genomics Consortium
- National Institute of Allergy and Infectious Diseases
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institutes of Health
- National Institute of Neurological Disorders and Stroke
- Pharmaceuticals and Medical Device Agency
- U.S. Food and Drug Administration
- World Health Organization

Academic Institutions

- The University of Arizona
- Arizona State University
- Baylor University
- University of California San Francisco
- University of Colorado-Denver
- Emory University
- University of Florida
- Johns Hopkins
- Mayo Clinic
- University of Texas Southwestern Medical Center
- Tufts University
C-Path Core Competencies

• Regulatory qualification of preclinical and clinical biomarkers for safety, efficacy, and trial enrichment

• Regulatory endorsement of disease models and clinical trial simulation tools

• Novel in vitro tools to expedite proof-of-concept

• Outcome assessment instrument development

• Clinical data standards development

• Secure data management, standardization, curation, database development
C-Path Accomplishments:
Drug Development Tools & Methodologies

✓ First imaging biomarker for trial enrichment qualified by FDA (Total Kidney Volume use in Polycystic Kidney disease)

✓ First imaging biomarker for trial enrichment qualified by the EMA (vMRI of hippocampus use in Alzheimer’s disease)

✓ First drug-disease-trial model for AD endorsed by the FDA & EMA

✓ First in vitro novel methodology qualified by EMA (Hollow Fiber System for use in TB drug development)

✓ Two Letters of Support from EMA for kidney injury biomarkers and skeletal muscle injury biomarkers

✓ Six Letter of Support from FDA for kidney injury biomarkers, skeletal muscle injury biomarkers, CSF in AD; vMRI in AD; Dopamine transport biomarker in PD

✓ First preclinical safety biomarkers (7) qualified by the FDA, EMA, and PMDA
Databases Accessible to Research Community
Shared as allowed by data owner.
Thank You

www.c-path.org