Welcome!

Duchenne Muscular Dystrophy Regulatory Science Consortium (D-RSC)

June 23, 2016

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D-RSC Team

- Jane Larkindale, Executive Director
- Pat Furlong, PPMD Co-Director
- Charles Lynn, Sr. Project Manager
- Klaus Romero, Director, Clinical Pharmacology
- Enrique Avilés, Chief Technology Officer
- Ann Robbins, Regulatory Consultant
- Ted Abresch, Duchenne Clinical Consultant

Plus scientific experts from consortium members

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D-RSC

"Why the need for the D-RSC?"

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- 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 Overview

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.

D-RSC Initial Objective 1

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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.

D-RSC Initial Objective 2

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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

D-RSC Initial Objective 3

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 phamacodynamic 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….

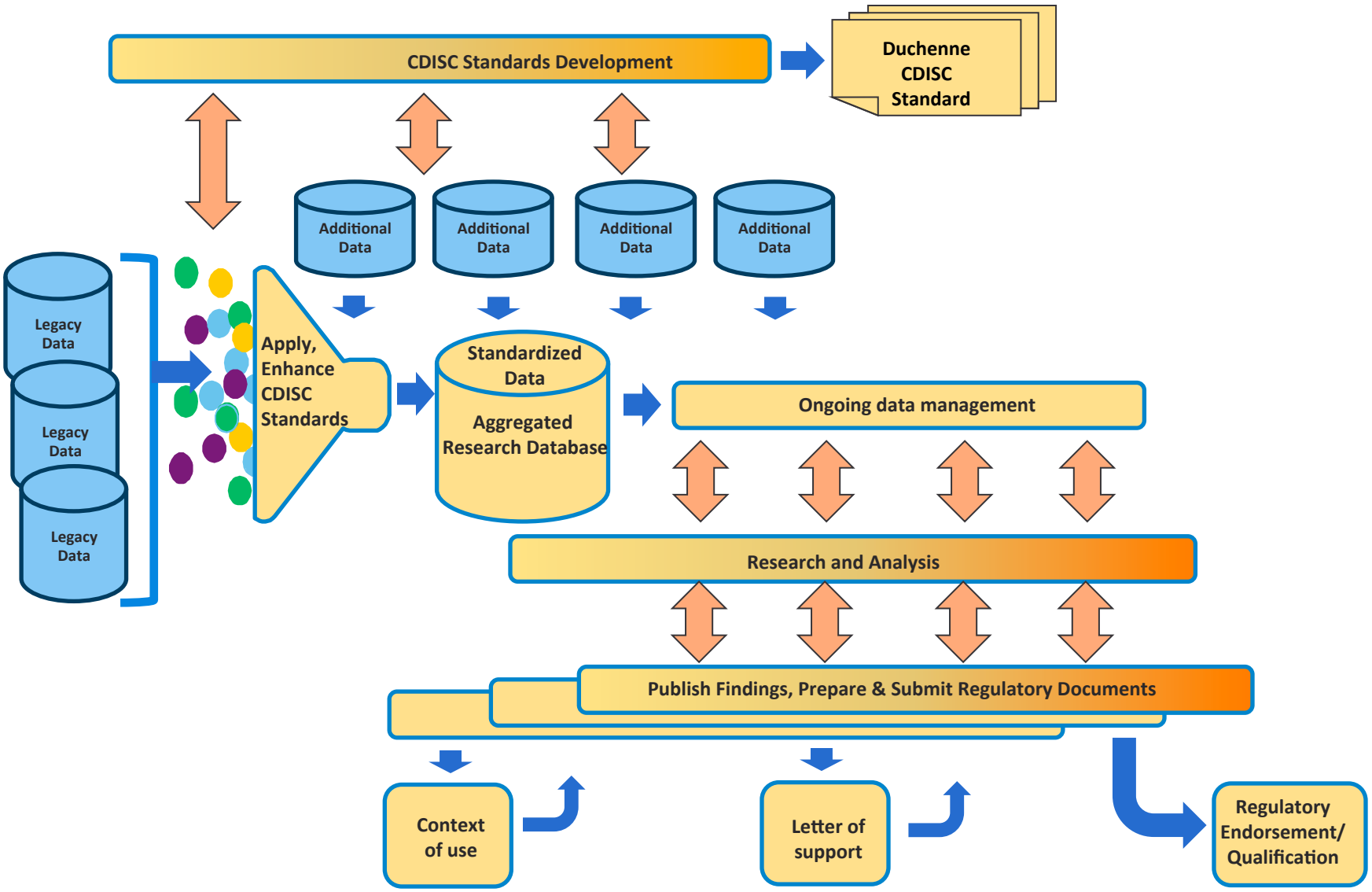
Additional Projects:

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



Data Sharing – Key Success Factors

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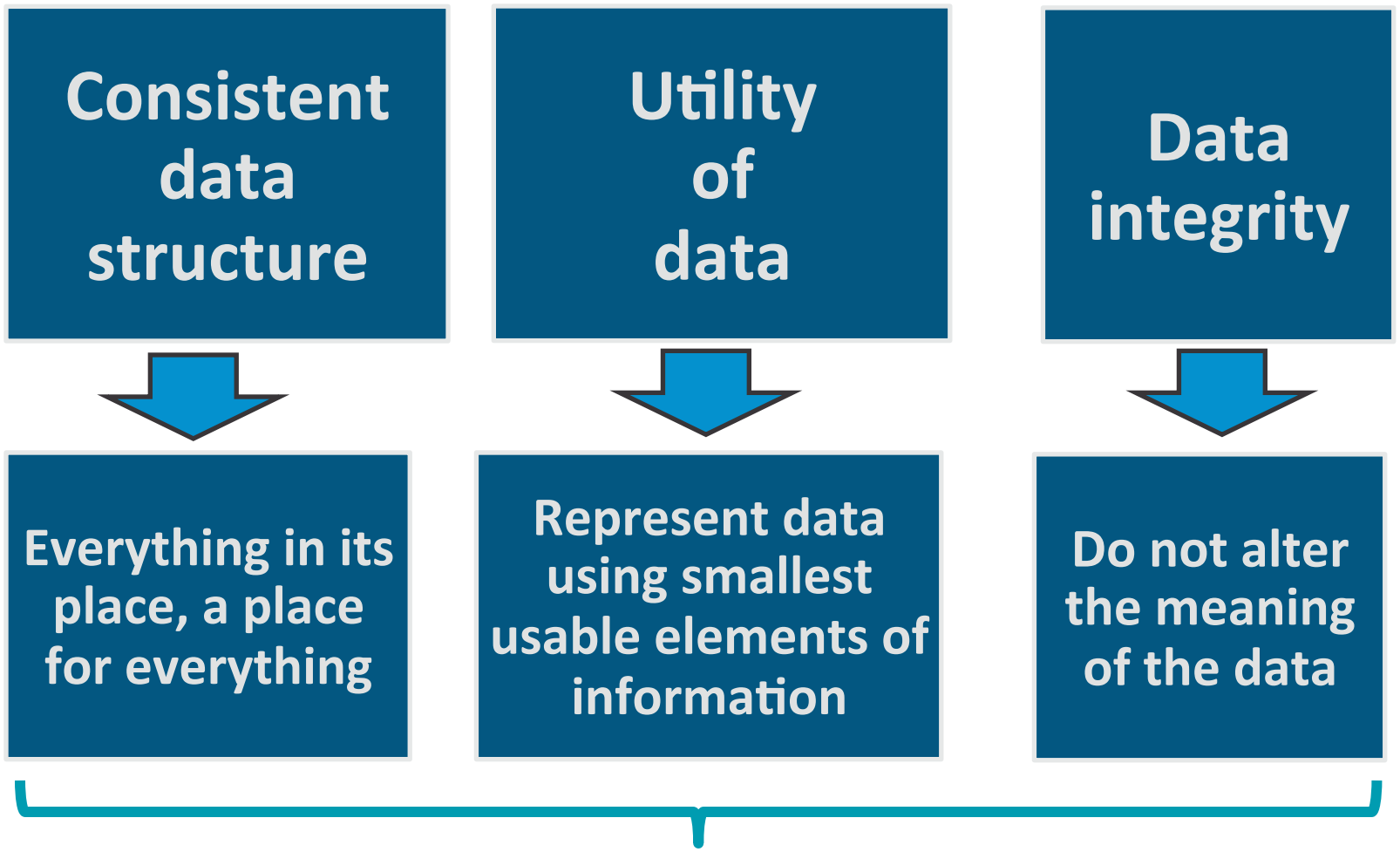
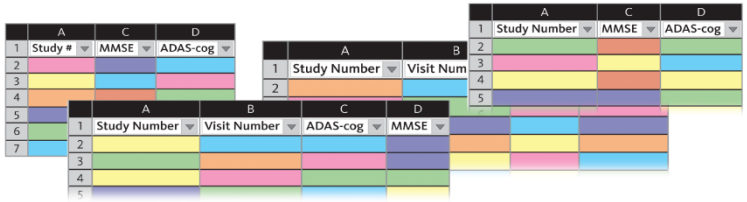


CDISC clinical data standards provide this capability

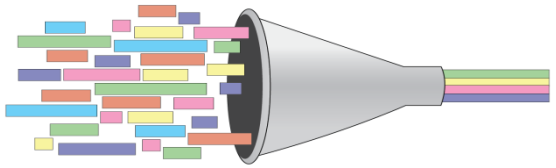
Value of Data Sharing, Standards, and Pooling

Start Point

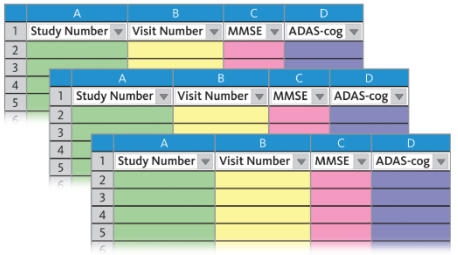
- Nine member companies agreed to share data from 24 Alzheimer's disease (AD) trials
- The data were not in a common format
- All data were remapped to the CDISC AD standard and pooled



Disparate Legacy Data



CDISC Data Standards



Integrated Data

Result

- 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

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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?

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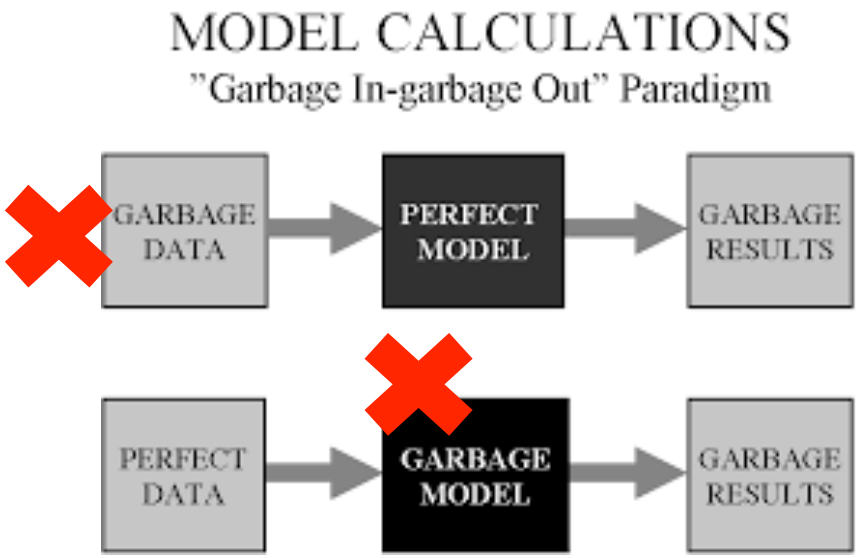
DISEASE PROGRESSION MODEL	**Understand Natural History:** • Understand / identify subgroups • Enrich clinical trials • Identify modifiers of progression • Identify responders to treatment
DISEASE / BIOMARKER MODEL	**Disease/Biomarker Model:** • Shows how the biomarker changes with disease progression • 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



Experienced CDISC database programmer

Experienced DDT qualification process

Database → Model → Qualification

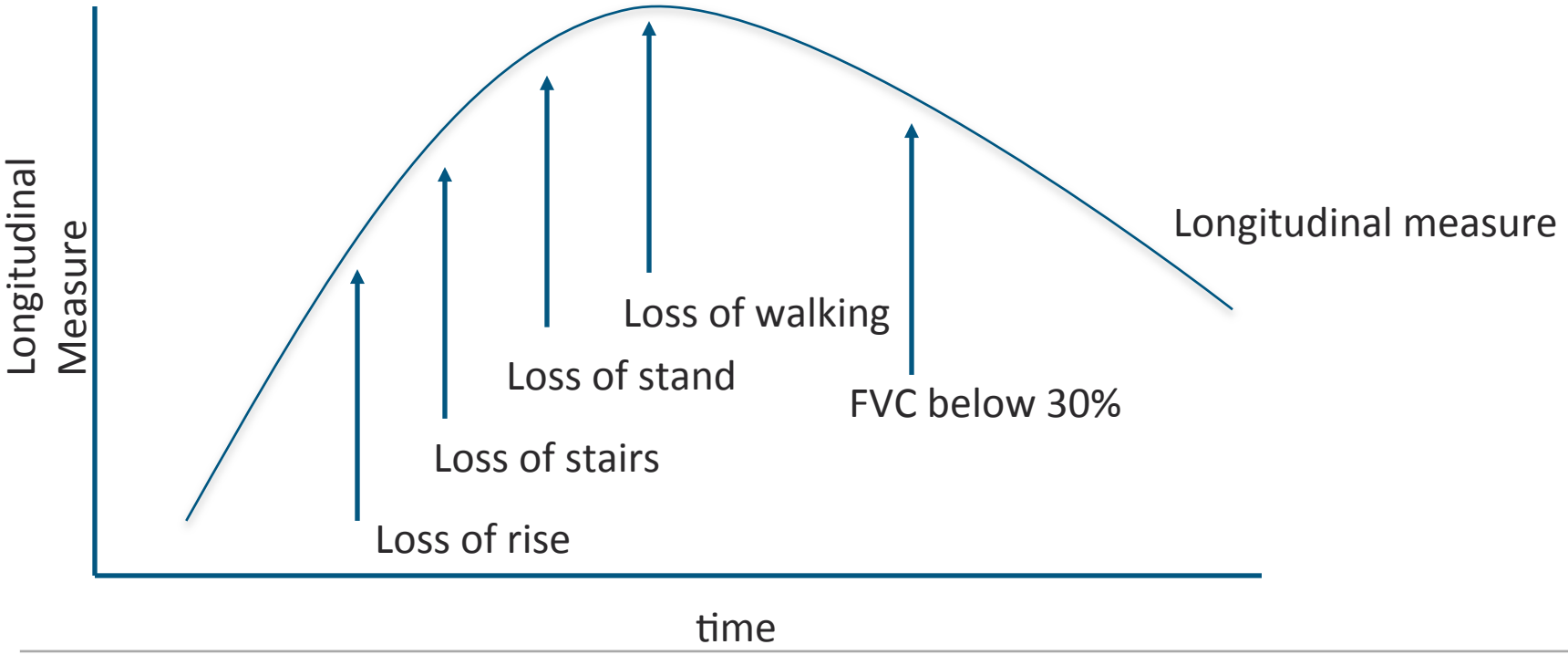
Experienced modeling team

Today: Data Inventory Step

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.



D-RSC Progress

Timeline

D-RSC
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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

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- 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

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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

SPONSORED RESEARCH AGREEMENT

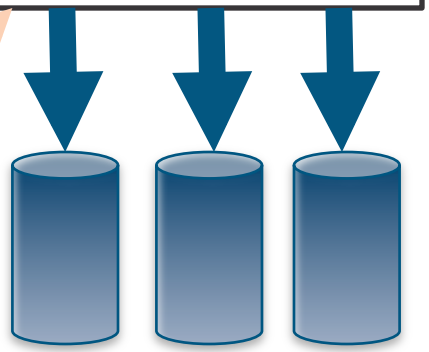
Critical Path Institute

- 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

Consortium

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

CONSORTIUM AGREEMENT



Deliverables

"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

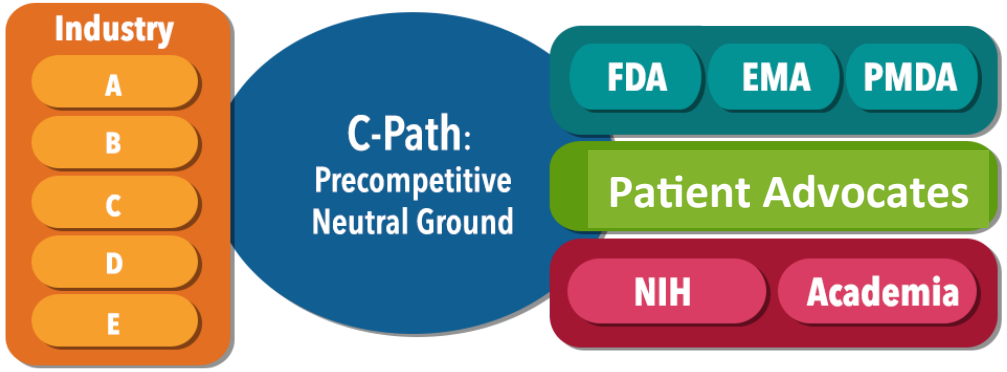
Academic
Pays no annual fee
Not contributing data
Has No vote

NIH and FDA
Advisors

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

FDA and EMA Qualification: A Formal Process of Review and Acceptance

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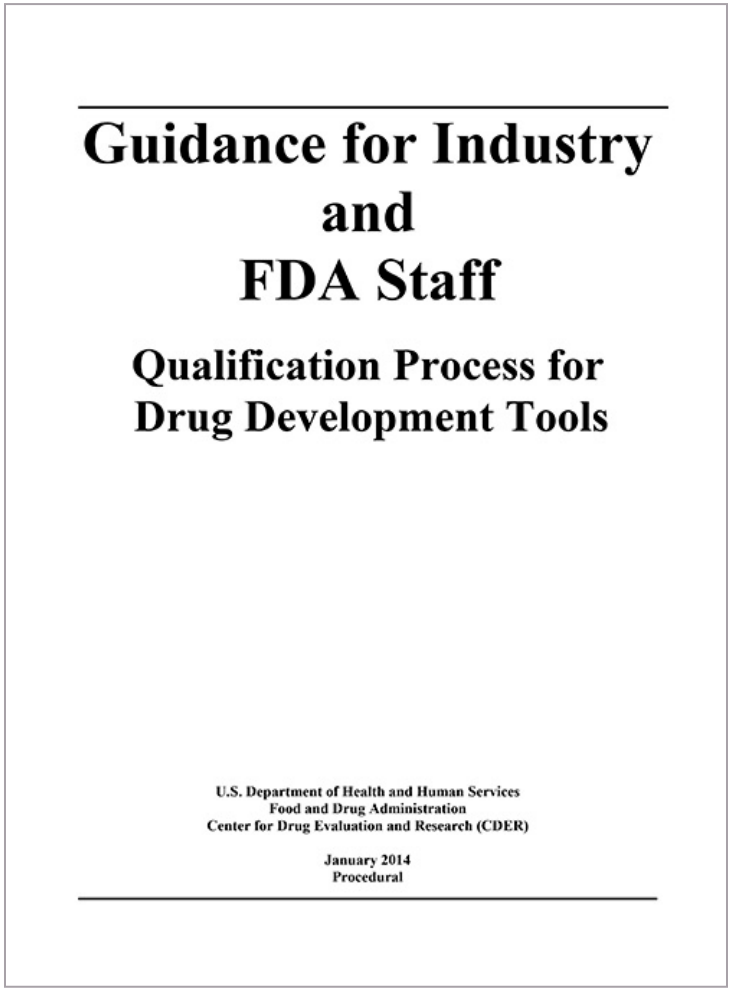
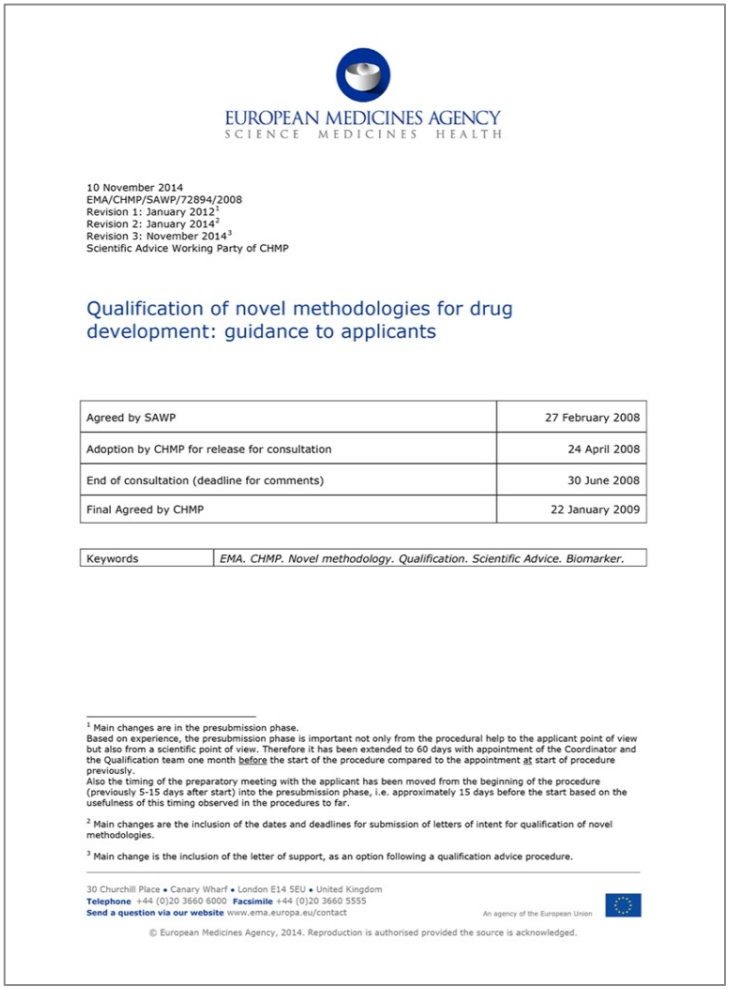


Guidance for Industry
and
FDA Staff

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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Keywords	*EMA. CHMP. Novel methodology. Qualification. Scientific Advice. Biomarker.*

[1] Main changes are in the presubmission phase.
Based on experience, the presubmission phase is important not only from the procedural help to the applicant point of view but also from a scientific point of view. Therefore it has been extended to 60 days with appointment of the Coordinator and the Qualification team one month before the start of the procedure compared to the appointment at start of procedure previously.
Also the timing of the preparatory meeting with the applicant has been moved from the beginning of the procedure (previously 5-15 days after start) into the presubmission phase, i.e. approximately 15 days before the start based on the usefulness of this timing observed in the procedures to far.

[2] Main changes are the inclusion of the dates and deadlines for submission of letters of intent for qualification of novel methodologies.

[3] Main change is the inclusion of the letter of support, as an option following a qualification advice procedure.

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Send a question via our website www.ema.europa.eu/contact

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

C-Path – December 2015

D-RSC benefits from C-Path consortia experience & results

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

CAMD — **Coalition Against Major Diseases**
Focusing on diseases of the brain

CFAST — **Coalition For Accelerating Standards and Therapies**
Data standards

CPP — **Critical Path for Parkinson's Consortium**
Enabling clinical trials in Parkinson's Disease

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

D-RSC — **The Duchenne Regulatory Science Consortium**
Duchenne Muscular Dystrophy

INC — **International Neonatal Consortium**
Neonatal clinical trials

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

PKD — **Polycystic Kidney Disease Outcomes Consortium**
New imaging biomarkers

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

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

PSTC — **Predictive Safety Testing Consortium**
Drug safety

PTC — **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

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Industry

- AbbVie
- Acorda Therapeutics
- Actelion Pharmaceuticals
- Allergan
- Almac
- Amgen
- AstraZeneca
- Biogen Idec
- Boehringer Ingelheim
- Bracket
- Bristol-Myers Squibb
- Celgene
- Cepheid
- CRF Health
- Daiichi Sanyko
- 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
- Santhera Pharmaceuticals
- 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

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- 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

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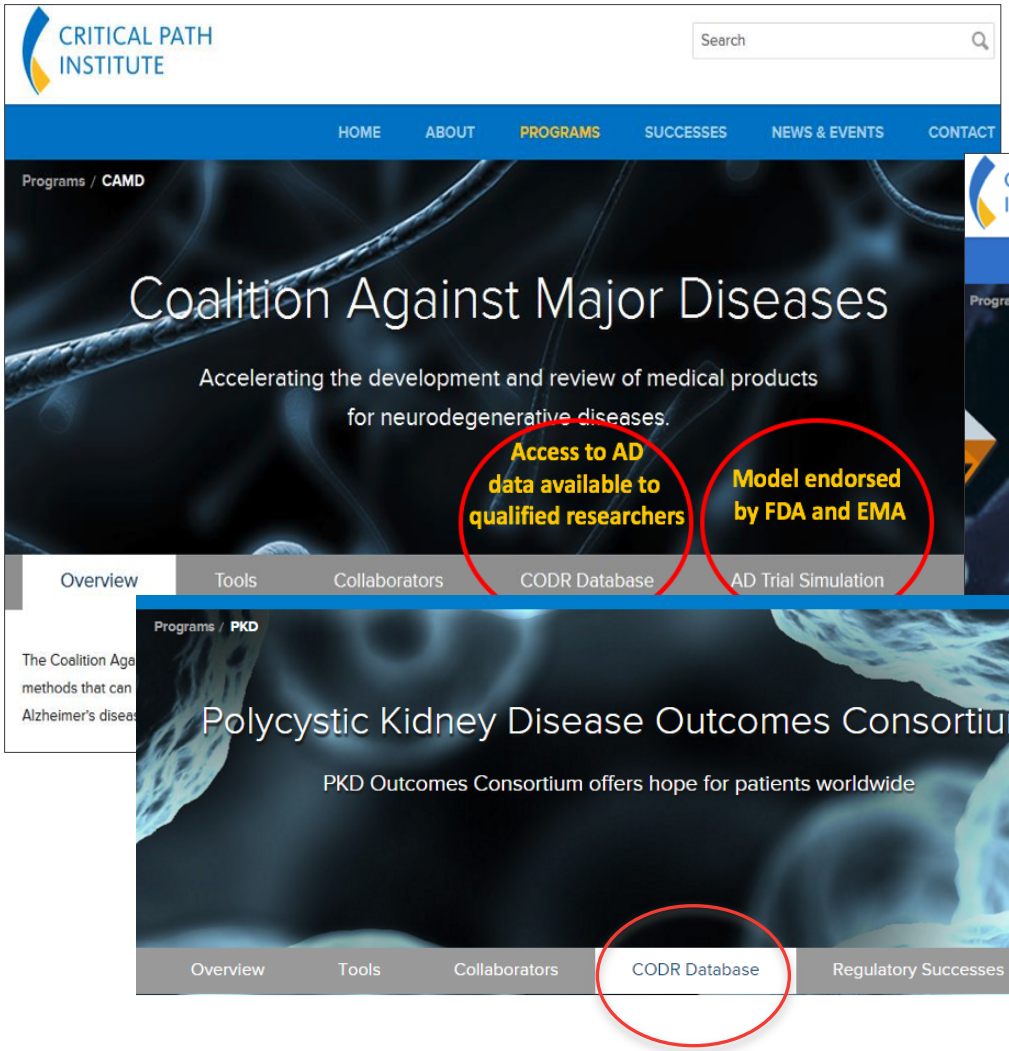
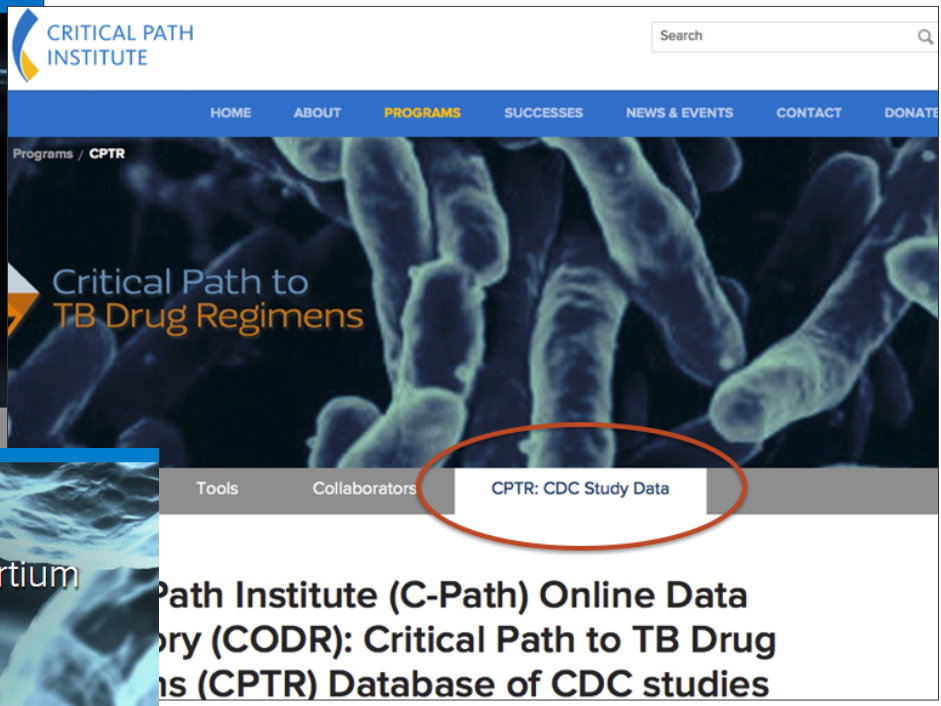
- ✓ First imaging biomarker for trial enrichment qualified by FDA (Total Kidney Volume use in Polycystic Kidney disease)
- ✓ First imaging biomarker for trial enrichment qualified by the EMA (vMRI of hippocampus use in Alzheimer's disease)
- ✓ First drug-disease-trial model for AD endorsed by the FDA & 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.



Critical Path Institute (C-Path) Online Data Repository (CODR): Polycystic Kidney Disease Outcomes Consortium's Database



Thank You

www.c-path.org

SCIENCE foundation ARIZONA
Innovation at Work

FLINN FOUNDATION

FDA

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