Now is a very hopeful time for development of therapies for Duchenne Muscular Dystrophy (DMD) – there are clinical trials of over 20 compounds currently ongoing. Unfortunately, however, several apparently promising drugs have not given us clear results in late stage trials, despite apparently positive early trials. This may be, in part, due to the selection of sub-optimal endpoints, or subpopulations of patients where those endpoints were unlikely to change in the course of the trial. This makes interpretation of the data difficult – in recent FDA submissions drug companies have relied on subgroup analyses and comparisons to external controls, which has resulted in debate as to the efficacy of the drugs.

Companies and researchers need clear biomarkers and endpoints, and an understanding of how they change in the disease populations so that new trials can be designed to be as efficient and informative as possible. D-RSC was set up by the Critical Path Institute and PPMD, with support from the FDA, to develop tools to make Duchenne trials better, and to inform the regulators about the disease and how it progresses in patients. The FDA has assigned a liaison to the consortium to ensure that all work products will be in line with FDA guidelines.

Has C-Path done this before?

- 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

What can a disease progression model do?

- Understand Natural History: • Understand / identify subgroups • Enrich clinical trials • Identify modifiers of progression • Identify responders to treatment
- Disease/Biomarker Model: • Shows how the biomarker changes with disease progression • Frequently required for qualification of imaging biomarkers
- Placebo Effect Model: • Understand disease progression • Accepted historical controls • Model replicates some placebos in trial, increases power of trial
- Drug-Disease Trial Model: • Simulate trial to optimize protocol • Quantitative trial enrichment • Reduces trial failure rate • informs biomarker discovery

What are the goals of D-RSC?

- 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, and then combined to build a pooled database of de-identified patient data 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 is defining the CDISC standardized data structure to be used in reporting Duchenne clinical data, which will be published after a period of public comment. Clinical Data Interchange Standards Consortium standards will be required for all FDA submissions from 2017. 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.

C-Path Achievements

- 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
- Multiple additional qualifications and letters of support for biomarkers and other tools
- Aggregated databases for three diseases available to all researchers through C-Path website, 4th available soon

D-RSC Achievements

- Five Consortium Members and three advisors
- Three datasets at C-Path (additional datasets close)
- Assignment of Dr. Ron Farkas as D-RSC FDA liaison
- Glen Huckolls (NINDS) and Tom Cheevers (NIAMS) engaged with consortium
- Over 50 one on one discussions with collaborators, getting buy in and support for natural history aggregation and modeling project
- Planning meeting at C-Path with clinical modeling expertise, planned annual meeting with experts for April 2016
- Initial Meeting with FDA Dec 15th, 2015

Data Sharing

- Data owners determine the level of sharing for their data contributions (just with C-Path, with the consortium or more widely)
- 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]
- Process of sharing data is not time consuming for the data owner
- Data owner may receive data back in CDISC format