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

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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 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

<table>
<thead>
<tr>
<th>Database Type of data</th>
<th>Number of patients</th>
<th>Age range</th>
<th>Length of follow-up</th>
<th>Types of variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC Davis Natural history</td>
<td>73</td>
<td>2-31 years</td>
<td>up to 10 years</td>
<td>Functional measures, respiratory measures, imaging</td>
</tr>
<tr>
<td>UC Davis Clinical measurement study</td>
<td>24</td>
<td>4-18 years</td>
<td>1 year</td>
<td>Functional measures, limited respiratory measures</td>
</tr>
<tr>
<td>Lilly Placebo arm of trial</td>
<td>115</td>
<td>7-18 years</td>
<td>up to 350 days</td>
<td>Functional measures, respiratory measures, cardiac measures</td>
</tr>
<tr>
<td>CHOP Clinical</td>
<td>66</td>
<td>10-35 years</td>
<td>up to 5 years</td>
<td>Respiratory measures</td>
</tr>
<tr>
<td>Lilly Placebo arm of trial</td>
<td>14</td>
<td>5-18 years</td>
<td>up to 5 years</td>
<td>FVC, drug effects, biomarkers</td>
</tr>
<tr>
<td>Sanofi Placebo arm of trial</td>
<td>372</td>
<td>Reports 1-115 years</td>
<td>none</td>
<td>Questionnaire</td>
</tr>
<tr>
<td>Cincinnati</td>
<td>97</td>
<td>7-15 years</td>
<td>up to 5 years</td>
<td>Respiratory measures, respiratory combi.</td>
</tr>
<tr>
<td>Imaging DMD Natural history</td>
<td>100</td>
<td>5-18 years</td>
<td>up to 7 years</td>
<td>Respiratory measures, limited respiratory measures</td>
</tr>
<tr>
<td>CHIRG DMD Natural history</td>
<td>440</td>
<td>5-20 years</td>
<td>up to 12 years</td>
<td>Functional measures, respiratory measures, respiratory</td>
</tr>
</tbody>
</table>

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

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.

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


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