Critical Path Institute
Coalition Against Major Diseases (CAMD)
Alzheimer’s Clinical Trial Database

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What We Do

DEVELOP “STANDARDS”

- Measurement standards
  - Molecular biomarkers for toxicity, efficacy and patient stratification
  - Imaging biomarkers for efficacy and stratification
  - Patient-, observer-, clinician- reported outcomes

- Methods standards
  - Disease models and clinical trial simulation tools
  - In vitro models

- Data standards
  - With CDISC, clinical data standards for therapeutic areas

ACQUIRE REGULATORY QUALIFICATION

- Recognition, endorsement for a given context of use
How We Do It

- Act as trusted neutral third party
- Convene consortia of industry, academia, and government for pre-competitive collaboration
  - The best science
  - Shared risk and costs
- Iteratively involve FDA in the development process
  - Regulatory participation, guidance
  - Official recognition through “qualification” of Drug Development Tools
    - DDTs = biomarkers, clinical outcome assessments, (animal models)
Non-Standardized Electronic Data Limits Quality and Efficiency of the Review

These issues also affect drug development tool qualification

- Extremely demanding data manipulations to answer basic review questions
  - Limits ability to ask in depth questions and address late-emerging issues in timely manner
  - Increases variability in quality of reviews
  - Reduces transparency and predictability
  - Creates delays and inefficiency in review process
Consortia Established

Six global consortia collaborating with 1,000+ scientists and 41 companies

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<thead>
<tr>
<th>Consortium</th>
<th>Description</th>
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<tbody>
<tr>
<td>PSTC</td>
<td>Predictive Safety Testing Consortium</td>
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<tr>
<td>PRO</td>
<td>Patient-Reported Outcome Consortium</td>
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<td>ePRO</td>
<td>Electronic Patient-Reported Outcome Consortium</td>
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<td>CAMD</td>
<td>Coalition Against Major Diseases</td>
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<tr>
<td>PKD</td>
<td>Polycystic Kidney Disease Consortium</td>
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<td>CPTTR</td>
<td>Critical Path to TB Drug Regimens</td>
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- **DRUG SAFETY**
- **DRUG EFFECTIVENESS**
- **UNDERSTANDING DISEASES OF THE BRAIN**
- **NEW IMAGING BIOMARKERS**
- **TESTING DRUG COMBINATIONS**

- **FDA**
- **CDISC**
  - Biomarkers
  - Patient Reported Outcome Instruments
  - Disease Progression Models
  - Data Standards
CAMD: Tools to Advance Effective Treatments for Alzheimer’s and Parkinson’s Disease

- Qualify biomarkers (FDA Draft Guidance 2010)
- Develop common data standards
- Create integrated databases of clinical trial data
- Develop “accepted for use” quantitative disease models

The first CDISC therapeutic area data standards were developed for Alzheimer’s disease, published September 2011

Nonmember participants: Academic key opinion leaders, CROs
CAMD Data Pooling: Building on Data Standards

- Nine member companies agreed to share data from 22 trials
- The data were not in a common format
- The data needed to be combined in a consistent manner
- All data were remapped to the CDISC standard and pooled

Start Point

Result

- A new in silico modeling tool was created through the application of data standards and is under review by the FDA

- Integrated database
- 22 studies, >6100 patients
- Database open to >200 qualified research teams in 35 countries
• Contributing organizations went through corporate approval procedures to share study data, de-identified for secondary use

• CAMD-AD data was subsequently de-identified further to HIPAA “Safe Harbor” requirements

http://privacyruleandresearch.nih.gov/pr_08.asp
What Was Learned?

ADAS-Cog Variability

- Cognition tests are used to assess Alzheimer’s patients

- Patients are asked to perform a set of tasks
  - Word recall
  - Follow a series of commands
  - Naming of objects
  - ....

- Different implementations of the test were found
  - Different number of questions
  - Different order of questions and tasks
  - Different scoring of same item

- These differences were identified and reconciled as a result of the Alzheimer’s data standards and mapping project

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Sources of Data for Building AD Model: Integration from Diverse Sources

- **Natural History**
  - Inter-patient variability
  - Patient specific factors
  - Imaging and CSF biomarkers

- **Treatment Effect**
  - Estimate data on drug treatment effects (magnitude, onset, offset)
  - 73 Trials (1990 to Present)
  - Inter-study variability

- **Placebo Effect**
  - 9 trials, 3223 patients
  - Inter-patient variability
  - Patient Specific Factors
Model Allows for Accurate Quantitative Predictions of Defined Patient Populations

- Mean (line) and 90% Credible Intervals (gray shaded area)
- 10 year prediction of disease progression as a function of baseline MMSE scores
- Patient selection
- Study size
- Study duration
- Study feasibility
- Study costs

- 65 y.o males
- non ApoE4 carriers

10 year prediction of disease progression as a function of baseline MMSE scores
Mean (line) and 90% Credible Intervals (gray shaded area)
Value Proposition

Research goal → shared data → data standards → integrated database → new drug development tools

Approach used for AD is being applied in other project areas to support development of new drug development tools for:

• Parkinson’s Disease
• Polycystic Kidney Disease
• Tuberculosis
The CAMD Data Challenge

Key Insights Gained

- Legacy data conversion is resource intensive but worthwhile for specific projects

- Assurance is needed that a specific dataset will be useful in achieving research/regulatory qualification objectives

- Selectivity is beneficial: convert only the needed data

- New insights can be obtained from data converted to a common standard and aggregated to enable queries and analysis

- Addition of standardized data from other sources (prospective, retrospective) becomes simplified and expands the power and utility of a standardized data resource
Drug Development Pipeline: Applicability of Data Standards

Primary application of CDISC clinical data standards

http://www.nature.com/horizon/chemicalspace/background/odyssey.html
Clinical Terminology Standards (Section XII E pg 28):

Using a public process that allows for stakeholder input, FDA shall develop standardized clinical data terminology through open standards development organizations (i.e., the Clinical Data Interchange Standards Consortium (CDISC)) with the goal of completing clinical data terminology and detailed implementation guides by FY 2017.

FDA Priorities for Therapeutic Area Data Standards

Priority Therapeutic Areas for Development

An initial inventory of data standards needs, resulted in the identification of 57 therapeutic areas prioritized into three tiers[1]. Further standardization of clinical study data specific to these and other therapeutic areas will facilitate the evaluation of medical products. To identify the preliminary priority areas several factors were considered: (1) areas of particular need, (2) areas with existing data standardization projects underway, and (3) areas with greater drug development pipeline activity. We encourage interested stakeholders to engage in and, whenever possible, sponsor these data standardization efforts.

Priority Disease/Domain Areas for Data Standardization

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<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
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<tbody>
<tr>
<td>Acne</td>
<td>Addiction</td>
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<tr>
<td>Alzheimer’s Disease*</td>
<td>Gastroesophageal reflux disease</td>
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<td>Anti-diabetic agents*</td>
<td>Pneumonia</td>
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<tr>
<td>Crohn’s Disease</td>
<td>Anticonvulsants</td>
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<td>Psoriasis</td>
<td>Influenza</td>
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<tr>
<td>Infecions of skin and/or subcutaneous tissue</td>
<td>Irritable bowel syndrome</td>
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<tr>
<td>QT Studies</td>
<td>Bipolar Disorder</td>
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<tr>
<td>Urinary tract infections</td>
<td>Lipid-altering drug groups</td>
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<tr>
<td>Treatment of postmenopausal osteoporosis</td>
<td>Treatment of overactive bladder</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Clonstridium difficile colitis</td>
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<tr>
<td>Schizophrenia</td>
<td>Major depressive disorder</td>
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<tr>
<td>Solid organ transplantation</td>
<td>Treatment of vasomotor</td>
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TransCelerate has defined five specific initiatives, one is focused on data standards, working with CFAST.
Sharing Clinical Research Data

Governance Considerations

- Rules for developing the data standards themselves
  - Collaborative expert input and consensus

- Rules of the road for merging data
  - Use high value data
  - Use data standards that the FDA accepts
  - Use data standards end-end

- Rules for accessing data
  - Obtain broadest possible data use agreement
  - De-identify data to HIPAA “Safe Harbor” requirements
  - Use access controls appropriate to use objectives

- Rules for access to qualified drug development tools
  - Place DDTs in the public domain to maximize use
Recommended Best Practices

- Data standards: use standards *ab initio* if they are warranted by the intended use
- Database design
  - Fully define & document database architecture
  - Define use cases in advance
  - Invest in ease of use
- Data access
  - Develop a data use agreement template
  - Define access levels specific to each project
  - Perform an independent security review
  - De-identify datasets to HIPAA “Safe Harbor” requirements

http://privacyruleandresearch.nih.gov/pr_08.asp
We want to thank the Food and Drug Administration and Science Foundation Arizona for their significant funding of our work.
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Alzheimer’s Disease-specific Therapeutic Area Supplement to the Study Data Tabulation Model User Guide

Prepared by the Coalition Against Major Diseases (CAMD)

http://www.cdisc.org/stuff/contentmgr/files/0/464c32d97e58d1e0640c77ab2809f0ef/misc/sdtmug_alzheimer__s_2011_09_23_final_revised.pdf