Lessons from the Development and Regulatory Evaluation of a Clinical Trial Simulation Tool for Alzheimer’s Disease

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Critical Path Institute
Why do drug development programs fail?

Reason by phase

Development stage

% Failures

Clinical safety
Efficacy
Formulation
Market potential
PK/Bioavailability
Strategic
Resources
Toxicology
COGS
Unknown
Other
Clinical Trial Simulations

Evaluate different design options

Drug-Disease-Trial Models

\[ \theta_{ipk} = E\left[\frac{ADAS_{ipk}}{70}\right]_{\text{patient } p} \]

\[ T_{pk} \sim \text{Weibull}(\alpha, h_{pk}) \]

Trial Execution

- \( X \) dose
- \( N \)
- Frequency of observations
- Inclusion/exclusion criteria

Simulated results

Trial optimization through simulations

Statistical Analysis

Design selection
C-Path: A Public Private Partnership

- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for pre-competitive sharing of data/expertise
  - The best science
  - The broadest experience
  - Active consensus building
  - Shared risk and costs
- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Official regulatory endorsement of novel methodologies and drug development tools
<table>
<thead>
<tr>
<th>Consortium Name</th>
<th>Focus/Description</th>
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<tbody>
<tr>
<td>Coalition Against Major Diseases</td>
<td>Focusing on diseases of the brain</td>
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<td>Critical Path to TB Drug Regimens</td>
<td>Testing tuberculosis drug combinations</td>
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<td>Multiple Sclerosis Outcome Assessments Consortium</td>
<td>Measuring drug effectiveness in MS</td>
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<tr>
<td>Polycystic Kidney Disease Consortium</td>
<td>New imaging biomarkers</td>
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<tr>
<td>Patient-Reported Outcome Consortium</td>
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<td>Predictive Safety Testing Consortium</td>
<td>Drug safety</td>
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<td>Coalition For Accelerating Standards and Therapies</td>
<td>Data standard</td>
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</table>

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

- **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
- CROnos
- Daiichi Sanyo
- Edetek
- Eisai
- Eli Lilly and Company
- EMD Serono
- Ephibian
- ERT
- Exco InTouch
- Forest Laboratories, Inc.
- Fujirebio Diagnostics
- GE Healthcare
- Genentech
- Genzyme
- GlaxoSmithKline
- Hoffmann-La Roche, Inc.
- Horizon Pharma
- ICON
- Ironwood Pharmaceuticals
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Medical Care Corporation
- Medidata Solutions
- Meso Scale Discovery
- Merck and Co., Inc.
- Millennium: The Takeda Oncology Company
- Mitsubishi Tanabe Pharmaceutical Commercialization, Inc.
- Pharsight/Certara
- Tanabe Pharma
- Novo Nordisk
- Orion Corporation
- Oracle
- Otsuka Pharmaceutical
- Pfizer
- PMDA Pharmaceuticals
- PHT
- Sanofi
- STC
- Shire
- Sunovion Pharmaceuticals
- TAG
- Takeda
- Teva Pharmaceuticals
- UCB
- Vertex

Nonprofit Research Organization

- Alzheimer's Association
- Alzheimer's Foundation of America
- Bill & Melinda Gates Foundation
- CDISC
- Engelberg Center for Health Care Reform
- EDCTP
- Flinn Foundation
- Foundation for National Institutes of Health
- National MS Society
- Parkinson's UK
- PKD Foundation
- Reagan-Udall Foundation
- Science Foundation Arizona
- SRI International
- Stop TB Partnership
- TB Alliance

Government and Regulatory Agencies

- Center for Disease Control
- 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
- U.S. Food and Drug Administration
- World Health Organization

Government and Regulatory Agencies

- 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
- Tufts University
• 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
Maximizing data to develop quantitative tools

Disparate Legacy Data

CDISC Data Standards

Integrated Data

CAMD database

The CAMD database is currently composed of the placebo arm data from clinical trials conducted by the member companies. These trials include drugs on the market or at different stages of development including termination.

Five companies:
- 9 studies
- 3179 Patients

Additional Data:
- ADNI
- Literature

https://codr.c-path.org/main/login.html

<table>
<thead>
<tr>
<th>Study #</th>
<th>Duration (weeks)</th>
<th>n of patient</th>
<th>Age (year)</th>
<th>Female (%)</th>
<th>Baseline MMSE</th>
<th>Year since diagnosis</th>
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<td>66</td>
<td>73.7 ± 9.6</td>
<td>54.5</td>
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<td>1009</td>
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<td>164</td>
<td>74.2 ± 6.4</td>
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<td>325</td>
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<td>51.1</td>
<td>20.9 ± 3.6</td>
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<td>3179</td>
<td>73.9 ± 8.2</td>
<td>55.3</td>
<td>20.3 ± 3.8</td>
<td>2.0 (&lt;1–20)</td>
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Relevant variables

- Longitudinal cognitive instrument:
  - ADAS-Cog: 11 items, 0-70 points

- Basal cognitive instrument:
  - MMSE: 8 items, 30-0 points

- Demographics:
  - Baseline age and gender

- Genetics:
  - APOE4 allele
Data integration for model development
<table>
<thead>
<tr>
<th>Baseline Severity (BMMSE)</th>
<th>Gender</th>
<th>APOE4 allele copies</th>
<th>Annual progression rate</th>
<th>Credible Interval (90%)</th>
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<td>1.42-6.57</td>
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<td>1</td>
<td>3.97</td>
<td>1.52-6.59</td>
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<tr>
<td>21</td>
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<td>2</td>
<td>4.88</td>
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<td>Female</td>
<td>2</td>
<td>1.37</td>
<td>0.02-4.53</td>
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</tbody>
</table>
Disease progression: 75-year-old men, by APOE4 and baseline severity
Some designs that can be simulated
Balancing power, sample size and duration, given varying effect magnitudes

91 Week Crossover
Versus
78 Week Parallel
By effect magnitude
Evolving dropout likelihood by baseline age and severity

Study 1014:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>639</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50-97</td>
</tr>
<tr>
<td>Females</td>
<td>359 (56%)</td>
</tr>
<tr>
<td>Males</td>
<td>280 (44%)</td>
</tr>
<tr>
<td>Follow-up range (days)</td>
<td>479-700</td>
</tr>
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</table>

External validation:
The model adequately describes independent data

Understanding completed trials

Real Results

![Graph showing ADAS-cog (change from baseline) over weeks with different lines for literature placebo, model prediction-placebo, model prediction-donepezil, Drug Y-placebo, and Drug Y-treatment. The y-axis represents ADAS-cog (change from baseline) scale from 0 to 10, and the x-axis represents weeks from 0 to 52. The graph shows a trend indicating worsening of ADAS-cog scores over time.]
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
The total journey took 1317 days (3 years, 7 months and 9 days).

• On June 12, 2013 the FDA determined the CTS tool was “Fit for Purpose.”

• On September 19, 2013 the EMA determined the CTS tool was “Qualified for Use.”
Main strategic lessons learned

• Use a consortium approach
• Provide clear context of use
• Establish partner relationship with regulators early in process:
  • Do not rush to submit a letter of intent, wait until there is clarity in position especially around the “context of use”
• Think about model support, enhancements, support infrastructure, etc.
  • Role for organizations such as ISCTM/academia
  • User communities
- Ten companies
- 24 studies
- 9500 Patients
- Accessible to >200 researchers

https://codr.c-path.org/main/login.html
Thank You

www.c-path.org