Increasing the Probability of Success for Alzheimer’s Disease Interventions through Modeling and Simulation: The Past, The Present & The Future

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Executive Director, Coalition Against Major Diseases
March 11, 2016
Critical Path Institute Consortia

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

- Coalition Against Major Diseases
  Focusing on diseases of the brain

- Coalition For Accelerating Standards and Therapies
  Data standards

- Critical Path for Parkinson’s Consortium
  Enabling clinical trials in Parkinson’s Disease

- Critical Path to TB Drug Regimens
  Accelerating the development of TB drug regimens and diagnostics

- The Duchenne Regulatory Science Consortium
  Duchenne Muscular Dystrophy

- International Neonatal Consortium
  Neonatal clinical trials

- Multiple Sclerosis Outcome Assessments Consortium
  Measuring drug effectiveness in MS

- Polycystic Kidney Disease Outcomes Consortium
  Focusing on diseases of the brain

- Patient-Reported Outcome Consortium
  Assessing treatment benefit

- Electronic Patient-Reported Outcome Consortium
  Electronic capture of treatment benefit

- Predictive Safety Testing Consortium
  Drug safety

- Pediatric Trials Consortium
  Developing effective therapies for children

- Biomarkers
- Clinical outcome assessment instruments
- Clinical trial simulation tools
- Data standards
- In vitro tools
CAMD is aimed at developing drug development tools that advance regulatory science, and accelerate the delivery of innovative treatments for Alzheimer’s disease and related neurodegenerative diseases that have impaired cognition and function.
CAMD’s 2016 Regulatory Pipeline

### Disease or Target

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<td>Hippocampal vMRI Biomarker</td>
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**Notes:**
- FDA:
  - Feasibility
  - Scoping
  - Research

- EMA: Submitted

**Letter of Support:**
OBJECTIVES

**Past:** Develop a comprehensive clinical trial simulation tool for the mild-to-moderate stages of AD
  - History; Example of use; Lessons learned

**Present:** To develop a quantitative understanding of MCI disease progression and apply it to enrich MCI clinical trials
  - Use of ADNI data & why importance of individualized data

**Future:** Develop a comprehensive clinical trial simulation tool that integrates clinical endpoints with imaging, biochemical and digital biosensor assessments from pre-symptomatic to MCI populations
Alzheimer’s Disease (AD) Stages:
Framing the dilemma of what to measure & when?

Unless different outcomes are validated, approvals will require patients to reach this stage of disease progression!

• Current outcomes insensitive
• Patient enrichment is critical

• Current outcomes focused on aMCI to Moderate AD

• Current PRO outcomes unreliable

Pre-Dementia  →  Dementia

Memory complaints  →  Cognitive Impairment  →  Cognitive, Functional & Behavioral deficits

Pre-Symptomatic  MCI / Prodromal AD  Mild  Moderate  Severe
No apparent symptoms  Symptoms  Current diagnosis & treatment

Johan Luthman (Eisai)
Using accepted outcome measures........

2014 CAMD Annual Meeting
- Richard Mohs (Lilly)

Symptomatic Treatment Effects on Cognitive Cognition Appear Before Effects on Function - Donepezil

Figure Legend: Least squares mean (± SEM) change from baseline in the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 457 were included in the intention-to-treat analysis at end point.

Figure 2. Kaplan–Meier survival estimates of time to clinically evident functional decline (by investigator, intent-to-treat population).

Our Challenges

Three key challenges arise as clinical trials for dementia reach earlier into the presymptomatic disease process:

• When assessing cognitive performance over decades, how can progression be consistently evaluated over time?

• How can the tools and data be standardized across the rapidly evolving technology platforms?

• Given that with current clinical instruments activities of daily living treatment changes cannot be measured before cognitive benefits (Rogers et al., 1998), more robust and sensitive assessment tools will be required to probe the earliest stages leading to dementia.
Dementia is co-morbid across many neurodegenerative diseases

Which drug [molecular target]?

.....in which patients?

Frequent Failure
Drug companies are looking to new tools to improve their odds in the development process because it’s currently such a long shot. The percentage of drugs in Phase I trials that advance to:

- Phase II trials: 65%
- Phase III trials: 22%
- Application for government approval: 13%
- Approval: 11%

Source: BioMedTracker data on more than 1,000 companies for 2003-12
The Wall Street Journal
Well Recognized Diseases/Disorders with Co-morbid Dementia

- Alzheimer’s Disease
- Parkinson’s Disease
- Lewy Body Dementia
- Frontal Lobe Dementia
- Down’s Syndrome
- Gaucher’s Disease
- Autism Spectrum Disorder
- Dravet’s Syndrome
- Huntington’s Disease
- Multiple Sclerosis
- Traumatic Brain Injury
- Vascular Dementia
- Congestive Heart Failure

Aging
Knowledge Management: “The Clinical Trialist’s Dilemma”

- The larger the “Knowledge Radius”, the more likely the team is to make a “good decision” BUT

- The larger the radius, the less likely it is that a single team/organization will have a “systematic” structure for integrating and managing the information (KM)

- “Human Factors”
  - Confirmation Bias
  - Framing and Anchoring
  - Availability Heuristic (Temporal and Vivid) (LPCF)
  - Weighting
Doing it Alone vs. Consortium Approach

Different Data = Different Results
AD Modeling Team Mission – February 2009

• To develop a quantitative model to describe the progression of cognitive changes in mild to moderate AD to test and optimize operating characteristics of trial designs for AD (via simulations based on the model).

• To submit the results of the analyses to regulatory agencies for review and qualification for potential use (as, defined by the “Context of Use”) to aid study design for teams involved in AD drug development

• Deliverables of a submission package for review, and tools, code and datasets for development team use
Diverse Work Team (2009)

- Brian Corrigan (Pfizer)
- Kaori Ito (Pfizer)
- James A. Rogers (Metrum)
- Daniel Polhamus (Metrum)
- Mahesh Samtani (J&J)
- Richard Meibach (Novartis)
- Richard Mohs (Lilly)
- Yaning Wang (FDA)
- Vikram Sinha (FDA)
- Maria Isaac (EMA)
- Lawrence Lesko (UoF)
- Lon Schneider (USC)
- Bill Thies (Alzheimer’s Association)

Broad Input from a variety of backgrounds
Start with the end in mind: A clear Context of Use

• **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
Step 1: Data Standards

Integrated Data

CDISC ‘Standardized Data’

Mixed Disparate Legacy Data

Integrated Data

Step 2: AD Drug-Disease-Trial Model
Integrating the Clinical Trialist’s World

How to request access
To CAMD database:
www.codr.c-path.org
Today >6500 patients
Step 3: Relevant Endpoints/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:
  - Number of APOE4 alleles

• Biomarkers
  - Not yet
Step 4 (use): Balancing power, sample size and duration, given varying effect magnitudes

91 week crossover versus 78 week parallel by effect magnitude
Step 5 (use): Evolving dropout likelihood by baseline age and severity
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.”
Lessons Learned from AD Modeling Team

• Key factors for success:
  - CAMD developed the integrated dataset using CDISC standard; data collected from literature, ADNI, and individual level data
  - CAMD member companies provided data from >6000 patients; largest pooled dataset available from randomized, DB, controlled trials
  - Establish partner relationship with regulators early in process
  - Provide clear context of use
  - Keep the team focused on the context of use
  - Regulators are open to endorse quantitative drug development platforms
  - Based on this case study, the process has been optimized
Requests for CAMD’s Clinical Trial Simulation Tool

CAMD’S CLINICAL TRIAL SIMULATION TOOL FOR ALZHEIMER’S DISEASE

30 Organizations (non-academic)

AstraZeneca
Biogen
Bristol-Myers Squibb
Lilly
Merck
Pfizer
Takeda

...and others

58 Individuals

16 Academic Institutions

Harvard University
Karolinska Institutet
LSE
Imperial College London
THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE
University of Florida
The University of Manchester
Penn
University of Southern California

...and others
Requests to Access CAMD’s AD Database

134 Organizations (non-academic)
Abbott
ALSTDI
ALZFORUM
BILL & MELINDA GATES foundation
GE Global Research
Genentech
GlaxoSmithKline
National Institutes of Health
The Michael J. Fox Foundation
...and others

312 Individuals

88 Academic Institutions

CAMD’S ALZHEIMER’S DISEASE DATABASE
CAMD has joined GAAIN
Three key challenges arise as clinical trials for dementia reach earlier towards the presymptomatic disease process:

• When assessing cognitive performance over decades, how can progression be consistently evaluated over time?

• How can the tools and data be standardized across the rapidly evolving technology platforms?

• Given that with current clinical instruments activities of daily living treatment changes cannot be measured before cognitive benefits (Rogers et al., 1998), more robust & sensitive assessment tools will be required to probe the earliest stages leading to dementia.
Developing a Comprehensive MCI Database (endpoints, covariate data) is a Critical Step for Success

MODEL CALCULATIONS
"Garbage In-garbage Out" Paradigm

- Experienced CDISC database programmer
- Experienced modeling team
- Experienced DDT qualification process

**Today:** Data Inventory Step
**Digital Measures of Health (DMH) – What?.. How?... Why?**

**The What:**
Data (signal output) collected from a biosensor that measures a biological recognition element

**The How:**
Continuous physiological monitoring with devices (wearables/smart phones, clothing, implants/ingestibles, remote biosensors)

**The Why:**
Improve our understanding of real-time changes in FUNCTION during the progression of life in health & disease

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**Wearable Sensors**

- **DIGESTIBLE SENSORS**
  - Sensor-enabled pill that can monitor patients’ adherence to medication.

- **WEARABLE SENSORS**
  - Workout gear measures muscle exertion and tracks data.

- **GLUCOSE SENSING CONTACT LENSES**
  - Google

**THE FUTURE OF SENSORS**

1. Passive data gathering
2. Meaningful interpretation
3. Internal sensors attached to body’s organs

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**FWD Health**
Dashboard Tracks Exercise Regimes For Lowered Insurance Prices
www.fwdhealth.co
**Digital Measures of Health: Biosensor Observed Measures**

**Value in Health** 18 (2015) 741-752

Fig. 3 – Attributes of outcome assessments. A specific outcome assessment is selected or created to operationalize measurement of the concept of interest. Outcome assessments are of two major types: clinical outcome assessments and biomarkers. Clinical outcome assessments have an attribute identifying the type of person whose judgment can influence the reported measurement. Clinical outcome assessments may be influenced by the judgment of the patient, clinician, or a nonclinician observer; they may also be a nonjudged recording of a task performed by the patient (performance outcome). Clinical outcome assessments may be directly reporting the meaningful feelings or functions selected as the potential treatment benefit, or may be reporting measurements that are thought to be indirectly informative regarding those feelings or functions (see Fig. 1). Biomarkers can only indirectly measure the meaningful aspect of health.

**Biosensor Observed Measures**
- Less ‘observer specific bias’
- No need for ‘observer training’
- Potential for lower cross-site variance of measures
- Reduced clinical fees
Can biosensor measurements ‘observe’ functionally meaningful changes before accepted outcome measures?

- Pain relievers must show at least a 1 point change in NRS before being considered clinically meaningful
- Clinical trials typically will require a pain score of ≥4.0 as an inclusion criterion

The regulatory endpoint for pain in clinical trials

11 point Numerical Rating Scale (NRS)


Dr. Jeffrey Kaye
DMHs enable a paradigm shift in assessing capabilities of daily living, CDLs [aka, ‘Quality of Life’, QoL]

**SUBJECTIVE**
Current Practice
In Drug Development

Efficacy

“Activities of Daily Living”
Challenges: Patient reported, subjective, memory-dependent, non-verifiable, not used in label claims

Safety

**OBJECTIVE**
Digital Measures
In Drug Development

Efficacy

“Capabilities of Daily Living”
Objective, verifiable, patient-independent outcomes for potential use in label claims; Surrogate for QoL

Safety
“Digital Biomarkers: Sensing Life Kinetics”
- Dr. Jeffrey Kaye, Director, Oregon Center for Aging & Technology

**Every Day Cognition:**
Medication adherence as a measure of cognitive function

- Adherence assessed continuously x 5 wks with MedTracker taking a
- Mean Age - 83 yrs
- Based on ADAScog: Lower Cognition Group vs Higher Cognition Group

![Graph showing adherence](image)

- Significantly Worse Adherence in Lower Cognition Group
- Median time within 53.4 mins of goal
- Median time within 12.0 mins of goal

**Differentiation of early MCI:**
Total Activity & Walking

- Activity patterns associated with mild cognitive impairment

![Graph showing activity levels](image)

- Trajectories of walking speed over time
  - Dodge, et al., *Neurology*, 2012

**Differentiation of early MCI:**
Night-time Behavior & Sleep


![Graph showing sleep patterns](image)

**Routine home PC use over time (without formal tests or queries)** detects change in those with MCI

- Mean 1.5 hours on computer/per day at baseline month
- Over time:
  - Less use days per month
  - Less use time when in session
  - More variable in use pattern over time

![Graph showing computer use](image)

Kaye, et al., *AAIC*, 2011
Improving clinical trials through continuous data collection:

Smaller samples, more precise estimates, faster, and ecologically valid

True “Precision Medicine” with “Real World Data”

Conventional Approach

Distribution can be generated for EACH individual within short duration data accrual periods

Walking Speed Observed During the First 90 days for 2 subjects

Your walking speed ≠ my walking speed OR Your computer use ≠ my computer use

Courtesy of H. Dodge
Transforming Clinical Trials with High Frequency, Objective, Continuous Data: “Smart Data” for Each Subject

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<tr>
<th>MCI Prevention Trial – Sample Size Estimates</th>
<th>Continuous Measures</th>
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<tr>
<td>LM Delayed Recall*</td>
<td>Computer Current Method Use**</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 50% EFFECT</td>
<td>688</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 40% EFFECT</td>
<td>1076</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 30% EFFECT</td>
<td>1912</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 20% EFFECT</td>
<td>4300</td>
</tr>
</tbody>
</table>

- Reduces required sample size and/or time to identify meaningful change.
- Reduces exposure to harm (fewer needed/ fewer exposed)
- More precise estimates of the trajectory of change; allows for *intra-individual* predictions.
- Provides the opportunity to substantially improve efficiency and inform go/no-go decisions of trials. *<14% of current patient costs with standard measures.*

Modeling and Simulation as a Tool to Enhance Understanding of Dementia

Putting it all together:
High dimensional data fusion model predicting MCI

24/7 Behavioral - Activity Data:
- Computer use, time out of home, etc.

Context:
- Weather, CCI, living in a retirement community, etc.

Weekly Self-Report:
- Mood, Pain, Falls, ER visits, Visitors, etc...

Annual Clinical Assessment:
- Cognition, physical function, genetics, biomarkers, etc.

Demographics:
- Age, education, socioeconomic status, etc.

Controls:
- Number of rooms in home, etc.

Outcome
- MCI Progression Transition

Kaye, AAIC, 2015

49,992,645 observations

[Image: Diagram depicting the integration of various data sources into a model predicting MCI progression.]

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Summary

• Analyses focusing on single biomarkers will unlikely provide a comprehensive picture of their contribution to understand disease progression.

• Disease progression modeling allows for a quantitative understanding of the interplay between sources of variability (biomarkers, baseline severity, genetics, demographics, etc.).

• In order to develop such models, patient-level data are required.

• A comprehensive expansion of the CAMD CODR database can provide the foundation for such disease progression modeling analyses.

• Regulatory review and endorsement of such disease progression models as quantitative-based clinical trial enrichment platforms provide the trust for sponsors and regulators to apply these platforms as drug development tools.

• Continuous collection of Digital Measurements of Heath will enable a future that uses “Real World Evidence” to practice “Precision Medicine”. 
Goals & Desired Outcomes

- View the current landscape of approaches to use biosensor technologies to assess changes in patient function across neurodegenerative diseases with impaired cognition.
- Understand the current gaps & barriers that impede the advancement of regulatory science progress for these technology platforms.
- Prioritize which gaps & barriers that would have the highest impact across more than one disease to advance regulatory science.
- Formalize the output of the meeting by publishing a manuscript detailing the findings and recommendations of the participants.
WCoP Pre-Meeting Workshop -
Role of Pharmacometrics in Regulatory Science

**WCoP PRE-MEETING WORKSHOP**

**ROLE OF PHARMACOMETRICS IN REGULATORY SCIENCE**

Sunday, August 21, 2016 | 08:30 AM – 04:00 PM

Brisbane Convention and Exhibition Centre, Meeting Room P3

**Workshop Goals & Desired Outcomes**

- Align on the intent and objectives of pharmacometrics within the regulatory science space
- Discuss value of quantitative drug-disease-trial models as drug development platforms
- Prioritize potential novel outcome measures as endpoints to be modeled for drug-disease trial models, such as digital biomarkers