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
a decade of excellence

10 YEARS

Critical Path Institute Consortia

CRITICAL PATH INSTITUTE

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

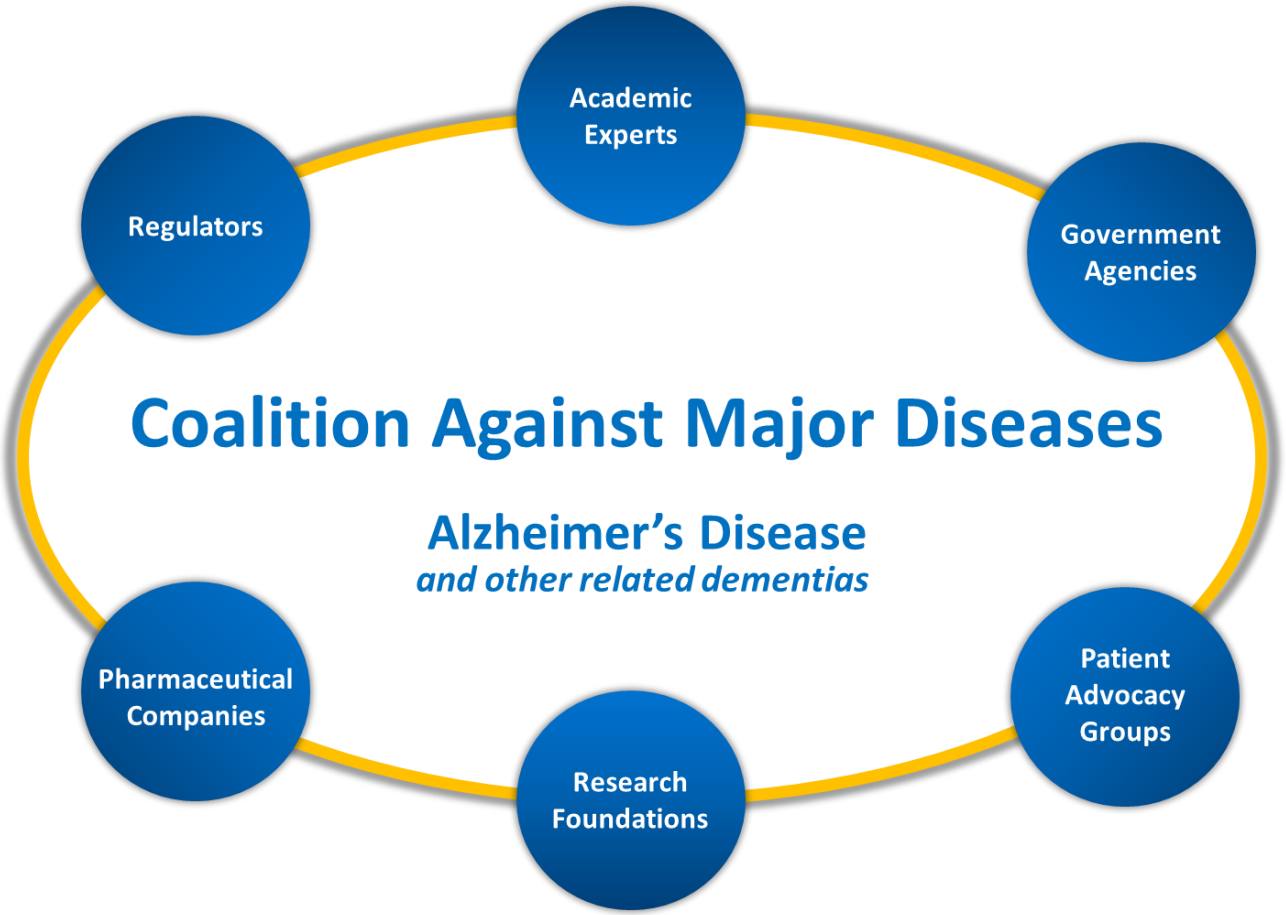
Electronic Patient-Reported Outcome Consortium
Electronic capture of treatment benefit

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 as a Consortium



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	Drug Development Tool	Feasibility[1]	Scoping[2]	Research[3]	Submitted[4]	Qualified[5]
Alzheimer's disease (AD)	Hippocampal vMRI Biomarker					
	CSF Biomarkers					
	Disease model of mild and moderate AD					
	Disease model of MCI/aMCI leading to AD					
Function & Cognition in Dementias	Digital Measures of Health in MCI leading to Dementia					

CAMD Alzheimer's Modeling Team

OBJECTIVES

Past: Develop a comprehensive clinical trial simulation tool for the mild-to-moderate stages of AD

- History; Example of use; Lessons learned

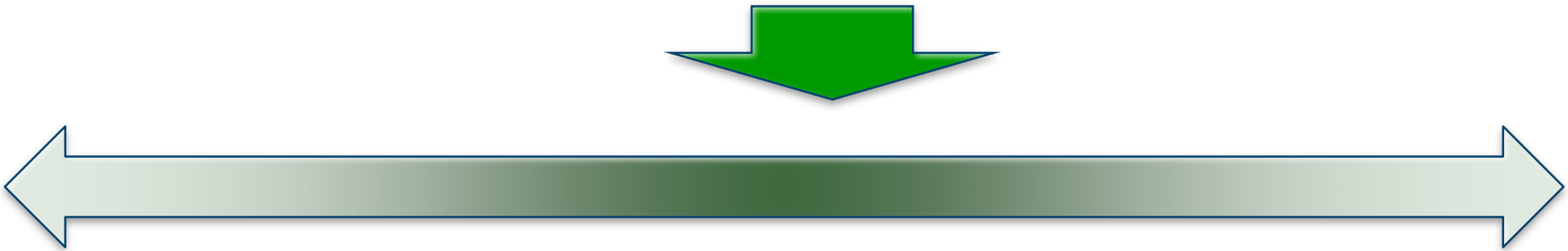
Present: To develop a quantitative understanding of MCI disease progression and apply it to enrich MCI clinical trials

- 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?

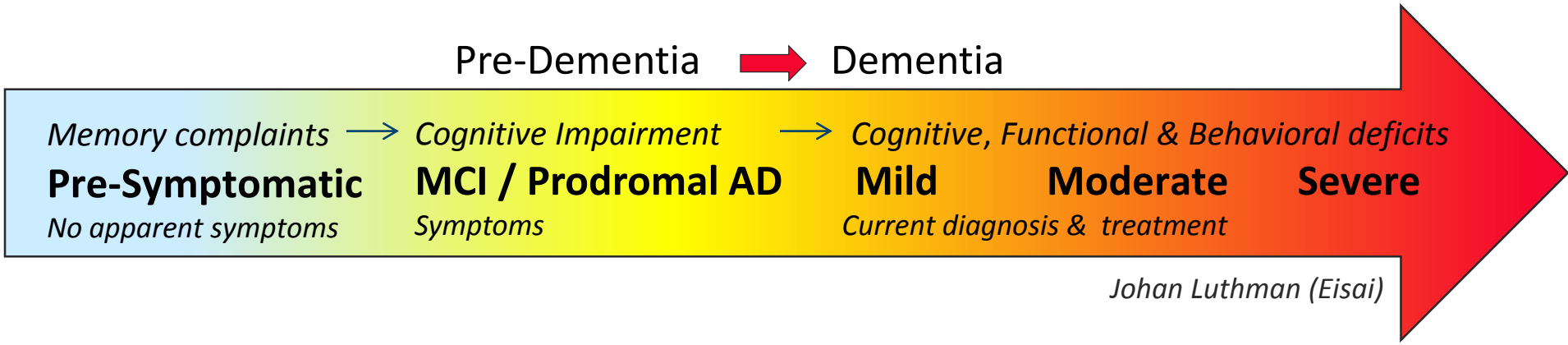
Unless different outcomes are validated, approvals will require patients to reach this stage of disease progression!



- **Current outcomes insensitive**
- **Patient enrichment is critical**

- **Current outcomes focused on aMCI to Moderate AD**

- **Current PRO outcomes unreliable**



Johan Luthman (Eisai)

Using accepted outcome measures……..

2014 CAMD Annual Meeting

- Richard Mohs (Lilly)

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

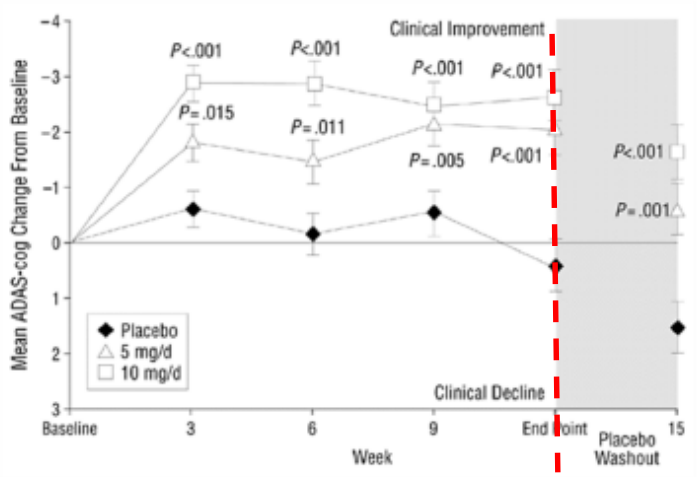


Figure Legend: Least squares mean (± SEM) change from baseline in the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized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

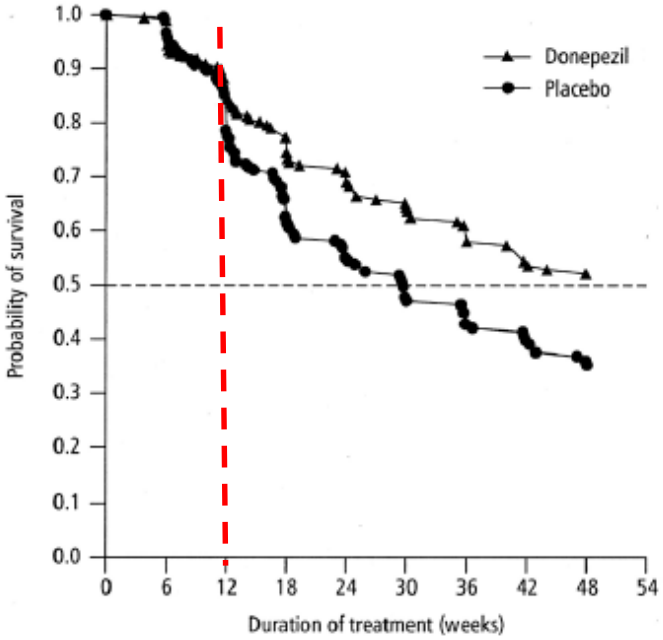


Figure 2. Kaplan–Meier survival estimates of time to clinically evident functional decline (by investigator, intent-to-treat population).

From: Rogers SL, et al. Donepezil improves cognition and global function in Alzheimer's disease. Arch Intern Med, 1998, 158:1021-1031. (Left) Mohs RC, et al. A one year, placebo-controlled preservation of function survival study of donepezil in patients with Alzheimer's disease. Neurology 2001; 57 (3): 481-488. .(Right)

Our Challenges

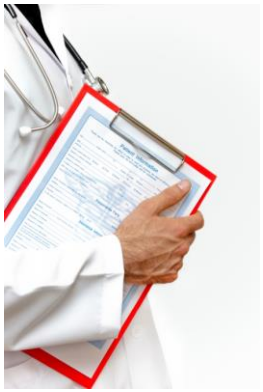
Three key challenges arise as clinical trials for dementia reach earlier into the presymptomatic disease process:

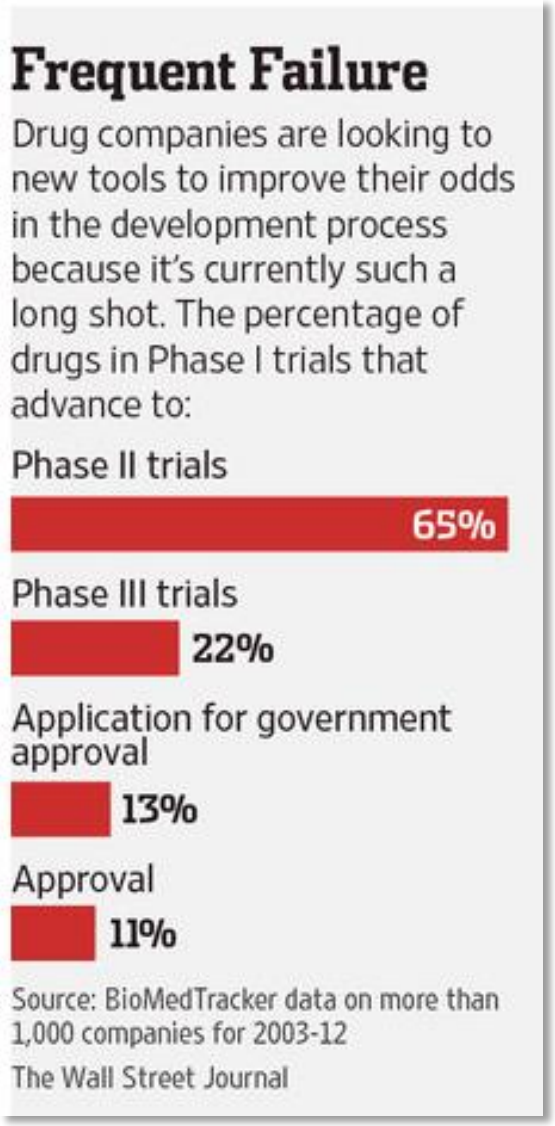
- When assessing cognitive performance over decades, how can progression be consistently evaluated over time?
- How can the tools and data be standardized across the rapidly evolving technology platforms ?
- Given that with current clinical instruments activities of daily living treatment changes cannot 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?





Well Recognized Diseases/Disorders with Co-morbid Dementia

Alzheimer's Disease

Parkinson's Disease

Autism Spectrum Disorder

Multiple Sclerosis

Frontal Lobe Dementia

Lewy Body Dementia

Dravet's Syndrome

Traumatic Brain Injury

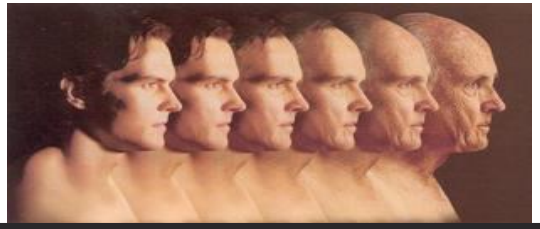
Down's Syndrome

Gaucher's Disease

Huntington's Disease

Vascular Dementia

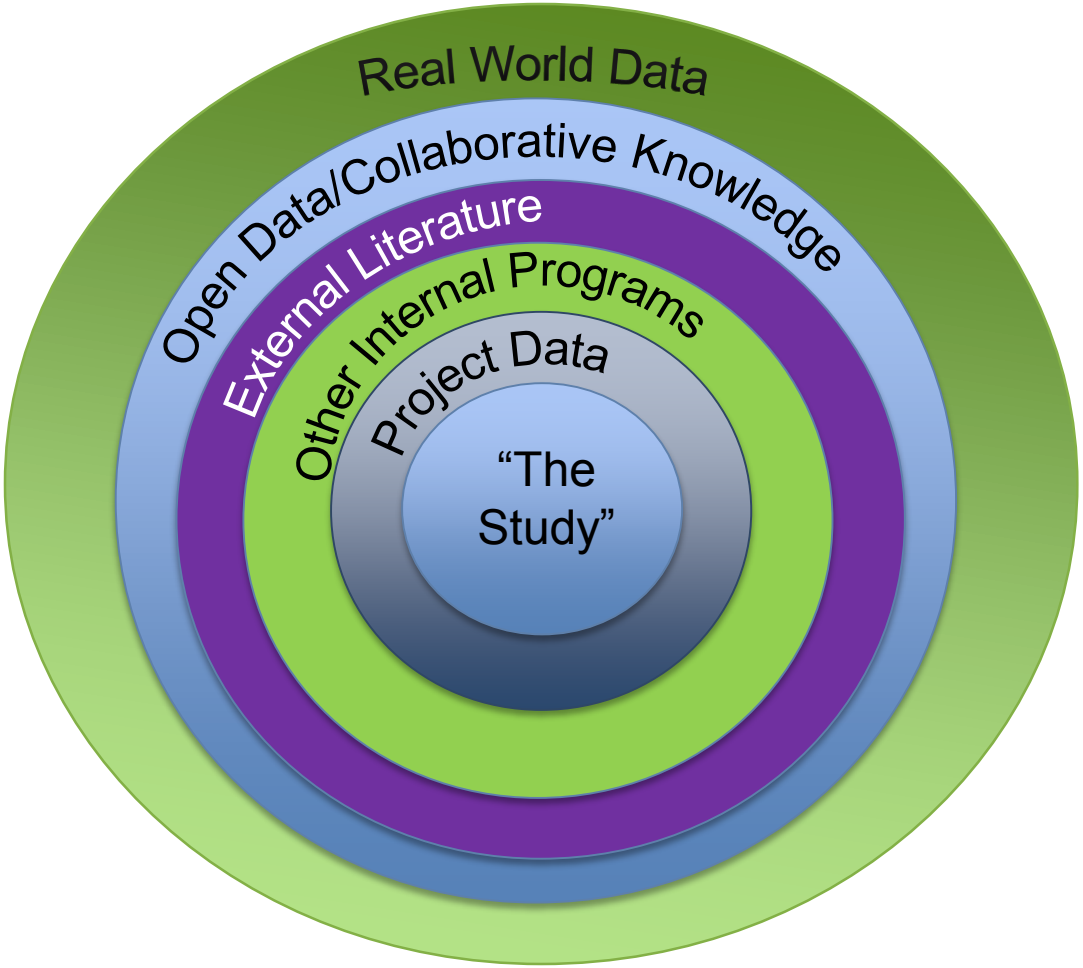
Congestive Heart Failure



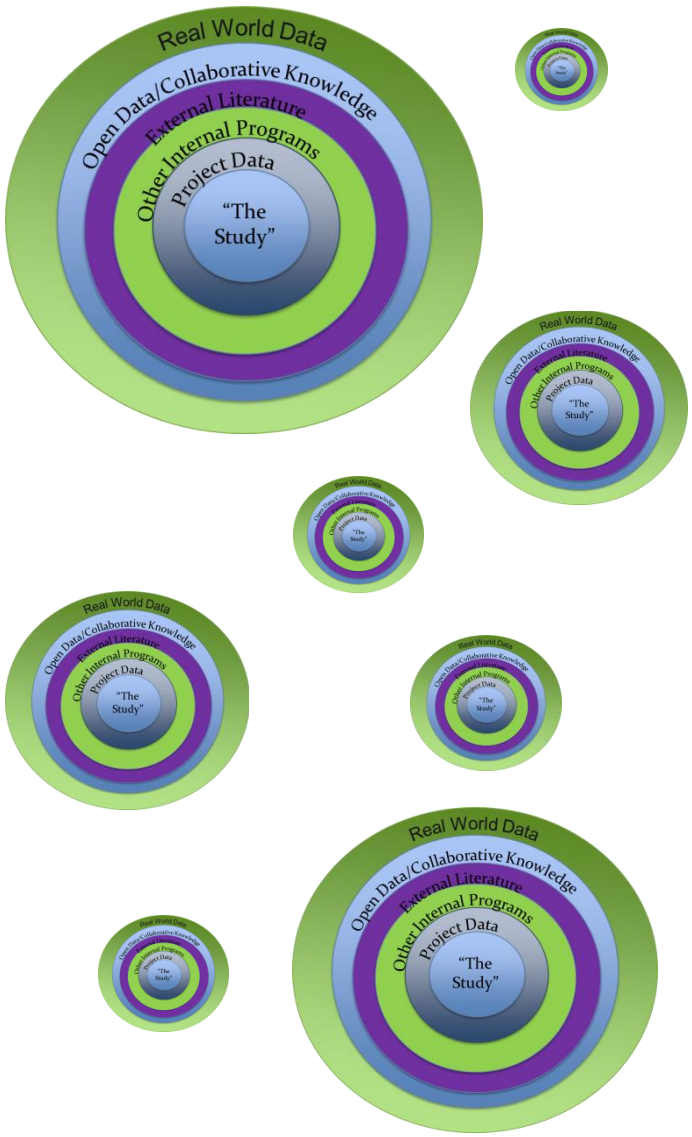
Aging

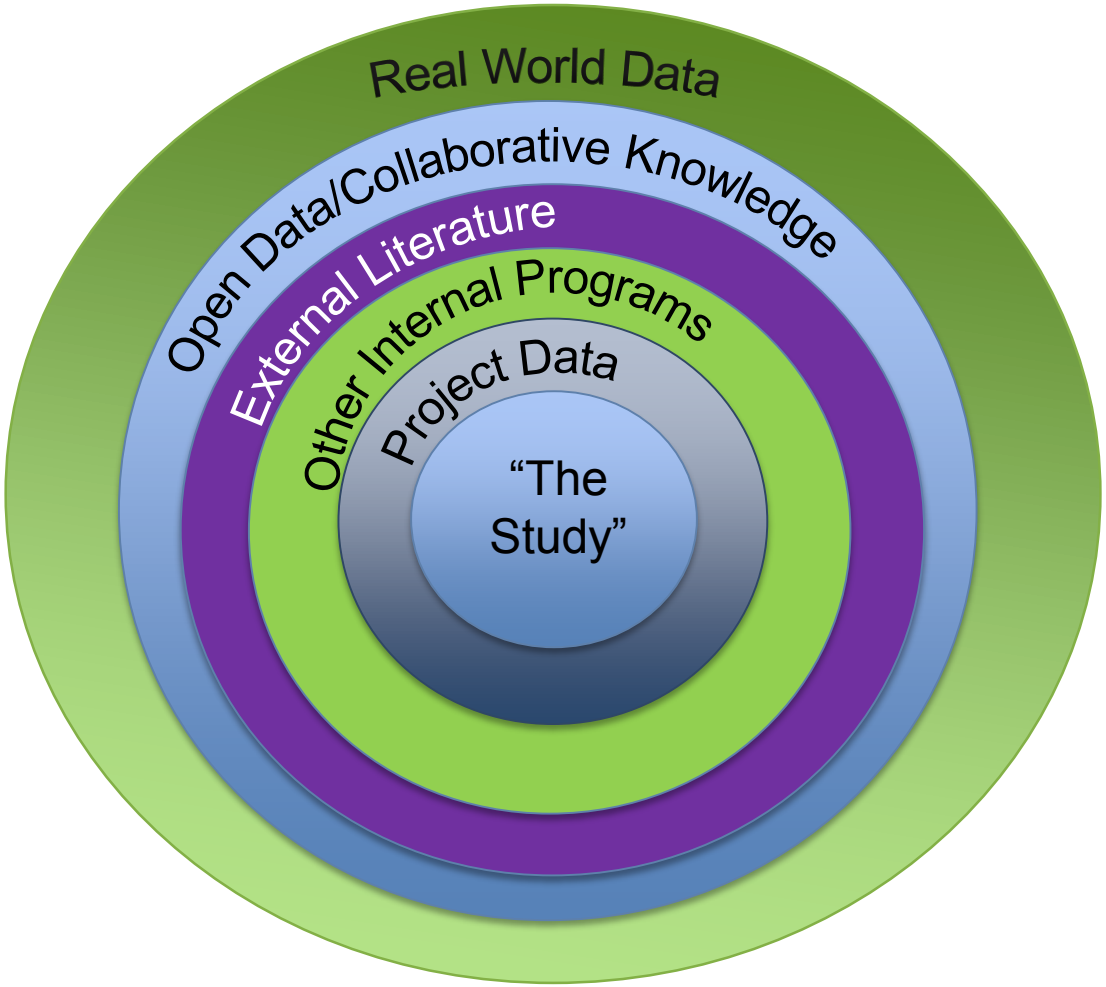
Knowledge Management:
"The Clinical Trialist's Dilemma"

- 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

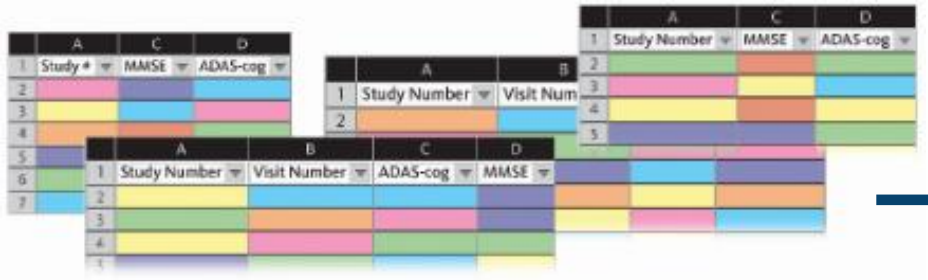
- **What it is based on:**

  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:**

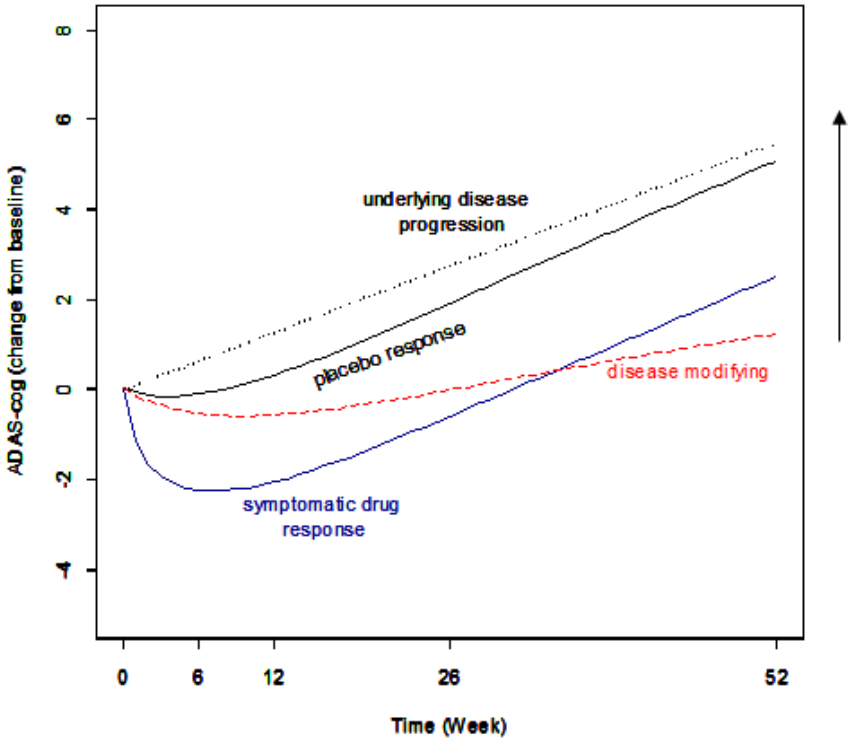
  Approve medical products without the actual execution of well conducted trials in real patients

Step 1: Data Standards



Mixed Disparate Legacy Data

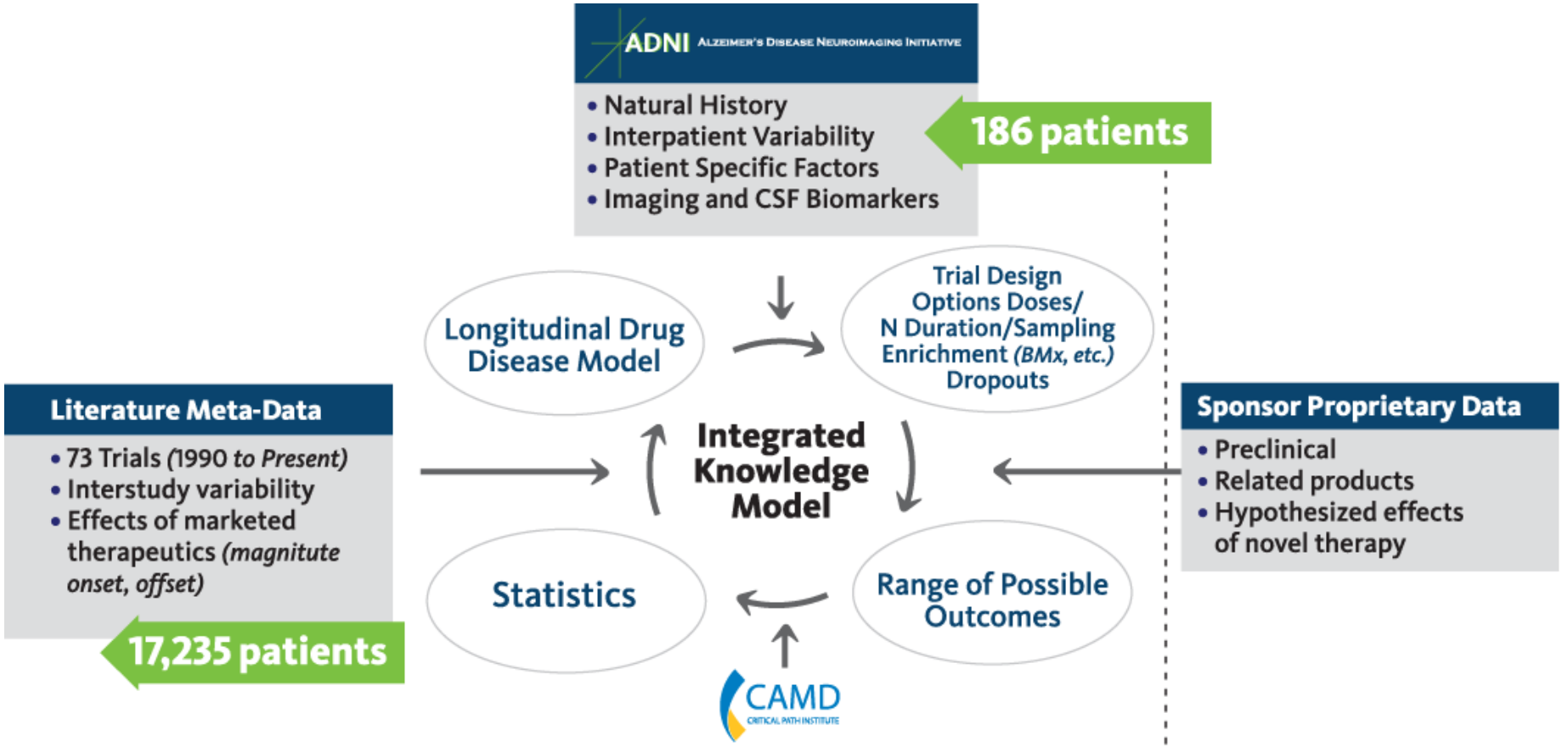
CDISC
'Standardized Data'



Integrated Data

Romero K., et al. Striving for an integrated drug development process for neurodegeneration: The Coalition Against Major Diseases. Neurodegen. Dis. Manage. 2011;1(5): 379-85.

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

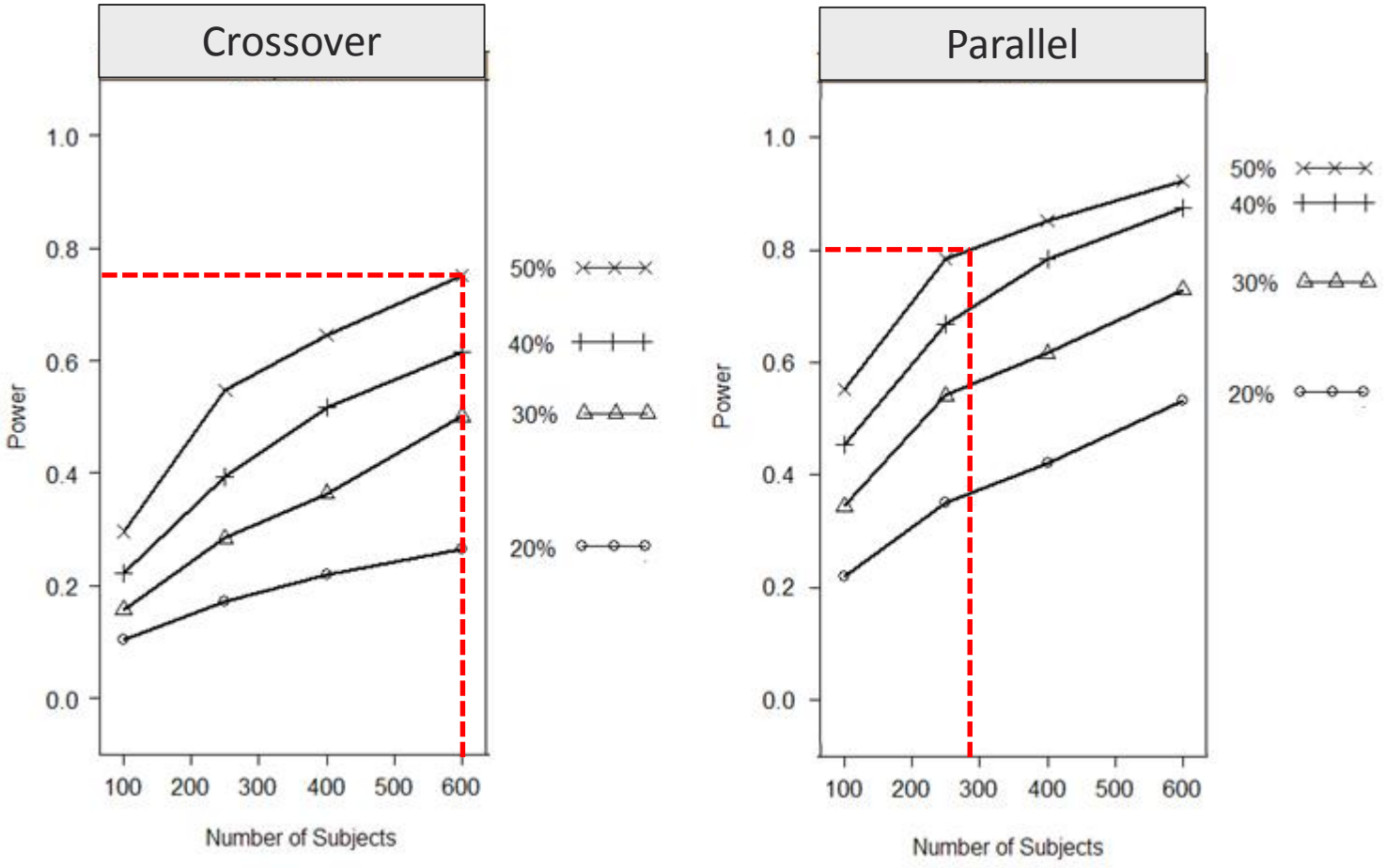
Step 4 (use): Balancing power, sample size and duration, given varying effect magnitudes

91 week crossover

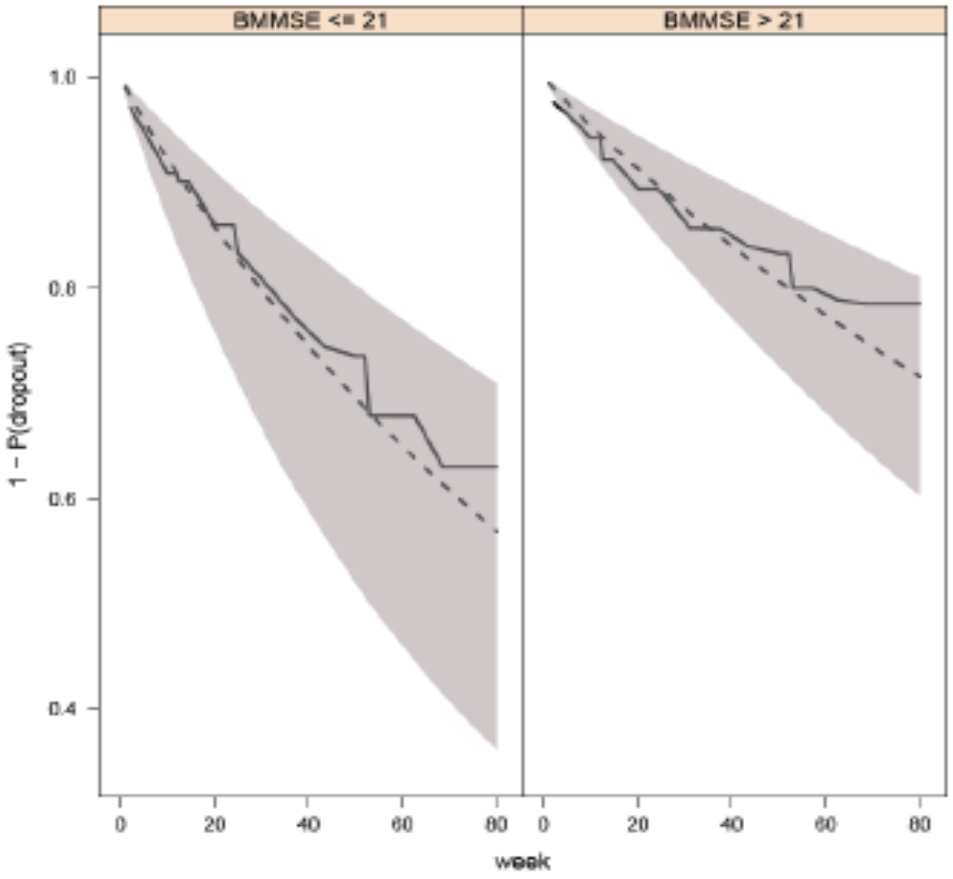
versus

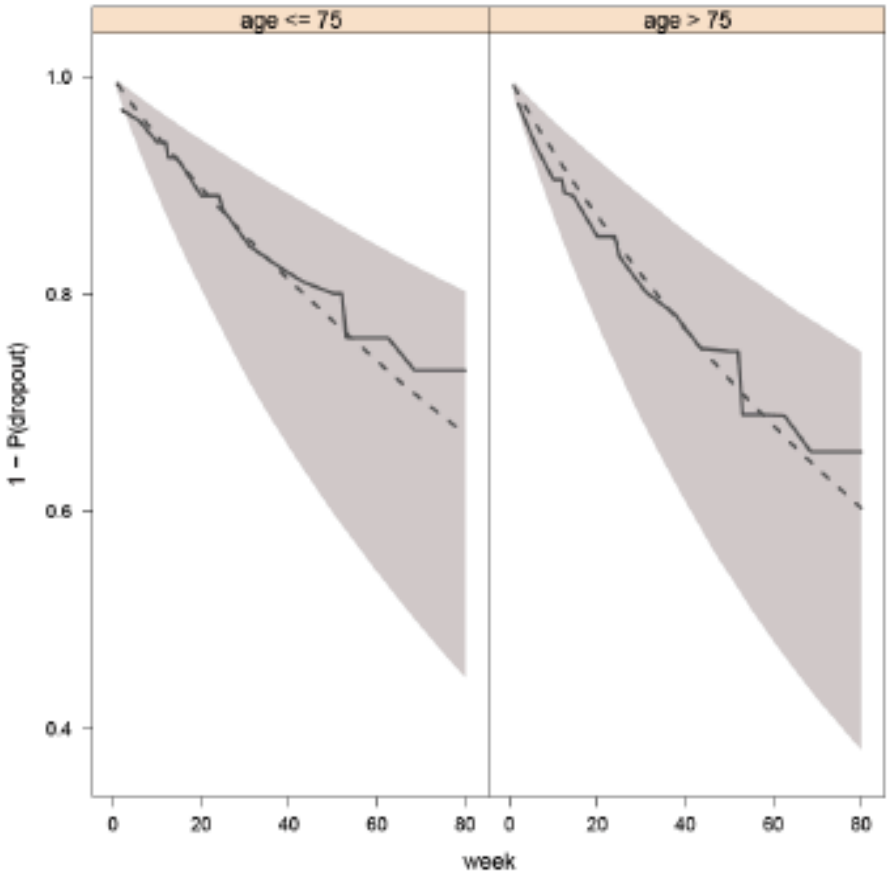
78 week parallel

by effect magnitude



Step 5 (use): Evolving dropout likelihood by baseline age and severity

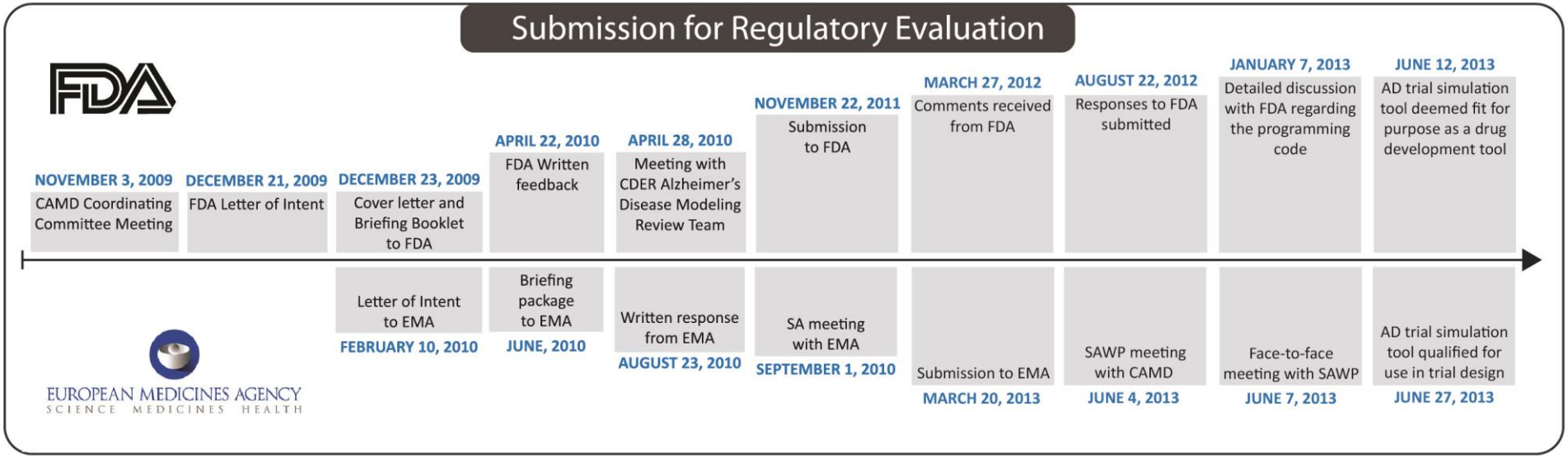




AD Drug Disease Trial Model - The Regulatory Path

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 The London School of Economics and Political Science
Imperial College London
UF University of Florida
Manchester 1824 The University of Manchester
Penn University of Pennsylvania
USC University of Southern California

...and others

Requests to Access CAMD's AD Database

CAMD'S ALZHEIMER'S DISEASE 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

Amherst College
Duke University School of Medicine
Emory University
Goethe Universität Frankfurt am Main
Harvard Medical School
Georgetown University Georgetown University Medical Center
Johns Hopkins University
Seoul National University
University of Aberdeen
The University of Auckland
University of Cape Town
Universitäts Klinikum Freiburg
...and others

CAMD has joined GAAIN

2016 – Understanding of Disease Progression in MCI

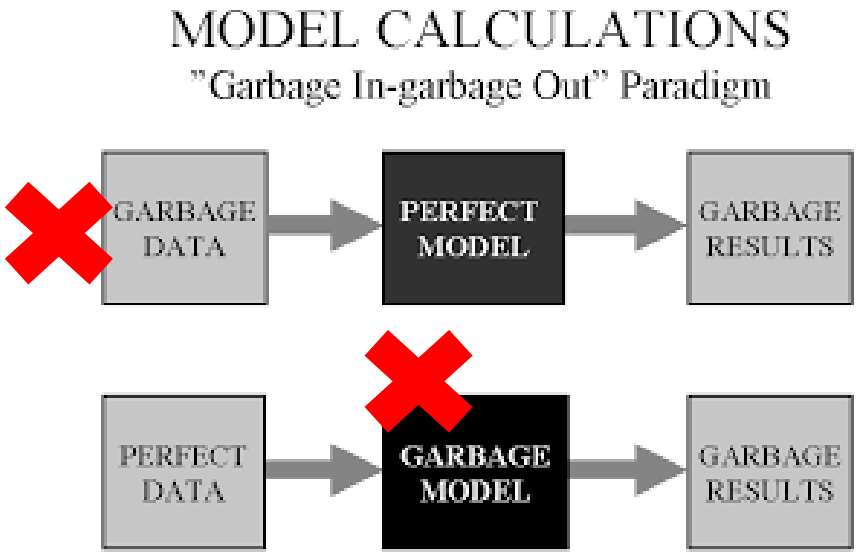
Three key challenges arise as clinical trials for dementia reach earlier towards the presymptomatic disease process:

- 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.

2016 CAMD Modeling & Simulation Team

Klaus Romero , Steve Arnerić, Volker Kern (C-Path)
Maria Isaac (EMA)
Vikram Sinha (FDA)
Yaning Wang (FDA)
Mahesh Samtani (Janssen R&D)
Sandra Allerheiligen (Merck)
Julie Stone (Merck)
Richard Meibach (Novartis)
Suzanne Hendrix (Pentara Corporation)
Brian Corrigan (Pfizer)
Kaori Ito (Pfizer)
Tim Nicholas (Pfizer)

Developing a Comprehensive MCI Database (endpoints, covariate data) is a Critical Step for Success



Experienced CDISC database programmer

Experienced DDT qualification process

Database → Model → Qualification

Experienced modeling team

Today: Data Inventory Step

Digital Measures of Health (DMH) – What?.. How?... Why?

The What:

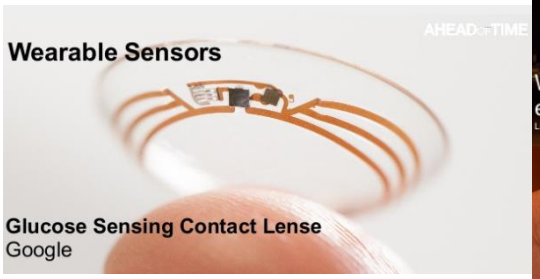
Data (signal output) collected from a biosensor that measures a biological recognition element

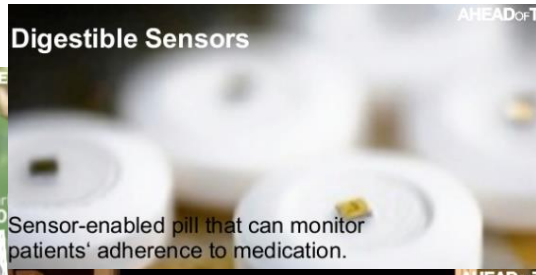
The How:

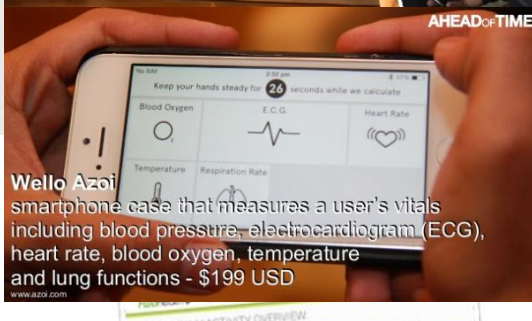
Continuous physiological monitoring with devices (wearables/smart phones, clothing, implants/ingestibles, remote biosensors)

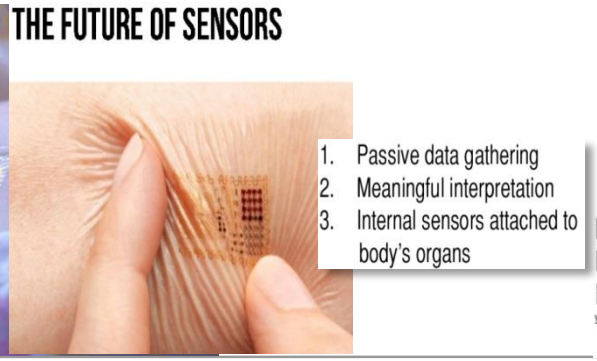
The Why:

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



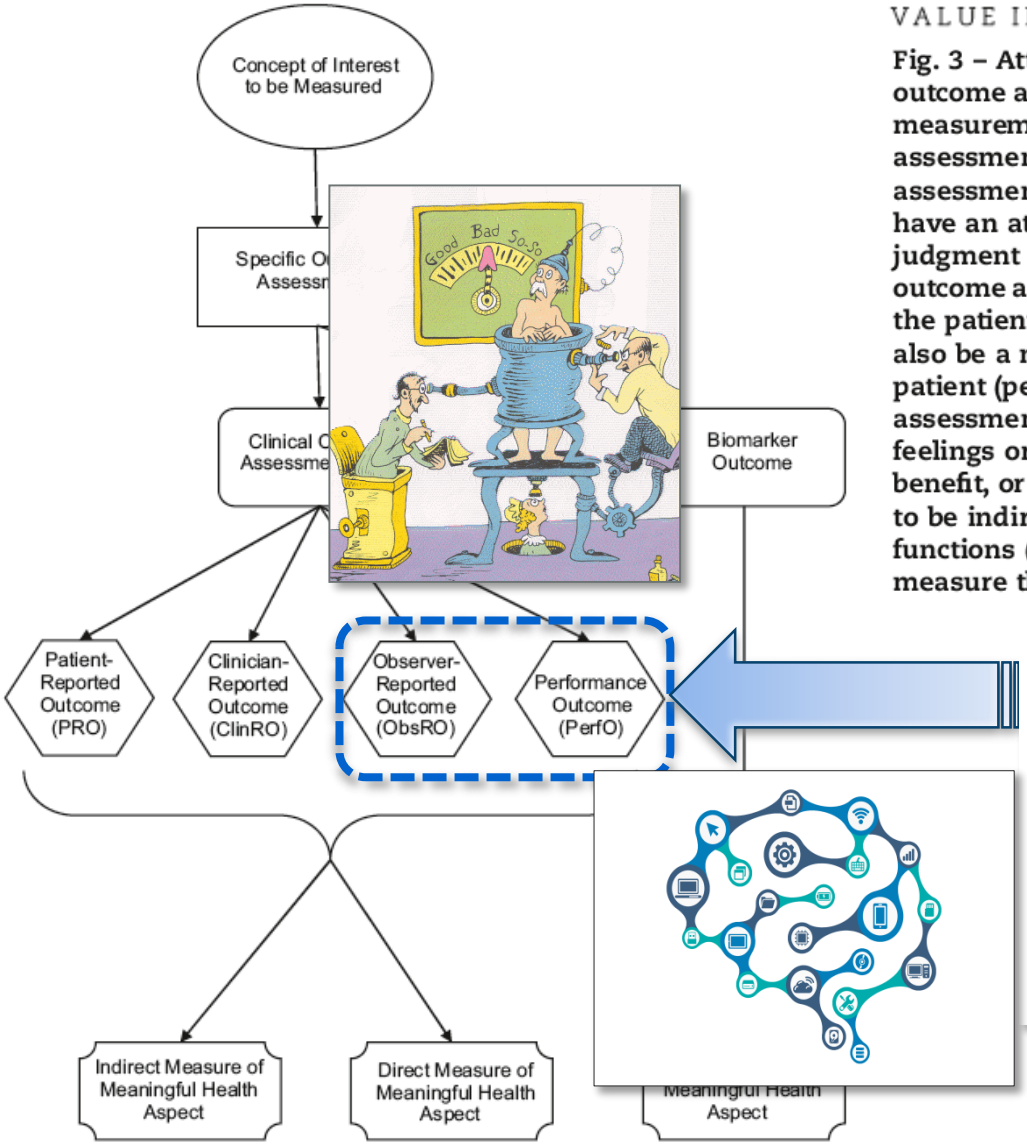






FWD Health
Dashboard Tracks Exercise Regimes For Lowered Insurance Prices
www.fwdhealth.co

Digital Measures of Health:
Biosensor Observed Measures



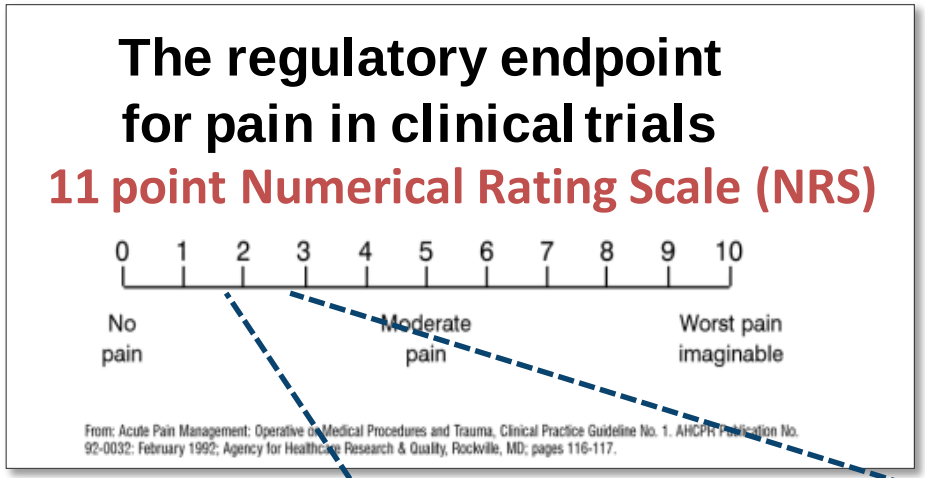
VALUE IN HEALTH 18 (2015) 741–752

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.

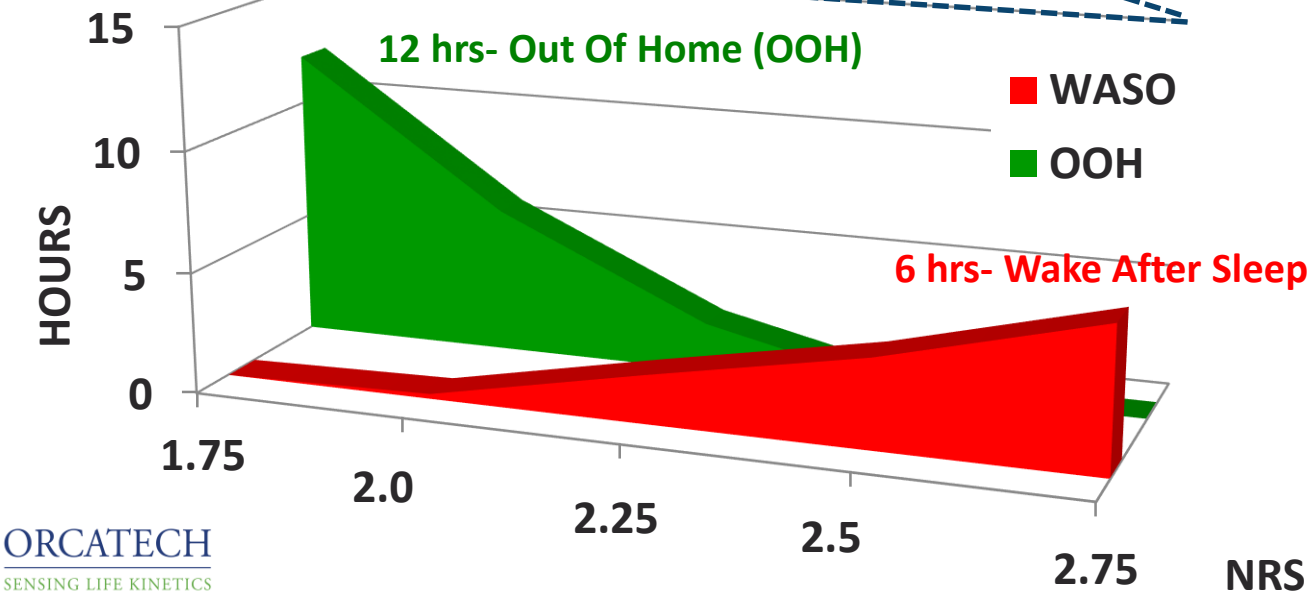
Biosensor Observed Measures

- 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



N=96
Age ≥ 65 yrs.

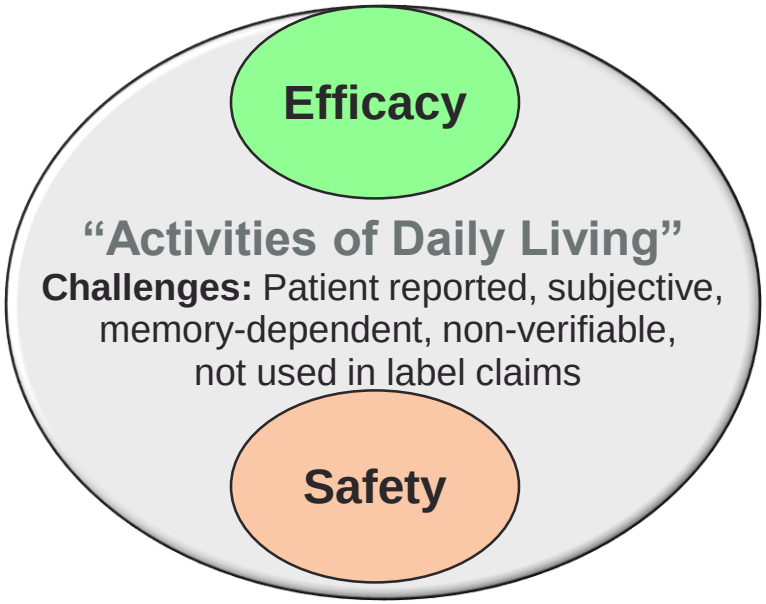
Dr. Jeffrey Kaye

DMHs enable a paradigm shift in assessing capabilities of daily living, CDLs [aka, 'Quality of Life', QoL]

SUBJECTIVE

Current Practice

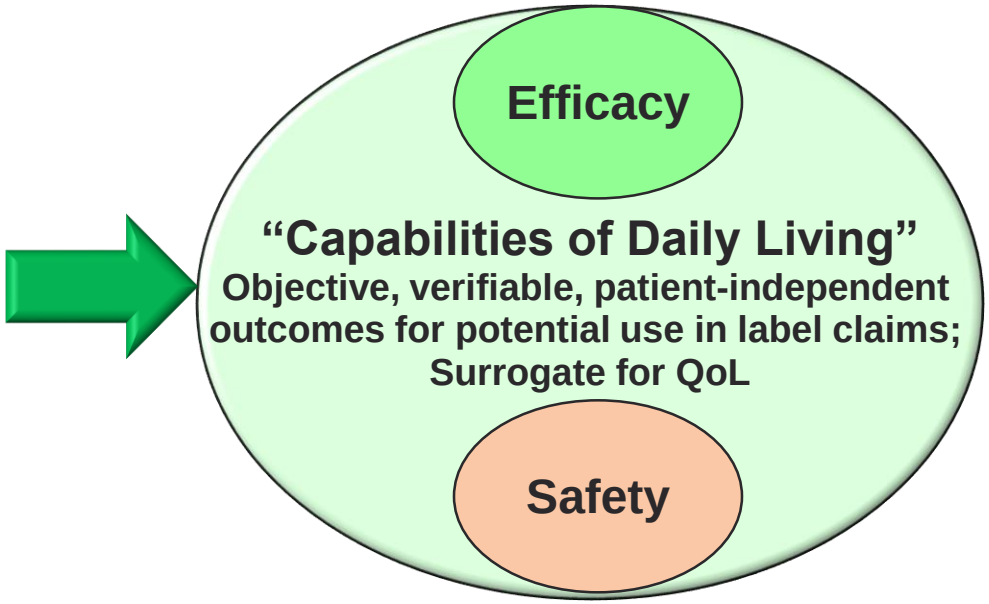
In Drug Development



OBJECTIVE

Digital Measures

In Drug Development



"Digital Biomarkers: Sensing Life Kinetics"

- Dr. Jeffrey Kaye, Director, Oregon Center for Aging & Technology

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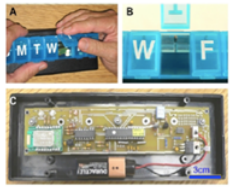
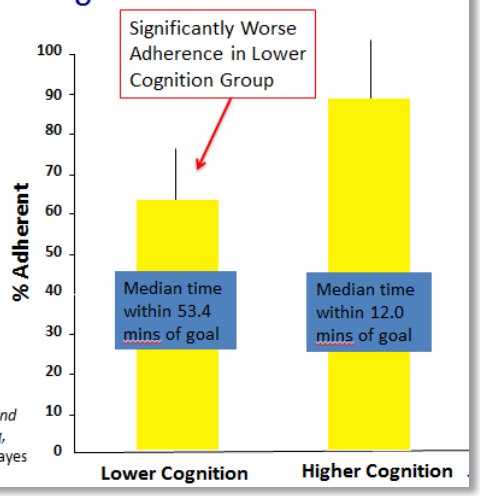
Every Day Cognition:
Medication adherence as a measure of cognitive function

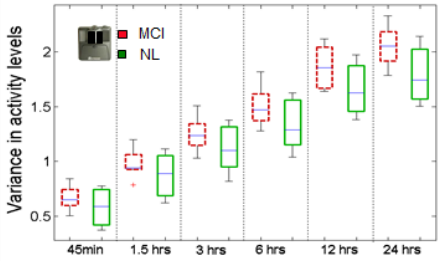


- Adherence assessed continuously x 5 wks with MedTracker taking a
- Mean Age - 83 yrs
- Based on ADAScog: Lower Cognition Group vs Higher Cognition Group

Hayes et al., *Proceedings : Engineering in Medicine and Biology Soc*, 2006; Leen, et al., *Technology and Aging*, 2007 ; Hayes et al. *Journal of Aging Health*, 2009; Hayes et al. *Telemedicine Jounal and E-Health*, 2009



Differentiation of early MCI: Total Activity & Walking



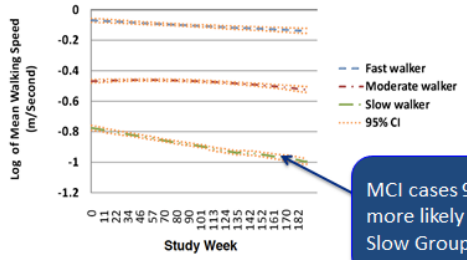
Activity patterns associated with mild cognitive impairment

Hayes et al. Alzheimers Dement, 2008

Trajectories of walking speed over time

Dodge, et al. Neurology, 2012

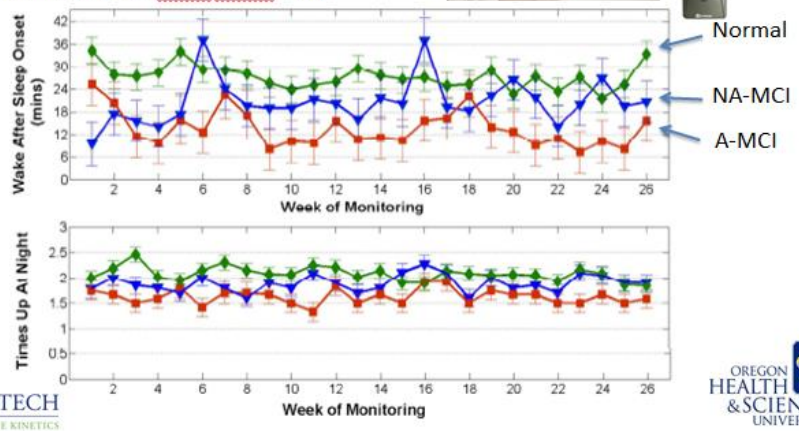
ORCATECH SENSING LIFE KINETICS



MCI cases 9X more likely in Slow Group

Differentiation of early MCI:
Night-time Behavior & Sleep

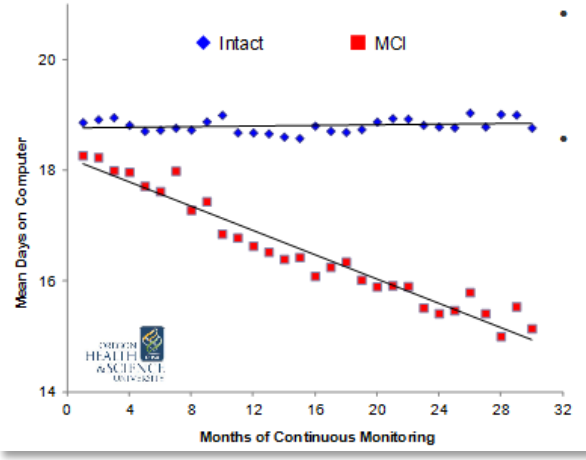
Hayes, et al. Alzheimer Dis Assoc Disord. 2014



ORCATECH SENSING LIFE KINETICS

OREGON HEALTH & SCIENCE UNIVERSITY

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*

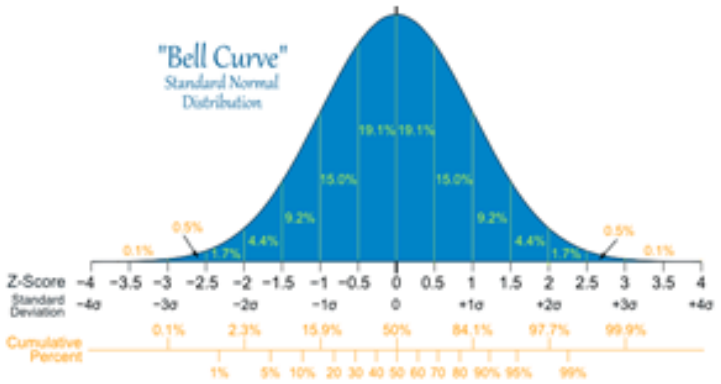
Kaye, et al. AAIC, 2011

Improving clinical trials
through continuous data collection:

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

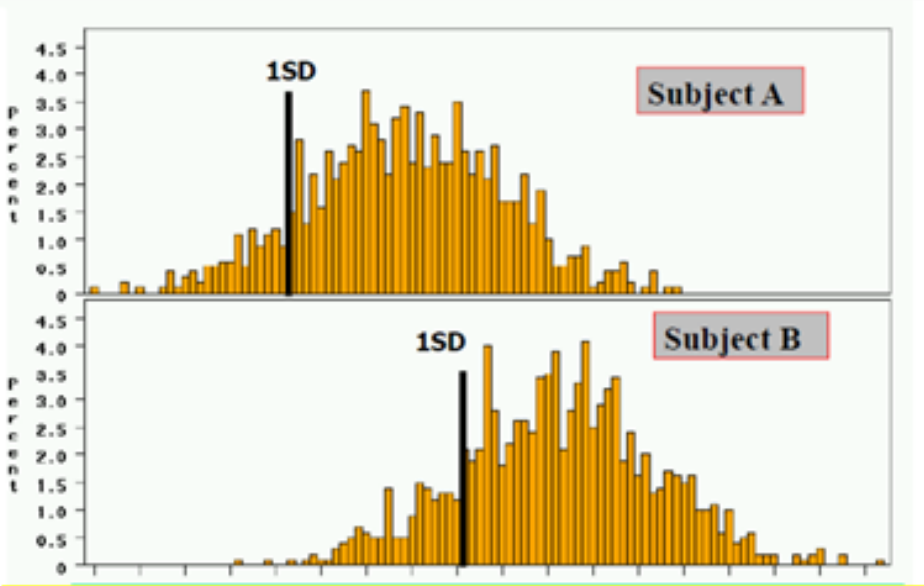
True "Precision Medicine" with "Real World Data"

Conventional Approach



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

Continuously Monitored Approach



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

ORCATECH SENSING LIFE KINETICS

MCI Prevention Trial – Sample Size Estimates

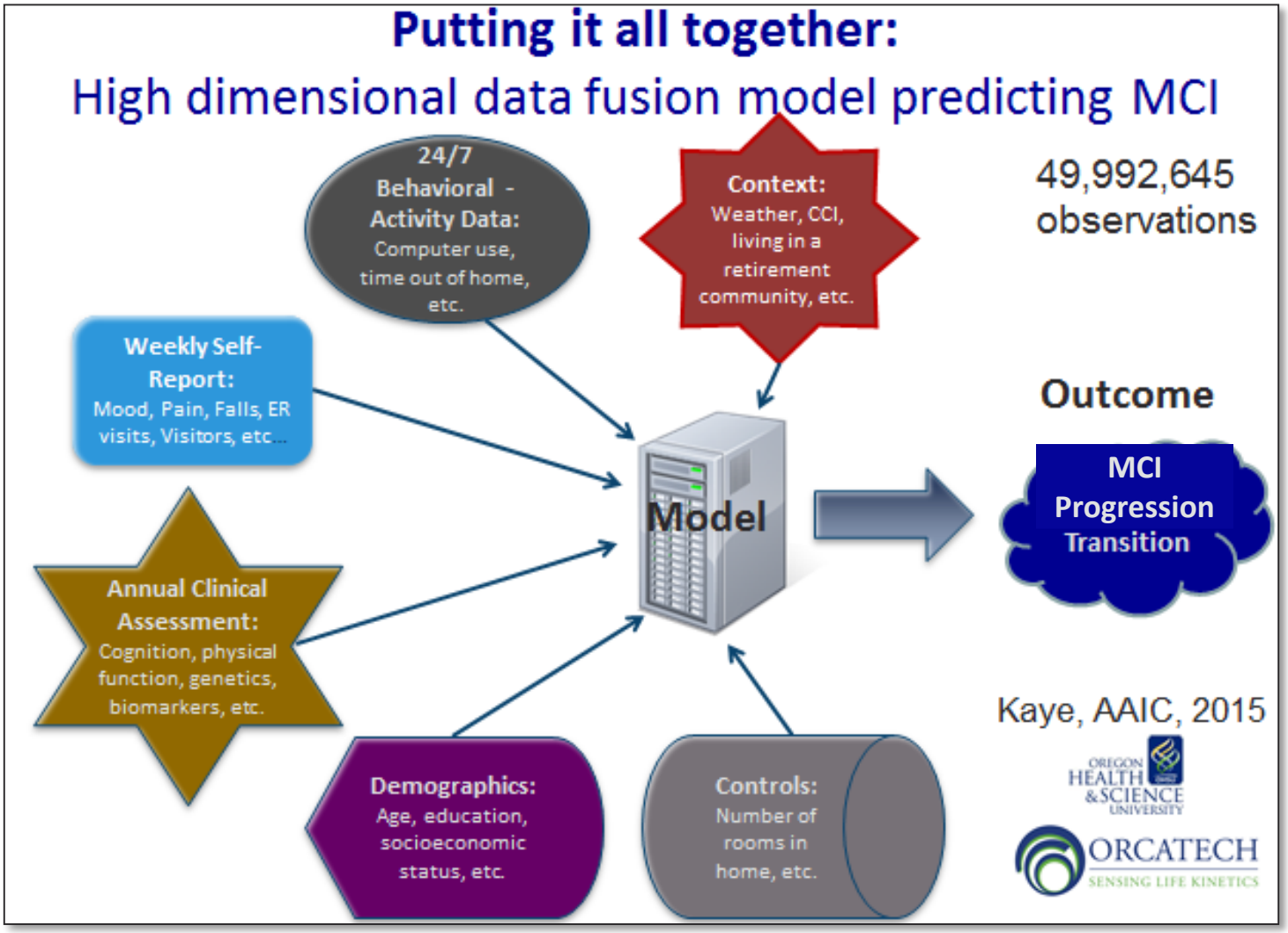
		Continuous Measures	
	LM Delayed Recall*	Computer Current Method Use**	Walking Speed**
SAMPLE SIZE TO SHOW **50% EFFECT**	688	10 [1.5%]	94 [13.7%]
SAMPLE SIZE TO SHOW **40% EFFECT**	1076	16 [1.5%]	148 [13.7%]
SAMPLE SIZE TO SHOW **30% EFFECT**	1912	26 [1.4%]	262 [13.7%]
SAMPLE SIZE TO SHOW **20% EFFECT**	4300	58 [1.4%]	588 [13.7%]

- 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.**

Dodge, et al., PLoS One, 2015

Modeling and Simulation as a Tool to Enhance Understanding of Dementia



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”.

FYI…

DIGITAL BIOMARKERS CONFERENCE

Use of Biosensors in Clinical Trials: Barriers & Solutions to the Current Landscape

March 31 and April 1, 2016

Bethesda North Marriott Conference Center

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

Thank You

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