Critical Path Institute

Accelerating drug development for Alzheimer's Disease through regulatory science

Martha A. Brumfield, PhD
President and CEO

Critical Path Institute Consortia

CRITICAL PATH INSTITUTE

Seven global consortia collaborating with 1300+ scientists and 60+ companies

CAMD CRITICAL PATH INSTITUTE	Coalition Against Major Diseases **UNDERSTANDING DISEASES OF THE BRAIN**
CPTR	Critical Path to TB Drug Regimens **TESTING DRUG COMBINATIONS**
CRITICAL PATH INSTITUTE MS National Multiple Sclerosis Society	Multiple Sclerosis Outcome Assessments Consortium **DRUG EFFECTIVENESS IN MS**
PKD CONSORTIUM CRITICAL PATH INSTITUTE	Polycystic Kidney Disease Consortium **NEW IMAGING BIOMARKERS**
PRO CONSORTIUM CRITICAL PATH INSTITUTE	Patient-Reported Outcome Consortium **DRUG EFFECTIVENESS**
ePRO CONSORTIUM CRITICAL PATH INSTITUTE	Electronic Patient-Reported Outcome Consortium **DRUG EFFECTIVENESS**
PSTC CRITICAL PATH INSTITUTE	Predictive Safety Testing Consortium **DRUG SAFETY**

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FDA

- ✓ Biomarkers
- ✓ Clinical Outcome Assessment Instruments
- ✓ Clinical Trial Simulation Tools
- ✓ Data Standards

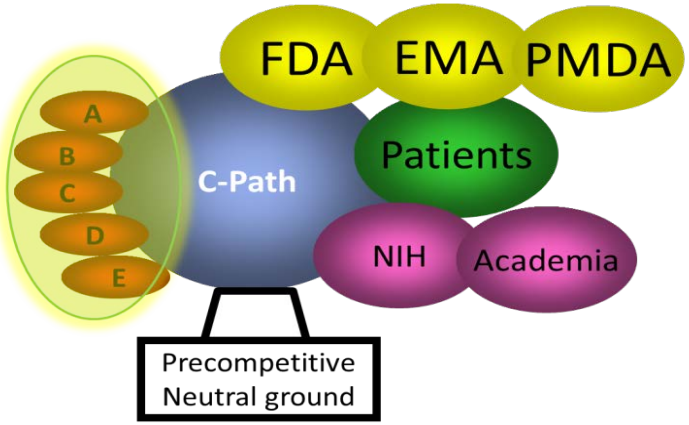
CDISC

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

C-Path's Role in Advancing Public Private Partnerships

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FOCUS ON U.S. DRUG DEVELOPMENT CONSORTIA

The driving role of consortia on the critical path to innovative therapies

Janet Woodcock, Martha Brumfield, Dalvir Gill and Elias Zerhouni

The Critical Path Institute: transforming competitors into collaborators

Martha Brumfield

The Critical Path Institute brings scientists from regulatory agencies, industry and academia together to improve drug development and regulatory processes.

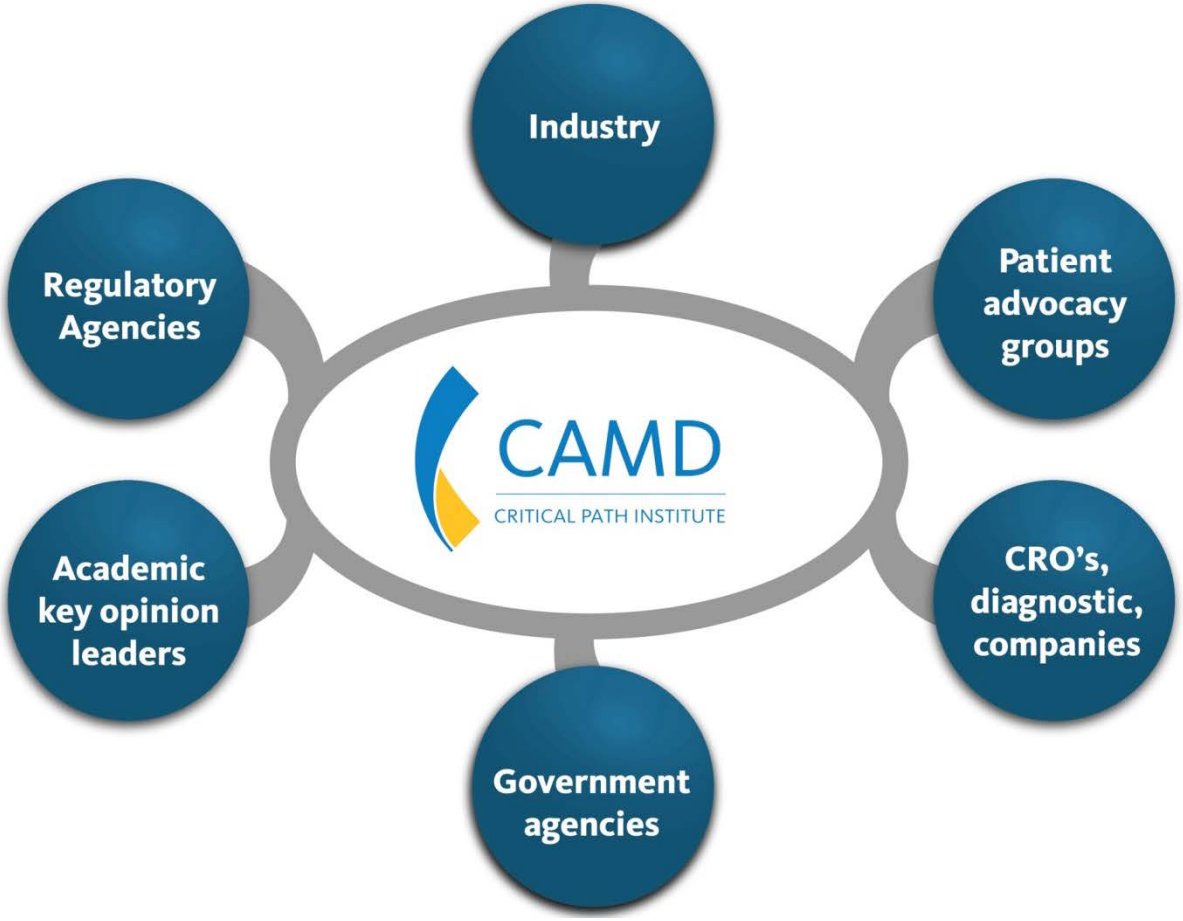
The Predictive Safety Testing Consortium and the Coalition Against Major Diseases

Diane Stephenson and John-Michael Sauer

The Predictive Safety Testing Consortium and the Coalition Against Major Diseases, both launched by the Critical Path Institute, provide valuable examples of the outcomes and lessons learned by different types of consortia working on new drug development tools.

CAMD's Mission

Critical Path Institute's Coalition Against Major Diseases (CAMD) accelerates the development of therapies for Alzheimer's and Parkinson's diseases by generating the best methods and tools for evaluating drug efficacy, expediting clinical trials, and streamlining review by regulatory agencies.



Alzheimer's Disease: the High Unmet Need for New Therapies

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Problem	Gap	CAMD Approach
High risk and increasing cost for AD drug development	Huge uncertainty in design of clinical trials	Regulatory endorsed clinical trial simulation tool
Lack of biomarkers for decision making	Highly variable subpopulations recruited into randomized clinical trials	Regulatory biomarker qualification for enrichment in randomized clinical trials
No effective therapy for modifying disease progression	Inadequate outcome measures for assessing efficacy of drugs in predementia stages	Innovative/sensitive clinical outcome assessment for efficacy of novel drug candidates

CAMD AD HV EMA Qualification Opinion

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 November 2011
EMA/CHMP/SAWP/809208/2011
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion of low hippocampal volume (atrophy) by MRI for use in regulatory clinical trials - in pre-dementia stage of Alzheimer's disease

ELSEVIER

Alzheimer's & Dementia 10 (2014) 421–429

Alzheimer's & Dementia

Featured Articles

Coalition Against Major Diseases/European Medicines Agency biomarker qualification of hippocampal volume for enrichment of clinical trials in predementia stages of Alzheimer's disease

Derek L. G. Hill[a], Adam J. Schwarz[b], Maria Isaac[c], Luca Pani[c], Spiros Vamvakas[c], Robert Hemmings[c], Maria C. Carrillo[d], Peng Yu[b], Jia Sun[b,e], Laurel Beckett[f], Marina Boccardi[g], James Brewer[h], Martha Brumfield[i], Marc Cantillon[j], Patricia E. Cole[b], Nick Fox[k], Giovanni B. Frisoni[g], Clifford Jack[l], Thomas Kelleher[m], Feng Luo[m], Gerald Novak[n], Paul Maguire[o], Richard Meibach[p], Patricia Patterson[q], Lisa Bain[r], Cristina Sampaio[s], David Raunig[t], Holly Soares[m], Joyce Suhy[u], Huanli Wang[f], Robin Wolz[a,v], Diane Stephenson[i,*]

Modeling Depends on Data!

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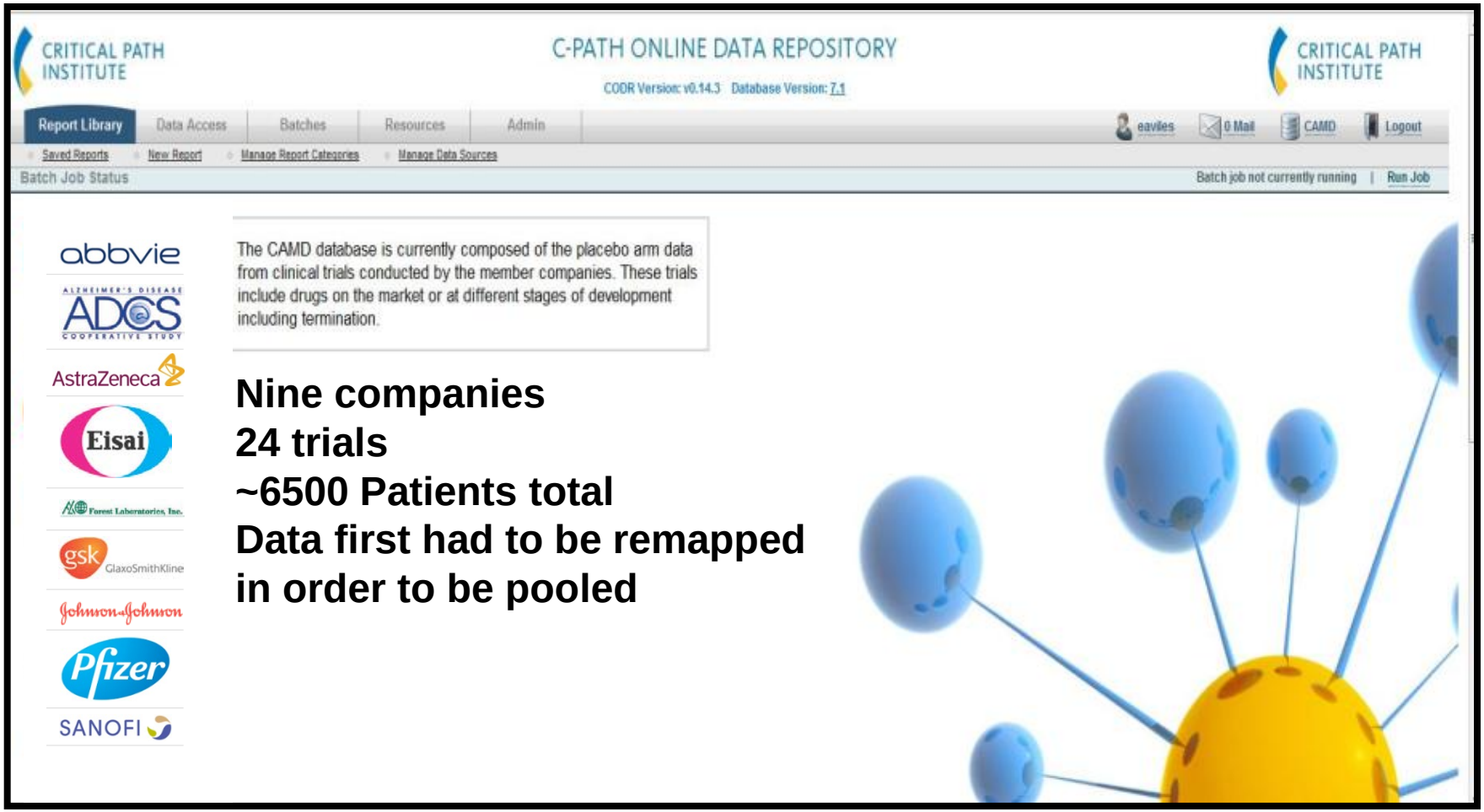

Value of Data Sharing, Standards, and Pooling

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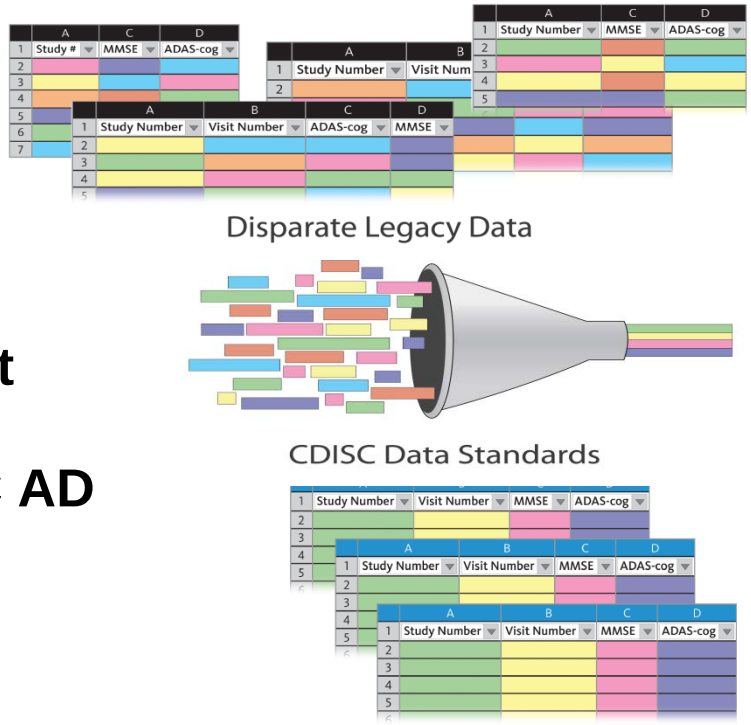
Start Point

- Nine member companies agreed to share data from 24 Alzheimer's disease (AD) trials
- The data were not in a common format
- The data were remapped to the CDISC AD standard and pooled



Result

- A new clinical trial simulation tool was created and has been the first model endorsed by the FDA and EMA
- Researchers utilizing database to advance our understanding of AD

CAMD Alzheimer's Disease Modeling Decisions--2013

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

June 12, 2013

Diane Stephenson, PhD
Executive Director, Coalition Against Major Diseases
Critical Path Institute

Dear Dr. Stephenson:

Please refer to your submission, provided on behalf of the Coalition Against Major Diseases (CAMD), which contains a package intended to support the utility of a trial simulation tool for planning certain clinical trials involving patients with mild to moderate dementia of the Alzheimer's type.

We have completed our review of your submission and have determined it is fit-for-purpose in the contexts, and with the caveats and constraints, outlined in this letter.

Goal and Intended Applications
The goal of the proposed simulation tool is to serve as a public resource for sponsors designing trials of new therapies for Alzheimer's disease (AD). CAMD intends that this simulation tool will provide quantitative support in the design and planning of clinical trials involving subjects with mild to moderate AD. The submission further suggests that the proposed tool could be used during all clinical stages of AD drug development, including proof-of-concept, dose-ranging, and confirmatory trial design and could encompass various types of treatment mechanisms (e.g. symptomatic and disease-modifying).

The submission outlines several intended applications of the proposed tool:

- Sample size calculations
- Determination of optimal trial durations and treatment effect measurement times
- Comparison of the sensitivity of competing trial designs to assumptions about the types of expected treatment effects (time to maximal effect, effects that increase or decrease over time)
- Determination of the most appropriate data analytic methods for novel trial designs

FDA Assessment
Quantitative disease-drug-trial models are potentially useful tools to represent the time course of clinical outcomes, placebo effects, drug pharmacologic effects and trial execution characteristics. The CAMD quantitative AD model was developed based on patient-level and summary data to support the design of future drug development studies in patients with mild to moderate AD. Different data resources (e.g., derived from literature, the AD Neuroimaging Initiative (ADNI), and CAMD database) were used to build up the current model and describe longitudinal changes in ADAS-Cog.

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12 July 2013
EMA/CHMP/SAWP/420174/2013
Human Medicines Development and Evaluation

Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease

Draft agreed by Scientific Advice Working Party	6 June 2013
Adopted by CHMP for release for consultation	27 June 2013[1]
Start of public consultation	19 July 2013[2]
End of consultation (deadline for comments)	27 August 2013[3]

Comments should be provided using this template. The completed comments form should be sent to Qualification@ema.europa.eu

Keywords	Qualification opinion, model of disease progression, mild and moderate Alzheimer's disease

[1] Last day of relevant Committee meeting.
[2] Date of publication on the EMA public website.
[3] Last day of the month concerned.

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An agency of the European Union

FDA fit-for-purpose decision on CAMD CTS tool. 2013
EMA qualification opinion on CAMD CTS tool. 2013

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Challenges in Outcome Measures for AD:

Measurement Aspects

- Excessive measurement variability
- Lack of sensitivity to change
- Site training inadequacies
- Challenges of very mildly affected patients
  - Functional measures less appropriate
- Disease-modification without improvement above baseline

Dr. Jeff Cummings
Cleveland Clinic

Pre-dementia Clinical Outcome Assessment (pCOA) Tool Project

Objective:
Advance through a formal regulatory path a composite clinical outcome assessment tool as a primary outcome measure for pre-dementia AD trials

Impact:
Regulatory accepted/qualified clinical outcome measure to be applied across targets and industry stakeholders

Members:
Alzheimer's Association, Boehringer Ingelheim, Merck, Takeda, Biogen Idec, Janssen, Eisai, Lilly, EMA, FDA

pCOA Path Aligns with Regulatory Recommendations

Guidance for Industry

Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease

Feb 2013

DRAFT GUIDANCE

"Because many of the assessment tools used to measure functional or global impairment in patients with dementia have not been validated for use in these early stage patients, we consider the use of a composite scale, validated in early stage patients to assess both cognition and function as a single primary efficacy outcome measure, to be appropriate."

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1 24 October 2013
2 EMA/CHMP/617734/2013
3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper on need for revision of the guideline on
5 medicinal products for the treatment of Alzheimer's
6 disease and other dementias
7

Major need: *The use of appropriate outcome measures with adequate clinical relevance to be used at any stage of the disease continuum.*

Efforts to Develop Improved Clinical Measures for Early Stage AD

Individual industry & academic efforts have proposed more sensitive and responsive instruments in early stage AD

- Some measures, especially cognitive, are more sensitive (e.g., delayed word recall, orientation, word recognition)

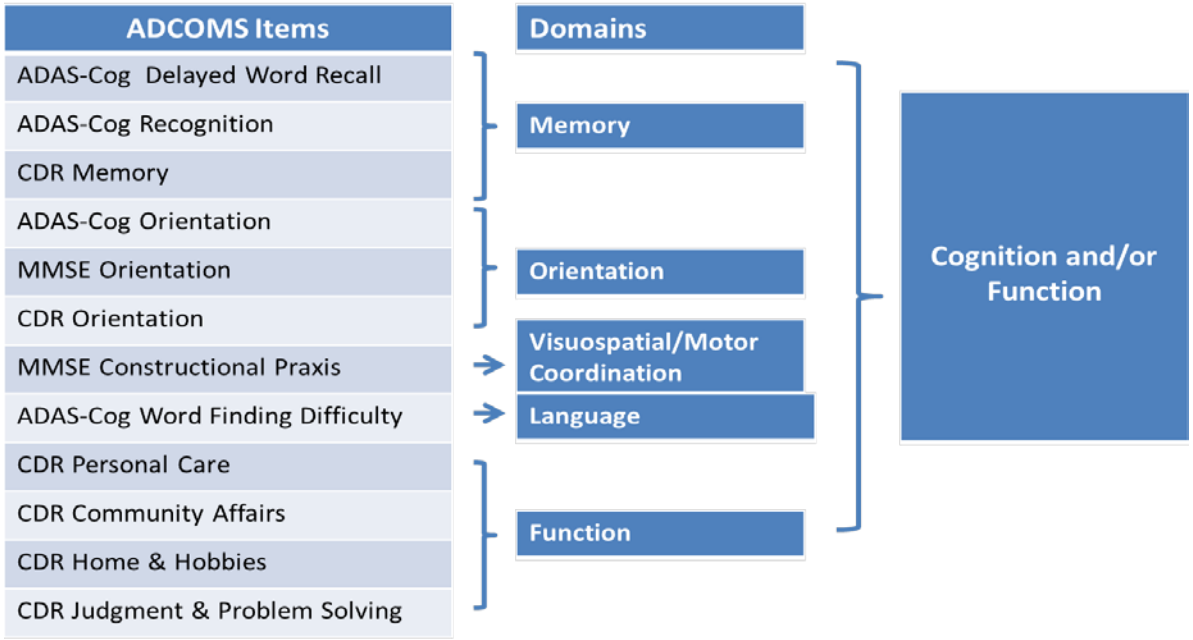
<u>Composite Clinical Endpoint</u> with items from established scales, e.g, ADAS-Cog, CDR-SB, and MMSE

- Selection of key items from existing instruments
  - ***Validity "borrowed" by using established, commonly used scales***
  - Emphasizing cognitive measures of performance

- General approaches:
  - Improved weighting of ADAS-Cog items (multivariate modeling)
  - Additive scales by combining ADAS-Cog with items from other instruments (CDR-SB, MMSE, FAQ, etc.)
  - A combination of both approaches

Composition of pCOA Proposed Composite

- ADCOMS composite measure includes both cognitive and functional components
- ADCOMS is a clinical composite score statistically derived from established validated clinical instruments using placebo data from multiple trials
- ADCOMS represents weighted linear combination of 12 items derived from ADAS-Cog, MMSE, and CDR-SB



Critical Success Factor: Agreement to share data with consortia from ongoing prospective trial; multiple companies sharing data

Clinical Meaningfulness - Importance

Critically important to regulators:

- Regulatory qualification of a proposed novel Outcome Measure
  - "Primary consideration is that the outcome must measure something that:
    - 1) matters clinically
    - 2) to the ***patient***"
- New drug approvals

Matters to payers[1]

e.g., Amyloid PET reimbursement

Essential to patients

[1]Foster et al., 2014

Analysis of Clinical Relevance and Clinical Meaningfulness

Quantitative measures

- Inclusion of accepted domains from CDR
- Conversion to AD Dementia & Time to Conversion

Qualitative measures

- Patient-Reported Outcome Measures

Leveraging Information from C-Path's PRO Consortium

C-Path's PRO Cognition working group developed 26-item developmental PRO instrument for early AD (amnestic MCI)

Measurement concepts emerged from review of the relevant literature, review of existing measure item content, consultation with experts in cognition research and patient care, feedback from the FDA's qualification review team, and qualitative information obtained from focus groups.

- Complex Activities of Daily Living
- Interpersonal Functioning

Sponsors during Qualitative Research:

- AbbVie
- AstraZeneca AB
- Boehringer Ingelheim Pharmaceuticals
- Bristol-Myers Squibb
- Eisai Inc.
- Janssen AI R&D, LLC
- Merck Sharp & Dohme Corp
- Novartis Pharma AG
- Pfizer, Inc.
- Roche

Patient and Informants Narratives
Frequency & Mapping to Composites

Methods: Two neuropsychologists independently assessed patient and informant narratives and then mapped onto items that comprise composite measures.

Results: Primary and secondary concerns of amnestic MCI (aMCI) participants and collateral informants mapped onto:

- Memory
- Executive Functioning
- Language
- Orientation

Overall, statistically-derived composites, including ADCOMs, were largely comprised of clinically meaningful items important to aMCI patients and informants.

Thus, composite measures integrate voice of the patient.

Critical for Success:
Aligning across consortia

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alzheimer's association
Research Roundtable

ADNI

ALZHEIMER'S DISEASE
ADCS
COOPERATIVE STUDY

ACT-AD
Accelerate Cure/Treatments for Alzheimer's Disease

Banner
Alzheimer's
Institute

Improved outcome measure

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

The New York Academy of Sciences
Building communities, advancing science since 1817

imi
Innovative Medicines Initiative

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Coalition Against Major Diseases
Accelerating the development and review of medical products for neurodegenerative diseases.
Access to AD data available to qualified researchers
Model endorsed by FDA and EMA
Overview
Tools
Collaborators
CODR Database
AD Trial Simulation
The Coalition Against Major Diseases (CAMD) is a public-private-partnership aimed at creating new tools and methods that can be applied to increase the efficiency of the development process of new treatments for Alzheimer's disease (AD) and Parkinson's disease (PD).
CAMD
Introduction
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Summary

- The EMA and FDA are supporting innovation in regulatory science specific to Alzheimer's disease.
- Each agency has provided scientific advice and consultation to CAMD's multiple projects, and has engaged fully to contribute toward meaningful advances.
- CAMD has worked to effectively align and synergize efforts across multiple initiatives but, for real progress, this needs to happen more.
- CAMD will continue the course to advance meaningful novel methodologies and drug development tools to aid in medicines development for Alzheimer's disease.

accelerate

innovate

collaborate

THANK YOU

C-Path gratefully acknowledges the support of

SCIENCE foundation ARIZONA
Innovation at Work

FLINN FOUNDATION

FDA

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