Coalition Against Major Diseases:

Viewing the 2013 Landscape

Diane Stephenson, Ph.D.
Executive Director, CAMD
Critical Path Institute

Goals for Today

- Celebrate accomplishments of CAMD
- Share knowledge and learning across teams
- Active dialogue to collectively identify ways to overcome challenges and barriers
- Open discussion among all parties of how to address unmet needs in drug development in Alzheimer's and Parkinson's Disease

CAMD Mission and Accomplishments

To advance innovative drug development tools through a regulatory path that accelerates therapies for neurodegenerative diseases.

Firsts:

- Therapeutic Area clinical data standards published by CDISC (AD and PD)
- Unified database of Alzheimer's disease clinical trial information provided by multiple pharmaceutical companies available to qualified researchers
- Clinical trial modeling and simulation tool endorsed by global regulatory agencies (FDA, EMA)
- Neuroimaging biomarker for Alzheimer's Disease qualified by a regulatory agency (EMA)

CAMD Members

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Government/Regulatory participants

- European Medicines Agency — Science Medicines Health
- FDA
- National Institute on Aging
- National Institute of Neurological Disorders and Stroke

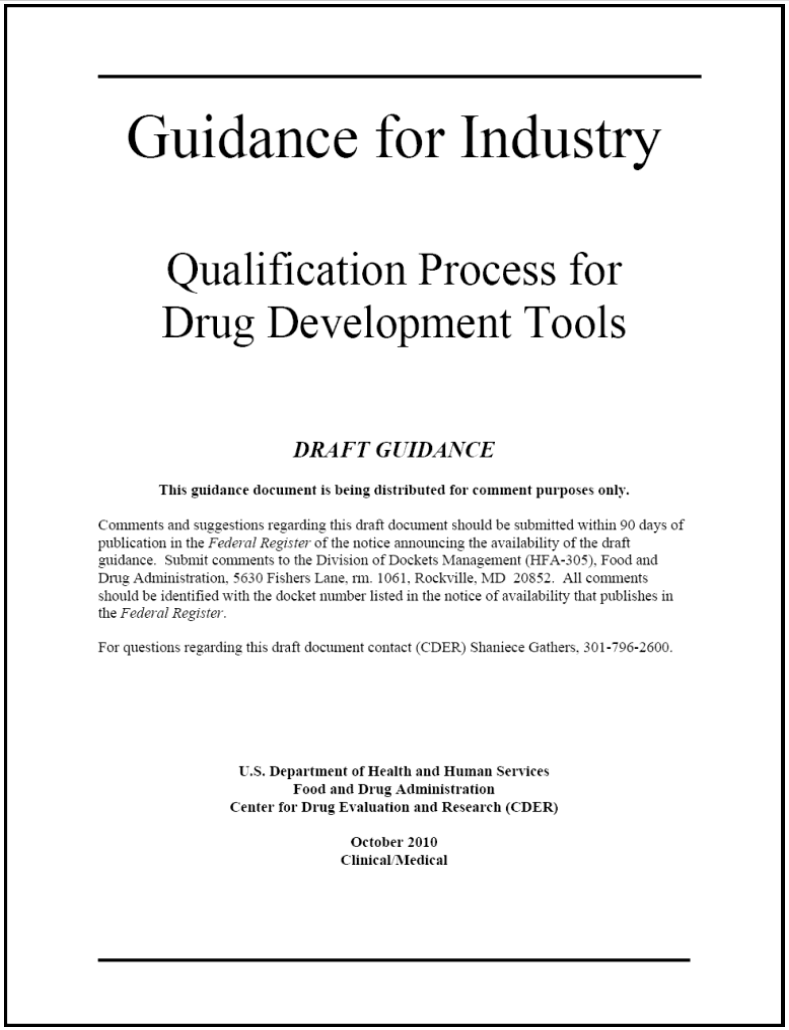
Industry members

- AstraZeneca
- GE Healthcare
- Meso Scale Discovery
- Boehringer Ingelheim
- GlaxoSmithKline
- Novartis
- Orion — Building Well-Being
- FUJIREBIO
- Bristol-Myers Squibb
- Pfizer
- Johnson & Johnson
- CROnos
- Lilly
- Roche Genentech — A Member of the Roche Group
- Eisai
- Medical Care Corporation
- Sanofi
- Takeda
- Forest Laboratories, Inc.
- Merck
- Teva

Non-profit research members

- Alliance for Aging Research
- alzheimer's association
- AFA — Alzheimer's Foundation of America
- US Against Alzheimer's — we can stop it by 2020.
- Parkinson's UK — Change Attitudes. Find a Cure. Join Us.

FDA and EMA Qualification: A Formal Process of Review and Acceptance



Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE

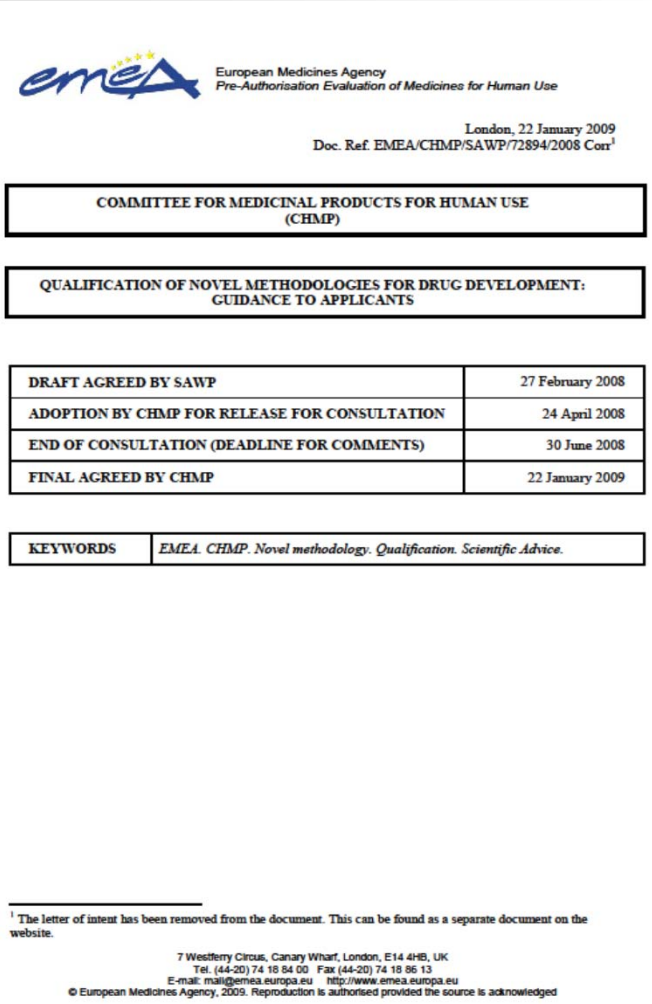
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shaniece Gathers, 301-796-2600.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical



European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 22 January 2009
Doc. Ref. EMEA/CHMP/SAWP/72894/2008 Corr[1]

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

QUALIFICATION OF NOVEL METHODOLOGIES FOR DRUG DEVELOPMENT: GUIDANCE TO APPLICANTS

DRAFT AGREED BY SAWP	27 February 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 April 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 June 2008
FINAL AGREED BY CHMP	22 January 2009

KEYWORDS	*EMEA. CHMP. Novel methodology. Qualification. Scientific Advice.*

[1] The letter of intent has been removed from the document. This can be found as a separate document on the website.

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Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

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 Modeling Team

Journey to Success

News Search

AD Trial Simulation Tool Receives Regulators' Blessings

AD Modeling Team Members:

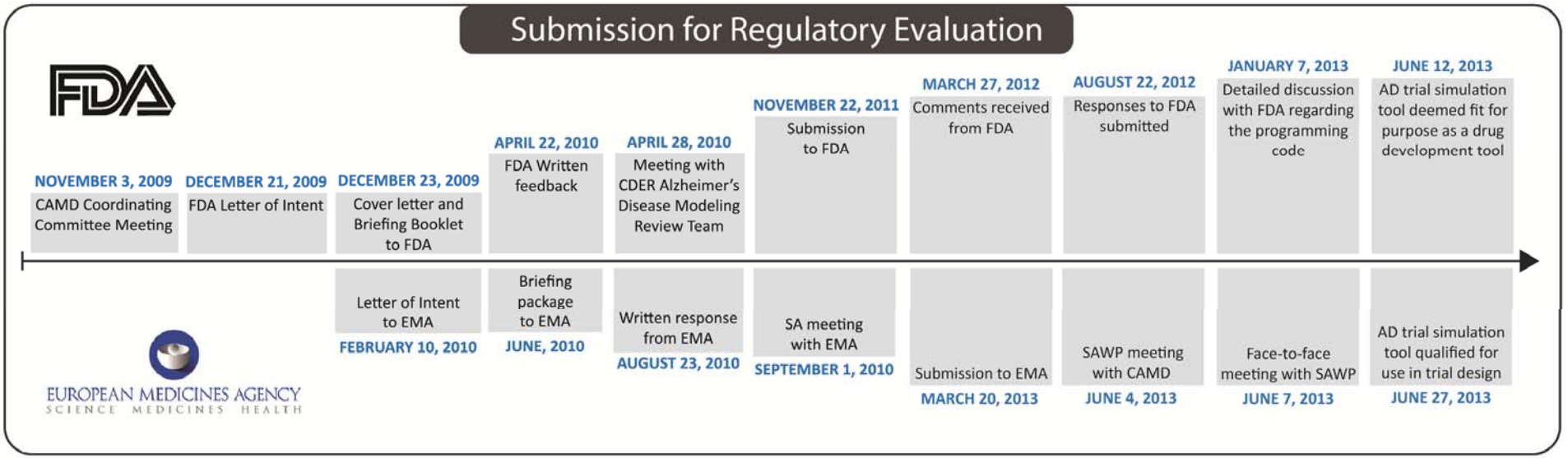
Klaus Romero
Brian Corrigan
Kaori Ito
Jim Rogers
Dan Polmamus
Richard Meibach
Richard Mohs

Yaakov Stern
Lon Schneider
Gary Cutter

Yaning Wang
Vikram Sinha
Li Zhang
Marc Walton
Nick Kozauer
Issam Zineh

Maria Isaac
David Brown
Jean Georges
Spiros Vamvakas
Robert Hemmings
Luca Pani

Special thanks to Bill Thies (Alz Assn), Eric Sokol (AFA)



C-Path AD model success

Registration is now open: Register Here for Discount

WHAT: MODELING & SIMULATION FOR MEDICAL PRODUCTS WORKSHOP

INTEGRATED APPROACHES TO MODELING & SIMULATION FOR DEVELOPING MEDICAL PRODUCTS AND REGULATORY REVIEW

WHEN: September 26, 2013
7:30 AM – 4:00 PM

WHERE: Washington, DC | The W Hotel

who has requested access to the CAMD clinical trial simulation tool?

7/12/2013	Novonordisk
7/22/2013	Envivo Pharma
7/23/2013	Lilly
7/24/2013	Böhringer-Ingelheim
7/29/2013	Lundbeck
8/6/2013	Biotie
8/6/2003	AZ
8/6/2013	Live
8/16/2013	Takeda
9/4/2013	Gene

09/26/2013 Astellas
09/28/2013 BMS
10/02/0213 Biosynetix
10/04/2013 Abbvie
10/07/2013 Quincy Bioscience
10/16/2013 Pharnext
10/24/2013 Evidera

Progress in Developing Therapeutic Area Data CDISC Standards

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www.cdisc.org/therapeutic

Clinical Data Standards

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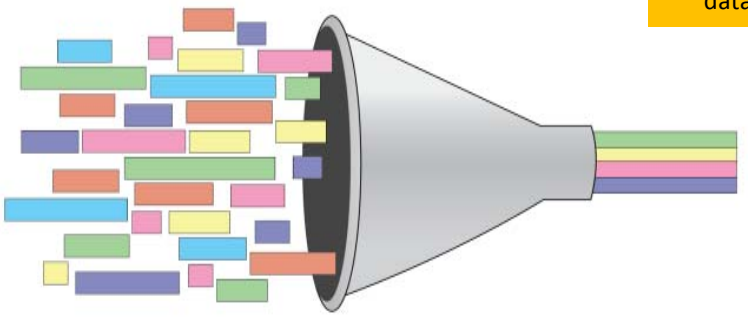
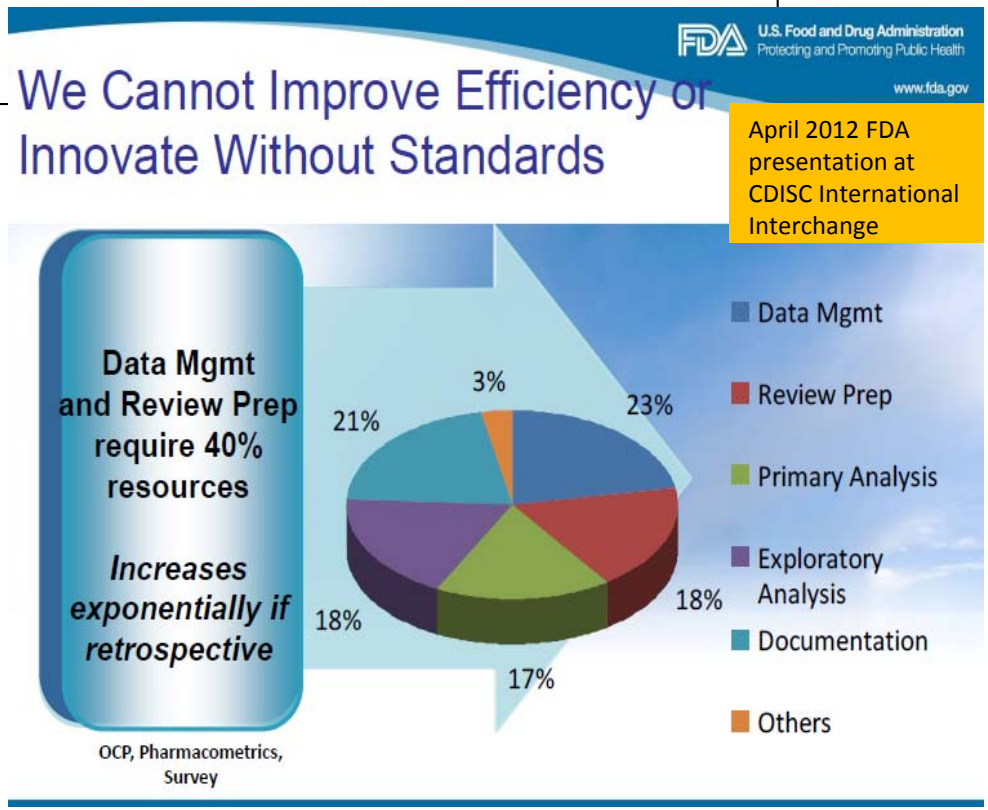
Value Proposition

- **Enable pooling of data that can generate new insights and surface subtle signals**

- **Improve the efficiency and effectiveness of regulatory reviews**
  (Standards will be required by 2017)



2010 C-Path CAMD –AD database



April 2012 FDA presentation at CDISC International Interchange

C-Path's Online Data Repository for Alzheimer's Disease

- **Nine companies remapped and pooled placebo data from 24 trials for ~6500 subjects**

- **Database open to >200 qualified research teams in 35 countries**

CAMD AD Database use is growing

Breakdown by Stakeholder Sector of 2013 Approved Applications (n=40)

- 15 from Academia
- 1 from Government
- 3 from Non-Profit
- 10 from Pharmaceutical
- 11 Other

Categories of Research Questions

Outcome measure Analyses
- Ueckert et al, (M. Karlsson, Pfizer)
- Yavorsky et al., CROnos

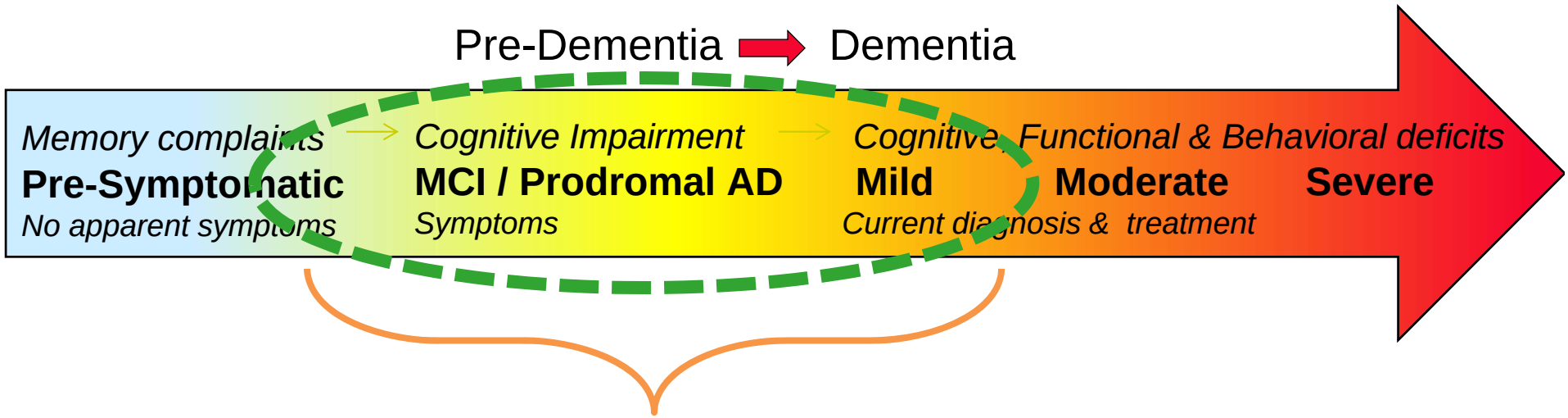
Patient heterogeneity
- Panegyres et al.

Biomarkers/Labs to assess risk factors
- Szalkai et al.

Technology development and innovation
- Kingery-Cogstate
- Oracle/C-Path collaboration

CAMD Clinical trial simulation tool/placebo response
- CAMD AD modeling team

How to Measure Cognitive Deficits in the Pre-Dementia Stages of the AD?



- Established Instruments to measure cognition lack sensitivity & responsiveness in early stages of the disease process
  - The registration standard Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) developed for moderate/dementia stages of AD
  - Major limitations of ADAS-Cog to detect and follow AD progression during pre-dementia stages

Johan Luthman, Merck

CAMD hippocampal volume team's recent publications

ELSEVIER

Alzheimer's & Dementia ■ (2013) 1–9

Alzheimer's & Dementia

Research Article

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[v], Robin Wolz[a], Diane Stephenson[i,*]

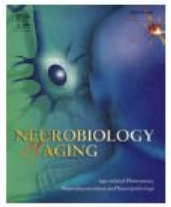
[a]IXICO Ltd., London, UK

Neurobiology of Aging xxx (2013) 1–11

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging



Operationalizing hippocampal volume as an enrichment biomarker for amnestic mild cognitive impairment trials: effect of algorithm, test-retest variability, and cut point on trial cost, duration, and sample size

Peng Yu[a], Jia Sun[a,b], Robin Wolz[c,d], Diane Stephenson[e], James Brewer[f], Nick C. Fox[g], Patricia E. Cole[h], Clifford R. Jack Jr[i], Derek L.G. Hill[c,g], Adam J. Schwarz[h,*], for the Coalition Against Major Diseases and the Alzheimer's Disease Neuroimaging Initiative

Parkinson's Disease:
The Challenge Shared with AD

Slow progressive neurodegeneration affecting multiple domains, with increasing burden over time

- Long prodromal period that precedes symptom onset

Symptomatic therapies available with decreasing efficacy over disease course

Insensitive outcome measures often impacted by factors other than treatment effect

High clinical failure rate for novel therapeutics

Clinical trials required to demonstrate efficacy, especially disease modification, are long and costly

- Trial outcomes and methods often confound symptomatic and disease modifying effects

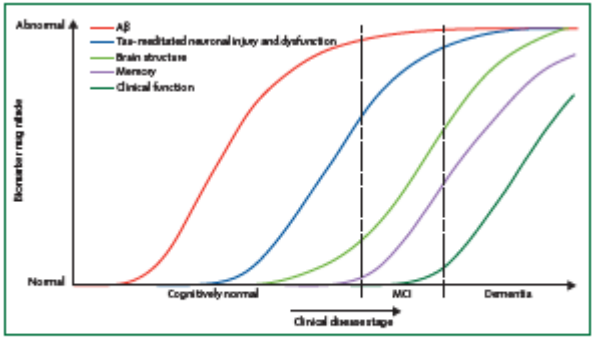
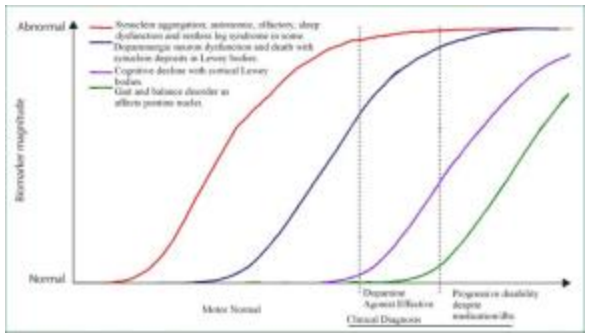


Figure 2: Dynamic biomarkers of the Alzheimer's pathological cascade
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

Jack et al. 2010

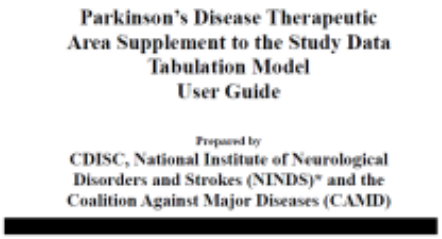


Schlossmacher

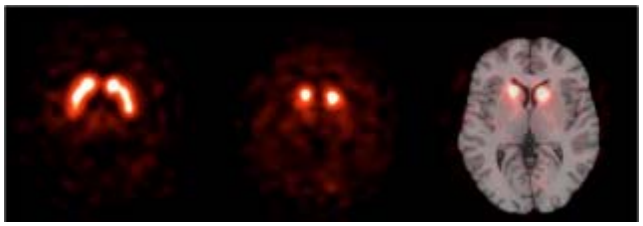
Tom Comery, CAMD annual meeting 2012

CAMD's Initiatives in Parkinson's Disease

- PD CDISC clinical data standards



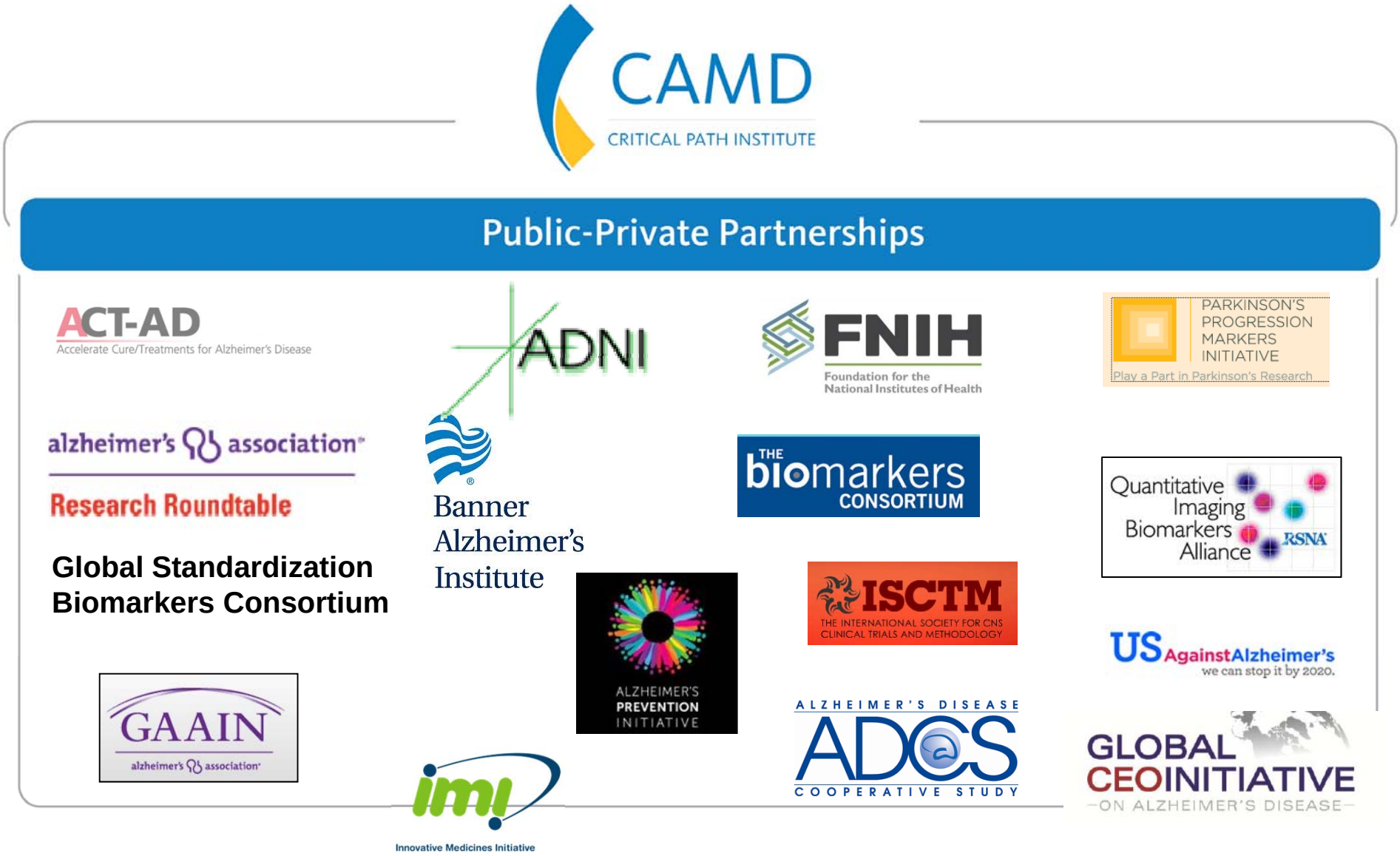
- PD imaging biomarker qualification team



SPECT imaging of DAT in healthy and PD

- Parkinson's UK joins CAMD
- PD modeling team formed (5 member companies, FDA)
- Educational awareness… precompetitive data sharing in PD

Critical Success Factors for CAMD: Aligning with Relevant PPPs



Regulatory Landscape Guides
CAMDs Path Forward

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Contains Nonbinding Recommendations
Draft – Not for Implementation

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

Additional copies are available from:

Office of Communication
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach and Development
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Food and Drug Administration
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Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

or

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Food and Drug Administration
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DSMICA E-mail: dsmica@cdrh.fda.gov; DSMICA Fax: 301-443-8818
(Tel) Manufacturers Assistance: 800-638-2041 or 301-443-6597
(Tel) International Staff: 301-827-3993
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2012
Clinical Medical

Guidance for Industry

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

DRAFT GUIDANCE

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For questions regarding this draft document contact Nicholas Kozauer at 301-796-2250.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2013
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