Advancing the Discipline of Regulatory Science for Medical Product Development: An Update on Progress and a Forward-Looking Agenda
An IOM Workshop

Innovation in Modeling and Integrating Information: The CAMD Knowledge Model for AD

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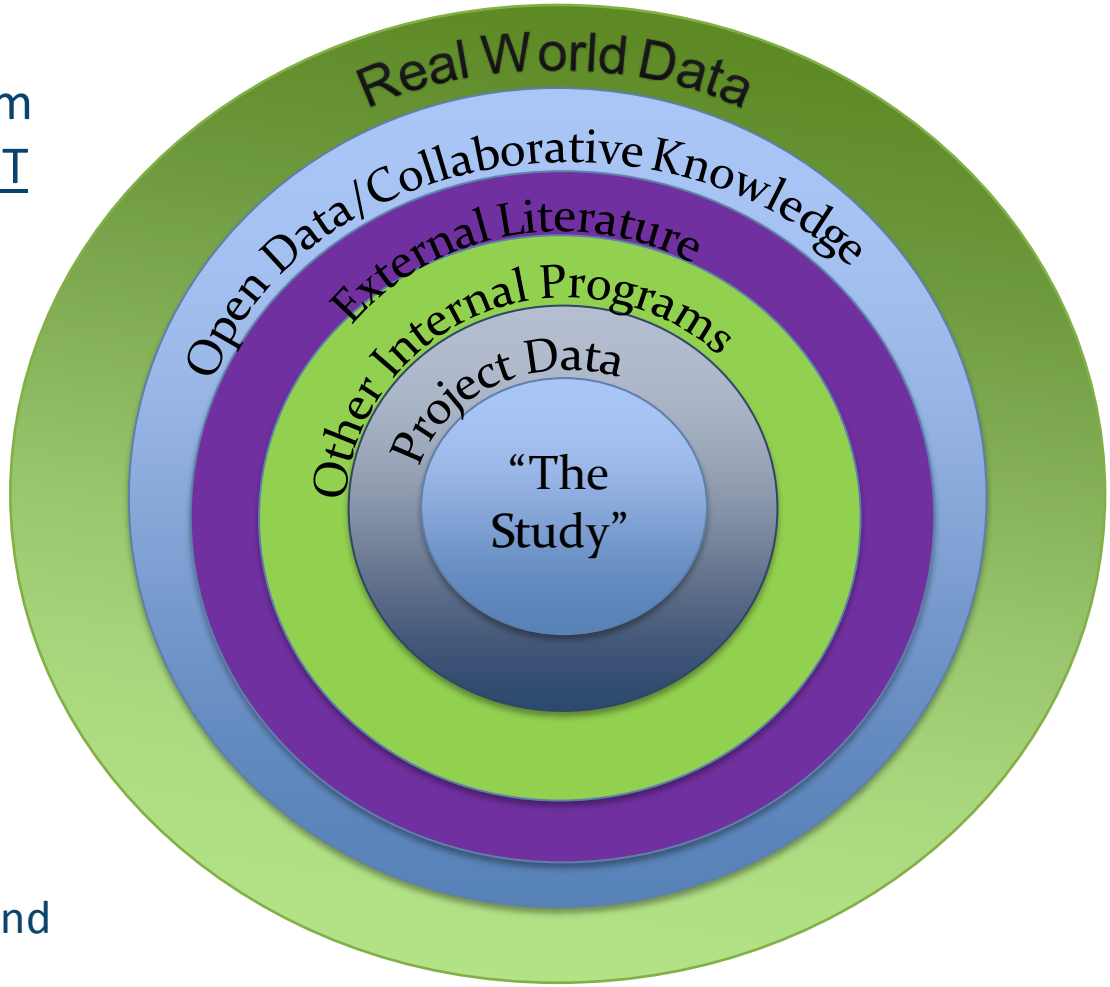
Agenda

- The Problem
  - The Trialist's Dilemma
  - limitations of "going it alone" in Model Based Drug Development (MBDD) in AD
- The Solution: CAMD
  - Data Standards
  - Data Collection
  - A Knowledge Model for Disease Progression
  - Qualification
- Lessons Learned

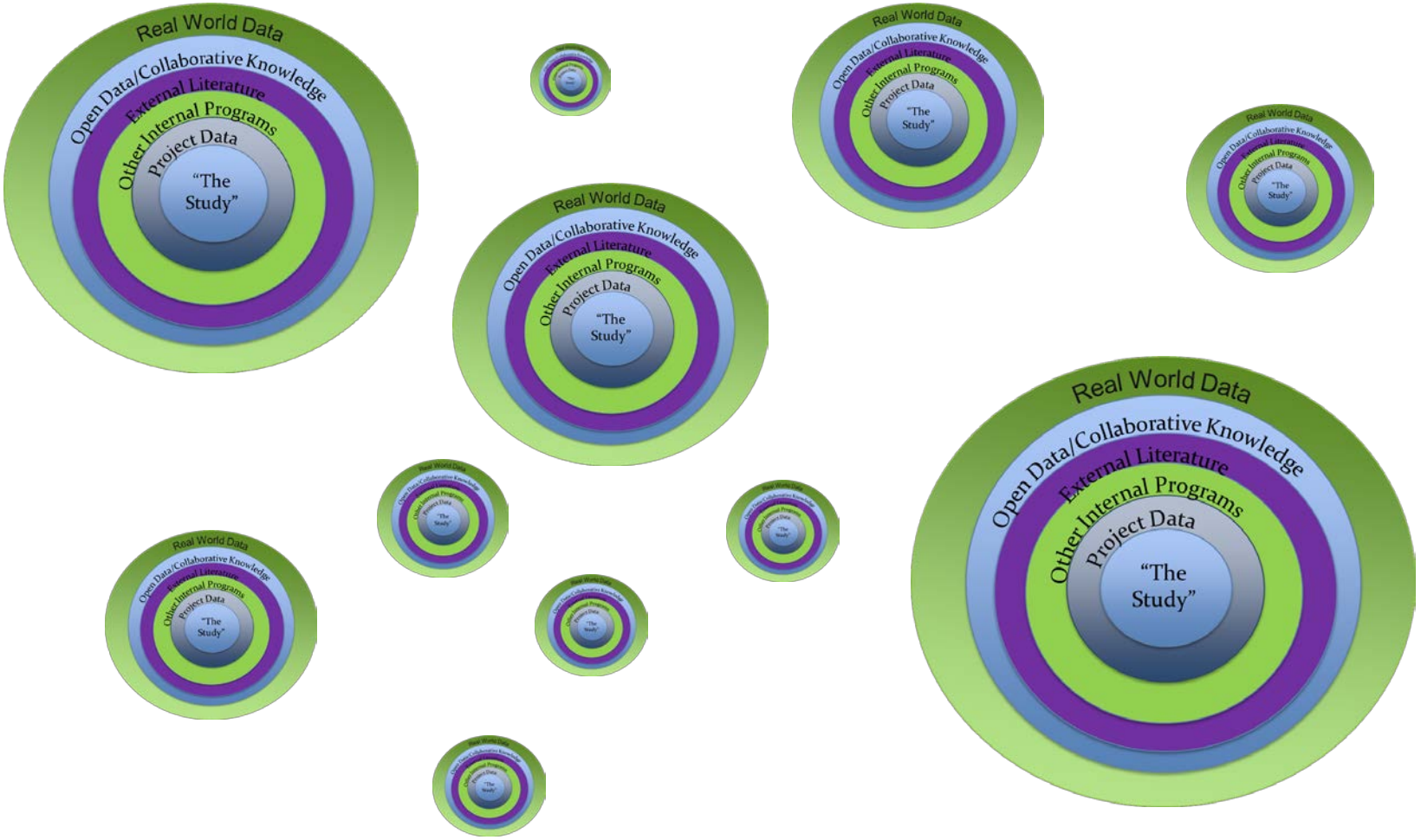
Knowledge Management: The Clinical Trialist's Dilemma

- 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 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



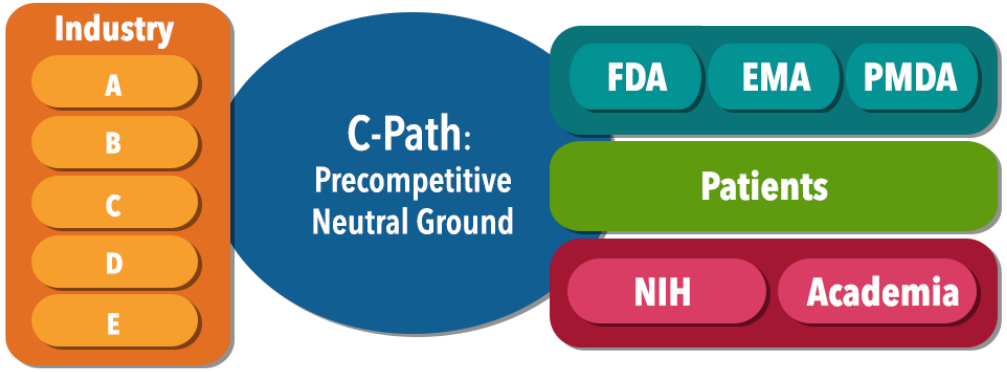
Going it Alone vs a Consortia Approach



Different Data = Different Results

C-Path: A Public Private Partnership

- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for 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 Collaborators

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Industry

- Abbvie
- Acorda Therapeutics
- Actelion Pharmaceuticals
- Allergan
- Almac
- Amgen
- AstraZeneca
- Biogen Idec
- Boehringer Ingelheim
- Bracket
- Bristol-Myers Squibb
- Celgene
- Cepheid
- CRF Health
- CROnos
- Daiichi Sanyko
- 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

- Alzheimerís Association
- Alzheimerís 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
- Parkinsonís 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

Diverse Work **Team**

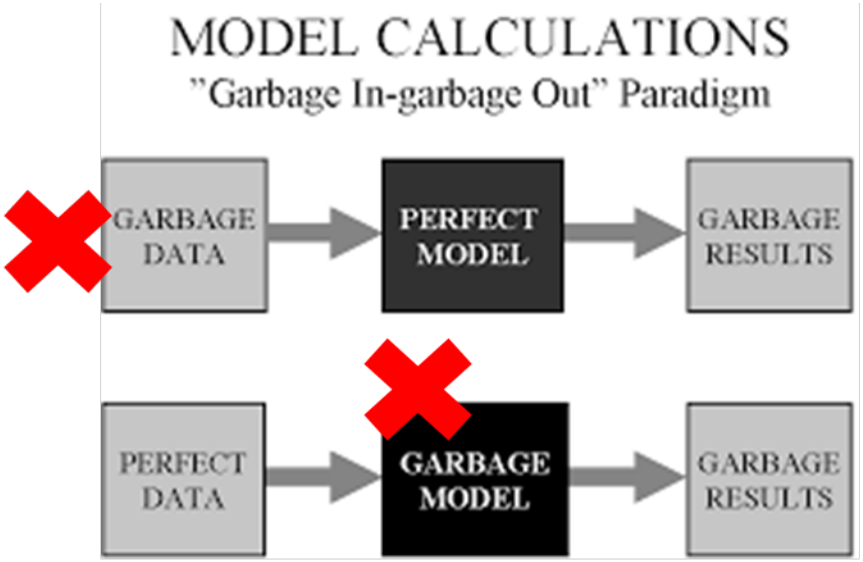
- Klaus Romero (CAMD)
- Kaori Ito (Pfizer)
- James A. Rogers (Metrum)
- Daniel Polhamus (Metrum)
- Mahesh Samtani (J&J)
- Richard Meibach (Novartis)
- Richard Mohs (Lilly)
- Yaning Wang (FDA)
- Vikram Sinha (FDA)
- Maria Isaac (EMA)
- Lawrence Lesko (UoF)
- Lon Schneider (USC)
- Bill Thies (Alzheimer's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

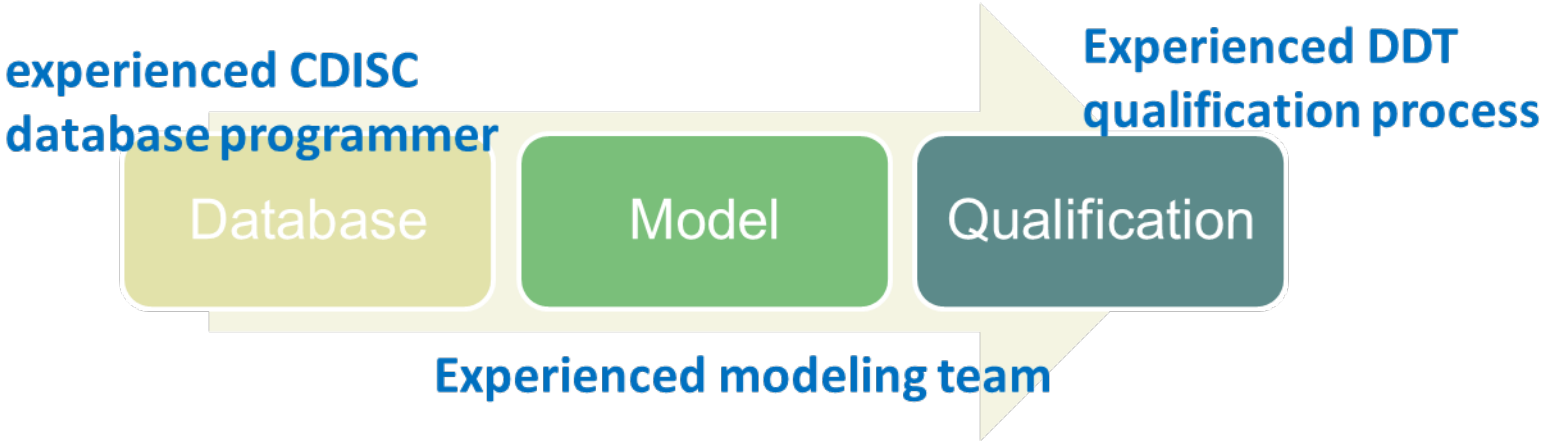
Broad Input from a variety of backgrounds

Clear Context of Use Summary

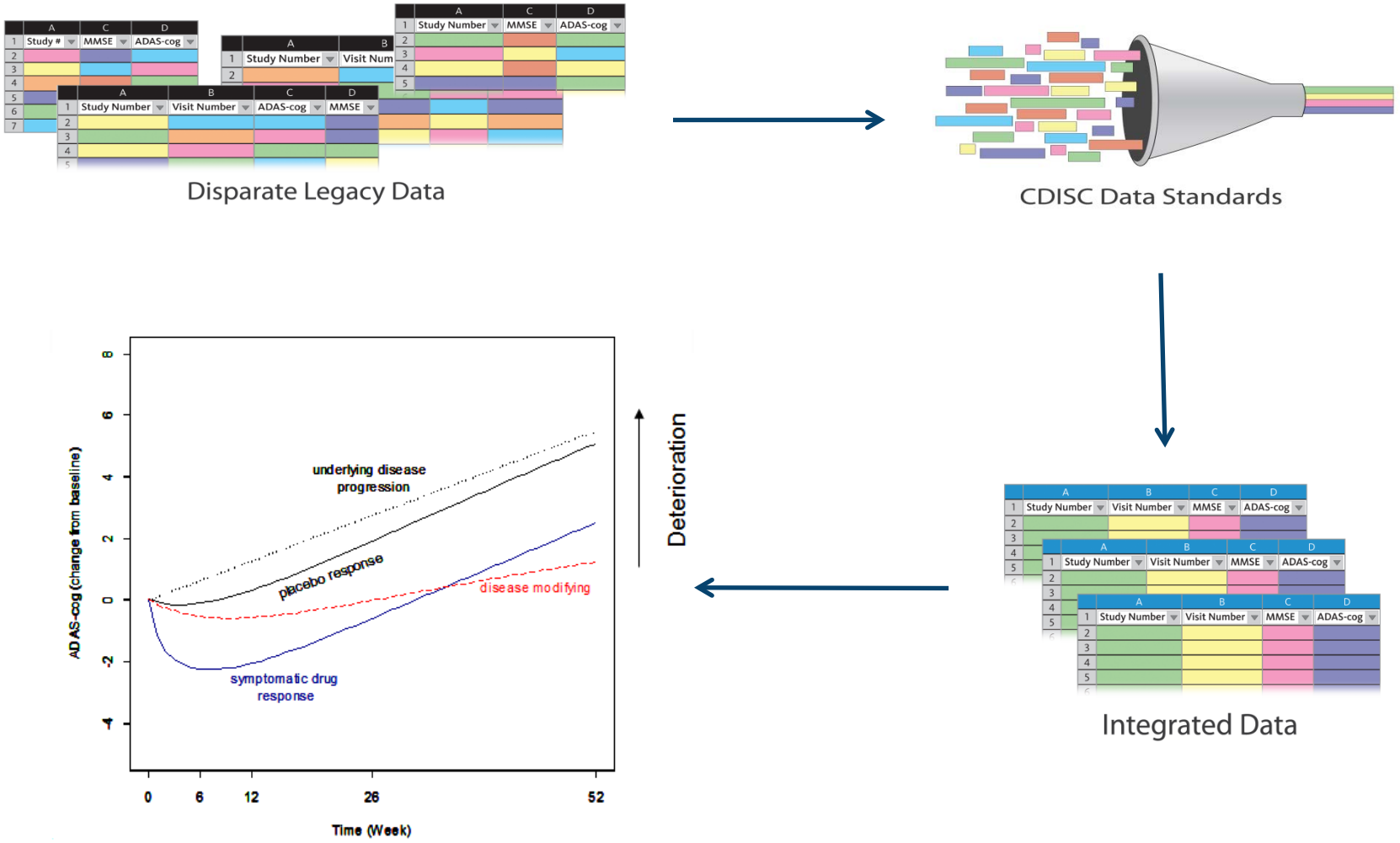
- What the tool is:
  - A clinical trial simulation tool to help optimize clinical trial design for mild and moderate AD, using ADAS-cog as the primary cognitive endpoint
- What it is based on:
  - A drug-disease-trial model that describes disease progression, drug effects, dropout rates, placebo effect, 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

Developing a Comprehensive Database (Endpoints, Covariate) is Critical for Success



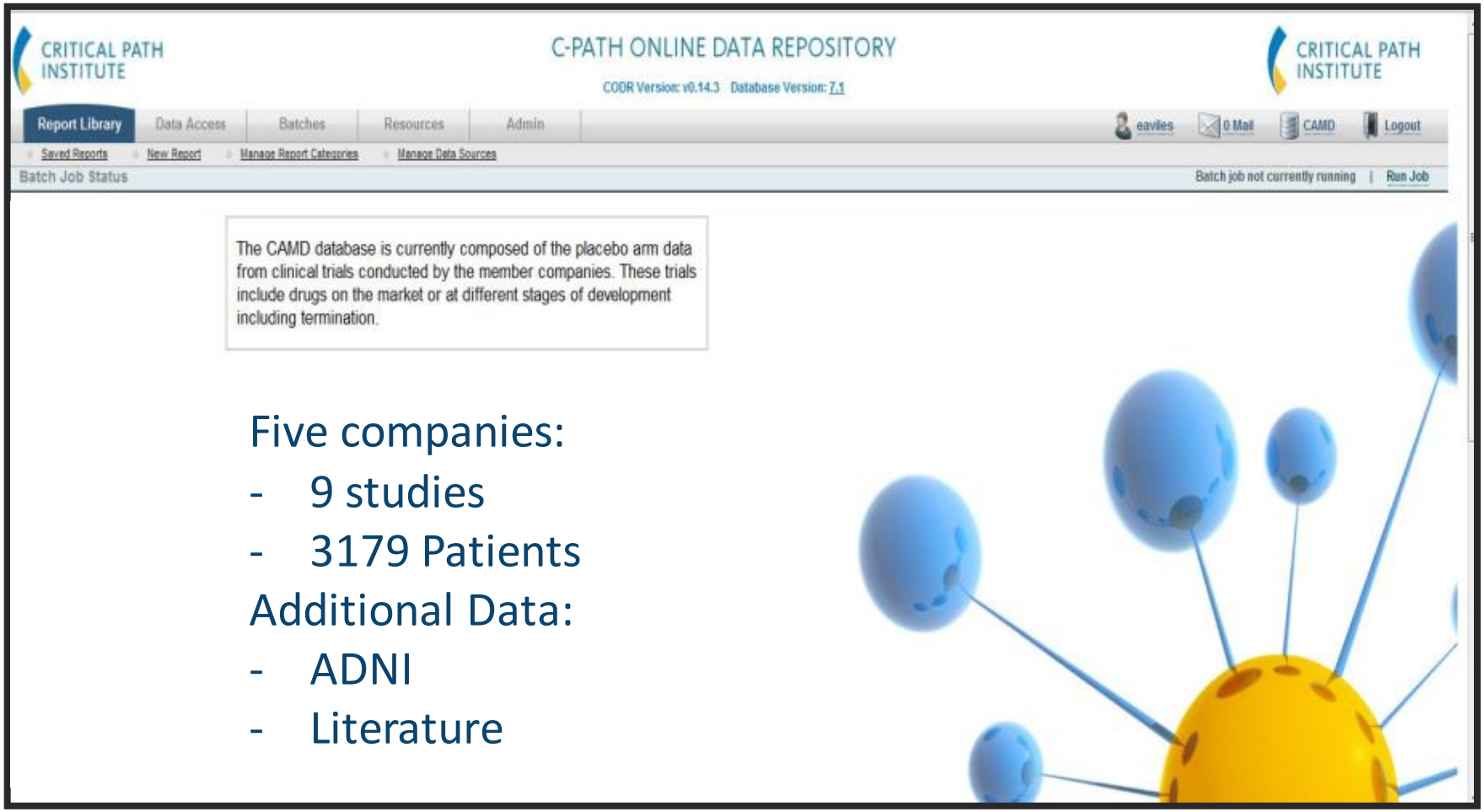


Step 1: Data Standards



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: CODR Database



Five companies:

- 9 studies
- 3179 Patients

Additional Data:

- ADNI
- Literature

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

Step 3: AD Drug-Disease-Trial Model

Integrating the Clinical Trialist's World

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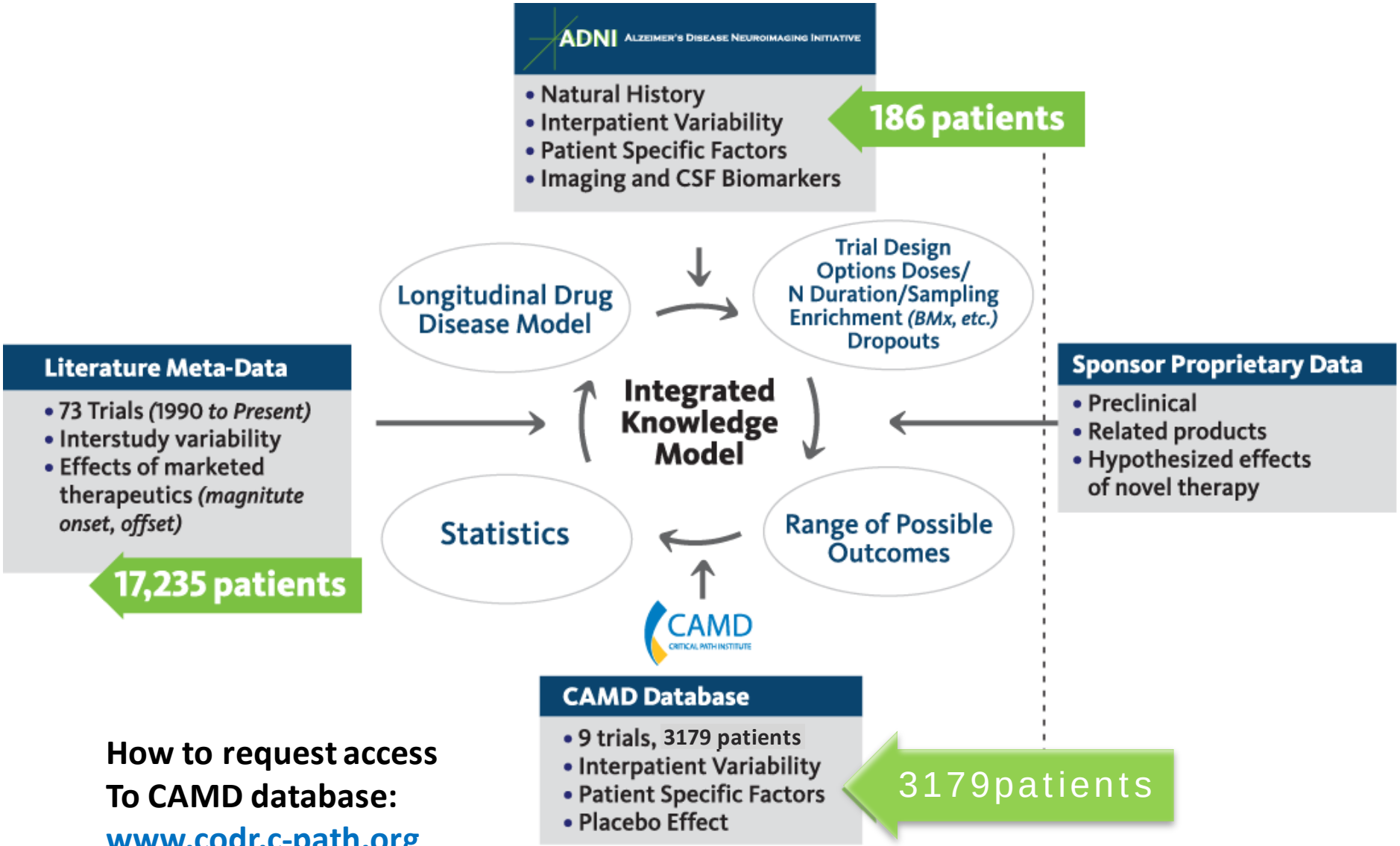


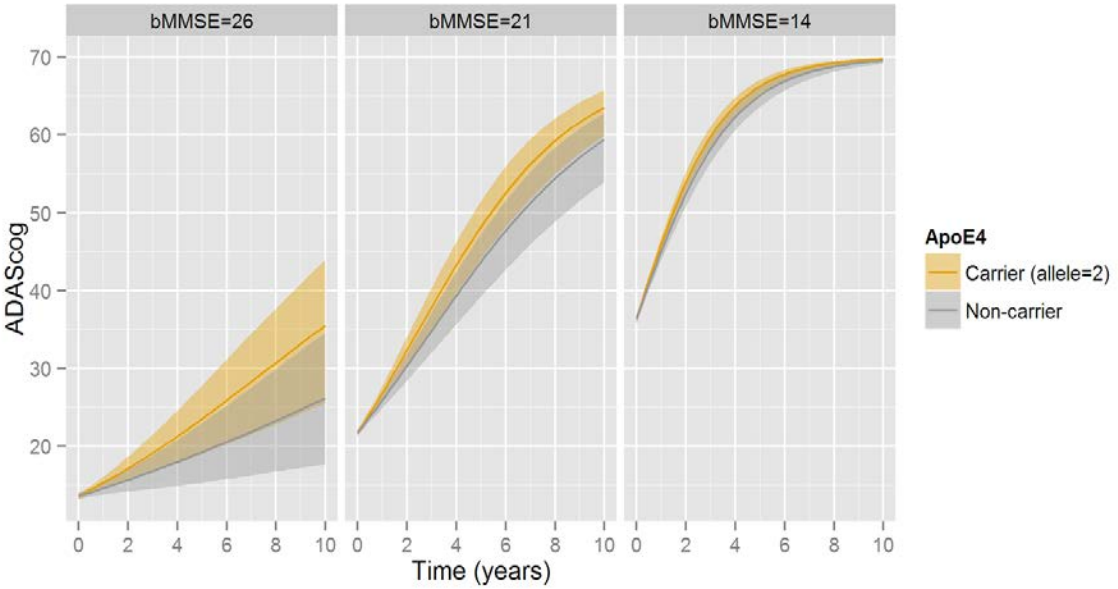
How to request access To CAMD database:
www.codr.c-path.org

Step 3a: 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:
  - APOE4 allele
- Biomarkers
  - Not yet

Step 3b: Peer Reviewed Quantitative Results

Baseline Severity (BMMSE)	Gender	APOE4 allele copies	Annual progression rate	Credible Interval (90%)
16	Male	0	7.07	4.48-9.42
16	Male	1	7.14	4.49-9.54
16	Male	2	8.03	5.20-10.40
16	Female	0	6.52	3.73-9.05
16	Female	1	6.53	3.88-9.04
16	Female	2	7.55	4.76-9.78
21	Male	0	4.43	1.99-6.94
21	Male	1	4.48	2.06-6.95
21	Male	2	5.43	2.82-8.06
21	Female	0	3.97	1.42-6.57
21	Female	1	3.97	1.52-6.59
21	Female	2	4.88	2.16-7.17
26	Male	0	1.69	(-)0.28-4.00
26	Male	1	1.70	(-)0.33-4.12
26	Male	2	2.39	0.34-4.90
26	Female	0	1.35	(-)0.61-3.78
26	Female	1	1.36	(-)0.68-3.71
26	Female	2	1.37	0.02-4.53



Disease progression: 75 year-old men, by APOE4 and baseline severity

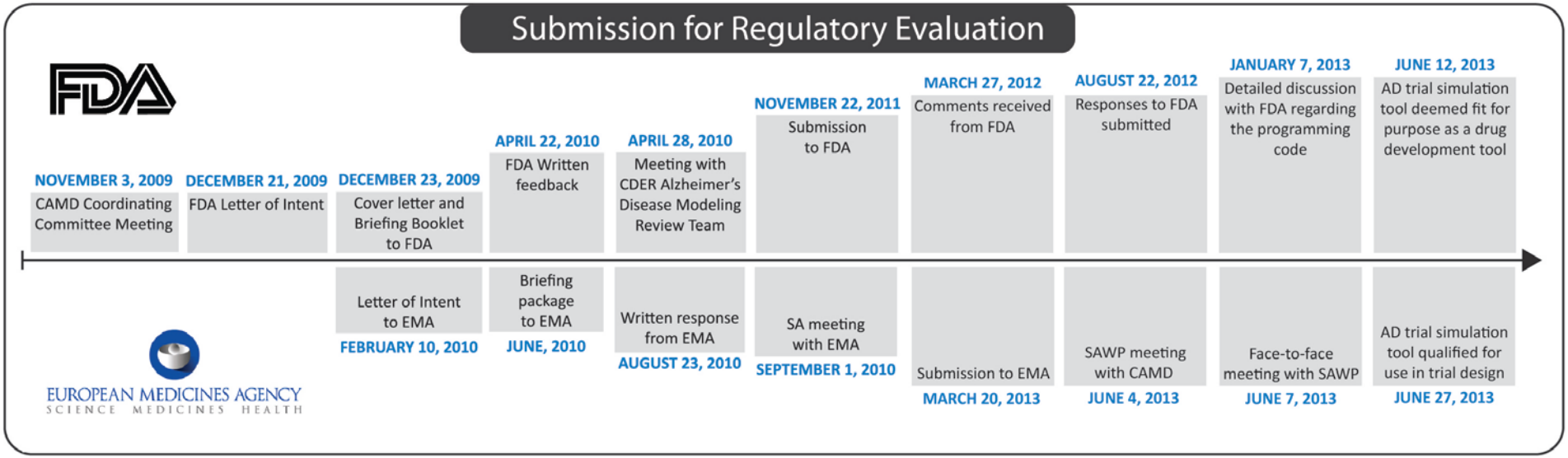
Rogers JA, et al. Alzheimer's disease modeling and simulation. J Pharmacokinet Pharmacodyn. 2012 Oct;39(5):479-98.

Step 4 The Regulatory Journey

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."
- A First for FDA

- On September 19, 2013 the EMA determined the CTS tool was "Qualified for Use."
- A First for EMA



Key Learnings with the Consortia Approach

- **Data standards critical**
- Partner with regulators early :
  - first example helped to drive “regulatory science”
  - Establish clarity in position especially around the “context of use”
- Think about model support, enhancements, support infrastructure, etc.
  - Role for organizations such as ISCTM/academia, professional organizations, others.
  - User communities
- Success Breeds Success
  - Ongoing Consortia initiatives in Parkinson’s and early AD
  - Preconference at AAPS later this month
- Most important equation
  - S=$f(t,p)$

Further Reading

- Rogers, JA, et al. Combining patient-level and summary-level data for Alzheimer's disease modeling and simulation: a beta regression meta-analysis. J Pharmacokinet Pharmacodyn (2012) 39:479–498 DOI 10.1007/s10928-012-9263-3
- 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.
- Lalonde, RL, et al. Model-based Drug Development. Clinical Pharmacology & Therapeutics, 82: 21–32. doi: 10.1038/sj.clpt.6100235