How can we achieve better understanding of disease progression and efficient clinical trial design in MCI populations?

CAMD modeling work group

Annual Meeting, 2015-10-15

Outline

Introduction

- History of AD modeling work group
- Example of use of model in AD clinical trial
- Lesson learned

Growing interests in MCI

- Understanding disease progression in MCI
- Modeling efforts with MCI (ADNI data)
- Why individual data is so important?

Key Message

AD Modeling Work Group Mission (2009-2013)

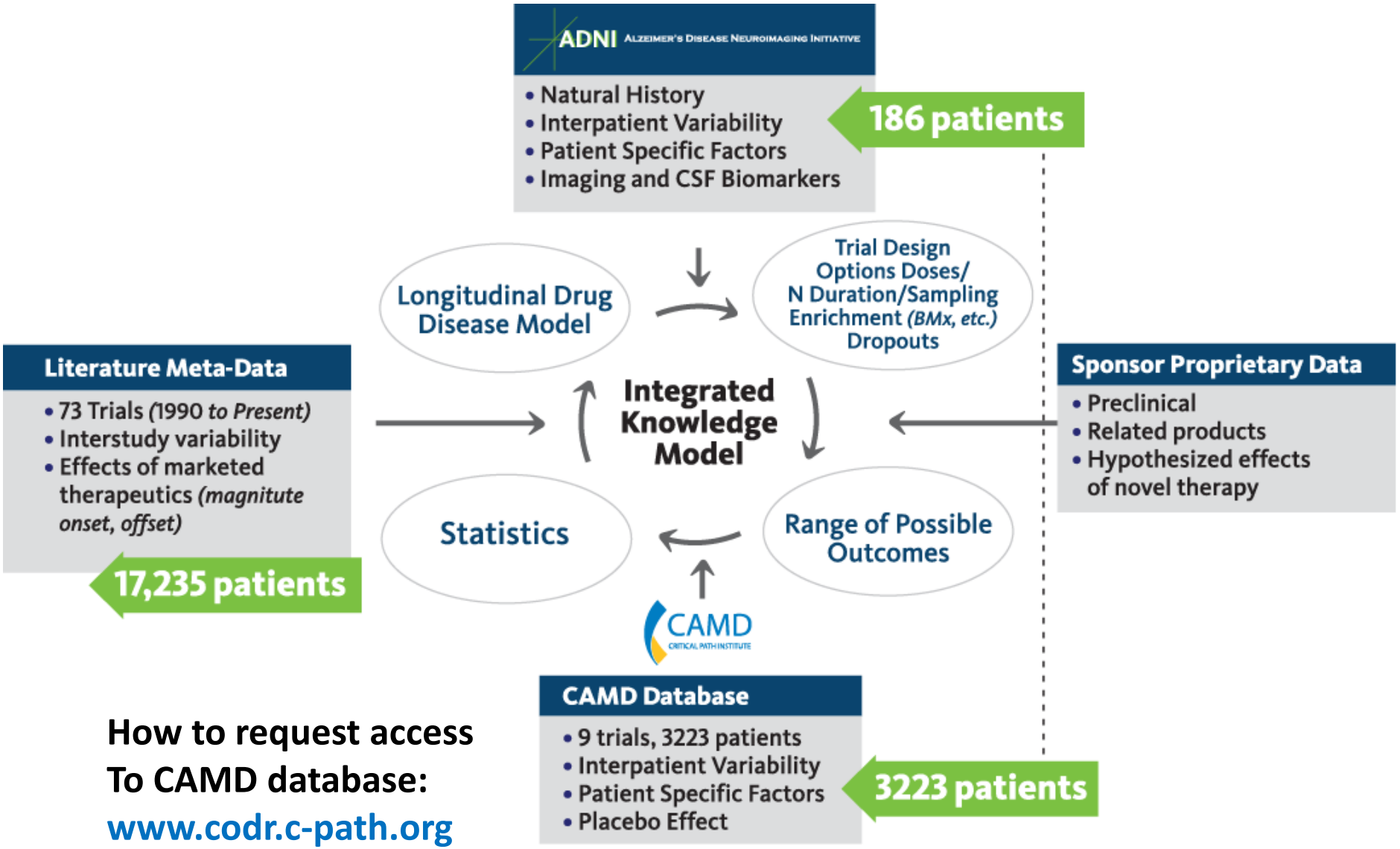
- To develop a quantitative model to describe the progression of cognitive changes in mild to moderate AD to test and optimize operating characteristics of trial designs for AD (via simulations based on the model).
- To submit the results of the analyses to regulatory agencies for review and qualification 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.

Model Developed with Broad Input From Consortium Members

Expert Panelists: **Richard Mohs, Lon Schneider, Yakov Stern, Mary Sano, Chris Weber, Gary Cutter, Rachel Doody**

AD Drug-Disease-Trial Model

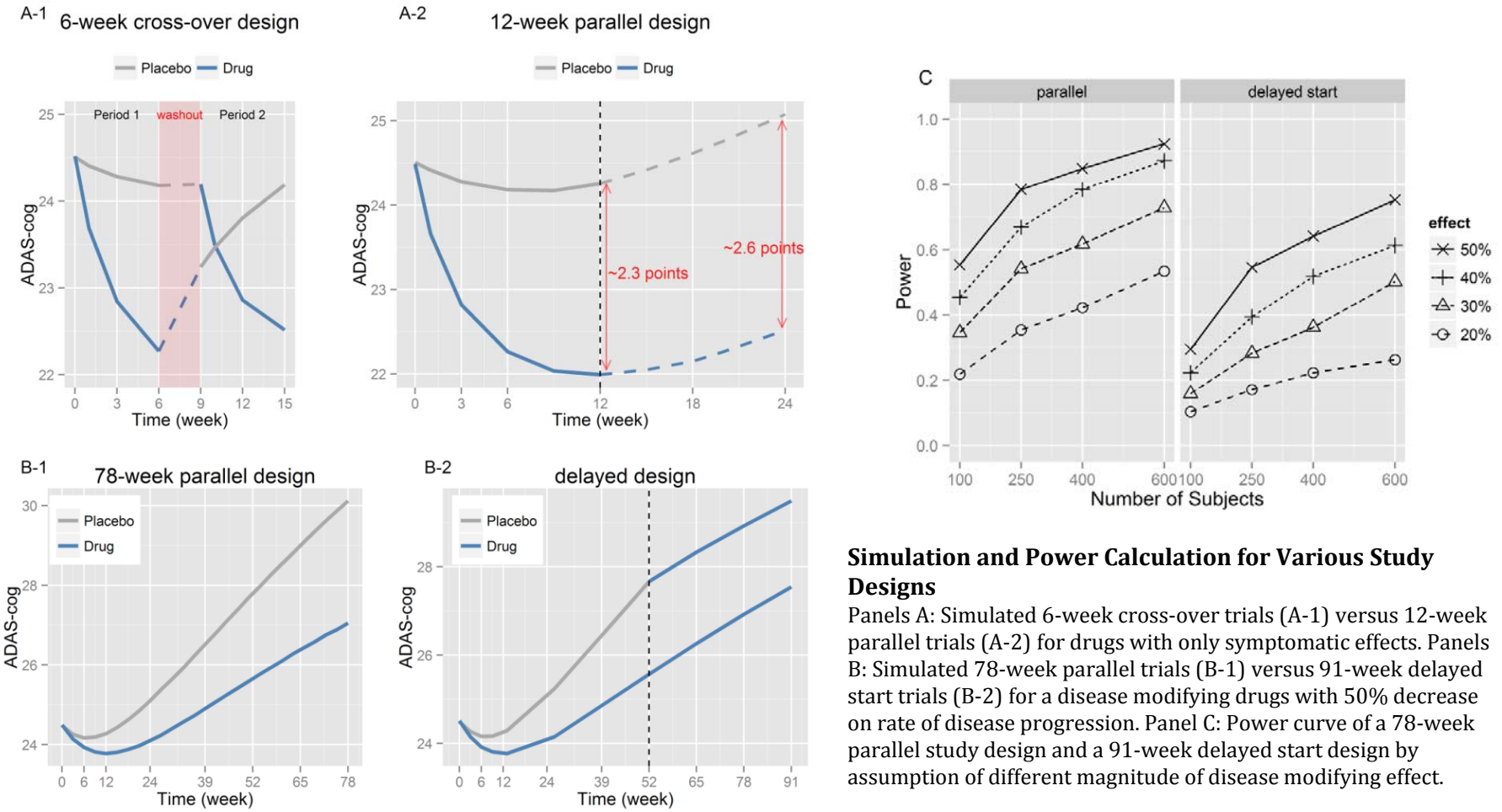
Integrating diverse data sources



How to request access To CAMD database:

www.codr.c-path.org

Simulation Examples



Simulation and Power Calculation for Various Study Designs

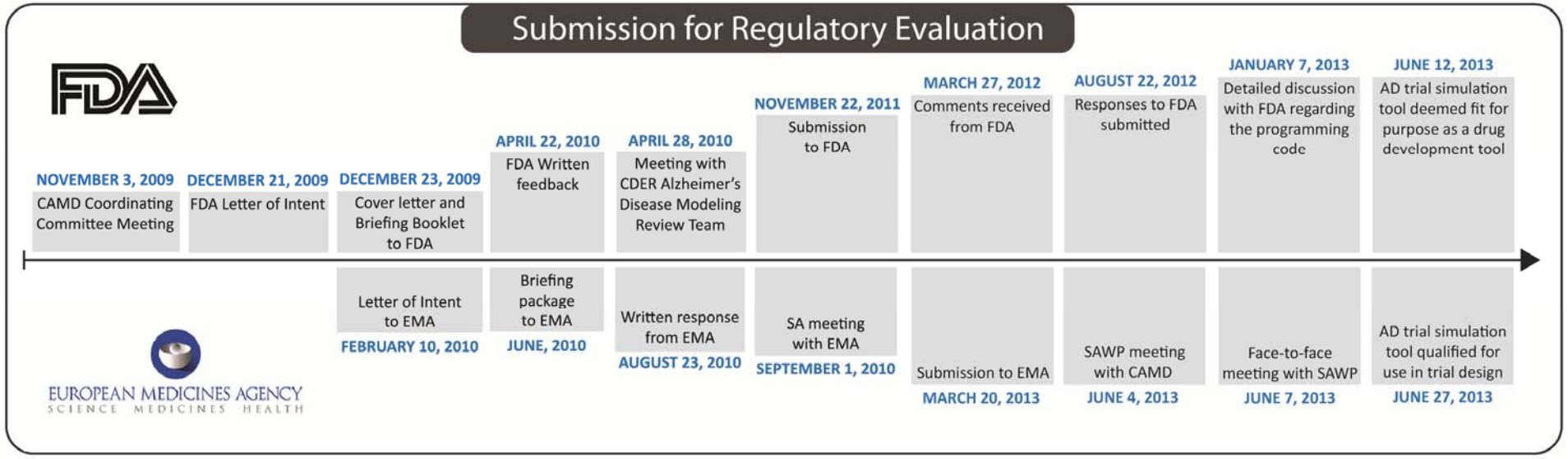
Panels A: Simulated 6-week cross-over trials (A-1) versus 12-week parallel trials (A-2) for drugs with only symptomatic effects. Panels B: Simulated 78-week parallel trials (B-1) versus 91-week delayed start trials (B-2) for a disease modifying drugs with 50% decrease on rate of disease progression. Panel C: Power curve of a 78-week parallel study design and a 91-week delayed start design by assumption of different magnitude of disease modifying effect.

Romero et al, Clinical Pharmacology & Therapeutics (2015), 97: 210–214. doi: 10.1002/cpt.16

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."

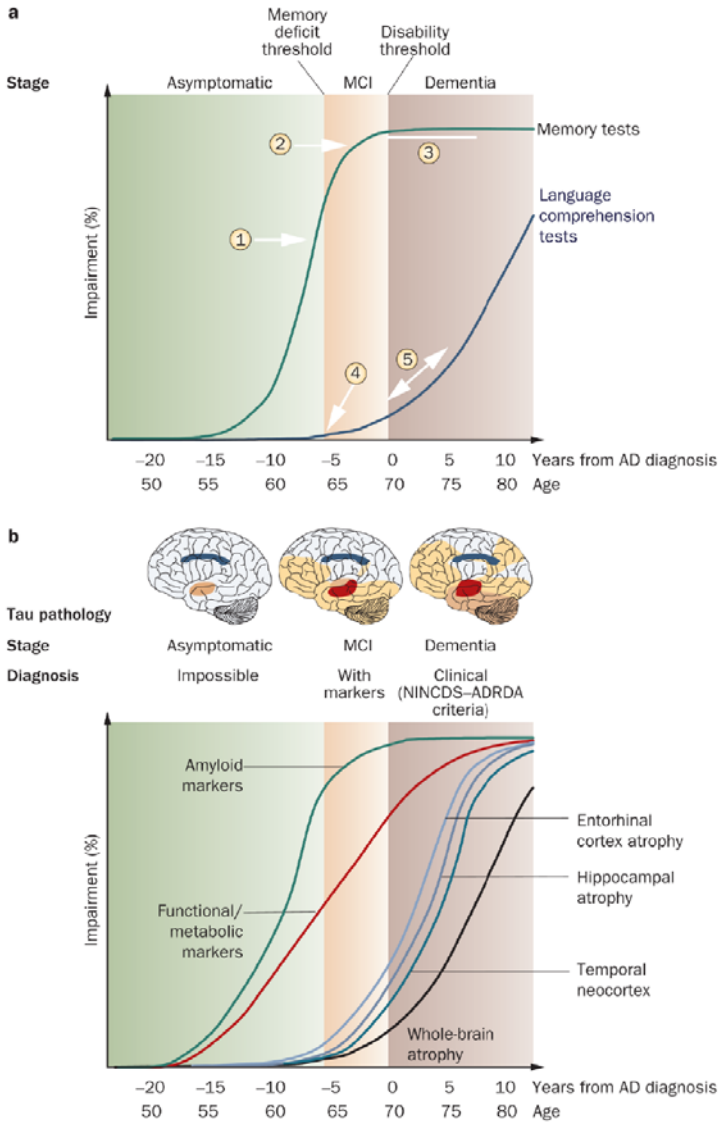


Lesson Learned
from AD Working Group

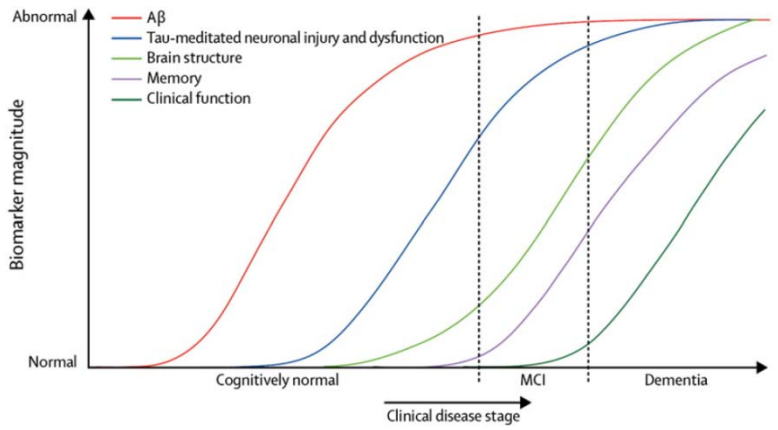
Important key factors for the success:

- CAMD developed the integrated dataset using CDISC standard; data collected from literature, ADNI, and individual level data
- CAMD member companies provided >5000 patients data; largest pooled dataset available from randomized, DB, controlled trials
- Establish partner relationship with regulators early in process
- Provide clear context of use

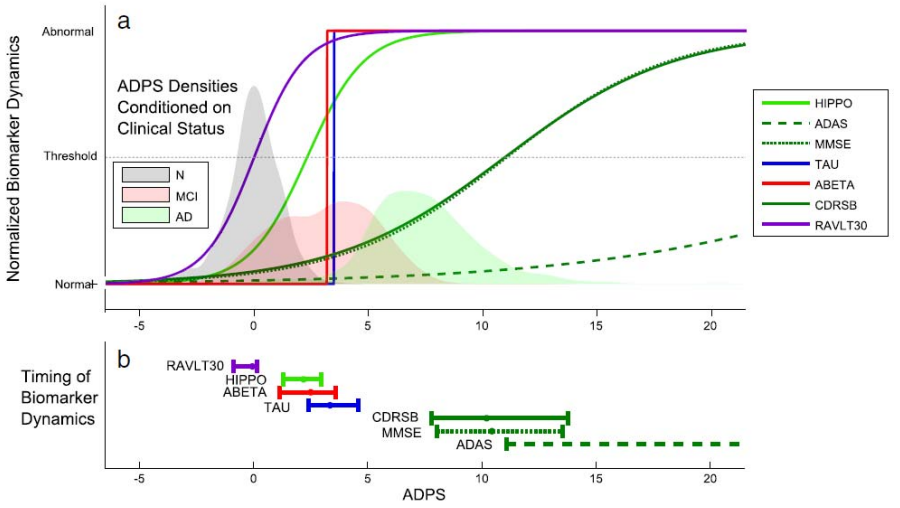
Recent Advances in the Understanding of the Underlying Pathophysiology of AD



Frisoni et al. *Nat Rev Nerol.* 2010



Jack et al. *Lancet Neurol.* 2010



Jedynak et al. *NeuroImage* 2012

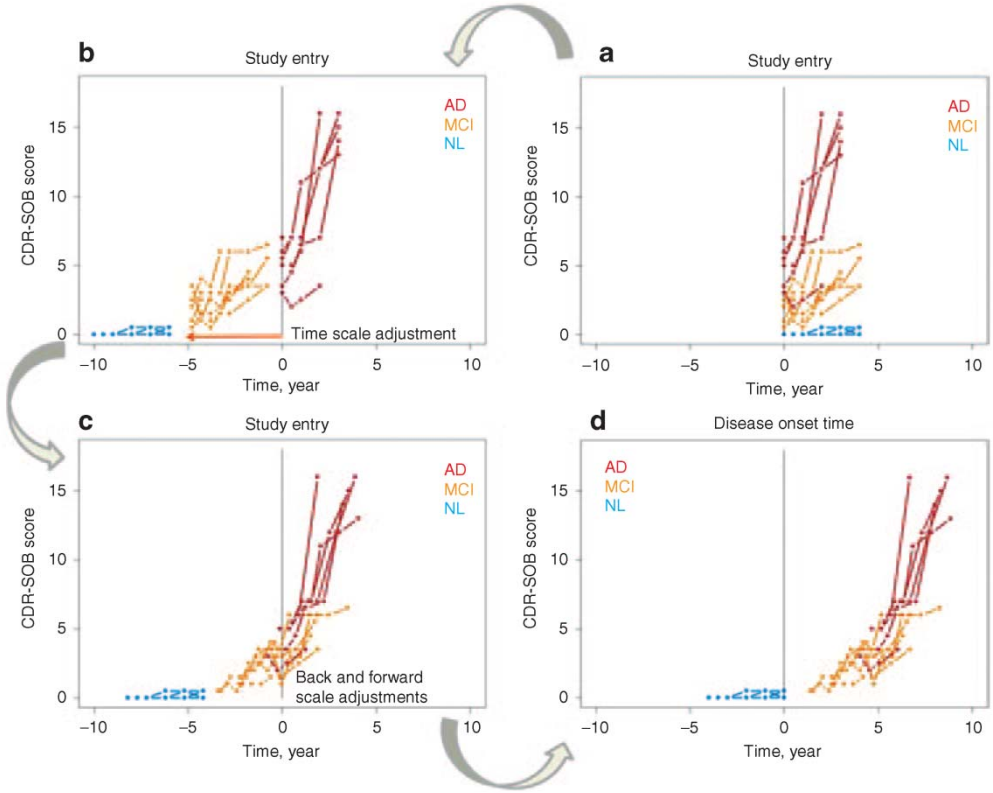
Understanding of Disease Progression in MCI

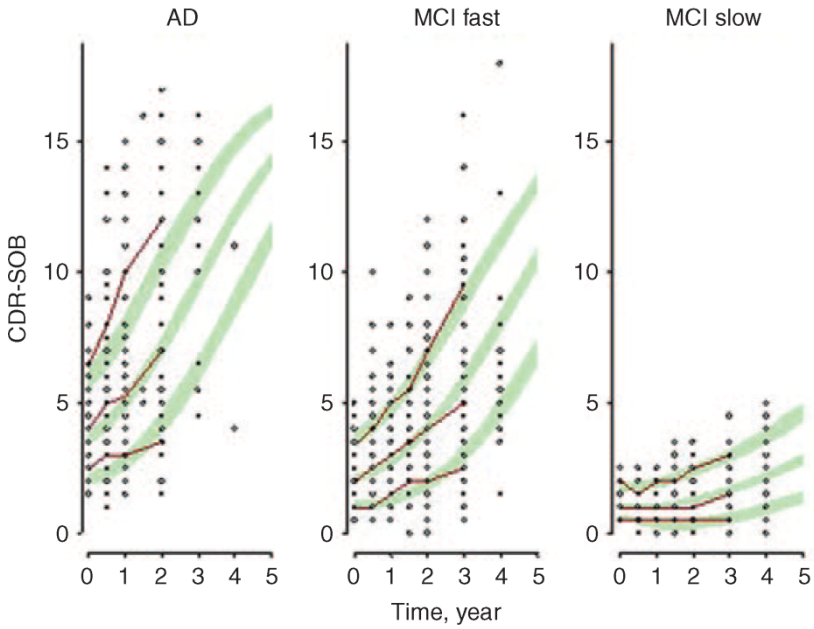
- Growing interest in starting to treat patients in the earlier stage even before the disease manifests clinical symptoms.
- Failing to demonstrate the efficacy with numerous new treatment modalities aimed at altering the disease progression.
- The EU/US/CTAD Task Force summarized existing and novel outcome assessments that may be useful in pre-dementia trials[1].
- FDA draft guidance[2] indicates CDR-SB as an example of a tool to assess disease progression as a single primary efficacy end point.

1. Vellas, et al. The journal of prevention of Alzheimer's disease. 2015;2(2):128-135. doi:10.14283/jpad.2015.55.
2. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf.

Disease Progression Model (1)

$$\frac{dA(1)}{dT} = \left(\text{RATE} + \left(A(1) \times \alpha\right)\right) \times \left(\frac{T^{30}}{\left(\text{DOT}^{30} + T^{30}\right)}\right)$$





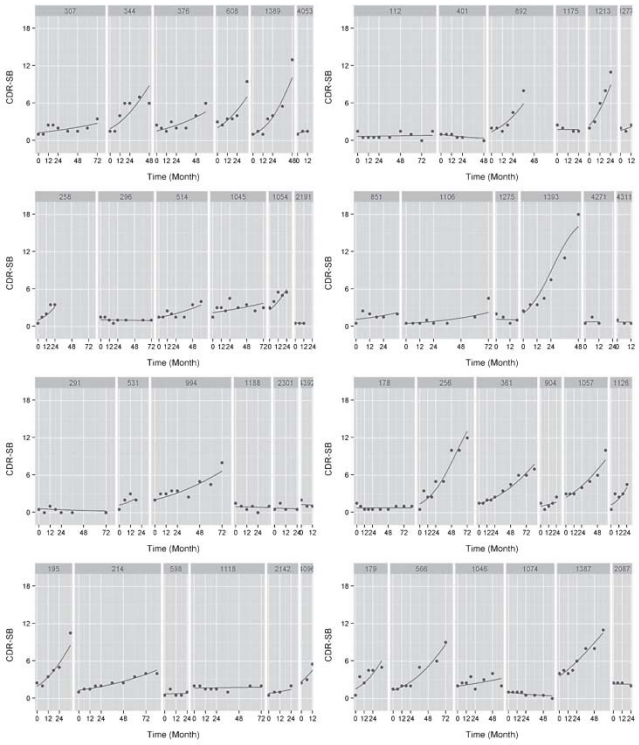
Delor et al. CPT-PSP(2013) doi:10.1038/psp.2013.54

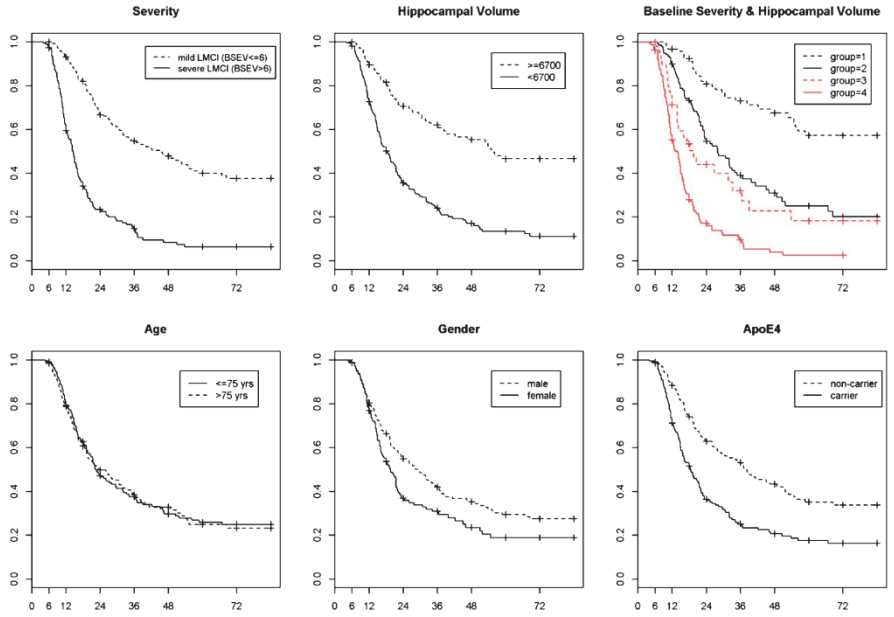
Disease Progression Model (2)

$$y \in (0,18) \mapsto z \in (0,1): \quad z = \frac{y-a}{b-a}$$

$$z(0,1) \mapsto x \in (-\infty,\infty): \quad x = h(y;\alpha) = \begin{cases} \log\left[\dfrac{(1-z)^{-\alpha}-1}{\alpha}\right] & \alpha \neq 0 \\ \log(-\log(1-z)) & \alpha = 0 \end{cases}$$

$$y = h\left(CDR\text{-}SB(t)\right) = \alpha_{INT} + \eta_{INT} + (\alpha_{SLP} + \eta_{SLP}) \cdot t + \varepsilon = \mu(t) + \varepsilon$$





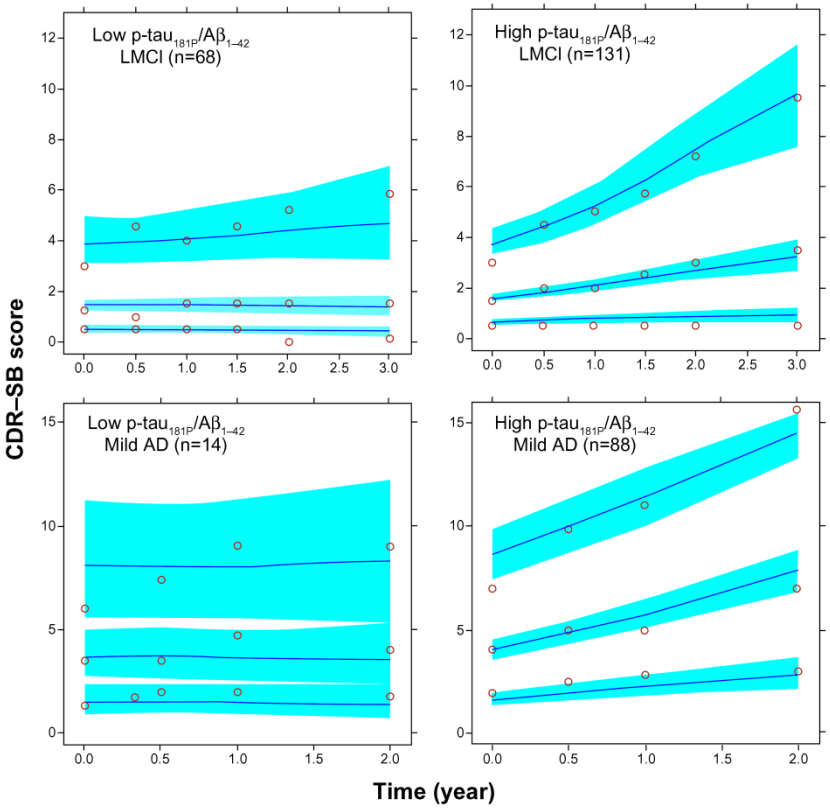
KM plot for 1 point change in CDR-SB by covariate of interest.

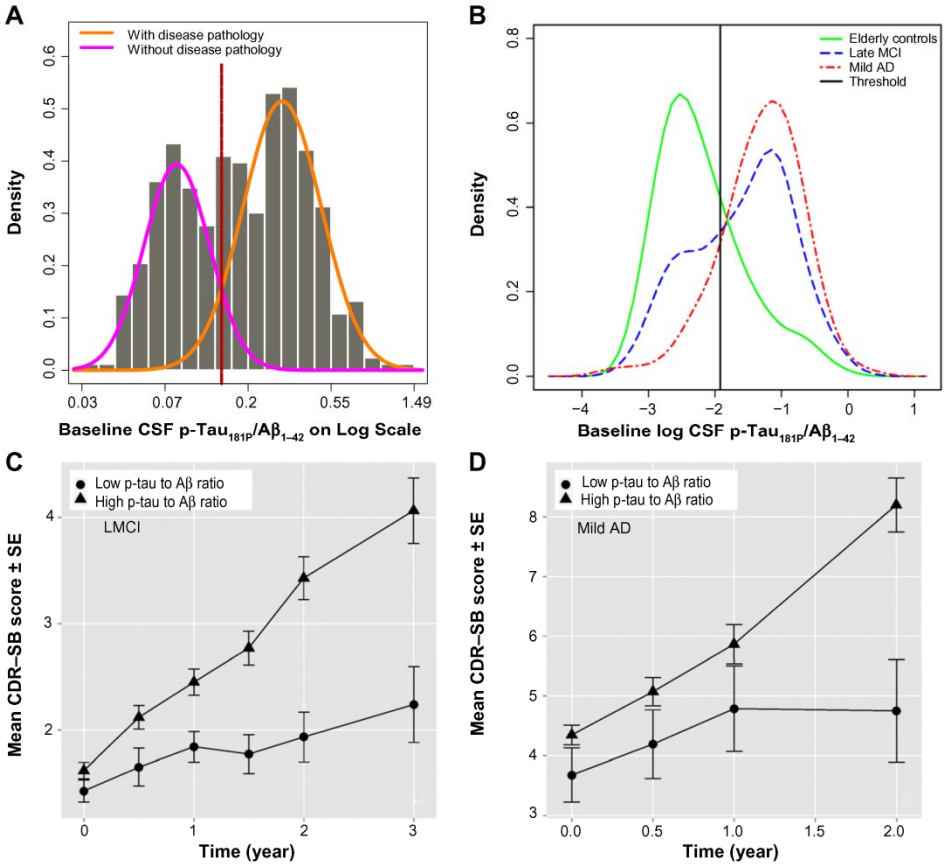
Ito et al. JAD 40 (2014) 967-979

Disease Progression Model (3)

$$\frac{dR_i}{dt} = \alpha_i \cdot R_i^{\beta}\left[1 - \frac{R_i}{18}\right];\ R_i(0) = R_{0i}$$

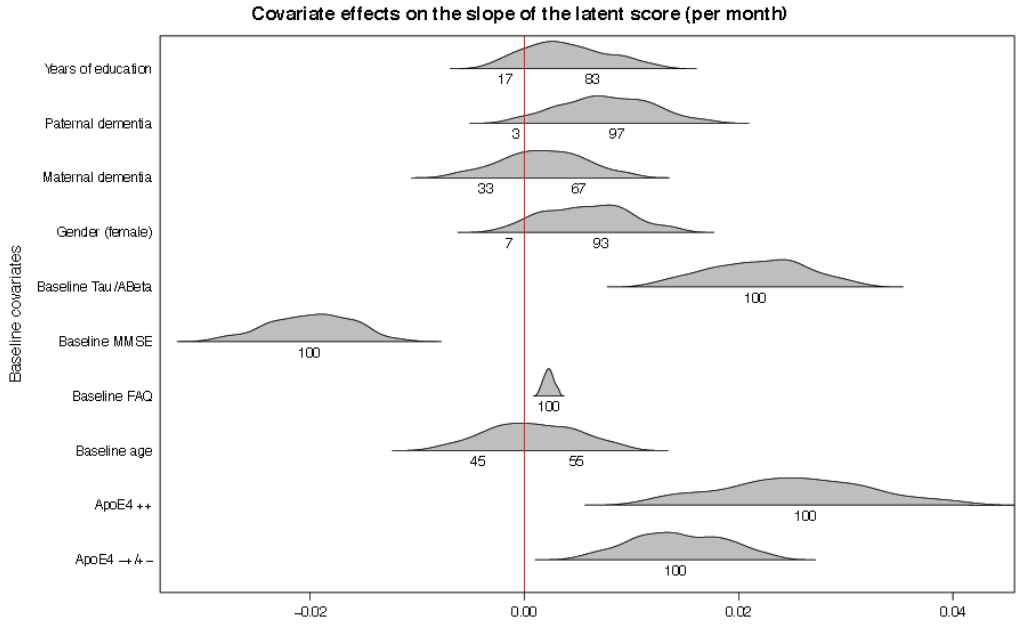
$$\mu(t, R_{0i}, \alpha_i, \beta) = \frac{R_i}{18}$$

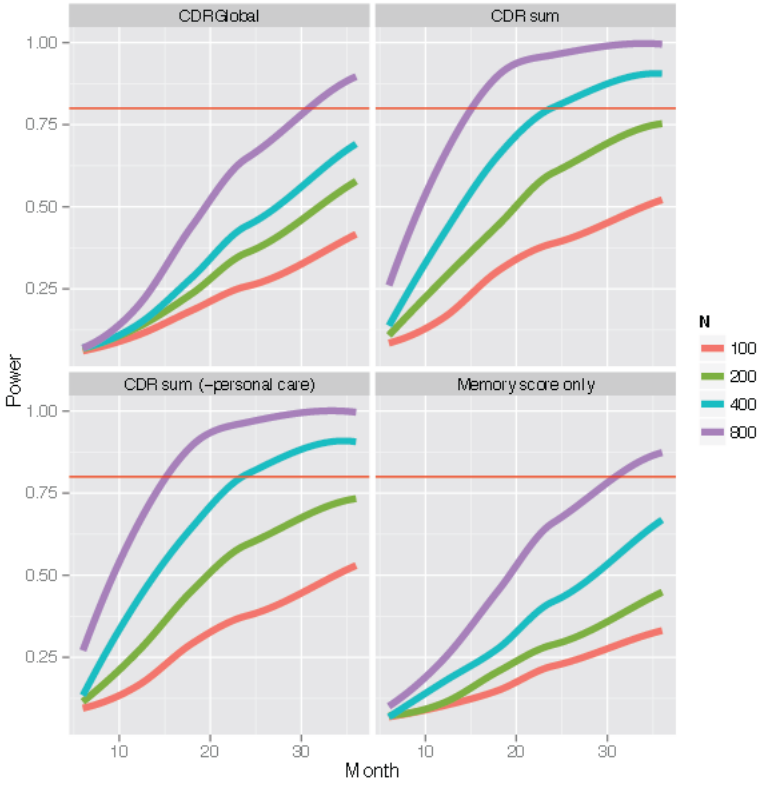




Samtani et al. Neuropsychiatric Disease and Treatment 2014:10 929–952

Disease Progression Model (4)





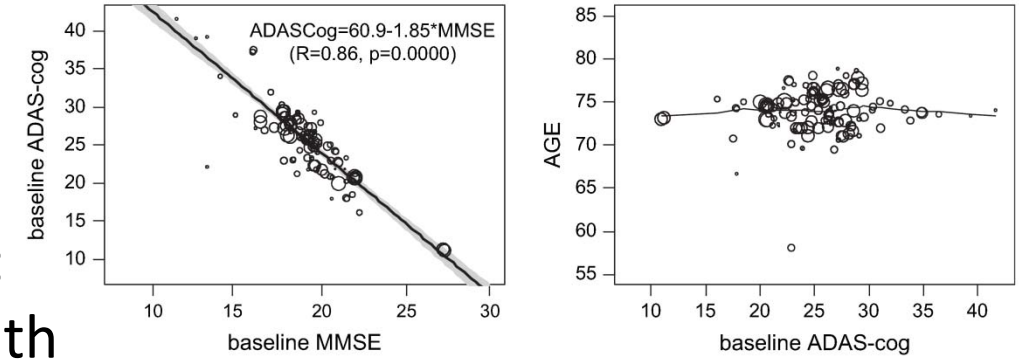
Clinical Dementia Rating Modeling and Simulation: *Joint progression of CDR and biomarkers in the ADNI cohort.*

Polhamus et al. AAIC poster (2013)

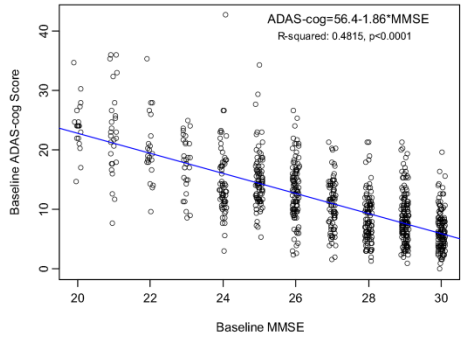
Why is Individual Data so Important?

- Individual data allow us to evaluate the covariate (predictor) effect for disease progression.
- Summary level meta-analysis: Potential "ecological bias"[1] with covariate effects
- Aggregation bias arises from the inability of aggregate data to characterize within-group variability in covariates[2].

Summary level data

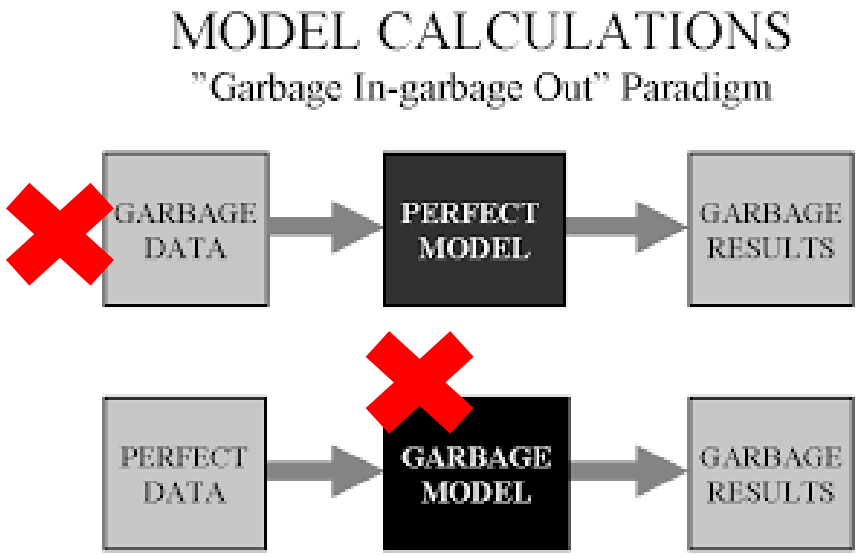


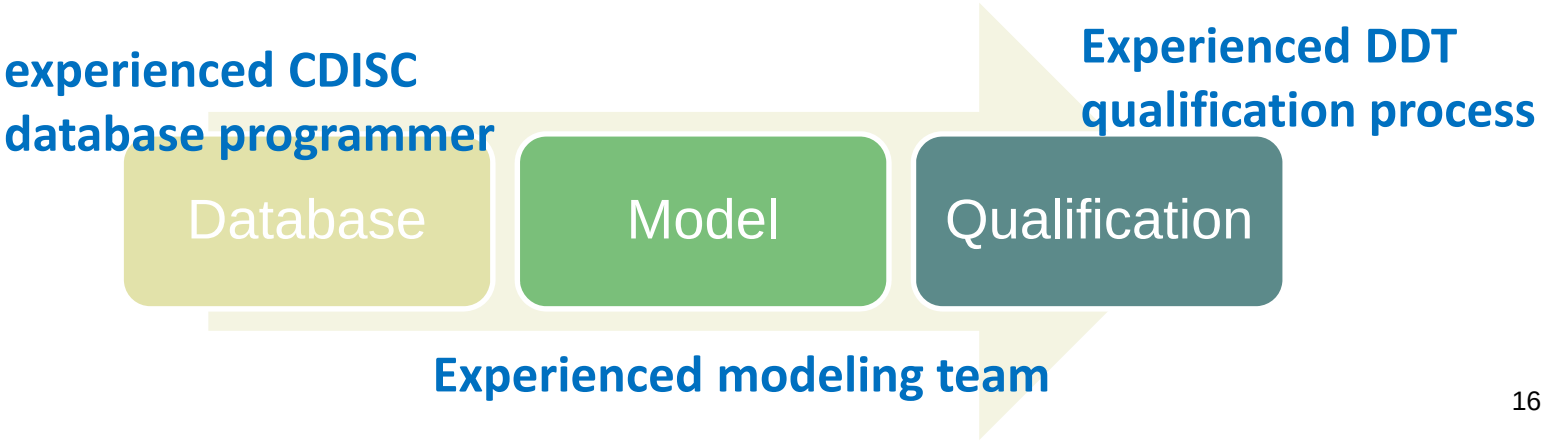
Individual level data



1. Berlin JA et al. Statist. Med. 2002; 21: 589-624.
2. J. Wakefield. Annu.Rev.Public Health.2008. 29:75-90.

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





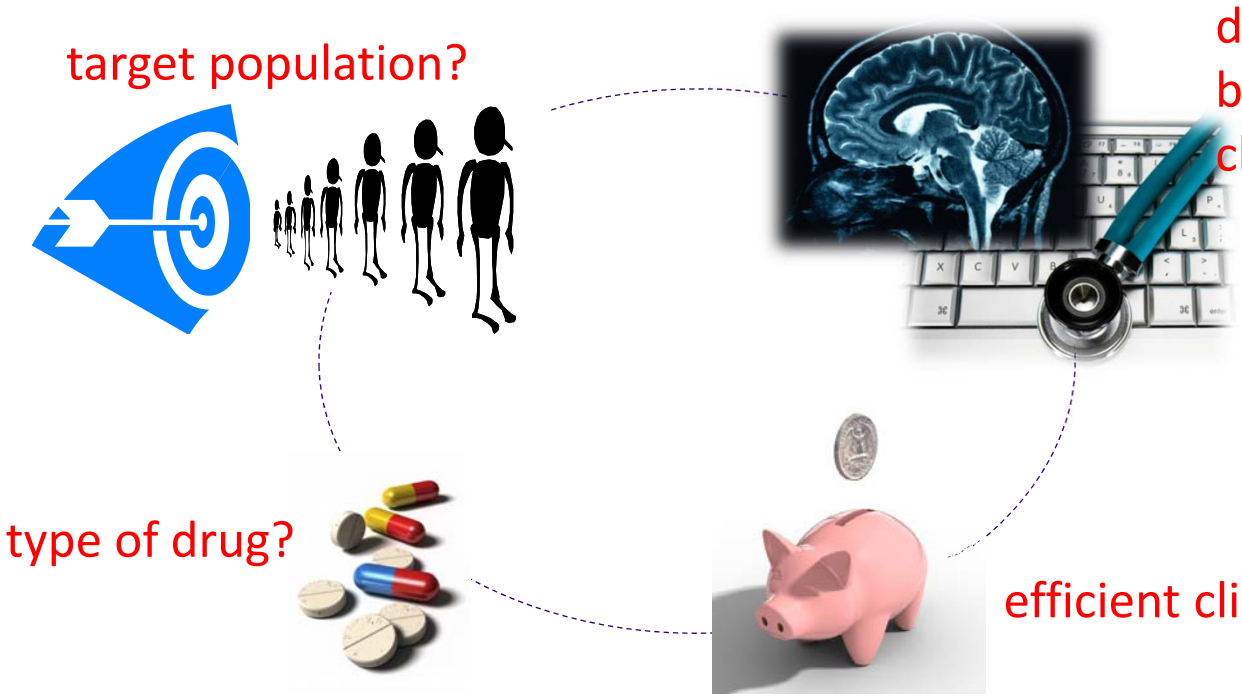
Cognitive Biases

"Cognitive biases are tendencies to think in certain ways that can lead to systematic deviations from a standard of rationality or good judgment, and are often studied in psychology and behavioral economics."

Belief bias	An effect where someone's evaluation of the logical strength of an argument is biased by the believability of the conclusion
Confirmation bias	The tendency to search for, interpret, focus on and remember information in a way that confirms one's preconceptions
Insensitivity to sample size	The tendency to under-expect variation in small samples

Accumulated controlled clinical data and appropriate mathematical model can help to avoid these biases

Connecting the Dots



Pharmacometrics approaches within consortia can help to understand critical questions in a systematic way by addressing issues quantitatively, and integrating knowledge/expertise across companies, regulators, and academia.

Summary

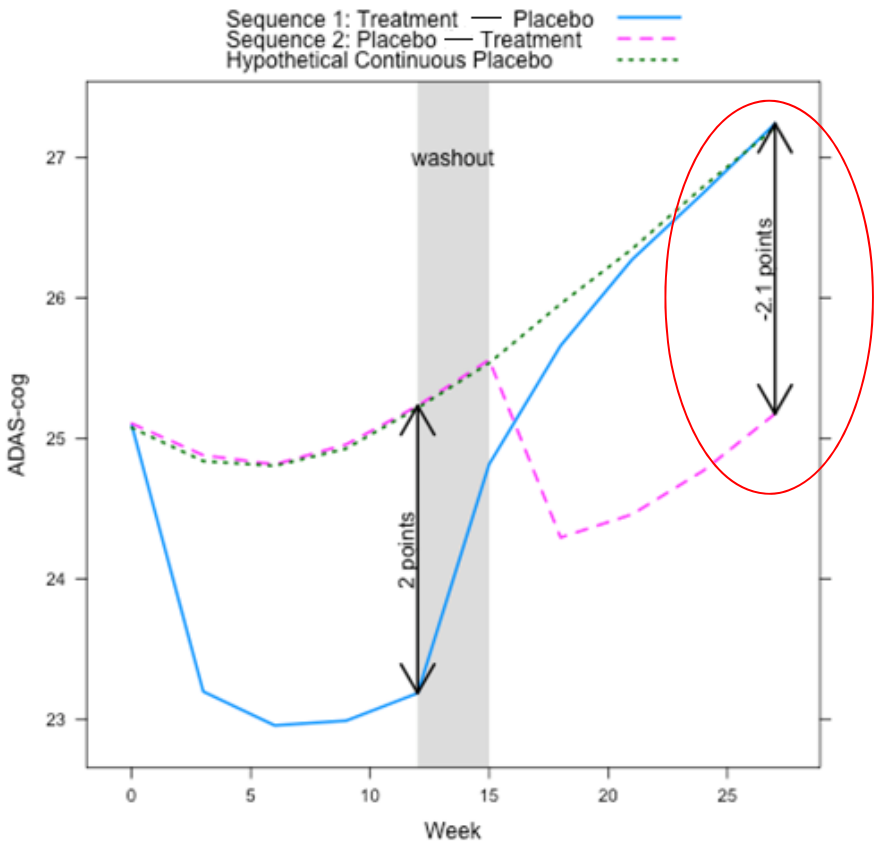
- Analyses focusing on single biomarkers will unlikely provide a comprehensive picture of their contribution to understand disease progression.
- Disease progression modeling allows for a quantitative understanding of the interplay between sources of variability (biomarkers, baseline severity, genetics, 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.

Acknowledgement

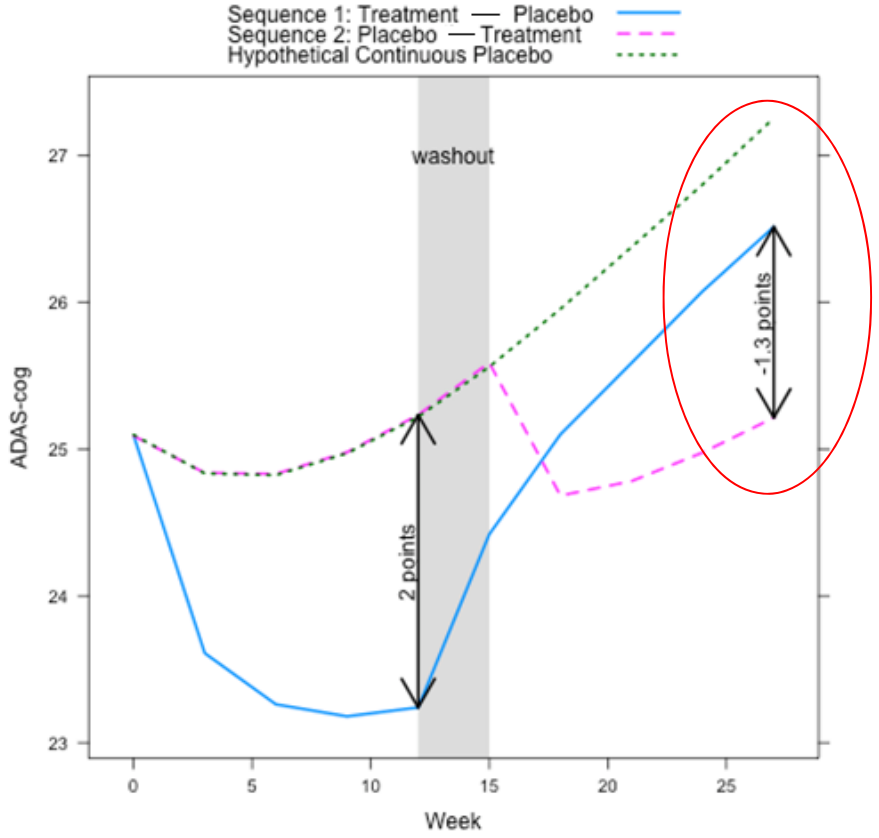
BACKUPS

Model Based Trial Simulation Example: Comparison of Different Drug Effect Type Scenarios in Early Development Study Designs

If symptomatic only



If symptomatic + Disease modifying



Model Based Trial Simulation Example: Comparison of Power, Sample size and DM Effect in Two Design Settings Where Normal Methodologies May Not Be Applicable

91-week Delayed-Start Design

Versus

78-week Parallel Study Design

By varying Disease Modifying Effects