Application of Modeling and Simulation to Support Clinical Drug Development Decisions in Alzheimer's Disease

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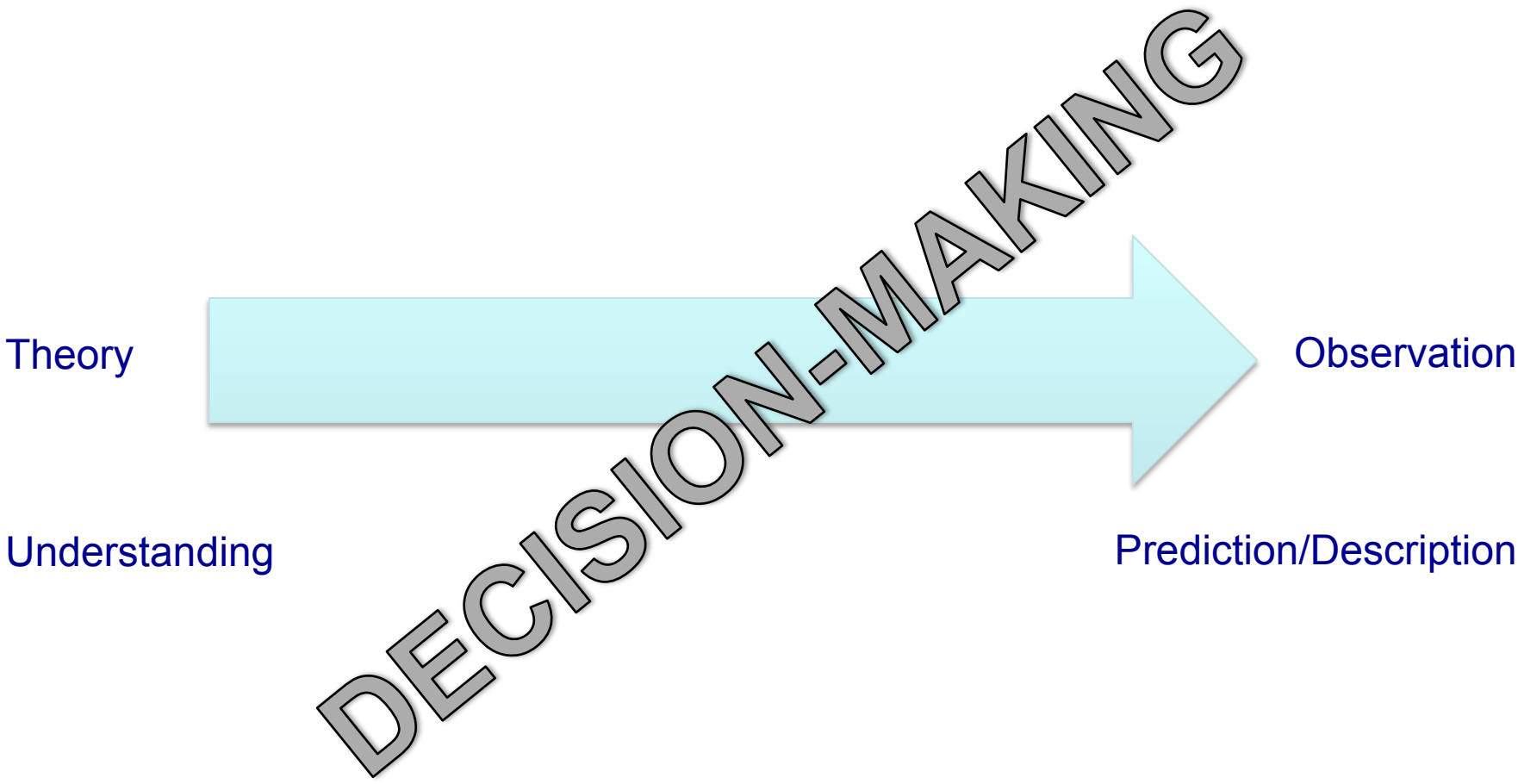
Overview

- Quantitative Decision Making in Drug Development
  - Understanding Questions
  - Developing Quantitative Decision Criteria
  - Modeling and Simulation to Support Decisions

- Examples in Alzheimer's Disease
  - Development Questions & Quantitative Criteria
  - Disease Progression Model Development
  - Applications:
    - Application to Proof of Concept Trials
    - Application in Adaptive Trial Designs
    - Biomarker-Based Decisions
    - Other Applications

Theory vs. Observation

Theory vs. Observation



Goal

Integrate current state of knowledge and decision-maker expertise with quantitative modeling/simulation to enable better decision making.

Ineffective M&S

My model is the best thing since sliced bread! Look at all these great diagnostic plots and see how much the objective function changed…

I don't understand this jargon. How does this help us make drug development decisions?

First, Listen and Understand

Understand the Development Questions

Rate the most challenging (1= least, 10=most) decisions in early development

Decision	Mean	SEM
Dose selection and prediction for FIH (translation from animals to man)	5.71	0.30
Assessment of maximum tolerated dose (MTD)	5.12	0.27
Uncertainty about relationship between biomarker(s) and clinical outcome(s)	8.08	0.21
Uncertainty about benefit-risk assessment moving from HV to patients	5.65	0.28
Dose/study design selection for POC (extrapolating from HV to patients)	6.49	0.26

Extracted from 2011 ASOP/ASCPT survey, to be presented in full:
March 13-14, 2012 Gaylord National Hotel
ASOP/ASCPT Preconference Symposium on Quantitative Decision Making in Development of Drugs and Biologics: What Can We Learn From Other Industries?

Rate the most challenging (1= least, 10=most) decisions in late development

Decision	Mean	SEM
Lack of sufficient information about safety	6.39	0.29
Difficulties in establishing a dose-response	7.27	0.28
Lack of reliable information on competitors	4.70	0.29
Consensus on which endpoints are most important	6.30	0.28
Consensus on picking a target value	6.33	0.28
Consensus on quantitative criteria for dose selection	7.18	0.26
Consensus on quantitative criteria for Go/No-Go decisions	7.77	0.27

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Quantitative Decision Criteria

AT LEAST 90% OF PATIENTS

effect size of + 3 points

average response rate of 85%

no more than 10 msec

15% BETTER THAN COMPETITOR

less Than 12% Incidence Rate

LESS THAN OR EQUAL TO 5 MMHG

Are quantitative decision criteria defined in advance of reviewing the data?

Milestone	Count	Percent
POC	43	63.2
Phase 2B	35	51.5
Phase 3	39	57.4
Phase 3 Dose Selection	24	35.3

If defined, are these criteria a constantly moving target?

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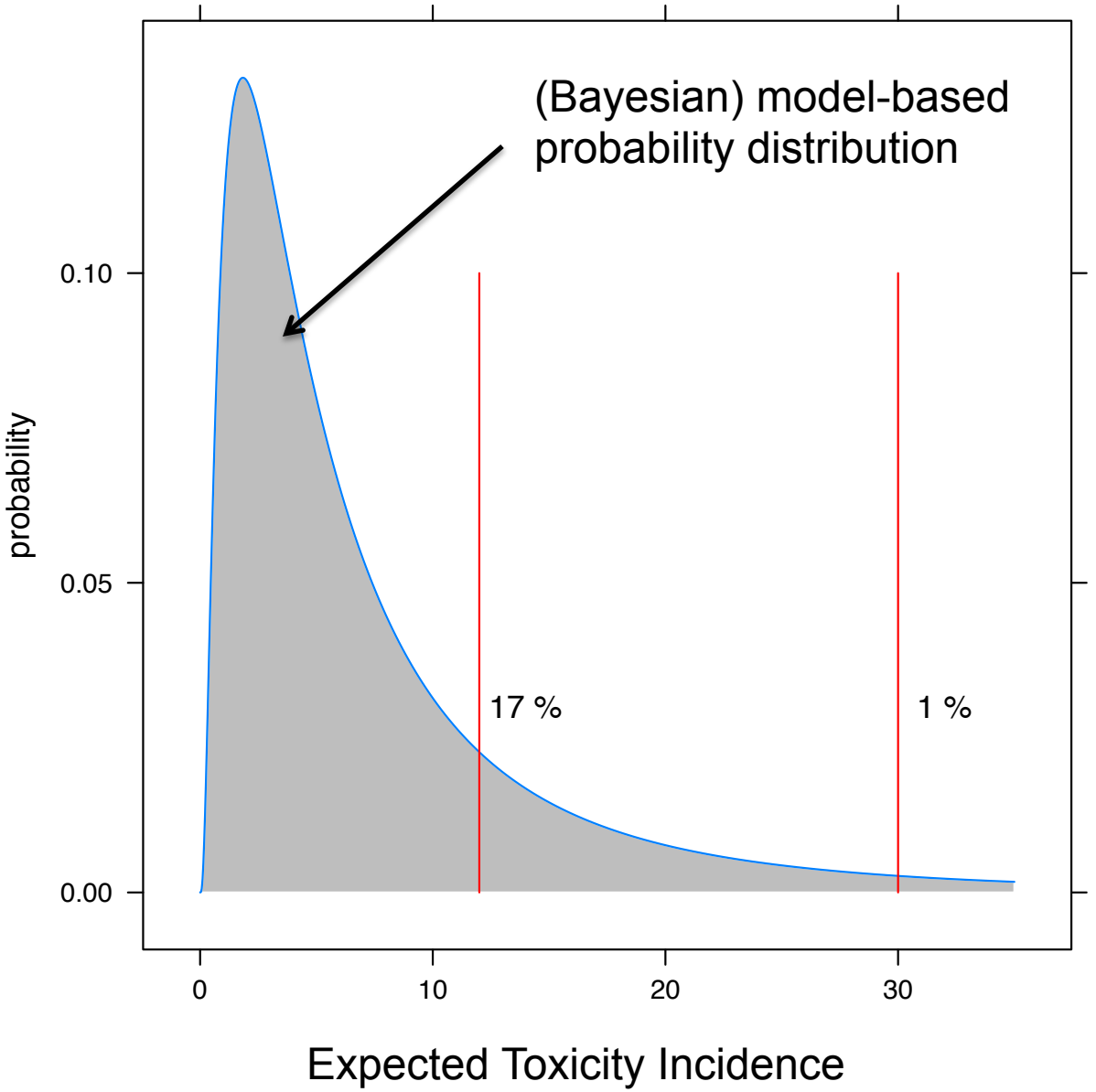
Focus M&S to Address Relevant Quantitative Questions



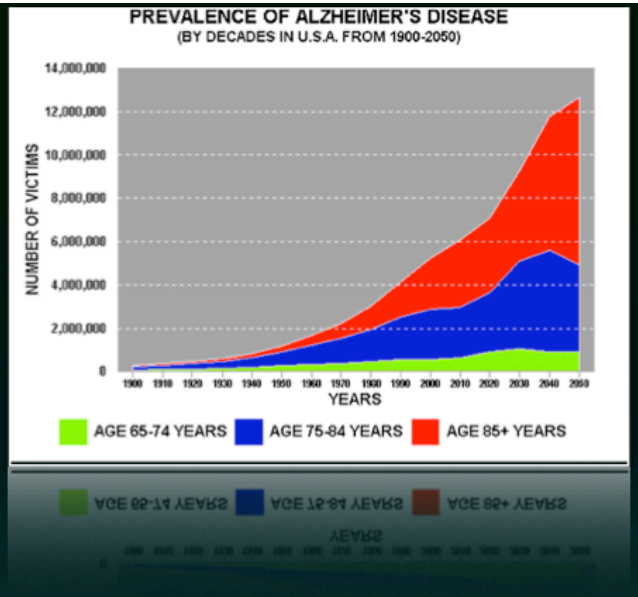
Given our current state of knowledge…

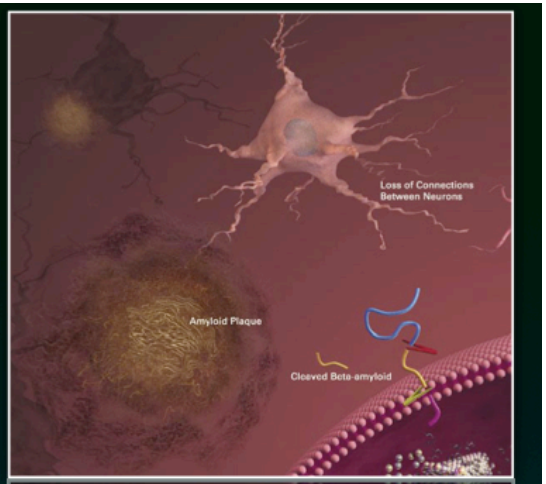
There is a 17% probability of tox. incidence being greater than 12%

But.. the probability of an incidence rate greater than 30% is very low.

Quantitative Drug Development Decision Making

Alzheimer's Disease





- Growing patient population
- Central nervous system disease mechanism
- Long-term trials
- Active R&D but lack of disease modifying therapies

Some Development Questions in AD

- How to design and interpret a POC study?
- What's the viability of a cross-over vs. parallel design?
- How do we efficiently select doses?
- What's the expected placebo response & duration?
- What trial duration and assessment schedule?
  - … for drug with anticipated symptomatic (Sx), disease modifying (DM), or both effects?
  - … if studying an early AD population?

More Development Questions in AD

- How would enrichment affect power of the design, and which endpoints should be used?
- Which covariates should be included in a pre-planned analysis?

- What's the probability of inferring DM mechanism and which design should we use?
- What's the impact of attrition on study design and interpretation?
- How do we interpret biomarker data without a causal link to efficacy?

AD Model Development

Brief History of Published AD Progression Models

- Disease progression model published by Holford and Peace[1]

$$E[S(t)] = S(0) + \alpha \bullet t + E_{PBO}(t) + E_{DRUG}(Concentration)$$

- Ito *et al*[2] developed meta-analytic version of this model (based on summary data) and applied it to new data.
  - Inclusion of new covariates (e.g. baseline severity) and modeled drug effect directly as a function of time and dose

$$E[S(t)] = S(0) + \alpha \bullet t + E_{PBO}(t) + E_{DRUG}(t, Dose)$$

- Gillespie *et al*[3] Bayesian Model-Based Meta Analysis
  - Simultaneous modeling of summary-level and patient-level data, constrains model to capped scale.

1 Holford, N.H. and Peace, K.E. Methodologic aspects of a population pharmacodynamic model for cognitive effects in alzheimer patients treated with tacrine. Proceedings of the National Academy of Sciences of the United States of America 89 (1992):11466–11470.

2 Disease progression meta-analysis model in Alzheimer's disease. Kaori Ito, Sima Ahadieh, Brian Corrigan, Jonathan French, Terence Fullerton, Thomas Tensfeldt, Alzheimer's Disease Working Group Alzheimer's & Dementia: The Journal of the Alzheimer's Association January 2010 (Vol. 6, Issue 1, Pages 39-53)

3 http://metrumrg.com/images/stories/publications/acop2009-adascog.pdf

Recent Bayesian Model-Based Meta-Analysis

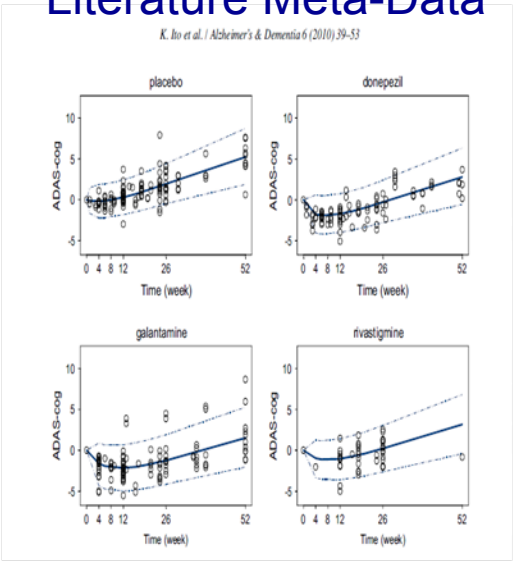
http://www.adni-info.org/

ADNI Defining Alzheimer's Disease

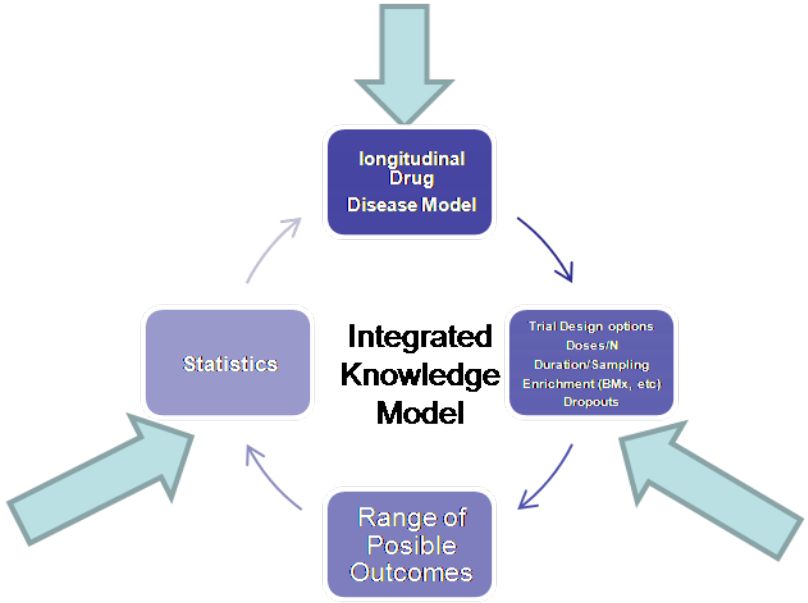
- Natural History
- Interpatient Variability
- Patient Specific Factors
- Imaging and CSF Biomarkers

Sub-populations
Normal (N=200)
MCI (N=400)
Mild AD (N=200)

Literature Meta-Data



- 73 Trials (1990 to Present)
- Interstudy variability
- Estimate of drug treatment effects (magnitude, onset, offset)

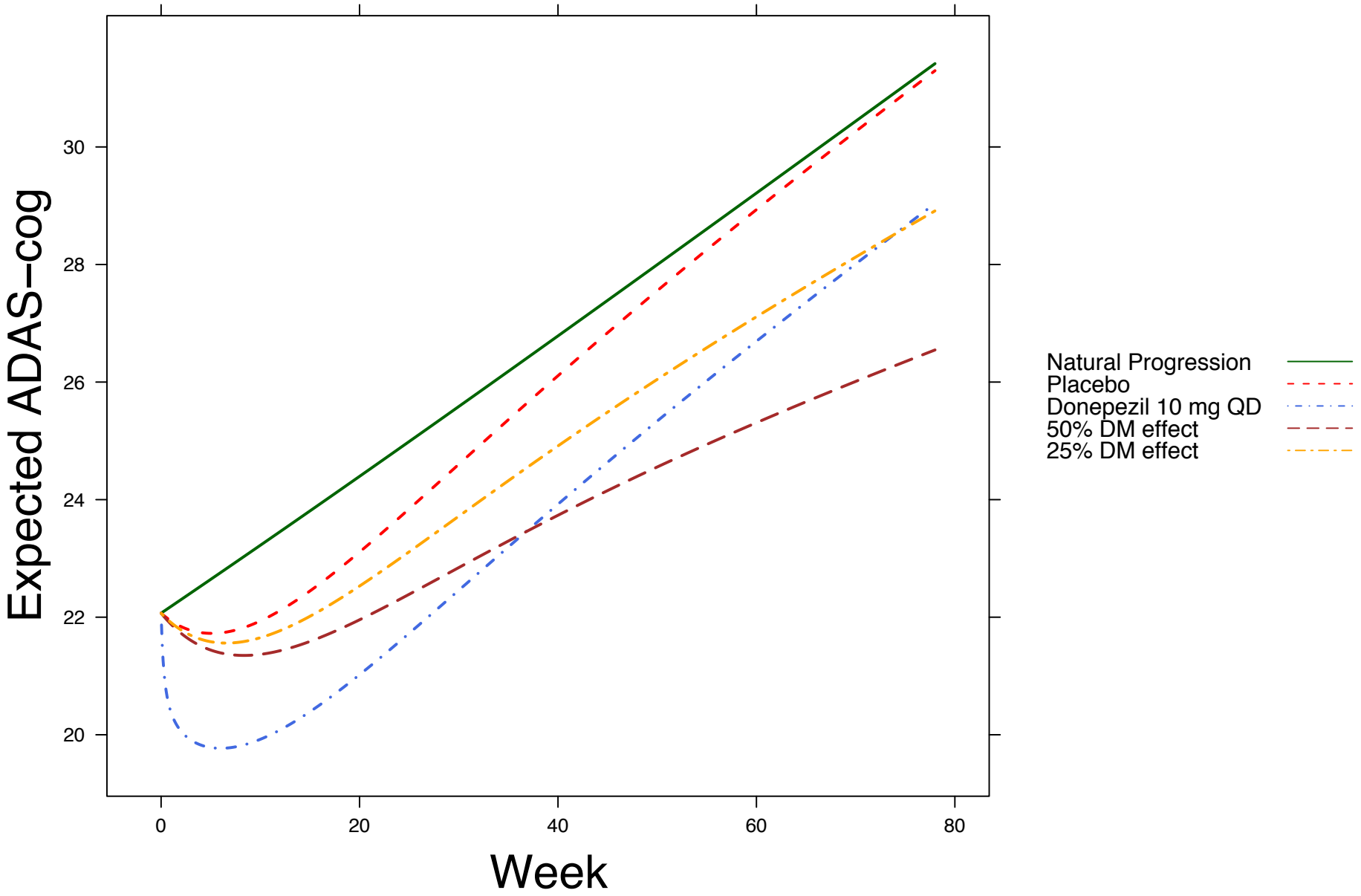


CAMD
CRITICAL PATH INSTITUTE

- 9 trials, 3223 patients
- Interpatient Variability
- Patient Specific Factors
- Placebo Effect

http://www.c-path.org/CAMD.cfm

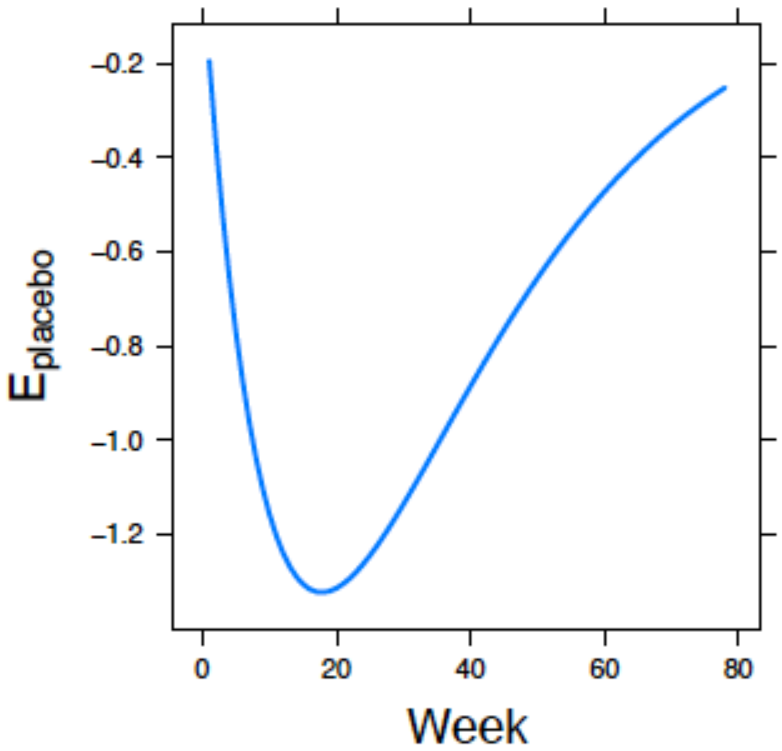
Disease Progression: ADAScog

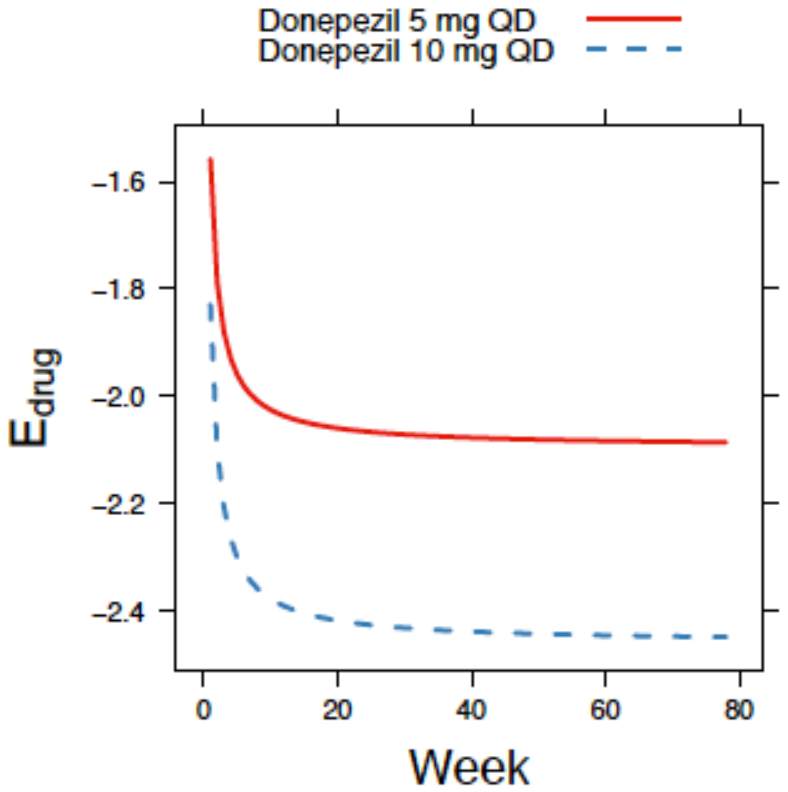


Fixed Effects Models for Placebo and Symptomatic Drug

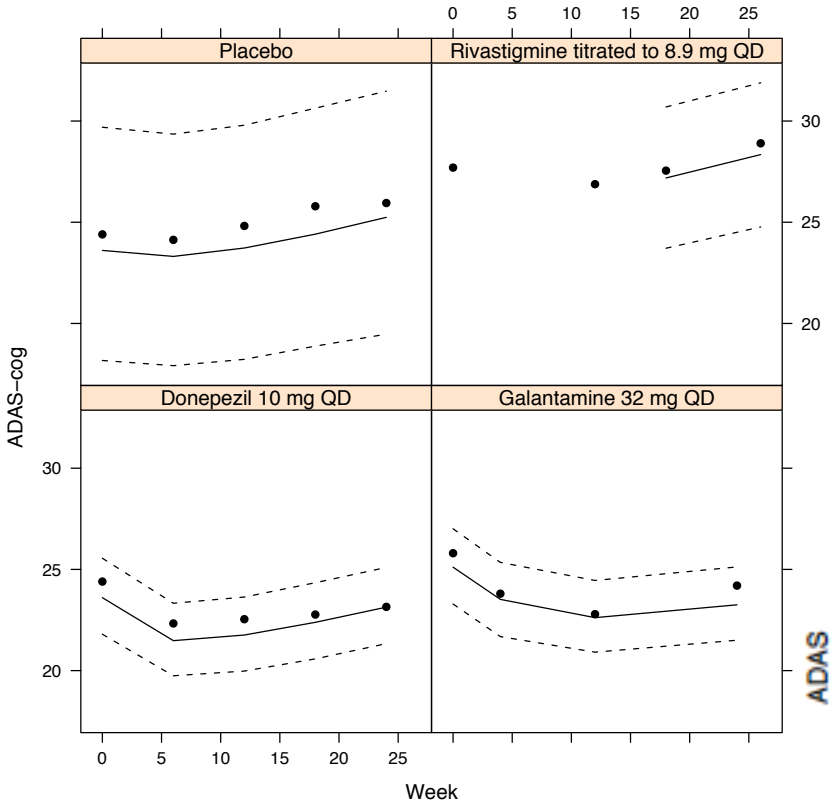
$$E_{\text{placebo},ipk} = \beta\left(e^{-k_{el}t_{ijk}} - e^{-k_{eq}t_{ijk}}\right)$$

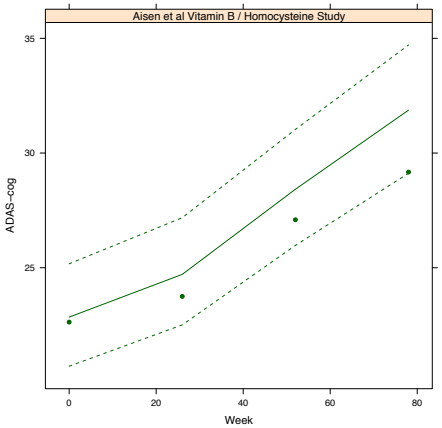
$$E_{\text{drug},idk} = \left(\frac{D_d}{D_{\text{ref},d}}\right)^{\gamma_d} \frac{E_{\Delta,d}\,t_{idk}}{ET_{50,d} + t_{idk}}$$

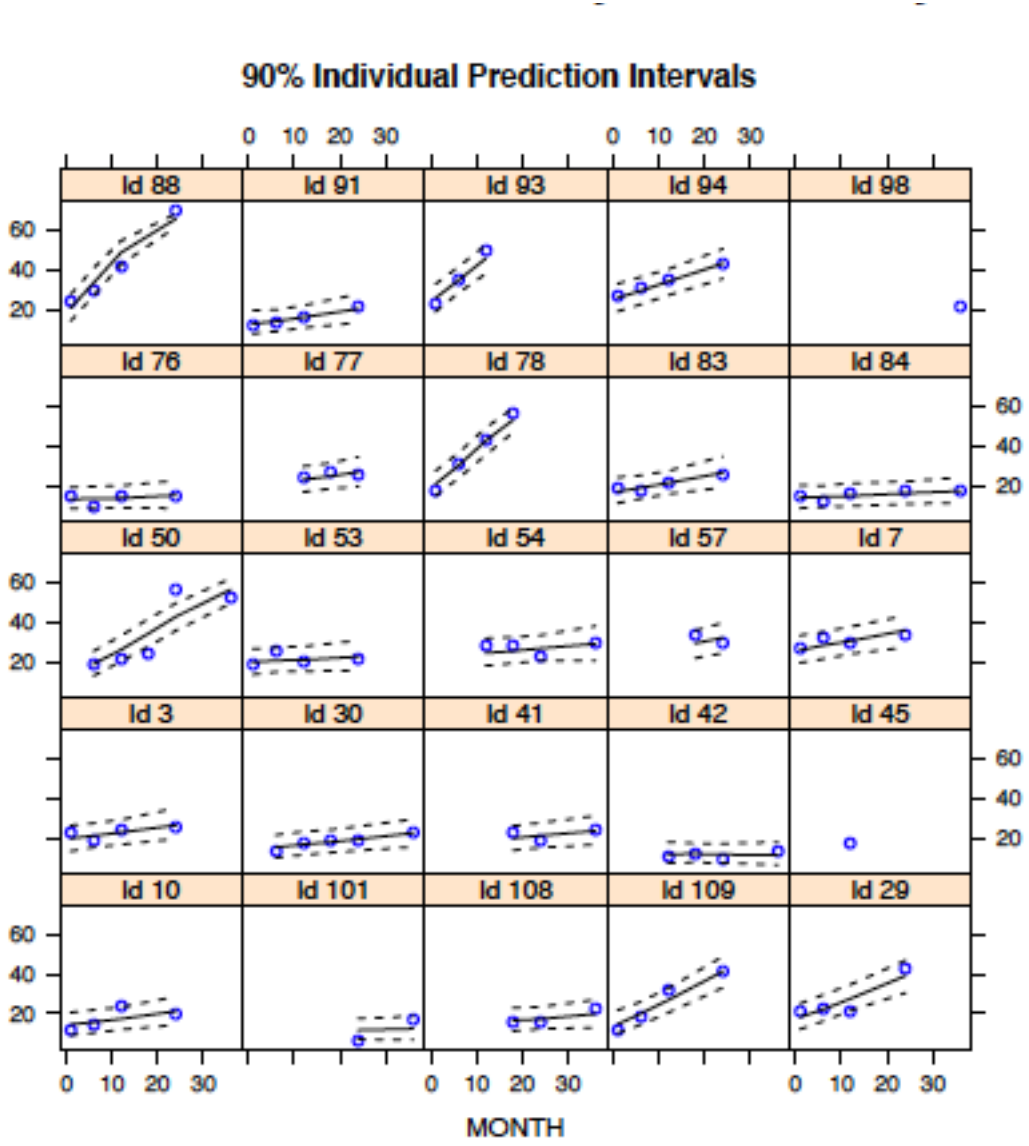




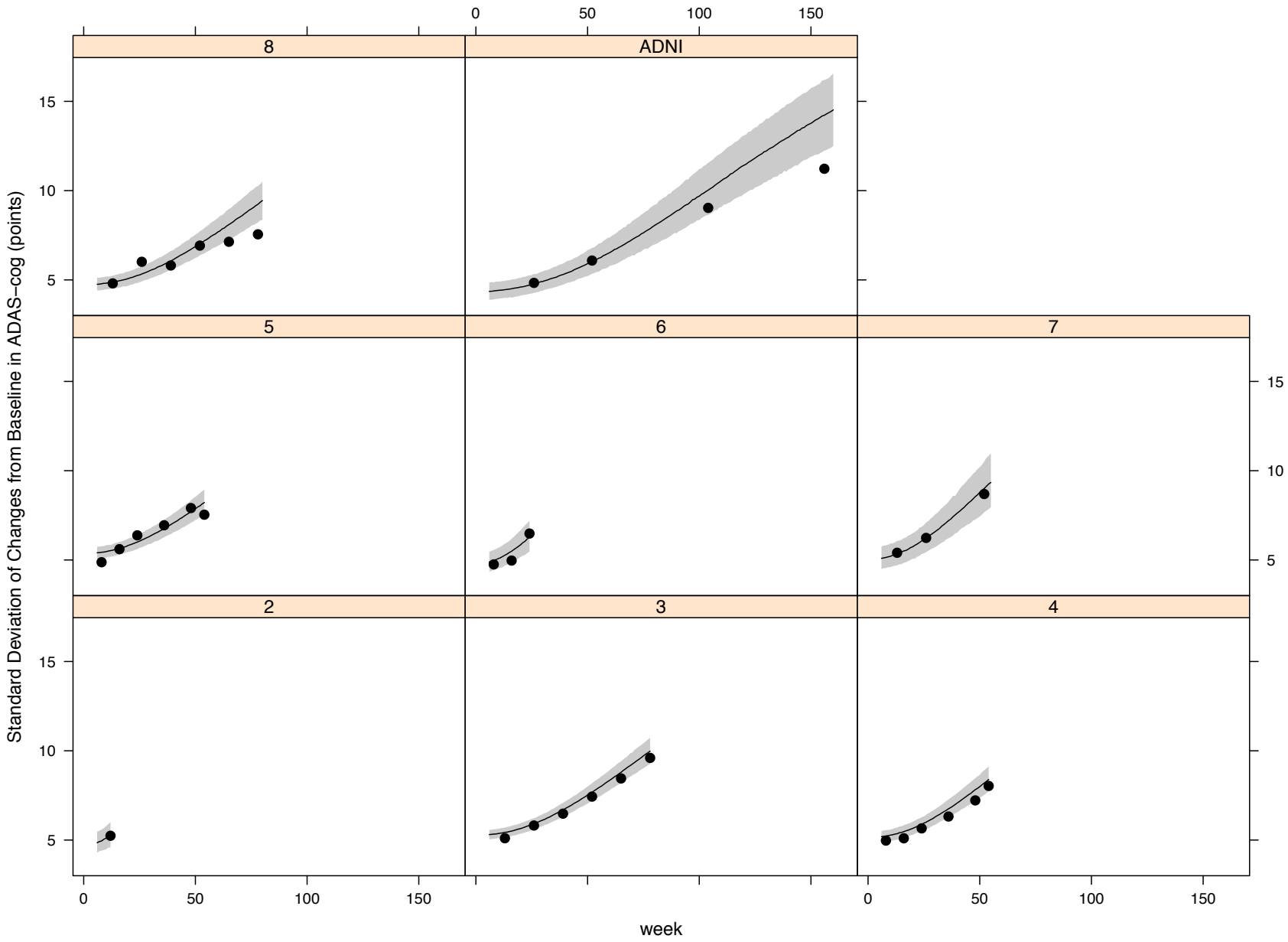
Disease Progression Model Predictions



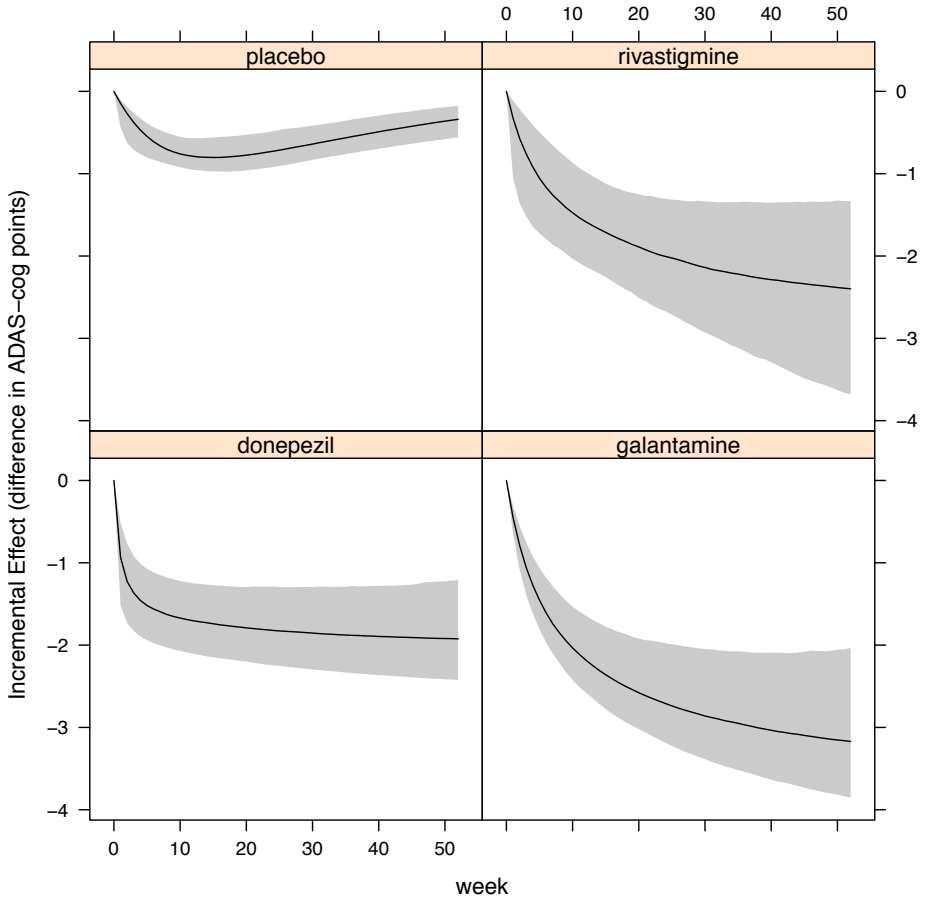


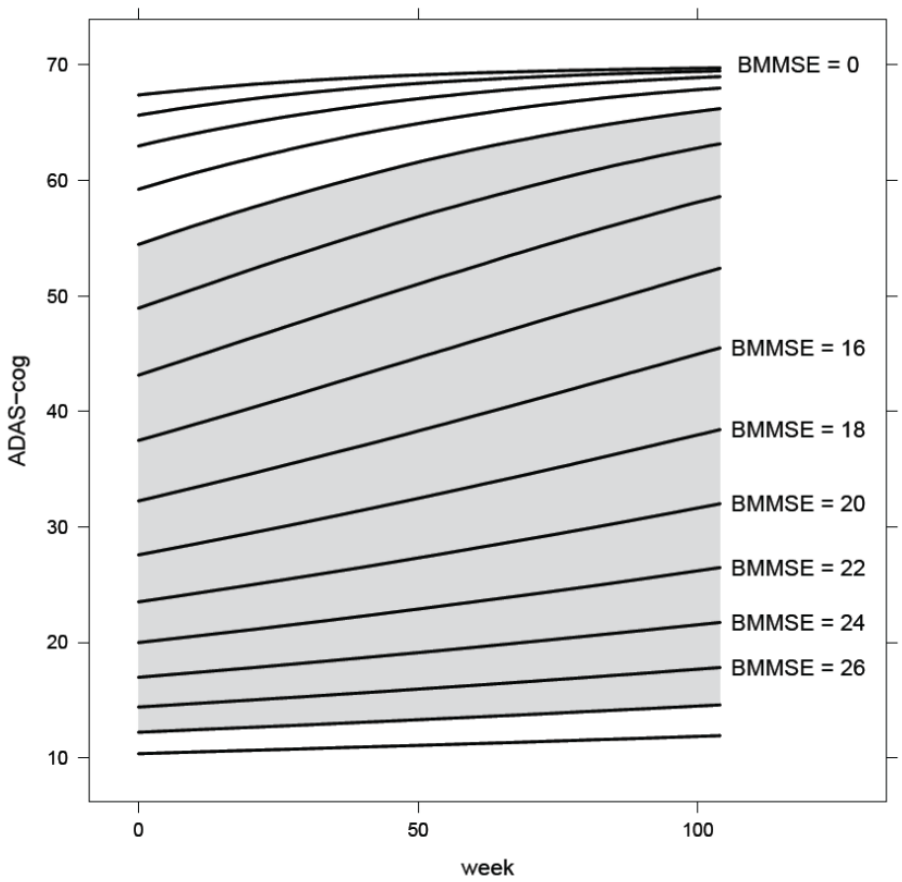


Posterior Prediction of CAMD Data Sets



Back to Some Questions…

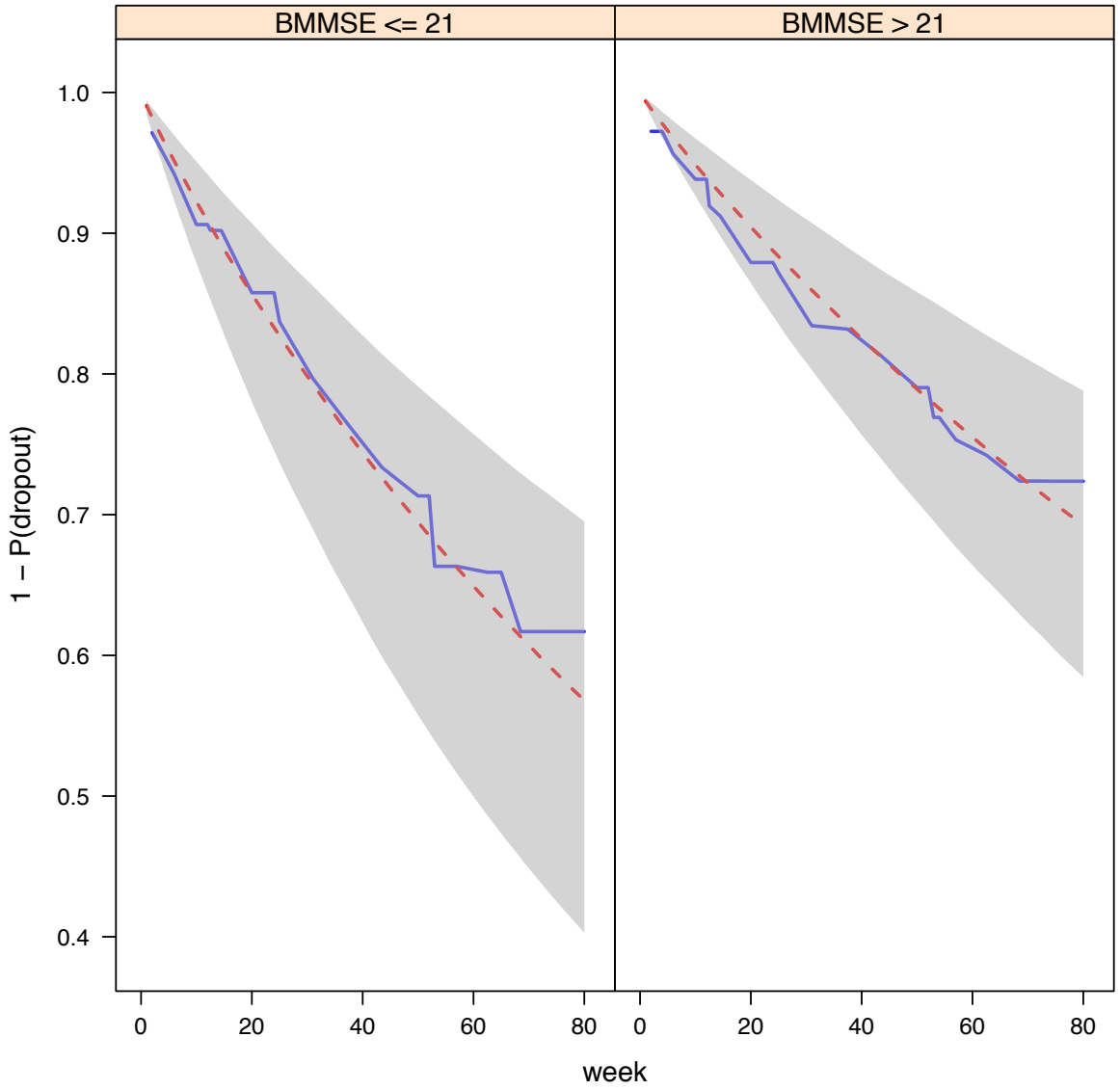




- What are expected placebo and competitor responses?

- What's the impact of baseline MMSE on rate of progression?

What's the relationship between covariates and dropout?



How does baseline status impact probability of attrition?

How do we adjust the study design/ analysis to accommodate?

Applications to Decision-Making in AD: Symptomatic Effects

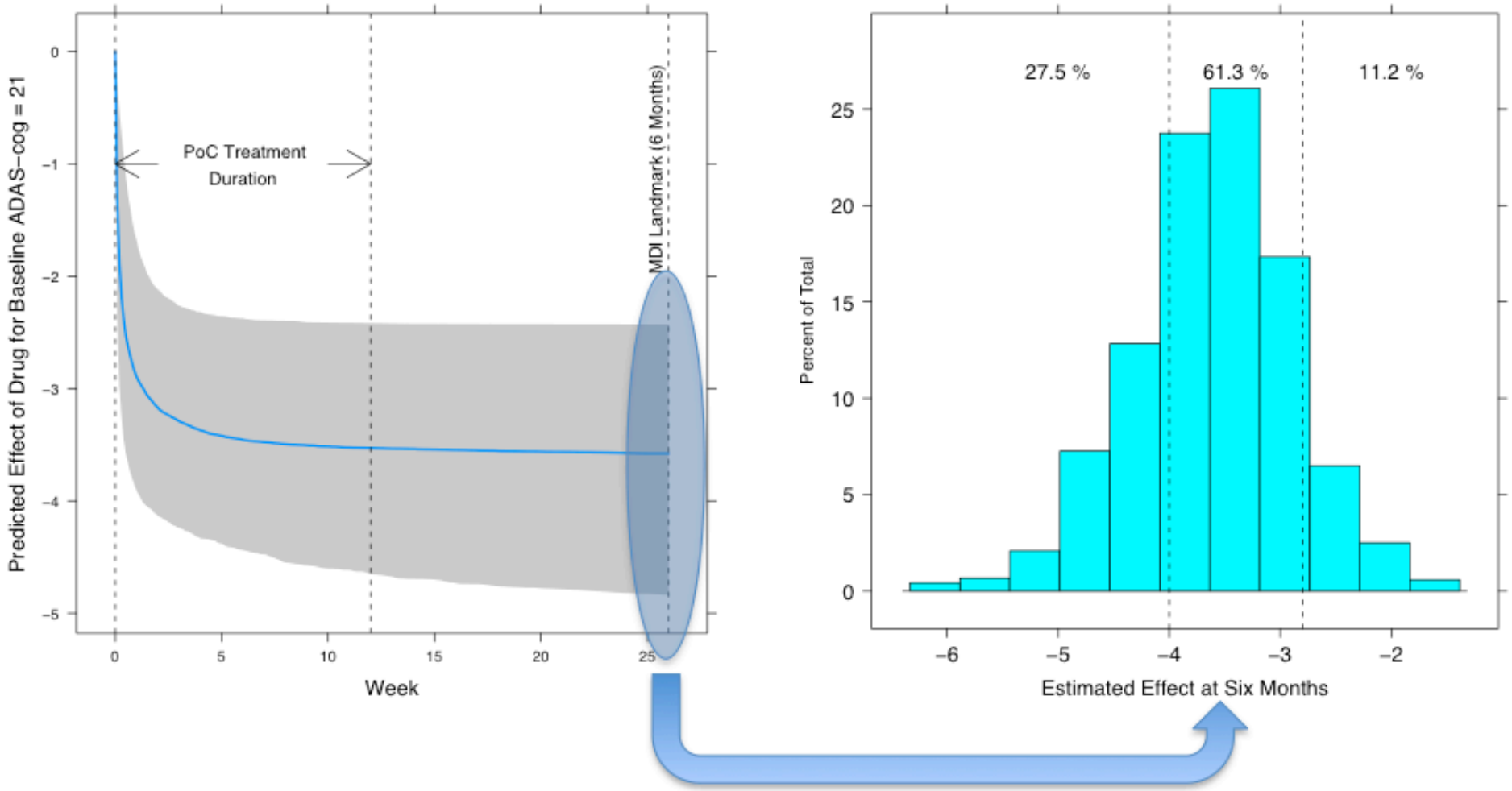
Proof of Concept (PoC) Trial Simulation

- Is further investment warranted for this drug & indication?
- Can we design an informative PoC study with a short trial duration?
  - Plan for a model-based analysis of PoC trial
    - Instead of traditional endpoint hypothesis testing vs. reference
  - Assess probability of achieving target product profile
    - Quantitative decision criteria based on 6-month ADAS-cog change from baseline relative to competing therapies
  - PoC decision based on posterior predictive distribution of 6-month outcomes, given shorter 6 or 12 week trials.
  - Trial simulations used to assess trial design performance
    - Trade-off between duration/cost & accuracy of trial results
    - Compared parallel and cross-over designs

Proof of Concept (PoC) Trial Simulation

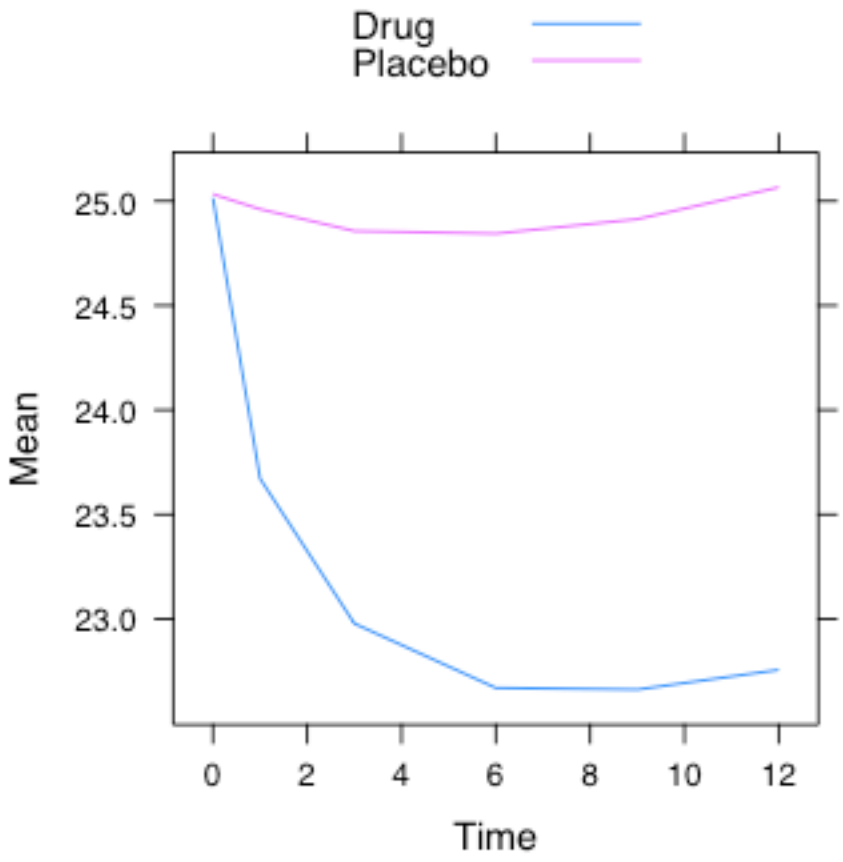
Target product response for change in ADAScog score at 6 months:

- must have -2.5 units
- wish for -4 units

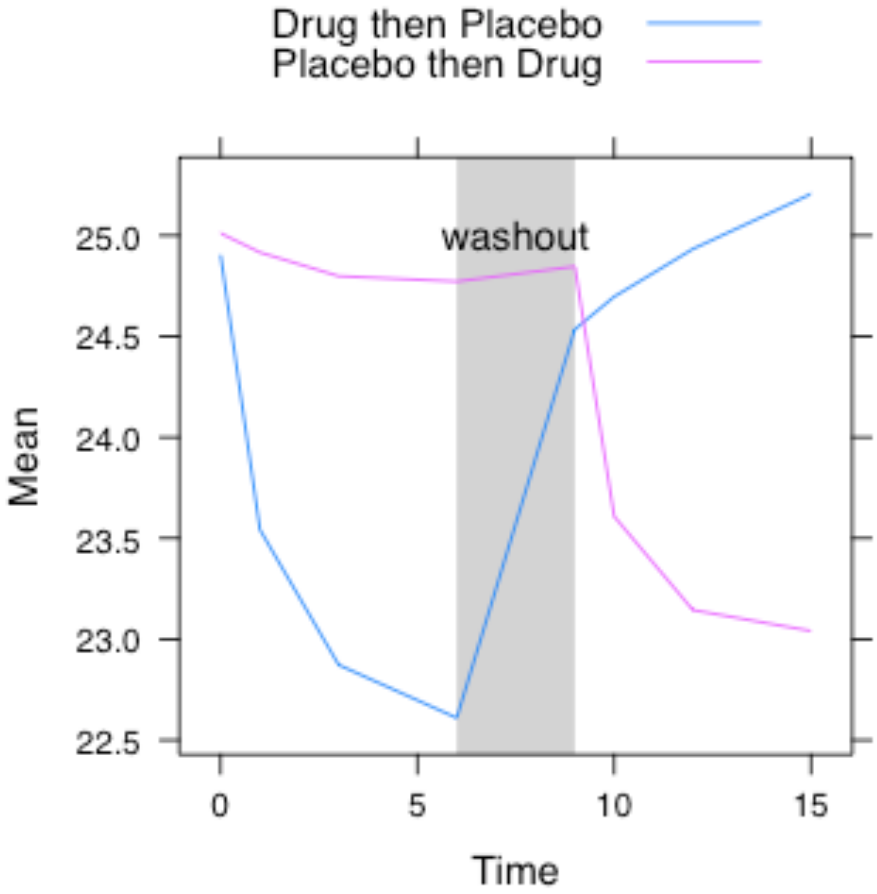


Exploring PoC AD Trial Design Options

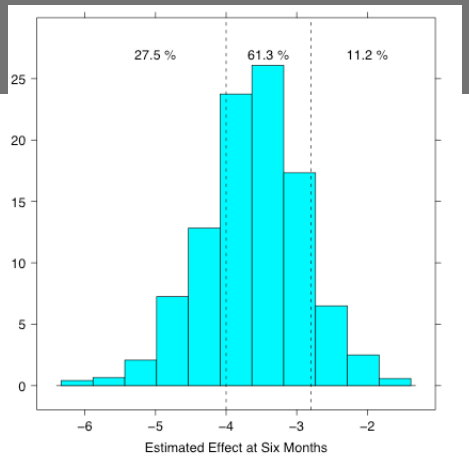
Parallel



Cross-Over



Exploring PoC AD Trial Design Options



Given quantitative criteria, explore performance under different assumptions about true drug characteristics.

Assuming drug reaches 50% of maximal effect at 4 weeks:

12 Week Parallel Design

Truth	Decision GO	NO GO
$E(6) = 2$	0%	100%
$E(6) = 4.5$	92%	8%

6 Week Cross-over Design

Truth	Decision GO	NO GO
$E(6) = 2$	10%	90%
$E(6) = 4.5$	92%	8%

$E(6)$ denotes placebo-adjusted drug effect at 6 months;
Table percentages based on 100 simulations

Bayesian Adaptive PoC/Dose-Finding Trial Design

Is it possible to gain efficiency in drug development through an adaptive approach vs. traditional process?

Traditional:

- Small PoC (2a) study in target population, usually at MTD
- Phase 2b study for dose finding
- Large Phase 3 confirmatory trial (sometimes in duplicate)

Adaptive:

- Stage 1: PoC and Initial Dose-Finding
- Stage 2: Definitive Dose-Finding
- Stage 3: Confirmatory Stage

Bayesian Adaptive PoC/Dose-Finding Trial Design

Stage 1: PoC and Initial Dose-Finding

- 9 dose levels of test drug, placebo, active comparator (AC)
- Adaptive treatment randomization
- Transition to Stage 2 when desired certainty in target dose range is reached, or stop if low probability of reaching target effect size.
- 12 week treatment duration

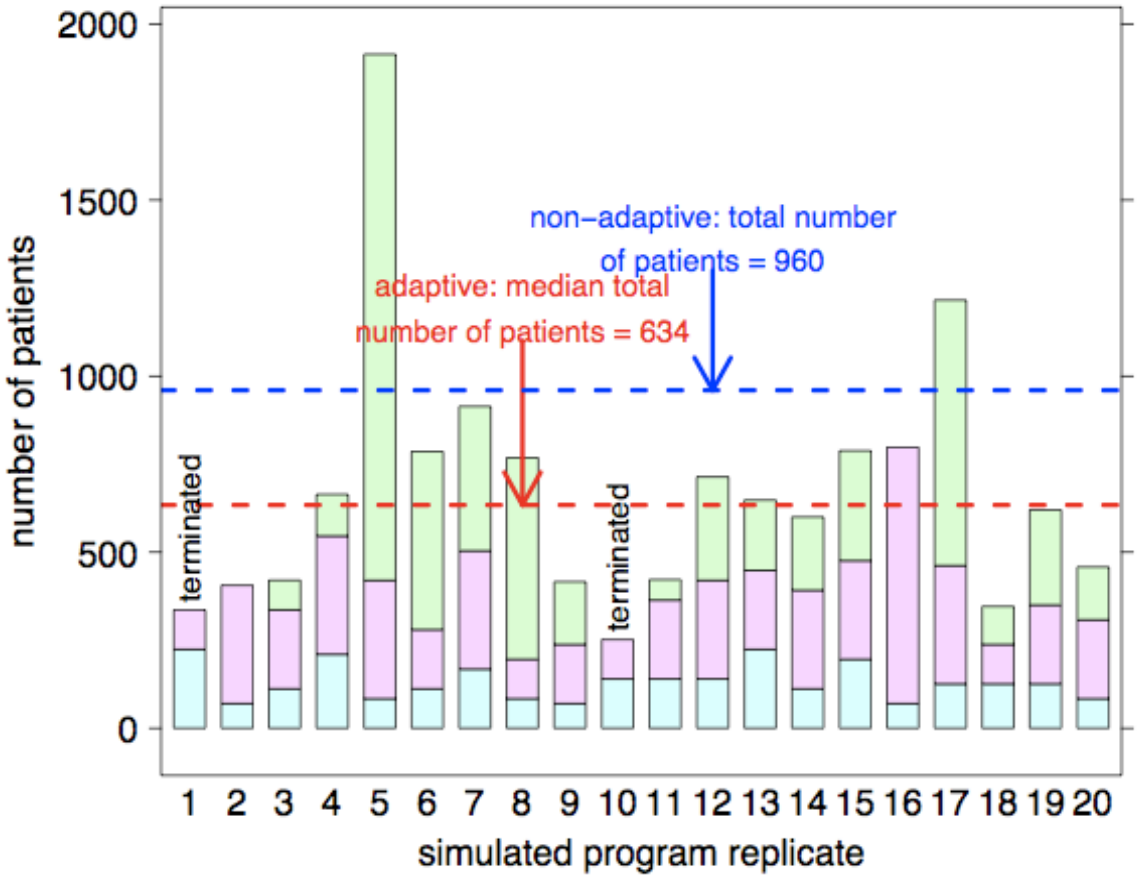
Stage 2: Definitive Dose Finding

- Seamless Phase 2/3 trial, 3 dose levels plus AC
- Transition to Stage 3 when target dose is determined with high certainty, or stop if low probability of reaching target effect size.

Stage 3: Confirmatory Stage

- 1 dose level vs. AC with 1 year treatment duration
- Conventional hypothesis testing for superiority to AC

Performance of Bayesian Adaptive Trial Design for AD



- 16/20 adaptive trials completed with fewer patients than non-adaptive
- 2 enrolled more patients
- 2 incorrectly terminated for futility

Subset of 20 trial simulations shown for illustrative purposes (actual total = 2000)

Applications to Decision-Making in AD: Disease Modifying Effects

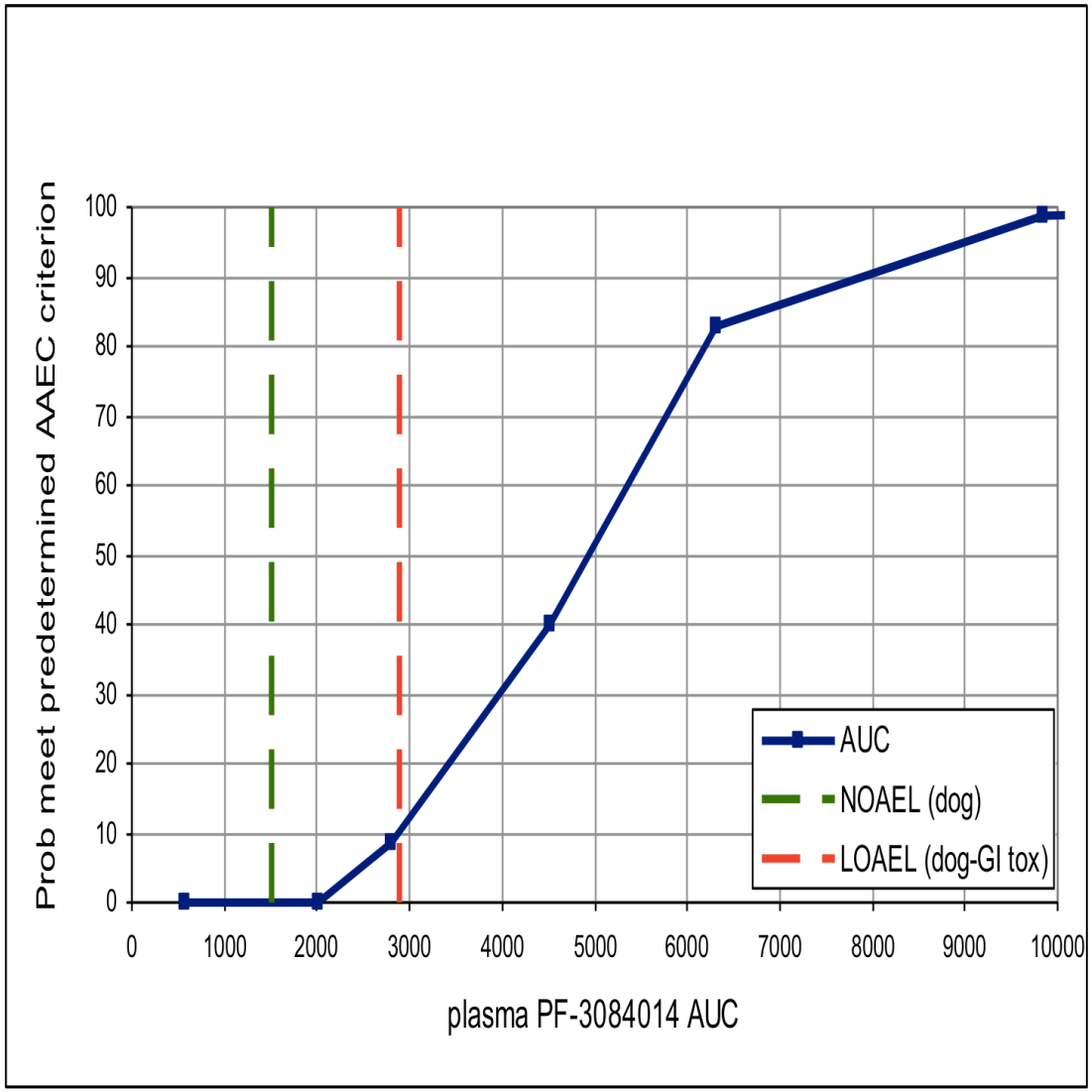
Biomarker-Based No-Go Decision

- Quantitative target: beta amyloid response (area above effect curve) defined based on MBMA of published data.

- PD model for biomarker developed from NCE data.

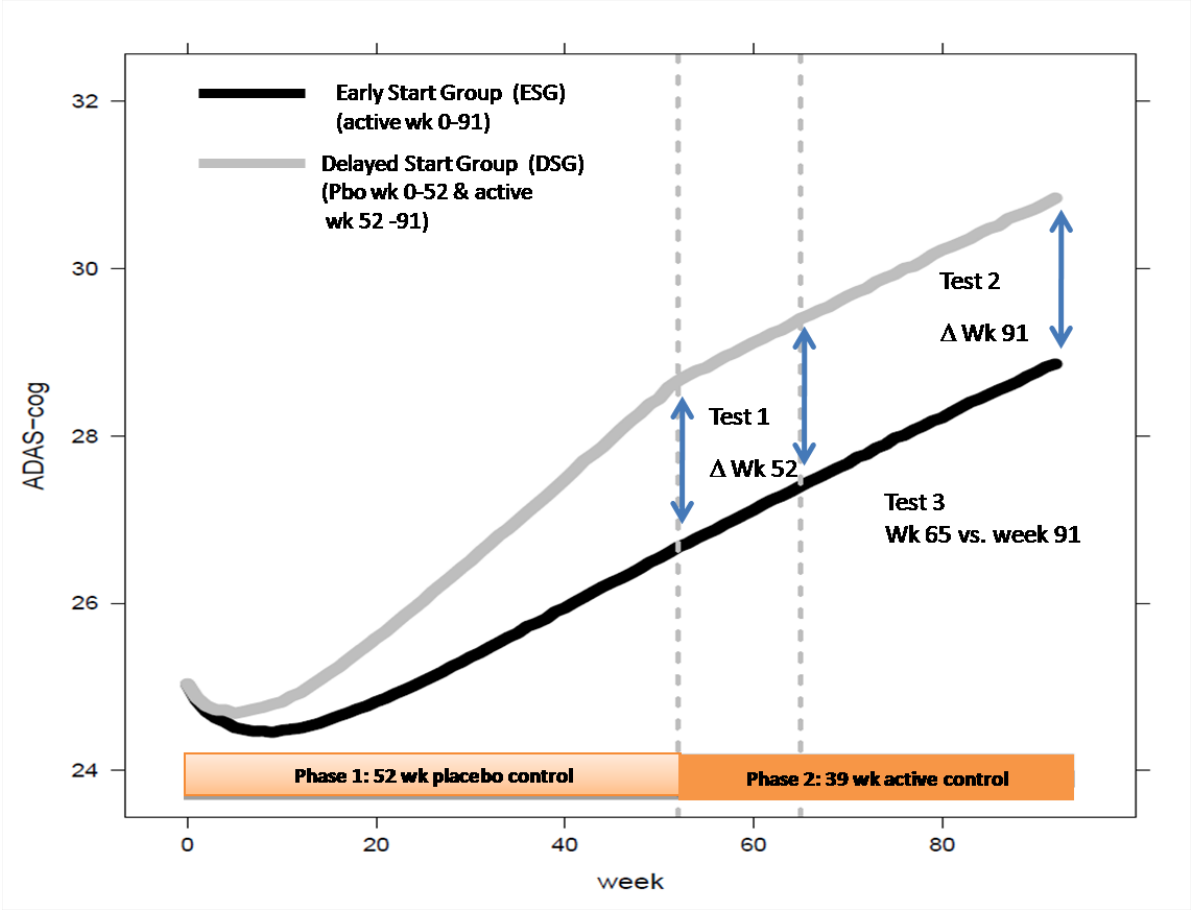
- Posterior probability of achieving target was too low given tox. coverage

- Terminated development



Ruolun Qiu[1], Susan Willavize[1], Terrence Fullerton[1], Marc R. Gastonguay[2]. Modeling and Simulation of Plasma Aβ in Human After Multiple Oral Doses of PF-3084014, a Potent Gamma Secretase Inhibitor. ACOP, 2009.

Exploring Trial Design Performance: Delayed Start



- Test 1: difference in ADAS-cog change from baseline between the placebo and study drug group at end of phase 1 (52 week).
- Test 2: difference in ADAS-cog change from baseline between early and delay start groups at end of phase 2 (91 week).
- Test 3: stability of the treatment difference, comparing the change from week 65 to week 91 for early versus delayed start groups.

Exploring Trial Design Performance

Which design will best support objectives?

- Comparison of a 78-week Parallel Study Design and a 91 Week Delayed Start Design by Assumption of Magnitude of Disease Modifying Effect

Effect	Design	P(reject H_0^1)	P(reject H_0^1 & H_0^2)	H_0^3 5% LB*	H_0^3 95% UB*
20 %	78 week parallel, n=600/arm	0.54			
20 %	91 week delayed start, n=600/arm	0.43	0.27	-0.757	0.733
30 %	78 week parallel, n=600/arm	0.76			
30 %	91 week delayed start, n=600/arm	0.66	0.46	-0.772	0.712
40 %	78 week parallel, n=600/arm	0.86			
40 %	91 week delayed start, n=600/arm	0.82	0.62	-0.783	0.696
50 %	78 week parallel, n=600/arm	0.93			
50 %	91 week delayed start, n=600/arm	0.90	0.74	-0.781	0.694

* Typical (median) lower and upper bounds for the (treatment-placebo) difference in mean change during the last 6 months of the trial.

- H_o^1 No difference in mean ADAS-cog change from baseline at week 52
- H_o^2 No difference in mean ADAS-cog change from baseline at week 91
- H_o^3 Difference in mean ADAS-cog change from week 65 to week 91 exceeds a given (as yet unspecified) threshold. (Null hypothesis to test non-inferiority, based on treatment-time interaction contrasts).

Summary

- Start with key development questions
- Define quantitative decision criteria
- Integrate (model) prior information on disease state, placebo response, competing therapies - with new data
- Build knowledge through iterative modeling, simulation, experimentation
- Goals:
  - Increase efficiency of decision-making and quality of information gained in clinical trials
  - Better trials, drugs, doses & patient outcomes

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  - METAMODL team

- Industry & Academic Collaborators

- CAMD Modeling and Simulation Working Group

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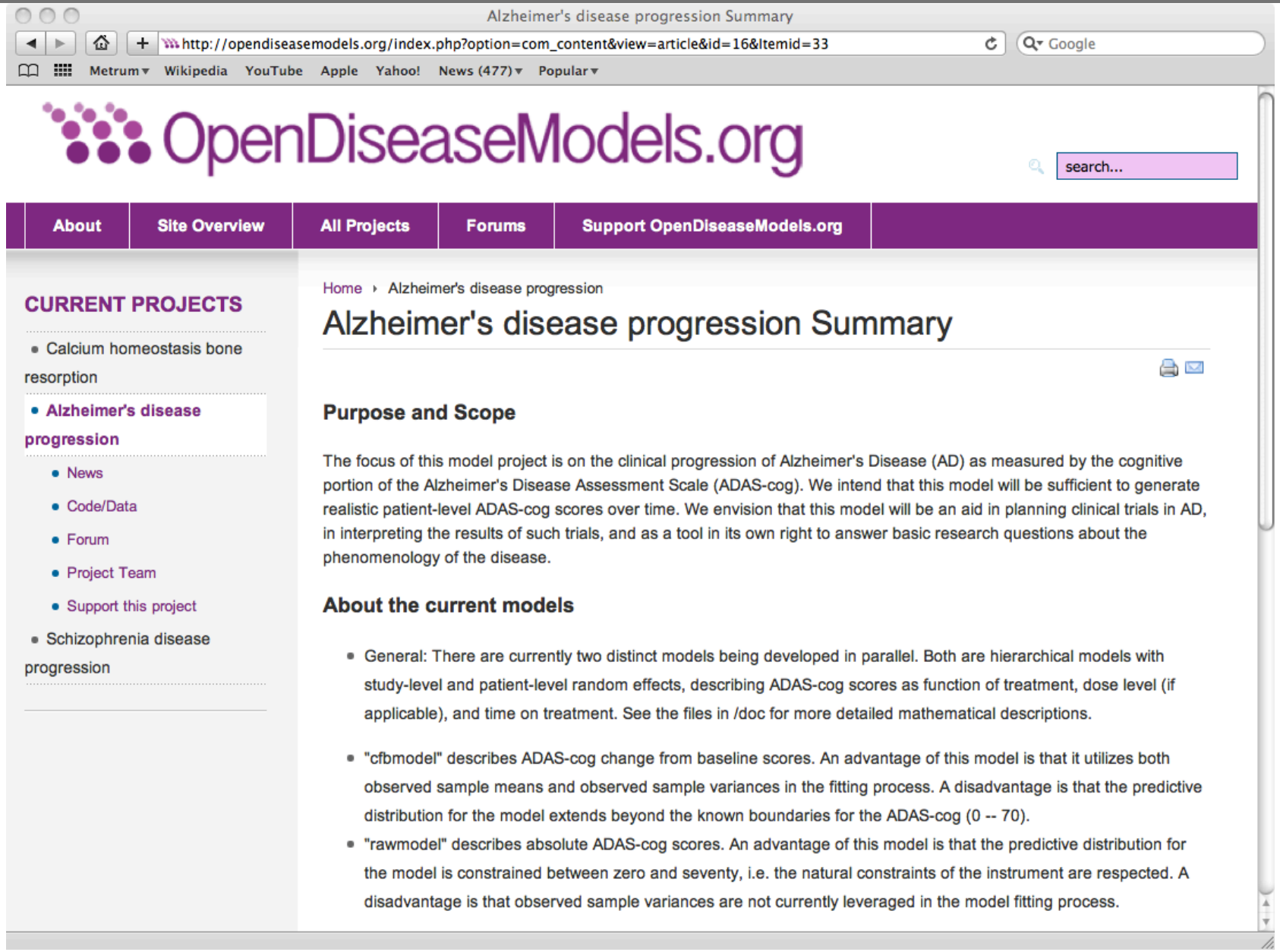
Results and validation of a population pharmacodynamic model for cognitive effects in alzheimer patients treated with tacrine.
Proceedings of the National Academy of Sciences of the United States of America **89** (1992):11471–11475.

Collaborative Model-Sharing (Public)



Collaborative Model/Meta-Data Sharing (Proprietary)

METAMODL

About | Model-based Meta-analysis | Splash

ABOUT METAMODL

- What is it?
- How will it change what you do?
- How is it different from other products?
- Features
- **Therapeutic areas**
- Implementation plan
- Contact us

About » Therapeutic areas

Therapeutic areas: current and planned

Therapeutic area	Data	Models	Availability
Osteoporosis/bone	Biomarkers for bone metabolism	Multi-level physiologic Now model of calcium homeostasis and bone turnover	Now
Alzheimer's disease	ADAS-Cog	ADAS-Cog as a function of Now drug, dose and time	Now
Osteoporosis/bone	Addition of bone mineral density and fractures	Model extended to bone mineral density and fractures	Q2 2011
Hepatitis C virus	RVR, EVR, SVR	Model for at least one end-point	Q2 2011
Multiple sclerosis			TBD
Type 2 diabetes			TBD
Type 1 diabetes			TBD
Macular Degeneration			TBD
Rheumatoid arthritis			TBD
Crohn's disease			TBD
Asthma			TBD
Oncology			TBD

Publicly Available Data for Model Development

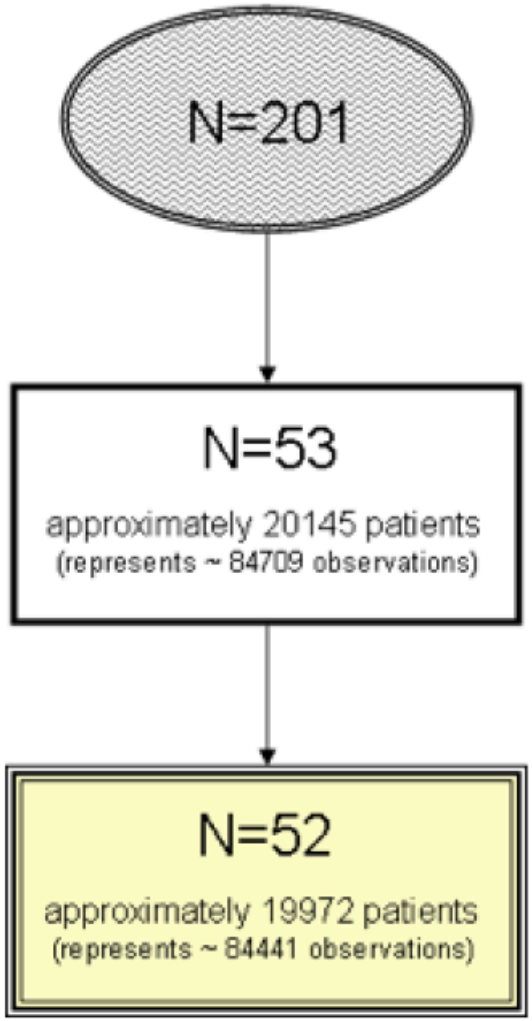
Alzheimer's Disease Neuroimaging Initiative (ADNI)
http://www.adni-info.org/

- Patient-level data
- Non-randomized, non-treatment study
- 2 to 3 year follow-up, with assessments roughly every 6 months
- Primary endpoints are imaging and biomarker endpoints, but ADAS-cog is assessed as well.

Sub-population	Number of subjects
Normal	200
MCI	400
Mild AD (MMSE 20-26)	200

Publicly Available Summary (Meta) Data

Data from systematic review of literature



Step 1: Literature Search Criteria

- Sources: all available clinical trials in National Institute for Clinical Effectiveness ("NICE"), Medline, Embase, SBAs at FDA's CDER website (years 1990-2008)
- Key search terms: AChE inhibitor names, endpoints names (ADAS-cog, MMSE, CIBIC, etc.), and clinical trials definitions (double-blind, randomized, etc.)

Step 2: Literature Acceptance Criteria

Accept:

Literature with ADAS-cog reported
if placebo group data is available from non-AChE study (i.e. Vitamin E study), keep only placebo data from that literature

Exclude:

- any duplicated literature (the same clinical data)
- duplicated data points reported with different analysis methods (selected OC over LCOF if available)
- an exploratory study (open study with number of patients <= 20)

Step 3: Further Refinement

One Study was removed from the analysis:

- only week 52 result (change from baseline) was reported, baseline ADAS-cog was not reported, and the drop-out rate was high [n=173 (baseline) to n=95 (week 52)], open study (rivastigmine)