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

Understanding

Observation

Prediction/Description
Theory vs. Observation

Theory → Understanding → Prediction/Description → Observation

DECISION-MAKING

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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

- Should We Invest Further?
- Will this trial succeed?
- What fraction of the treatment population?
- What's the target product profile?
- What dose is necessary for efficacy?
- Is toxicity a concern at this dose?
- Are we better than the competitors?

Should We Invest Further?
Rate the most challenging (1= least, 10=most) decisions in early development

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

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

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

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Quantitative Decision Criteria

- **Less than or equal to 5 mmHg**
- **Less than 12% Incidence Rate**
- **Rate of at least 90% of patients**
- **Effect size of +3 points**
- **No more than 10 msec**
- **15% better than competitor**
Are quantitative decision criteria defined in advance of reviewing the data?

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>POC</td>
<td>43</td>
<td>63.2</td>
</tr>
<tr>
<td>Phase 2B</td>
<td>35</td>
<td>51.5</td>
</tr>
<tr>
<td>Phase 3</td>
<td>39</td>
<td>57.4</td>
</tr>
<tr>
<td>Phase 3 Dose Selection</td>
<td>24</td>
<td>35.3</td>
</tr>
</tbody>
</table>

If defined, are these criteria a constantly moving target?

*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?*
Focus M&S to Address Relevant Quantitative Questions

Given our current state of knowledge…

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

But.. the probability of an incidence rate greater than 30% is very low.
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\(^1\)

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

- Ito \textit{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

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

- Gillespie \textit{et al}\(^3\) Bayesian Model-Based Meta Analysis

  - Simultaneous modeling of summary-level and patient-level data, constrains model to capped scale.

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Recent Bayesian Model-Based Meta-Analysis

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)

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

http://www.c-path.org/CAMD.cfm
Disease Progression: ADAScog

Expected ADAS–cog vs Week

- Natural Progression
- Placebo
- Donepezil 10 mg QD
- 50% DM effect
- 25% DM effect
Fixed Effects Models for Placebo and Symptomatic Drug

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

\[ E_{\text{drug,ik}} = \left( \frac{D_d}{D_{\text{ref,d}}} \right)^{\gamma_d} \frac{E_{\Delta,d}t_{idk}}{ET_{50,d} + t_{idk}} \]
Disease Progression Model Predictions

- Placebo
- Rivastigmine titrated to 8.9 mg QD
- Donepezil 10 mg QD
- Galantamine 32 mg QD

90% Individual Prediction Intervals

Week

ADAS-cog

 MONTH

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Posterior Prediction of CAMD Data Sets

![Graph showing changes in ADAS-cog points over weeks for different subjects.](image)
- 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

Drug
Placebo

Drug then Placebo
Placebo then Drug

Mean

Time

Mean

Time

washout

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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

<table>
<thead>
<tr>
<th>Truth</th>
<th>Decision</th>
<th>GO</th>
<th>NO GO</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E(6) = 2$</td>
<td>0%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>$E(6) = 4.5$</td>
<td>92%</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>

6 Week Cross-over Design

<table>
<thead>
<tr>
<th>Truth</th>
<th>Decision</th>
<th>GO</th>
<th>NO GO</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E(6) = 2$</td>
<td>10%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>$E(6) = 4.5$</td>
<td>92%</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>

$E(6)$ denotes placebo-adjusted drug effect at 6 months;
Table percentages based on 100 simulations
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 Qiu¹, Susan Willavize¹, Terrence Fullerton¹, Marc R. Gastonguay². 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**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Design</th>
<th>P(reject $H^1_0$)</th>
<th>P(reject $H^1_0$ &amp; $H^2_0$)</th>
<th>$H^3_0$ 5% LB*</th>
<th>$H^3_0$ 95% UB*</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 %</td>
<td>78 week parallel, $n=600/arm$</td>
<td>0.54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 %</td>
<td>91 week delayed start, $n=600/arm$</td>
<td>0.43</td>
<td>0.27</td>
<td>-0.757</td>
<td>0.733</td>
</tr>
<tr>
<td>30 %</td>
<td>78 week parallel, $n=600/arm$</td>
<td>0.76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 %</td>
<td>91 week delayed start, $n=600/arm$</td>
<td>0.66</td>
<td>0.46</td>
<td>-0.772</td>
<td>0.712</td>
</tr>
<tr>
<td>40 %</td>
<td>78 week parallel, $n=600/arm$</td>
<td>0.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 %</td>
<td>91 week delayed start, $n=600/arm$</td>
<td>0.82</td>
<td>0.62</td>
<td>-0.783</td>
<td>0.696</td>
</tr>
<tr>
<td>50 %</td>
<td>78 week parallel, $n=600/arm$</td>
<td>0.93</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 %</td>
<td>91 week delayed start, $n=600/arm$</td>
<td>0.90</td>
<td>0.74</td>
<td>-0.781</td>
<td>0.694</td>
</tr>
</tbody>
</table>

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

- $H^1_0$ No difference in mean ADAS-cog change from baseline at week 52
- $H^2_0$ No difference in mean ADAS-cog change from baseline at week 91
- $H^3_0$ 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
Acknowledgements

- Metrum Research Group Staff (www.metrumrg.com)
  - Bill Gillespie
  - Dan Polhamus
  - Jim Rogers
  - METAMODL team

- Industry & Academic Collaborators

- CAMD Modeling and Simulation Working Group
References

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A disease progression meta-analysis model in Alzheimer’s disease.
*Alzheimer’s & Dementia* (Accepted May 13, 2009).

Holford, N.H. and Peace, K.E.
Methodologic aspects of a population pharmacodynamic model for cognitive effects in alzheimer patients treated with tarcine.

Holford, N.H. and Peace, K.E.
Results and validation of a population pharmacodynamic model for cognitive effects in alzheimer patients treated with tarcine.
Collaborative Model-Sharing (Public)

Alzheimer's disease progression Summary

Purpose and Scope

The focus of this model project is on the clinical progression of Alzheimer's Disease (AD) as measured by the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog). We intend that this model will be sufficient to generate realistic patient-level ADAS-cog scores over time. We envision that this model will be an aid in planning clinical trials in AD, in interpreting the results of such trials, and as a tool in its own right to answer basic research questions about the phenomenology of the disease.

About the current models

- General: There are currently two distinct models being developed in parallel. Both are hierarchical models with study-level and patient-level random effects, describing ADAS-cog scores as function of treatment, dose level (if applicable), and time on treatment. See the files in /doc for more detailed mathematical descriptions.

- "cflmodel" describes ADAS-cog change from baseline scores. An advantage of this model is that it utilizes both observed sample means and observed sample variances in the fitting process. A disadvantage is that the predictive distribution for the model extends beyond the known boundaries for the ADAS-cog (0 -- 70).

- "rawmodel" describes absolute ADAS-cog scores. An advantage of this model is that the predictive distribution for the model is constrained between zero and seventy, i.e., the natural constraints of the instrument are respected. A disadvantage is that observed sample variances are not currently leveraged in the model fitting process.
### Therapeutic areas: current and planned

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

<table>
<thead>
<tr>
<th>Sub-population</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>200</td>
</tr>
<tr>
<td>MCI</td>
<td>400</td>
</tr>
<tr>
<td>Mild AD (MMSE 20-26)</td>
<td>200</td>
</tr>
</tbody>
</table>
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, SBA at FDA's CDER website (years 1990-2006)
- 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)