Model-Based Decision Making in Drug Development

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“As to methods, there may be a million and then some, but principles are few. The man who grasps principles can successfully select his own methods. The man who tries methods, ignoring principles, is sure to have trouble.”

- Ralph Waldo Emerson

Uses of Simulation

Analysis

- Model checking (e.g. predictive checks)

Illustration

- Summarize and illustrate data/concepts
- Integrate knowledge across multiple sources

Exploration

- Interpolate between observed data or extrapolate to new conditions
- Express expected range of variability and/or uncertainty in response relationship

Decision-Making

- Quantify probability of outcome given potential decision paths

Outline

- **Define the Problem/Question**
- Translate into Quantitative Terms
- Define Prior Knowledge, Assumptions, Constraints
- Model Development and Model Checking
- Plan and Execute Simulation
- Summarize and Present Results

Models are Knowledge Management Tools

Models allow us to integrate our knowledge of biological systems with emerging data, as compounds move through development.

- Prior knowledge and assumptions about the underlying physiology, pathology, and pharmacology.
- In vitro data (potency, binding affinity)
- Data from preclinical studies (PK, PD, ADME, Toxicology)
- Clinical data (PK, AEs, biomarkers, clinical endpoints, variability)

The model becomes a mathematical representation of our accumulated knowledge, which can be used to answer drug development questions.

The structural and statistical components of the model determine what questions it can be used to answer.

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Simulations allow us to extract information from models

A model is a mathematical representation of our accumulated knowledge about the relevant physiology and pharmacology.

Through simulation, the model can be used to answer questions in a **quantitative** fashion, throughout drug development.

- What clinical effect might be observed if this target is inhibited?
- What will be the likely effect of this combination therapy?
- What is a safe starting dose in humans?
- What dosing regimen will optimize benefit / risk?
- What dose has a high probability to differentiate current standard of care?
- Are dose adjustments needed for this population?

This enables informed decision-making in every phase of development.

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Defining the Question

The question should guide model development and evaluation.

- What model structure and components are needed?
- What data features must be reproduced?

The question to be answered also guides simulation design.

- What simulation structure / components are needed?

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Listen and Understand

Listening is not done until you can re-state the specific problem or questions, constraints and concerns, accurately.

"Whoever best describes the problem is the one most likely to solve it"

Dan Roam

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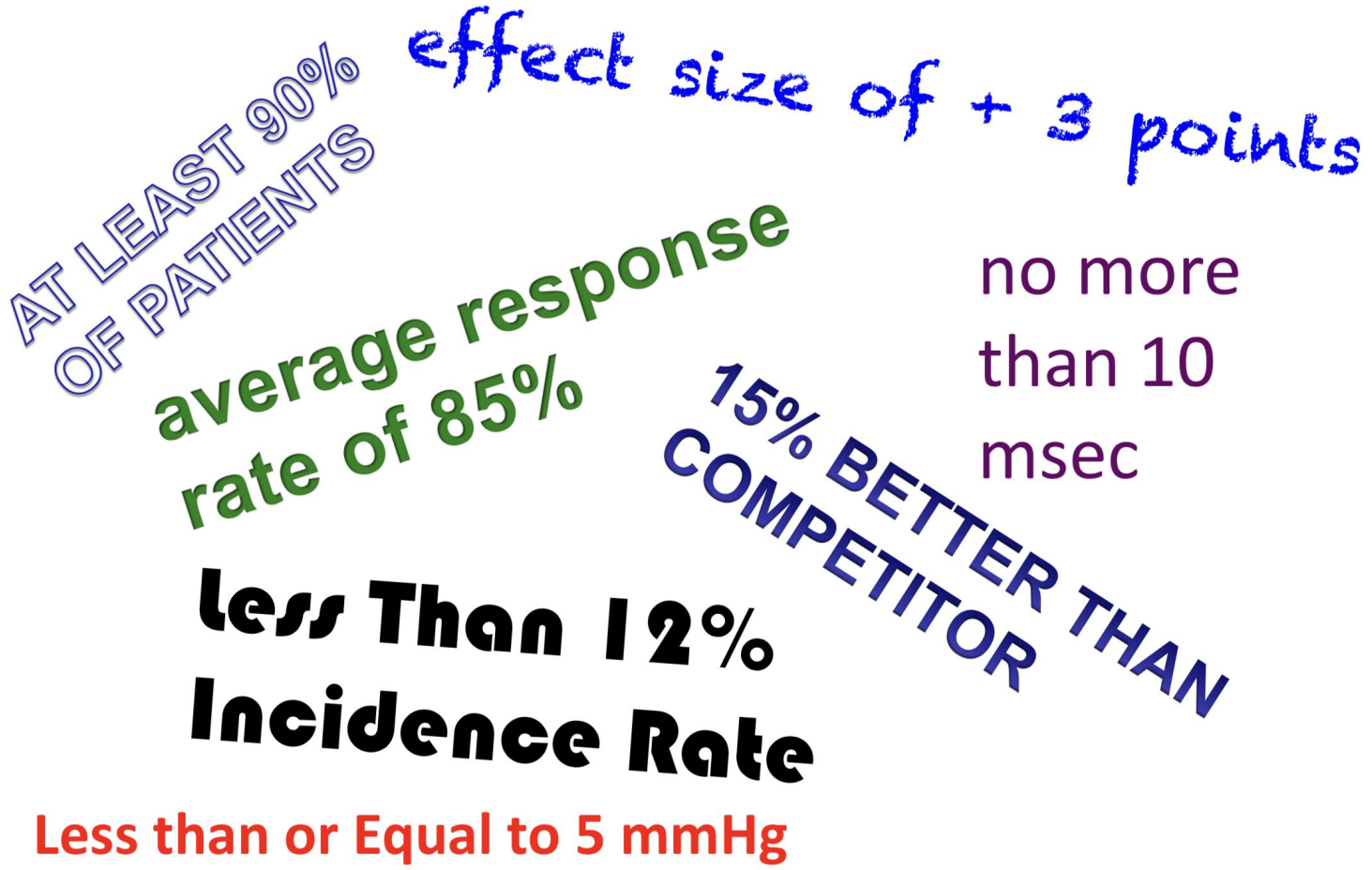
Question must be Specified Quantitatively

The question must be translated into quantitative terms prior to simulation.

Requires specific quantitative definitions of clinically relevant effect size or response rate.

Quantitative questions are often best framed as a probabilistic statement.



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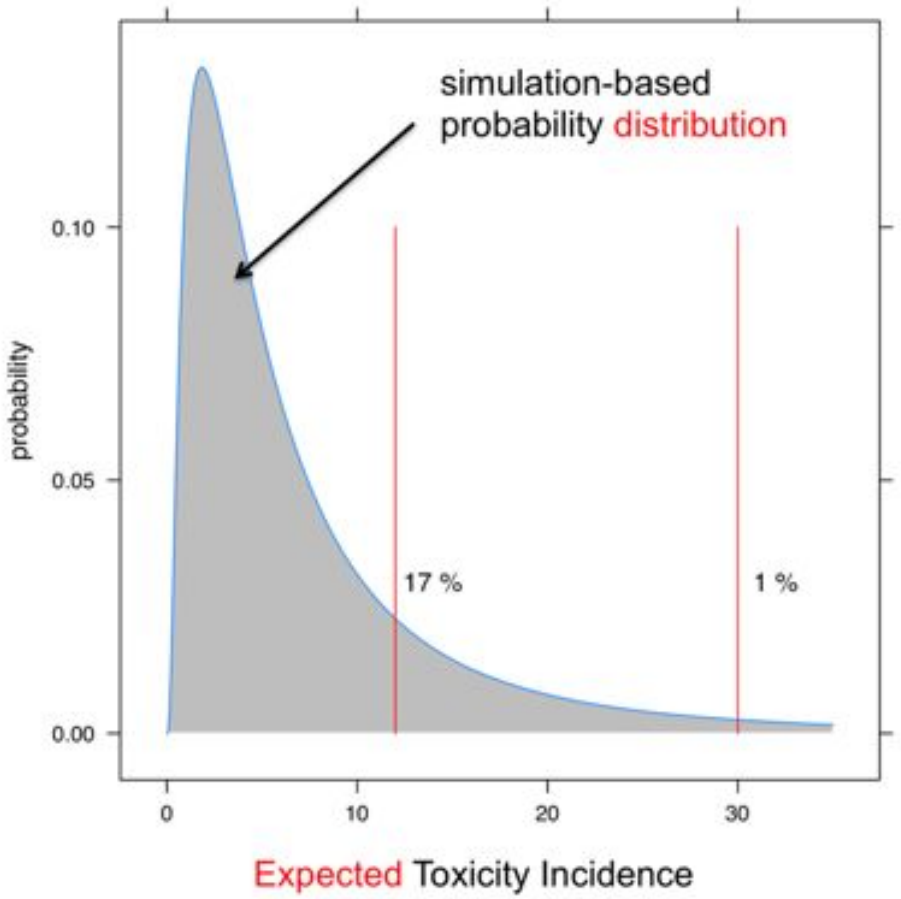
Probability of Achieving Quantitative Criteria

Key Question: Is toxicity a concern at this does?

Quantitative Translation: To be competitive with SOC, toxicity incidence must be less than 30%. What's the probability?

What's the probability that tox incidence < 12%?

Defining quantitative criteria is key to formulating M&S strategy.



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MBMA for Indirect Comparison of Efficacy

- Linagliptin (10 trials) vs. Sitagliptin (15 trials)
- No trials with head-to-head comparison

- **Key Question**: Are these drugs different with respect to efficacy?
- **Quantitative Translation**: What's the **probability** that the placebo-adjusted difference in mean change from baseline HbA1c at 24 weeks between Linagliptin (5mg) and Sitagliptin (100mg) is less than +/- 0.1%?

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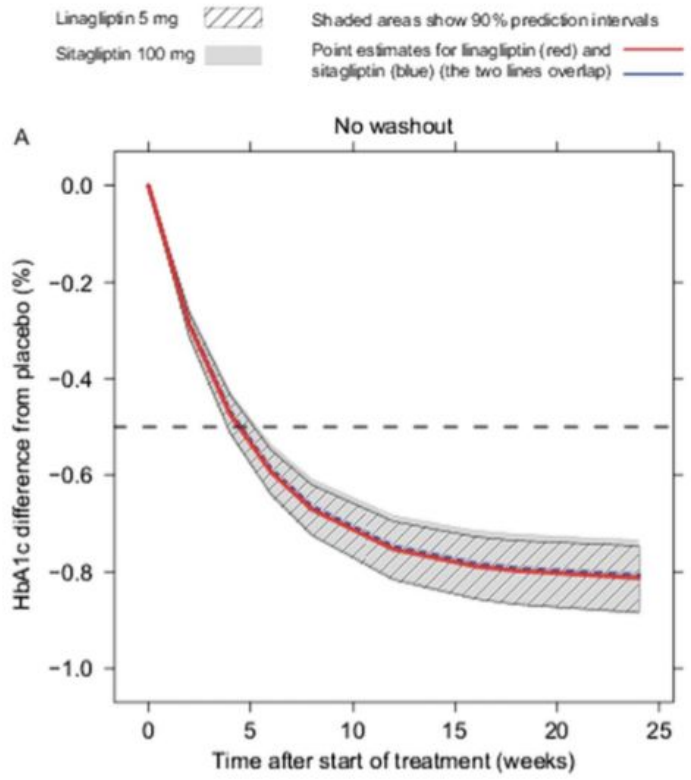
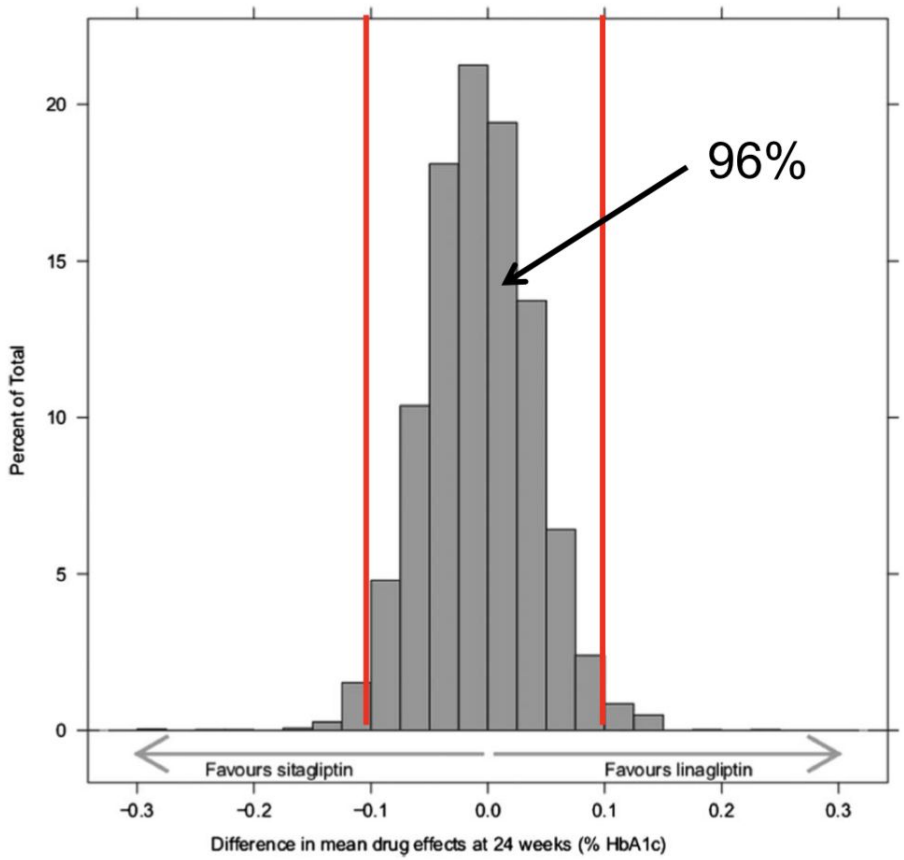
Probability Distribution of Expected Response





Gross JL, Rogers J, Polhamus D, Gillespie W, Friedrich F, Gong Y, Monz BU, Patel S, Staab A, Retlich S. A novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medications: an example using DPP-4 inhibitors, sitagliptin and linagliptin, in treatment of type 2 diabetes mellitus BMJ Open 2013, 3:e001844.

Posterior distribution for the difference in effect estimates between linagliptin (5 mg) and sitagliptin (100 mg) at 24 weeks.

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Prior Knowledge

Results from prior modeling exercises

- Model structure and parameters (fixed and random effects)
- Some measure of parameter uncertainty
  - Variance-covariance matrix of estimates
  - Bootstrap parameter distributions
  - Bayesian posterior distributions

Review of literature in this disease indication

- Ranges of plausible values
- Model structures
- Clinically important effect size
- Model-based meta analysis
- Natural history disease database

Poll experts/team members: everyone's view can be part of the simulation

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Assumptions and Constraints

What assumptions will be necessary to implement the simulation model?

- Is there a gap in current knowledge? e.g. we have no data and will assume that exposure-response is the same in adults and children.
- Do you have estimated covariance matrix of random effects or will assumptions be made about covariance structure?
- Will simulation outcome include subjective specifications? e.g. what is a clinically-important change in effect size?

What constraints are there on the possible decision path?

- Limited sample size for trial design
- Limited budget for next development phase
- Limited dose multiples
- Limited trial duration

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Model Development

Which components of the model will be necessary to implement a simulation that addresses the quantitative question?

- Endpoints
  - PK, PD, clinical outcomes
- Covariate relationships
  - Is covariate model development necessary?
  - Simulate joint distribution or re-sample from database?
- Trial-related processes
  - Drop-out, non-compliance, titration, re-randomization
- Random effects hierarchy
  - Inter-individual, inter-occasion, residual variability, parameter uncertainty?
  - Covariance of random effects

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Model Checking

Basic Model Evaluation

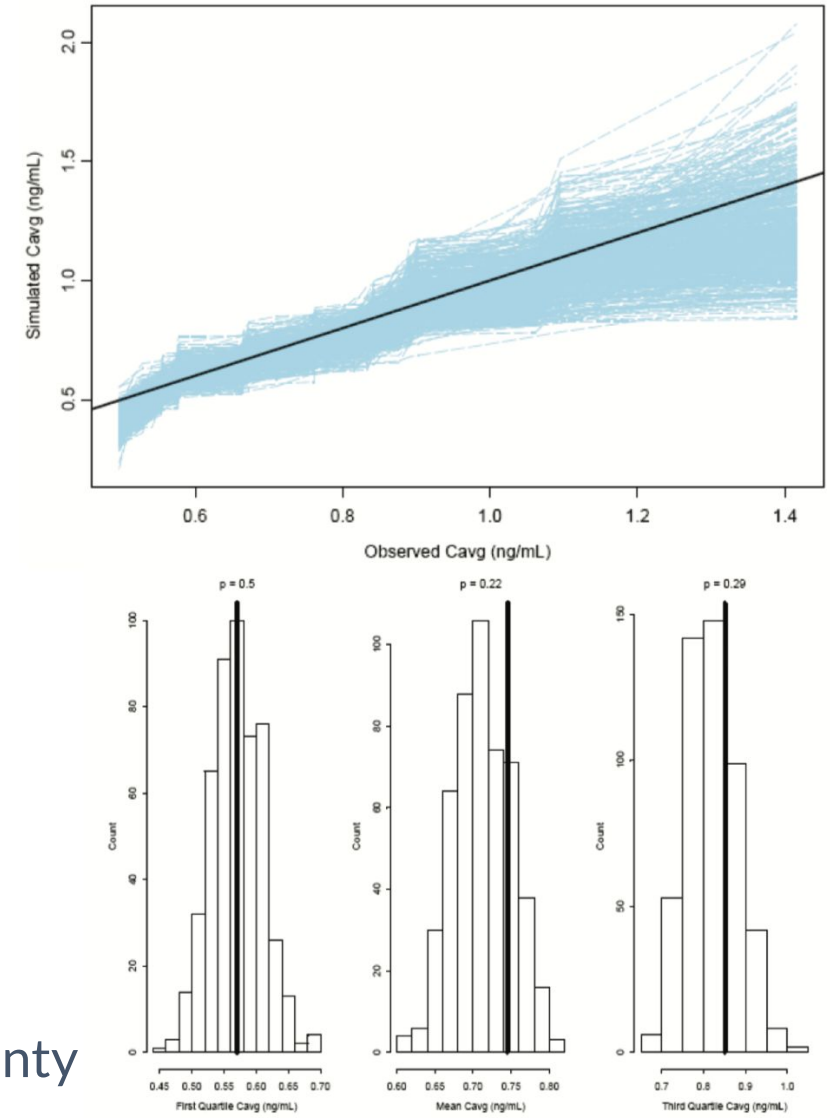
- Plausibility of parameter estimates and model structure
- Compare with prior knowledge
- Convergence, global minimum, stable parameter estimates
- Goodness of fit diagnostic plots

Focused Predictive Checks

- What data features are important for decision-making?
- Raw endpoint vs change from baseline.
- Are particular timepoints critical?
  Longitudinal vs snapshot model.

Probabilistic Statements

- Requires joint probability distribution of parameter uncertainty



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Nobody's Perfect …

"**Our** simulations show that our drug performs very well compared to the competitor... we should use M&S more often."

"**Your** simulations show that our drug doesn't perform very well... there must be something wrong with your model."

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Lack of Alignment on Methods

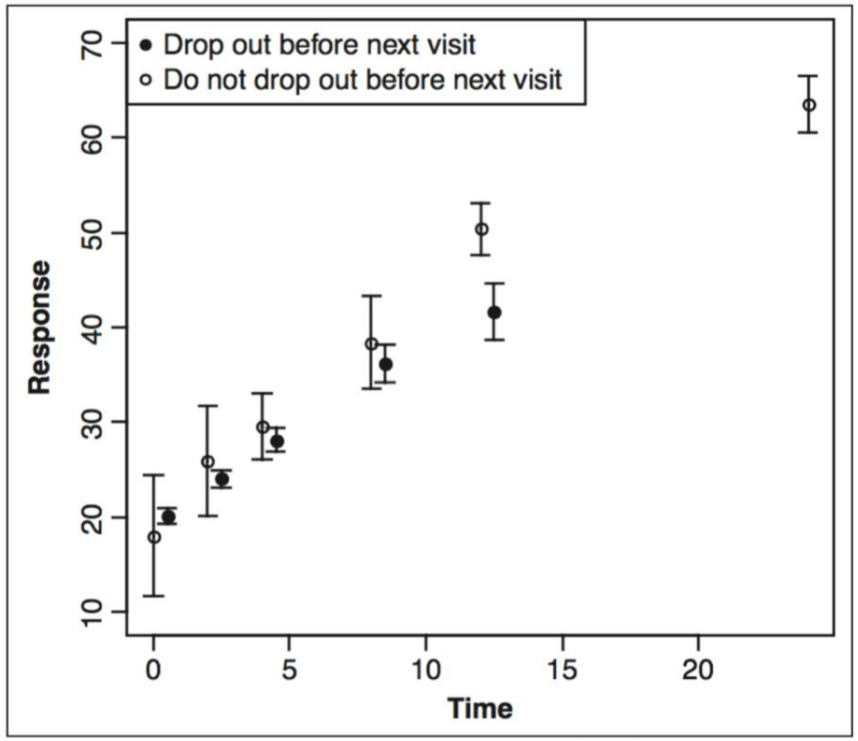

Figure 1. Longitudinal response data are plotted vs. time in arbitrary units, conditioned on drop-out status at next visit. Points and error bars represent mean and standard deviation of responses for subjects who drop out before the next visit (closed circles) and for subjects who do not drop out before next visit (open circles).

- Assessment of expected efficacy at new dose
- 25% dropout in Phase 2a Study

Statistics	Pharmacometrics
D-R model based on landmark data	Repeated measures PK-PD model
Completers only	NLME model and simulation
New dose efficacy is favorable	New dose efficacy insufficient

Missing data in model-based pharmacometric applications: points to consider. Gastonguay, Marc R, French, Jonathan L, Heitjan, Daniel F, Rogers, James A, Ahn, Jae Eun, and Ravva, Patanjali. J Clin Pharmacol. 2010 50 (9) 63S-74S.

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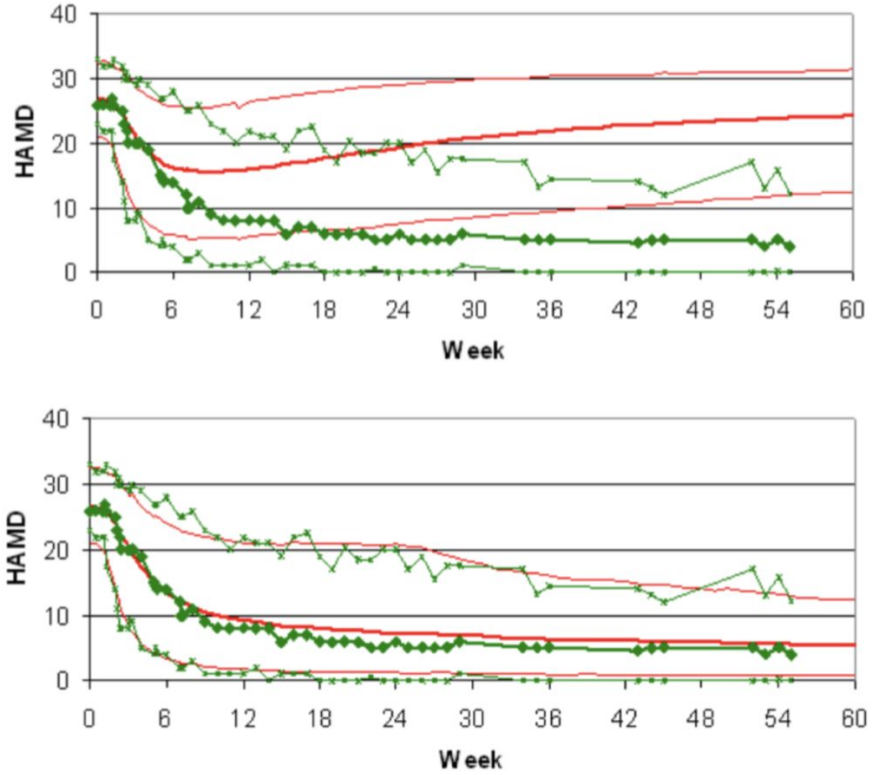
Poor Presentation and Poor Communication

Pharmacometrics presented longitudinal Monte Carlo simulations across doses.



A tutorial on Visual Predictive Checks.
Nick Holford, Mats Karlsson. Page 17 (2008)

Stats presented a table of point estimates for the change from baseline response by dose.

How were they received?

Statistics	Pharmacometrics
Looks great!	Must be something wrong
Immediate acceptance	Scrutiny & criticism of model
Let's move ahead	Your analysis is not needed

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Presentation of Results

- Presentation of results should be based on a re-statement of key questions in quantitative form.
- Focus presentation of results to one or two key graphics or tables.
- Often useful to present probability of achieving the stated quantitative question.
- Not so useful to present p-values, model diagnostics and goodness of fit statistics.
- Too much technical detail can distract from the message.

Emphasize the important findings (don't emphasize how you got there)

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Create Shared Commitment

Encourage and enable the non-tech customer to become part of the quantitative decision-making process from the start.

Successful communication of results in the final presentation begins with initial communication about the project.

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Beginning with the End in Mind

Share a mock-up of the planned deliverable for the key messages (figure, table, web app), etc.

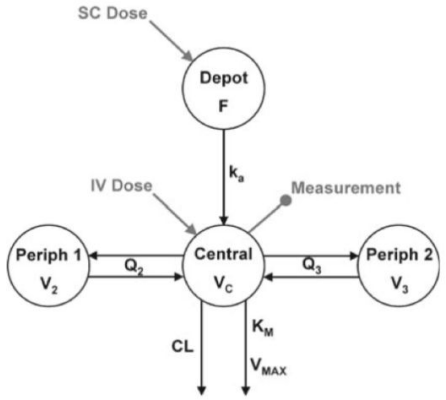
- Adjust to input from non-technical collaborator
- This forces you to have a solid understand of what you are setting out to achieve, and provides a clear expectation of the deliverable.

Keep non-technical team members involved in defining key M&S assumptions (biology and pharmacology) and constraints (realities of clinical program).

- Should be **OUR** model not **YOUR** model.

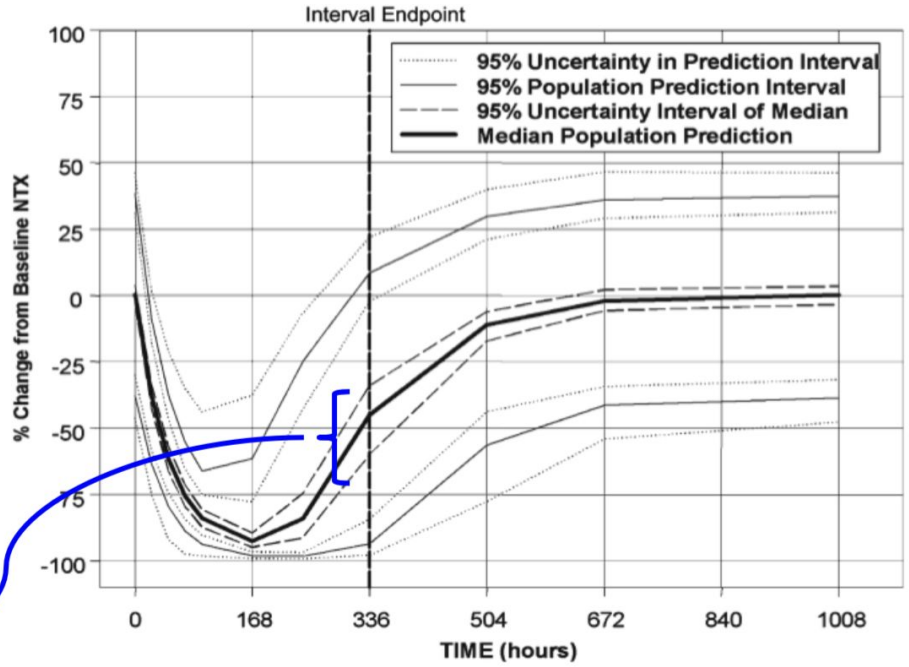
Probably Too Much Detail

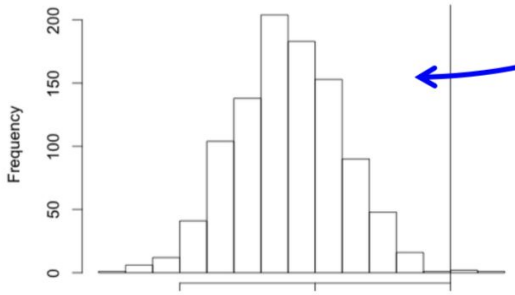
Fig. 1 Final compartmental model for Fc-OPG pharmacokinetics. V_C is the central compartment volume of distribution, V_2 and V_3 are the peripheral compartments' volumes, Q_p is the intercompartmental clearance between the central compartment and compartment p, CL is the linear clearance from serum, and V_{max} and K_M describe Michaelis–Menten elimination. Subcutaneously injected compound had a first-order absorption rate of k_a and a bioavailability of F. See text for more details



$$\frac{dNTX(t)}{dt} = k_{syn}\left(1 - \frac{I_{MAX}C_{OPG}(t)}{IC_{50} + C_{OPG}(t)}\right) - k_{\deg}NTX(t)$$

population variability and parameter uncertainty





Typical change from baseline NTx at 336 hours

Fig. 7 Simulation of 200 replicate trials, each with 200 subjects, based on a single SC dose of 3 mg/kg, reflecting cohort 4 dosing in the original data set (body mass was assumed to be 70 kg for all subjects). The thick solid line represents the median value of all median NTX percent changes from baseline (across the 200 simulated trials; one median value is obtained from each simulated trial). The dashed lines delimit the 95% uncertainty interval for the population median value. The thin solid lines show the median values of all 95% population variability prediction intervals (across the 200 simulated trials). The dotted lines show the 95% uncertainty interval in the population 95% prediction intervals. The vertical dashed line intersects the computed profiles at 2 weeks after drug administration, and it helps to gauge visually how effective a biweekly dosing regimen might be. See text for further details

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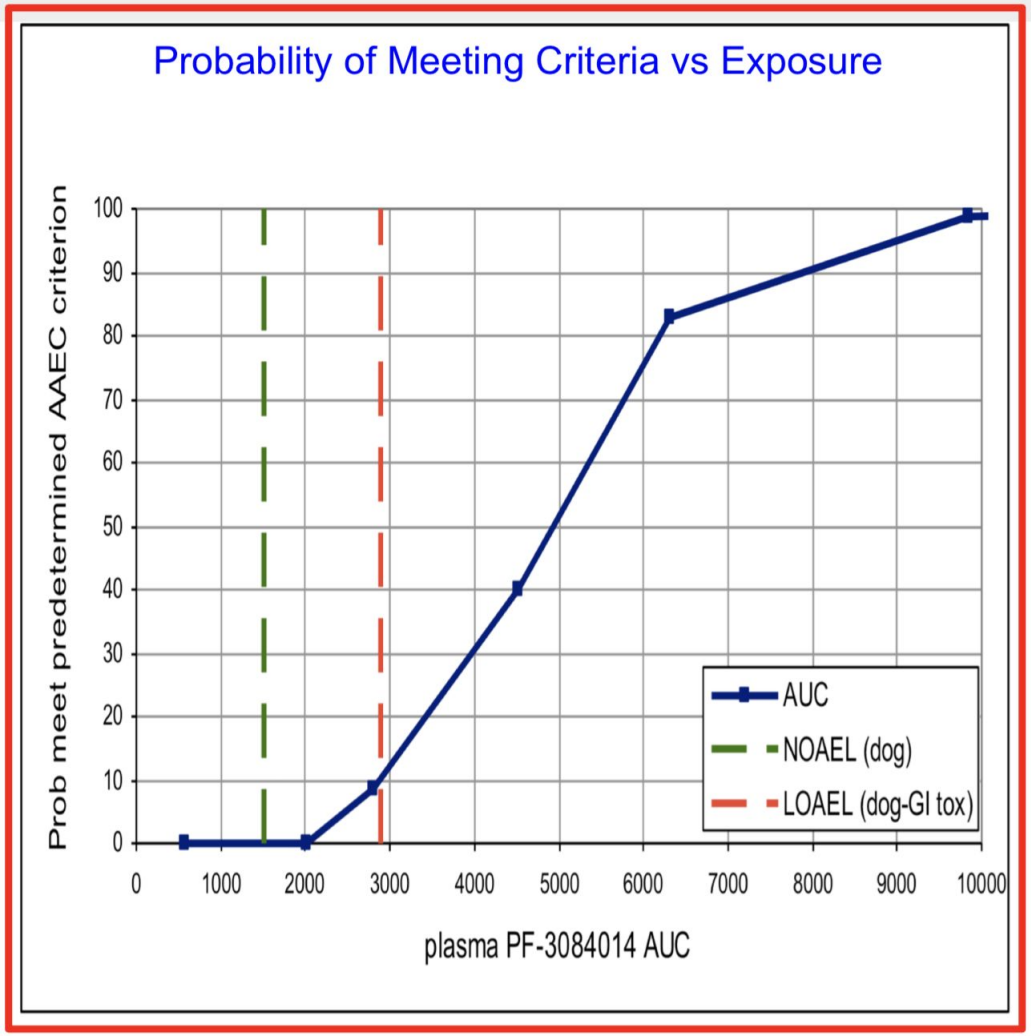
Clear and Concise

Biomarker-based No-Go Decision

- Quantitative target: typical beta amyloid response (area above effect curve) defined based on MBMA of published data.
- PD model for typical biomarker response developed from individual level 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.

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Breakout Session

Form groups to discuss example of translating development question into quantitative criteria.

- Convert general questions to specific quantitatively defined questions.

See example questions on following slide.

Question 1: Are exposures in pediatric patients similar to adults?

Question 2: Do the POC trial results support continued development?

Question 3: Is the proposed PK sampling scheme adequate?

Question 4: Which doses should we select for the Phase 2b trial?

Question 5: How do we decide between these 2 proposed Phase 3 trial designs?

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the end

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