IMMPACT-VIII

Early Clinical Study Designs, Emphasizing Proof-of-Concept Trials

June 12-14, 2008

Arlington, VA

PK-PD Modeling and Dosage Determination for Proof-of-Concept Trials

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METRUM
RESEARCH GROUP

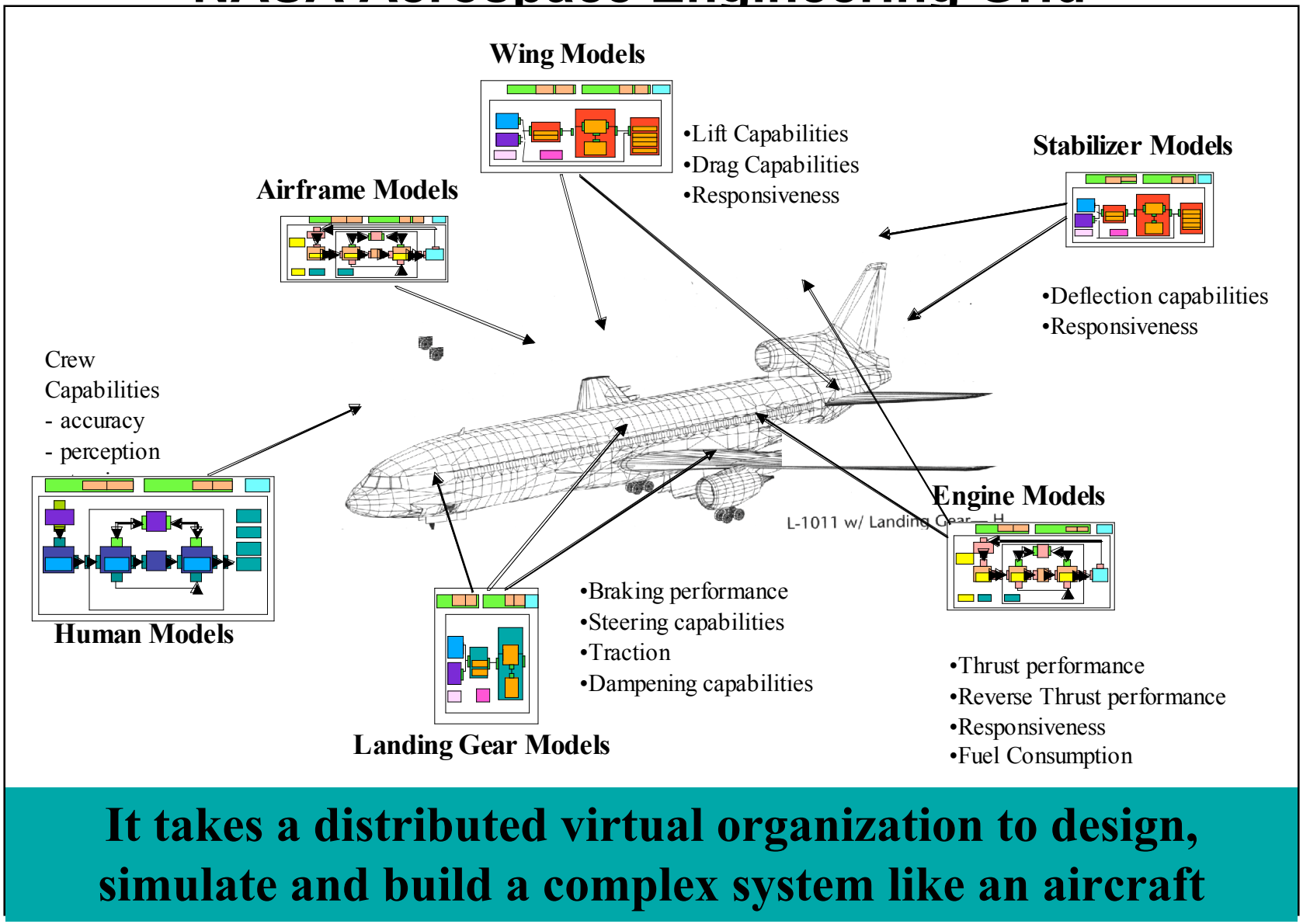
Overview

- PK/PD (Exposure-Response) and Model-Based Drug Development

- Role of Exposure-Response Modeling in Proof-of-Concept Trials
  - Planning and Design
  - Analysis and Quantitative Support for PoC Determination
  - Building Knowledge for Later Stage Development
  - Other examples of E-R utility

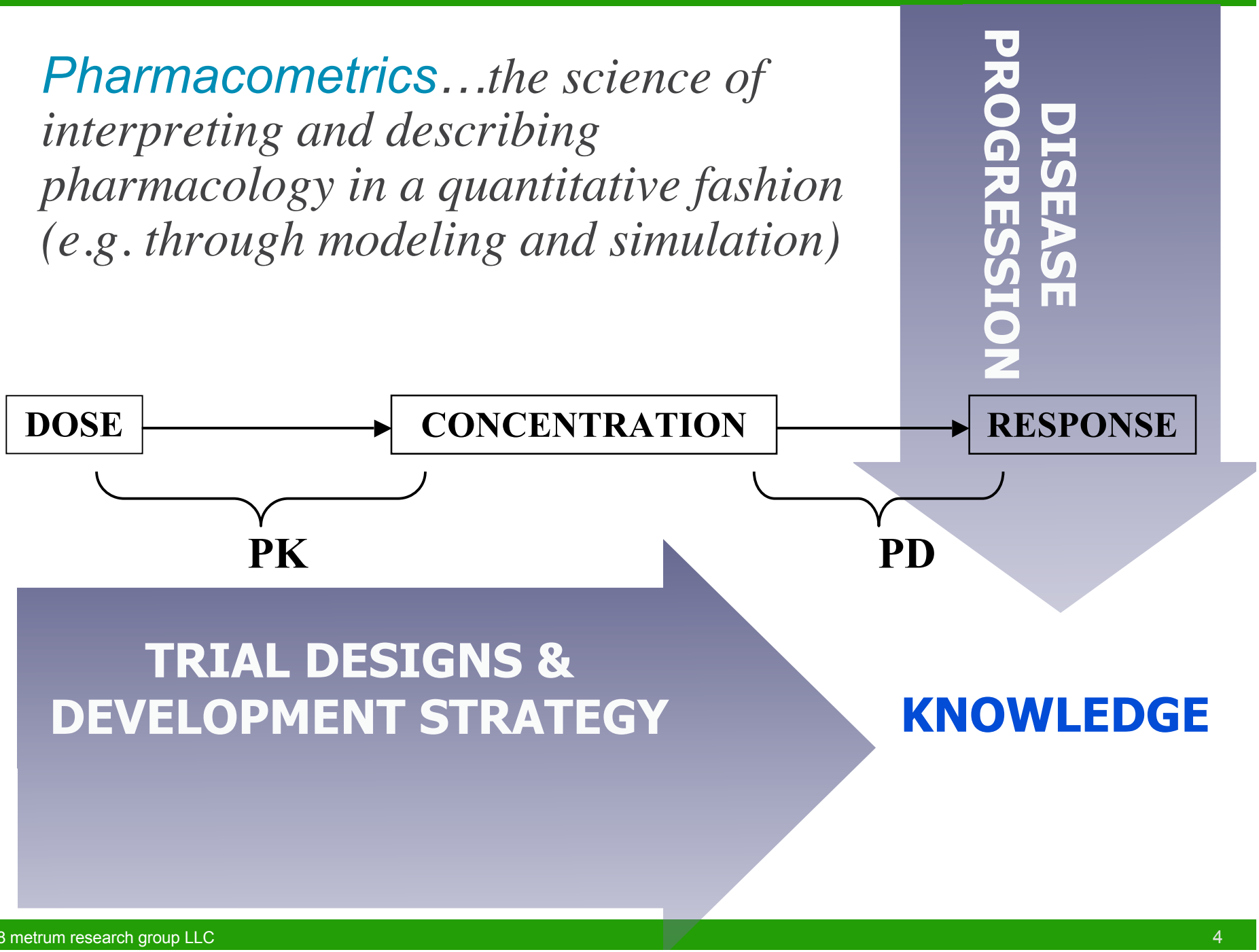
- Summary Points

Innovation: Planes are modeled long before takeoff NASA Aerospace Engineering Grid



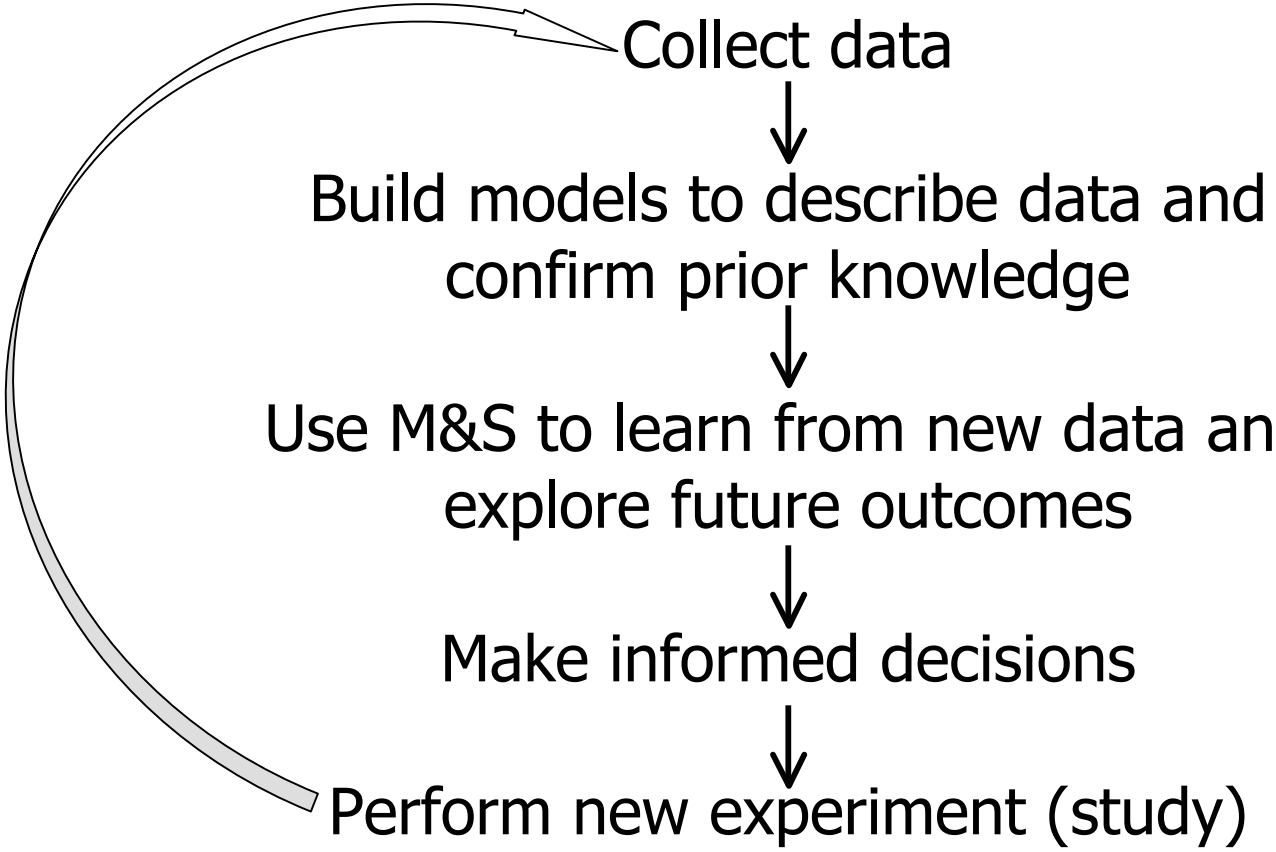
It takes a distributed virtual organization to design, simulate and build a complex system like an aircraft

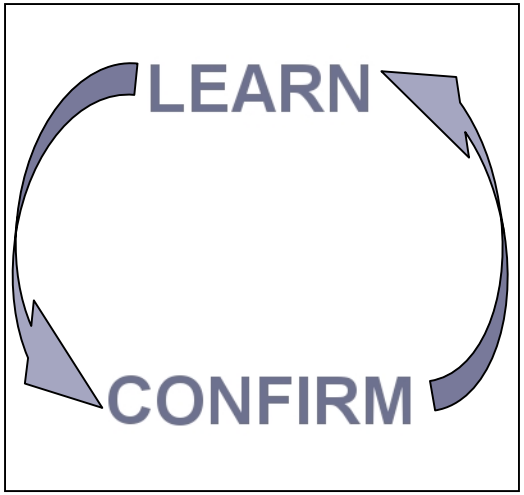
Pharmacometrics…the science of interpreting and describing pharmacology in a quantitative fashion (e.g. through modeling and simulation)



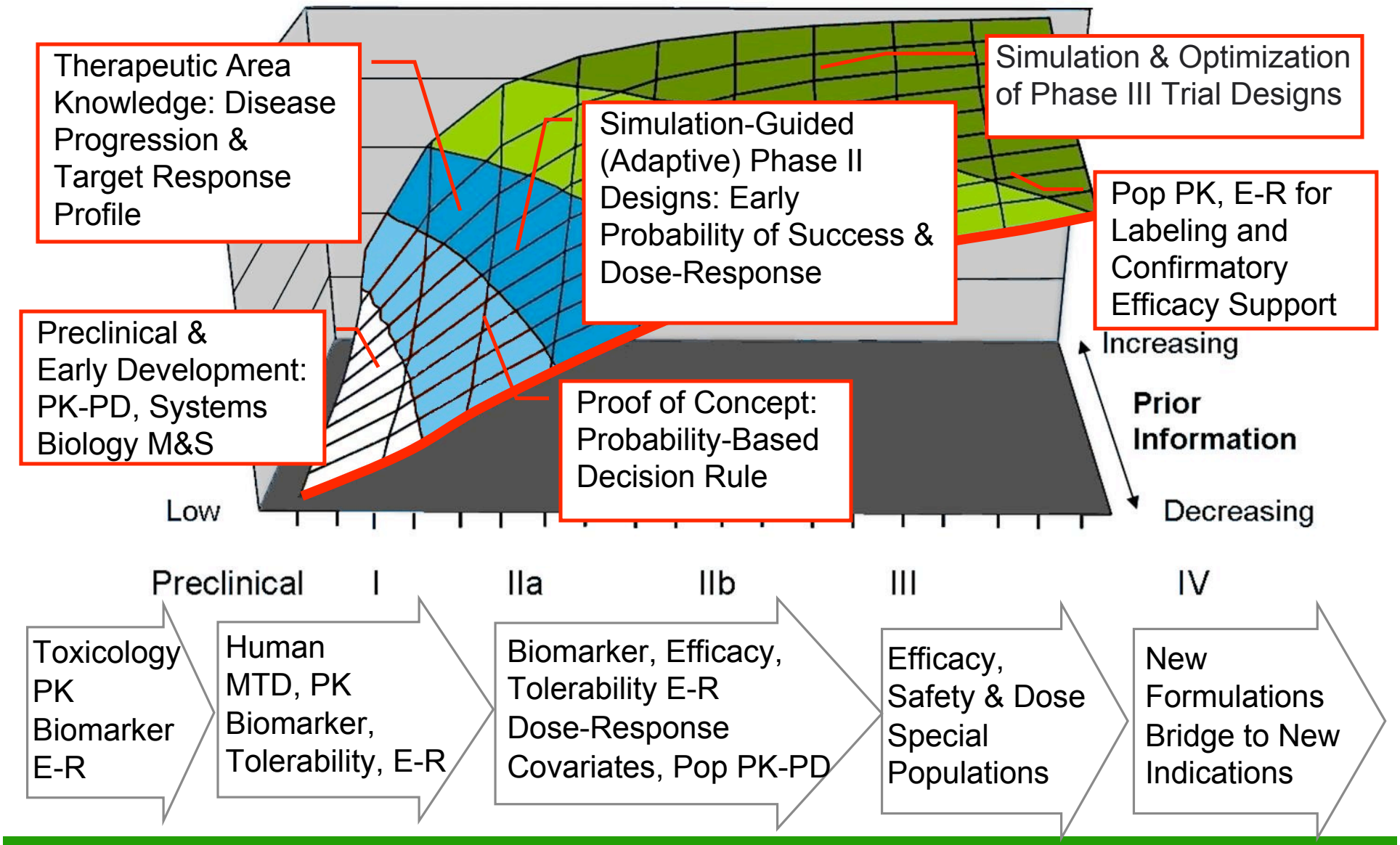
Modeling and Simulation: A Tool to Facilitate the Learn-Confirm Continuum

Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther 1997; 61(3):275-91.

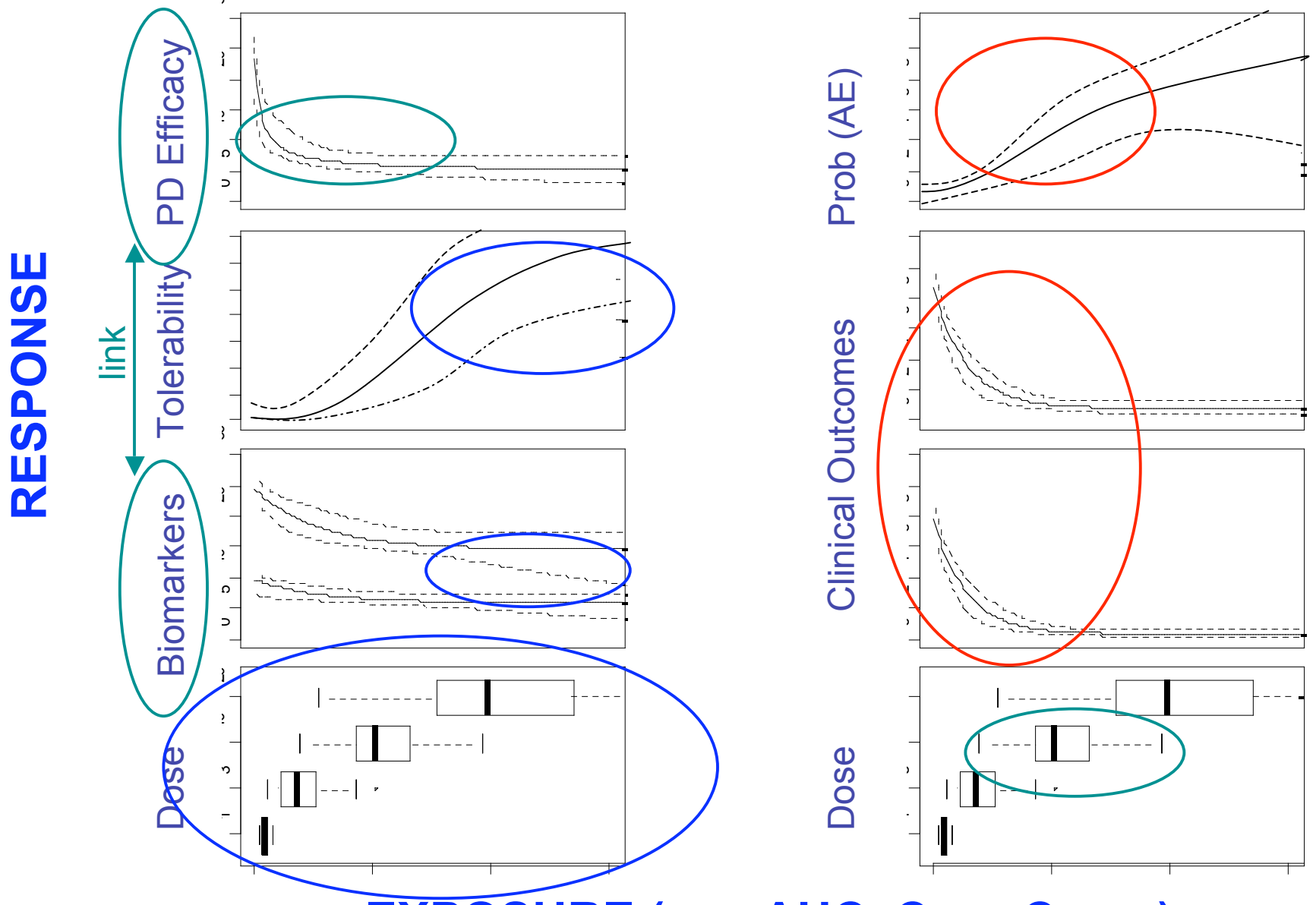




M&S Throughout Drug Development

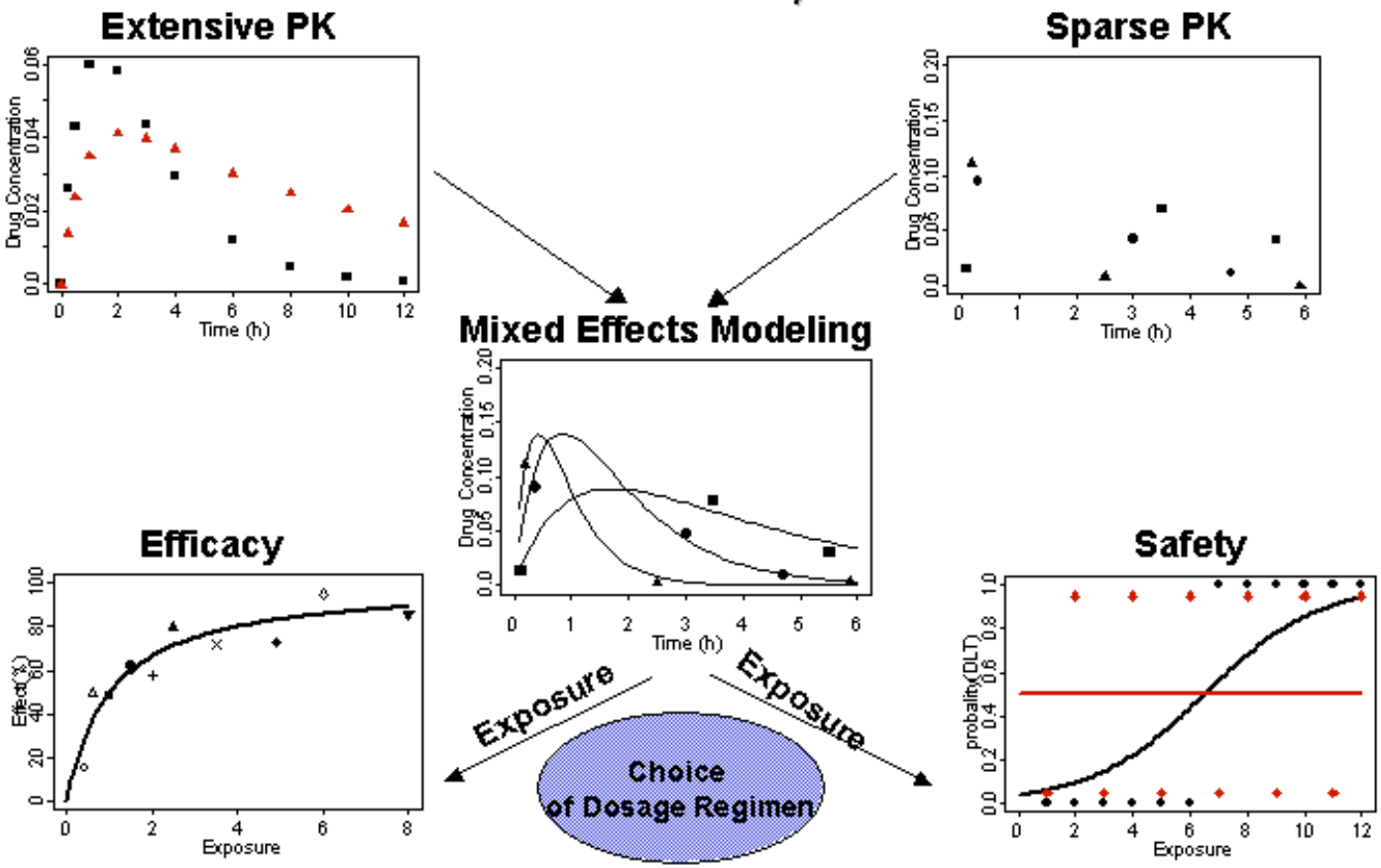


What to Learn?



Regulatory Support for M&S

Population Pharmacokinetic and Dynamic Modeling
A Fundamental Tool to Characterize Exposure-Response Relationships



http://www.fda.gov/oc/initiatives/criticalpath/presentations.html

Regulatory Support for M&S: Guidance Documents

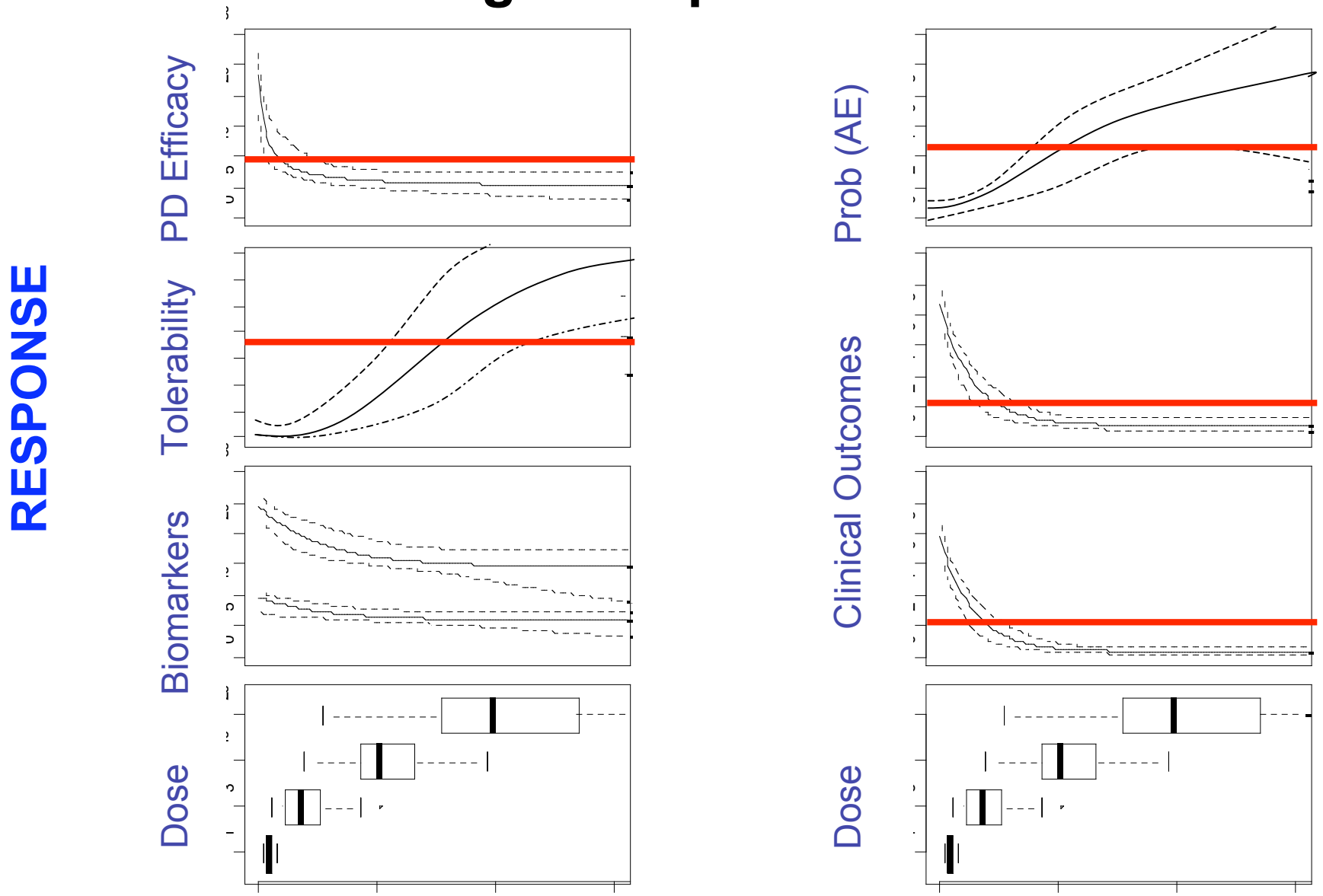
- Population Pharmacokinetics (FDA and EMEA)
- Exposure-Response Relationships (FDA)
- Dose-Response Information to Support Drug Registration (ICH-E4)
- General Considerations for the Clinical Evaluation of Drugs (FDA 77-3040)
- General Considerations for Pediatric Pharmacokinetic Studies (FDA)
- Pharmacokinetics in Patients with Impaired Renal Function (FDA)
- Pharmacokinetics in Patients With Impaired Hepatic Function (FDA)
- Studies in Support of Special Populations: Geriatrics (ICH-E7)
- Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH-E5)
- Clinical Investigation of Medicinal Products in the Pediatric Population (ICH-E11)

Determination of PoC

- Primary Challenge: Define decision criteria for PoC determination
  - Proof of mechanism
  - Statistically significant efficacy response with approval endpoint
  - Acceptable probability of achieving multivariate target response profile
  - Comparability to active control

- Once defined, probability of meeting PoC decision criteria for different trial designs can be explored through modeling and simulation

Target Response Profile



PK and Exposure-Response M&S Opportunities in PoC

- PK Modeling
  - Understand PK in target population and possibly reduce inter-individual variability in exposure to increase signal/noise: dosing individualization
  - Select PoC doses with minimal exposure overlap
  - Explain unexpected outcomes (e.g. unknown phenotypic differences in PK)
  - Adjust for formulation differences
- E-R Modeling
  - Assessment of E-R relationships for multiple endpoints (e.g. after dose-ranging based on efficacy endpoint)
  - Basis for trial simulations: explore performance/options *in silico* before initiating clinical trial

Impact of E-R Varies with PoC Trial Designs

MTD-Type PoC Design

- Typically 1 active treatment dose vs. reference treatment
- Dose selected based on Phase I MTD
- Standard pair-wise statistical comparison

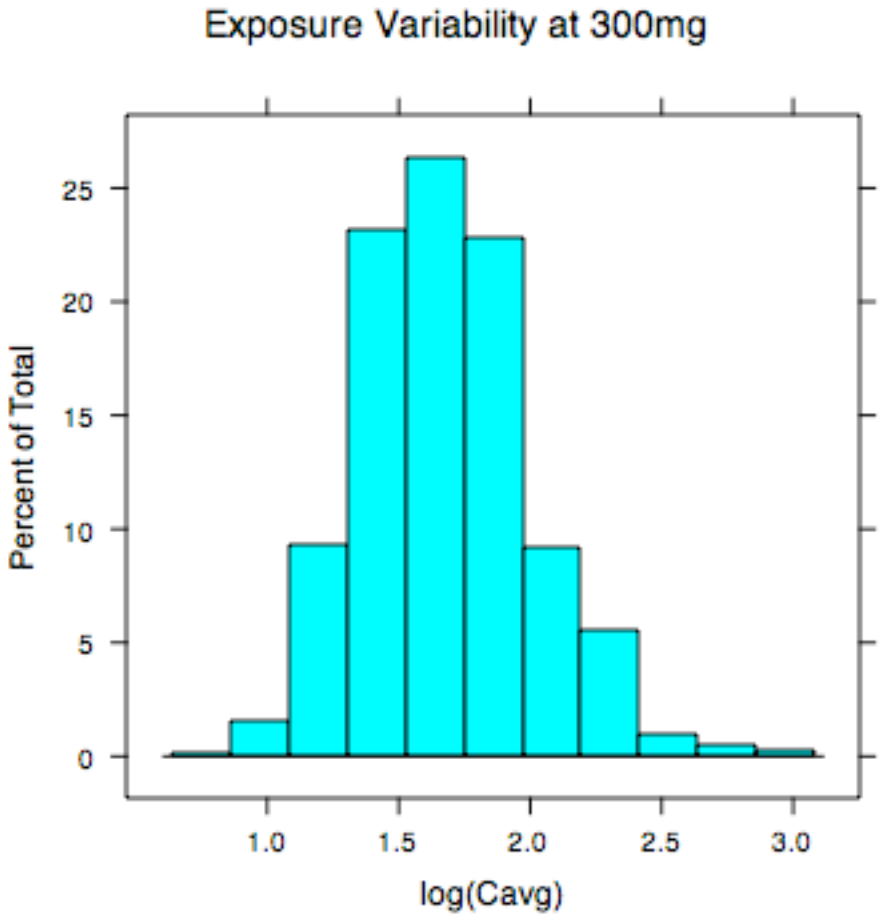
Dose-Ranging PoC Design

- Multiple doses investigated
- Dose-range informed by preclinical data, Phase I, biomarker, competitor data
- Model-based data analysis
- Often multi-variable PoC assessment

Exposure-Response in MTD-Type PoC: Proceed with Caution

- Single active treatment arm at MTD (300 mg) vs. Placebo
- Obtain PK in all individuals
- Explore resulting relationship between exposure (Cavg) and Response (1 observation per individual)

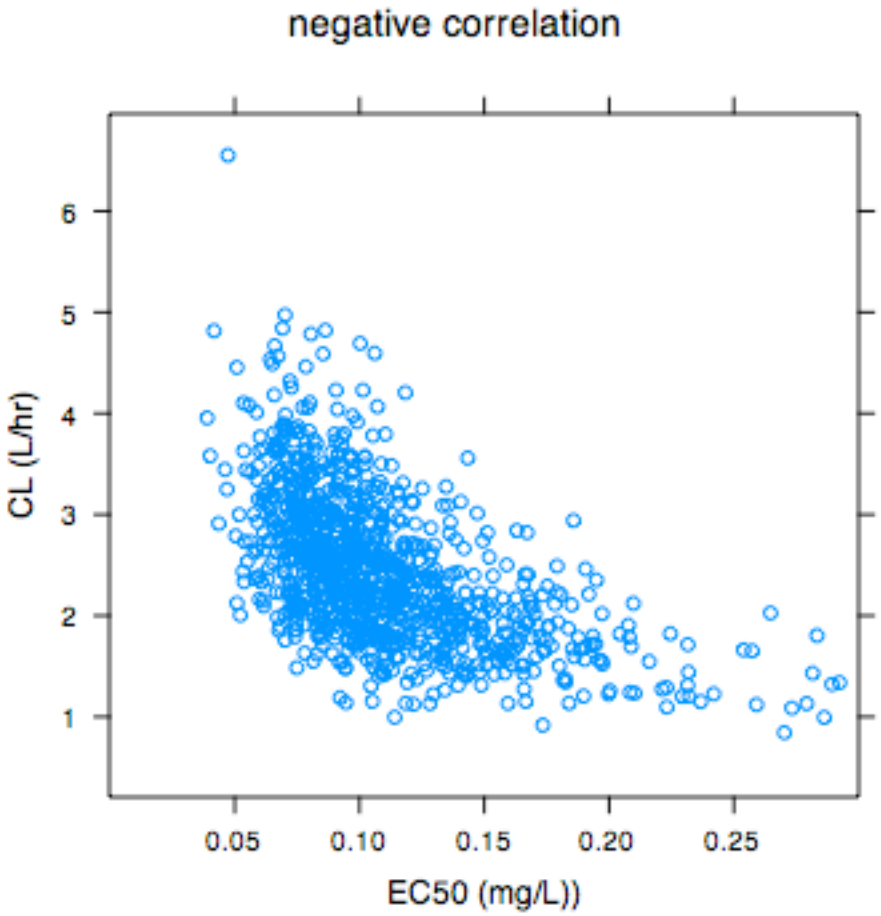
- Can we make an accurate assessment of the PK-PD relationship from this design?

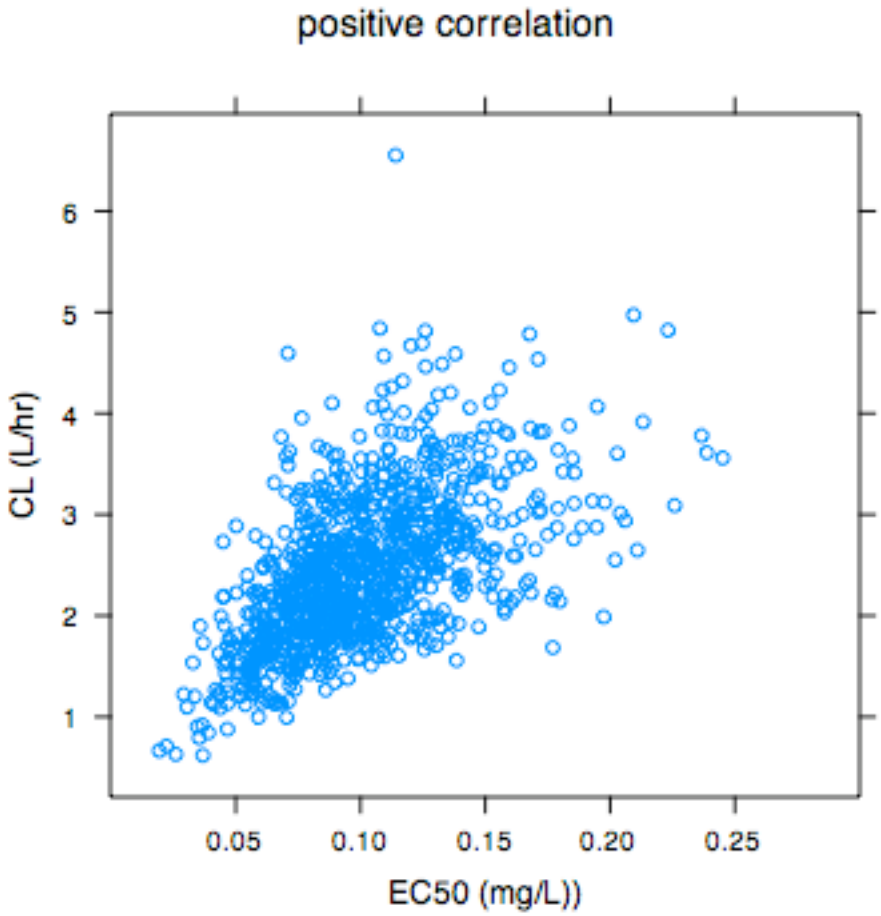


Problem described in: Nedelman JR, Rubin DB, Sheiner LB. Diagnostics for confounding in PK/PD models for oxcarbazepine. Stat Med. 2007 Jan 30;26(2):290-308.

Exposure-Response in MTD-Type PoC

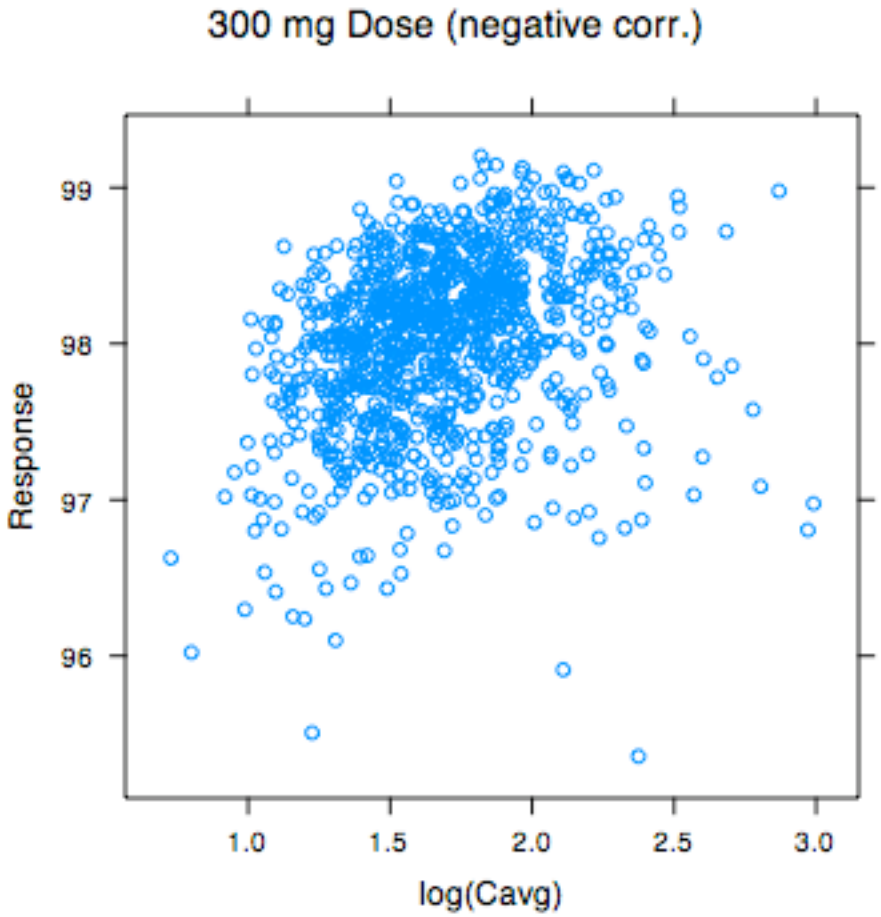
- Consider possible inter-individual correlation between PK and PD

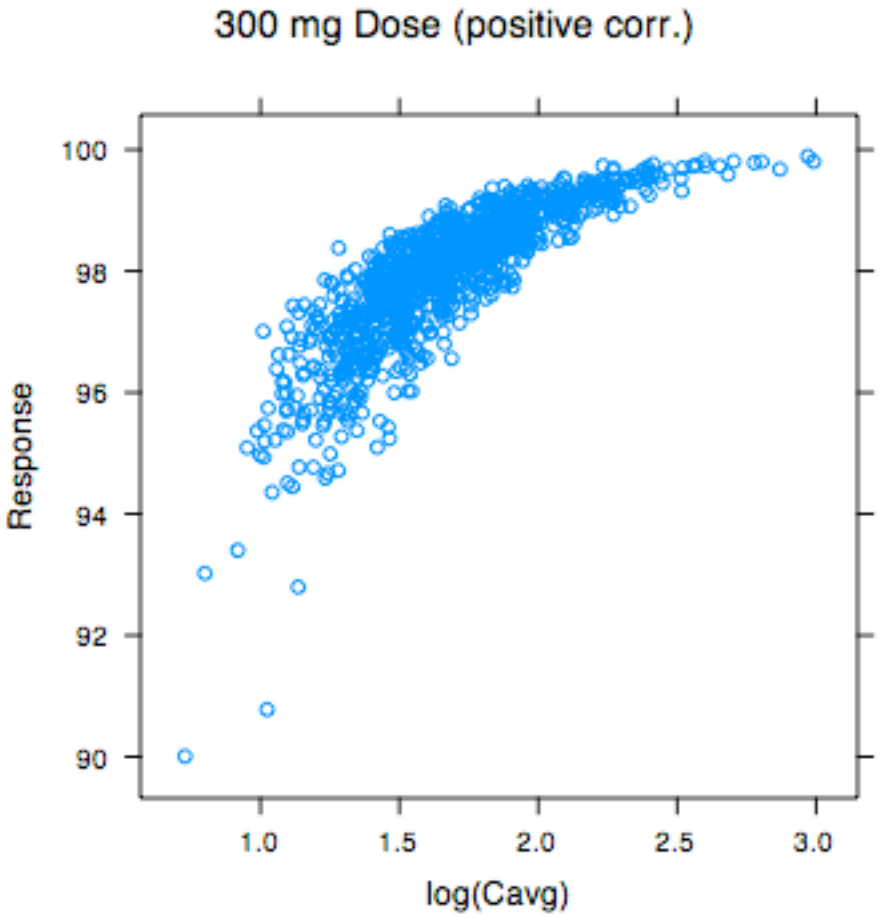




Exposure-Response in MTD-Type PoC

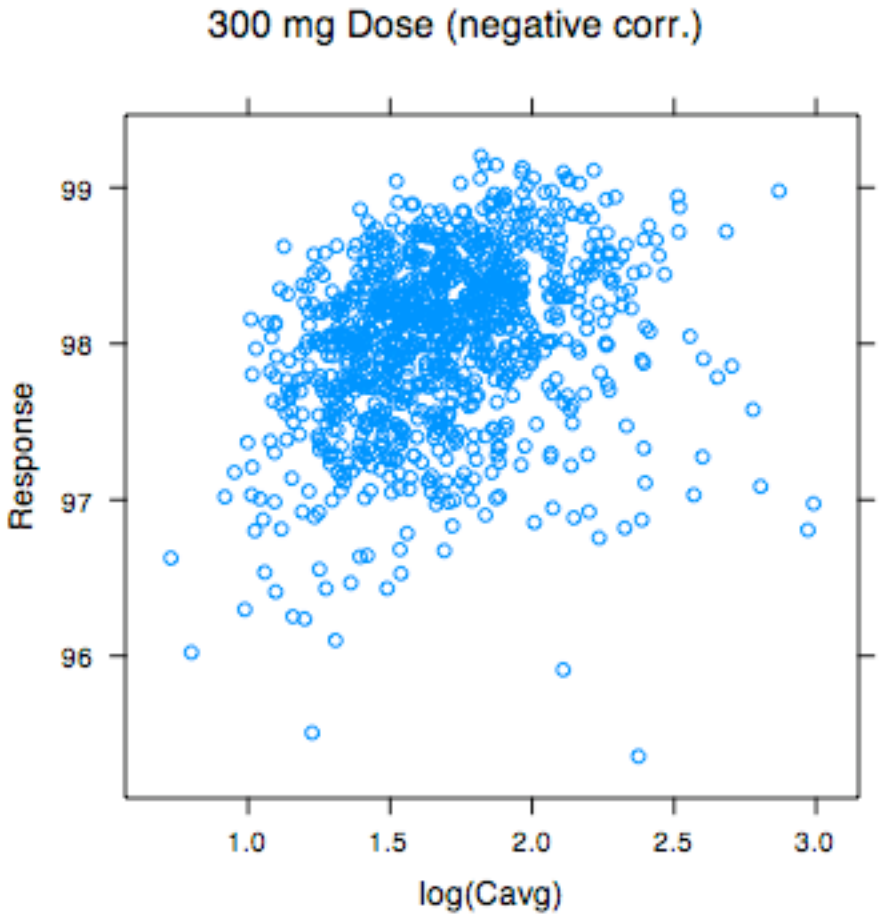
- Resulting exposure-response relationships are misleading

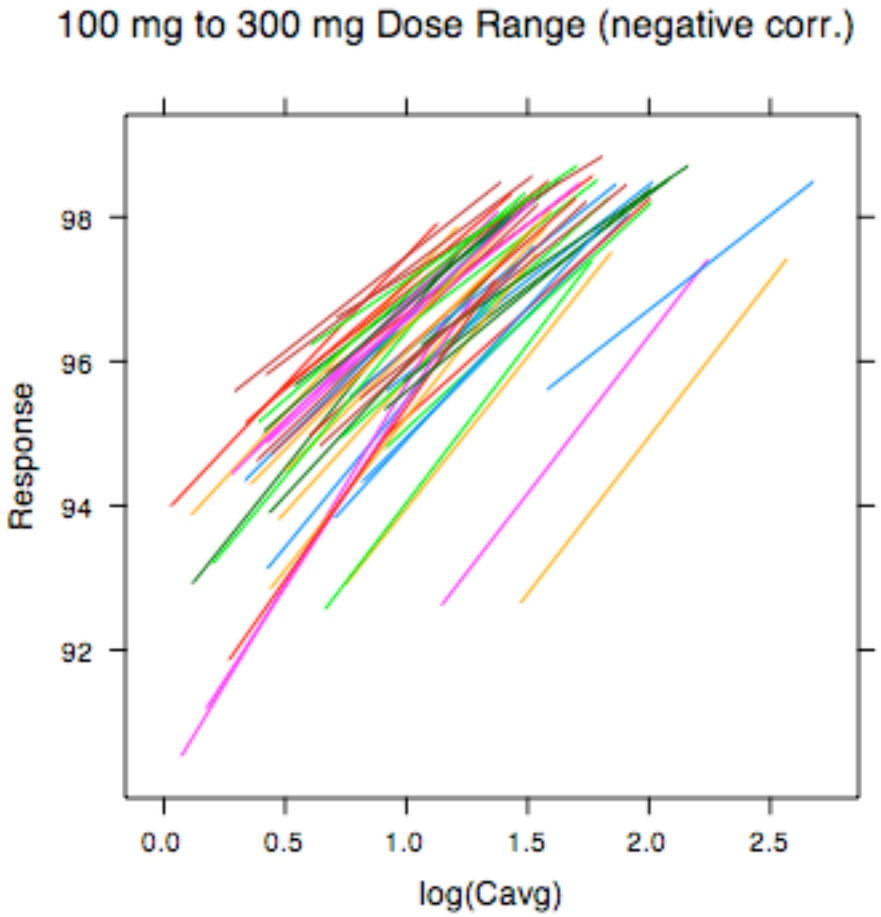




Exposure-Response in MTD-Type PoC

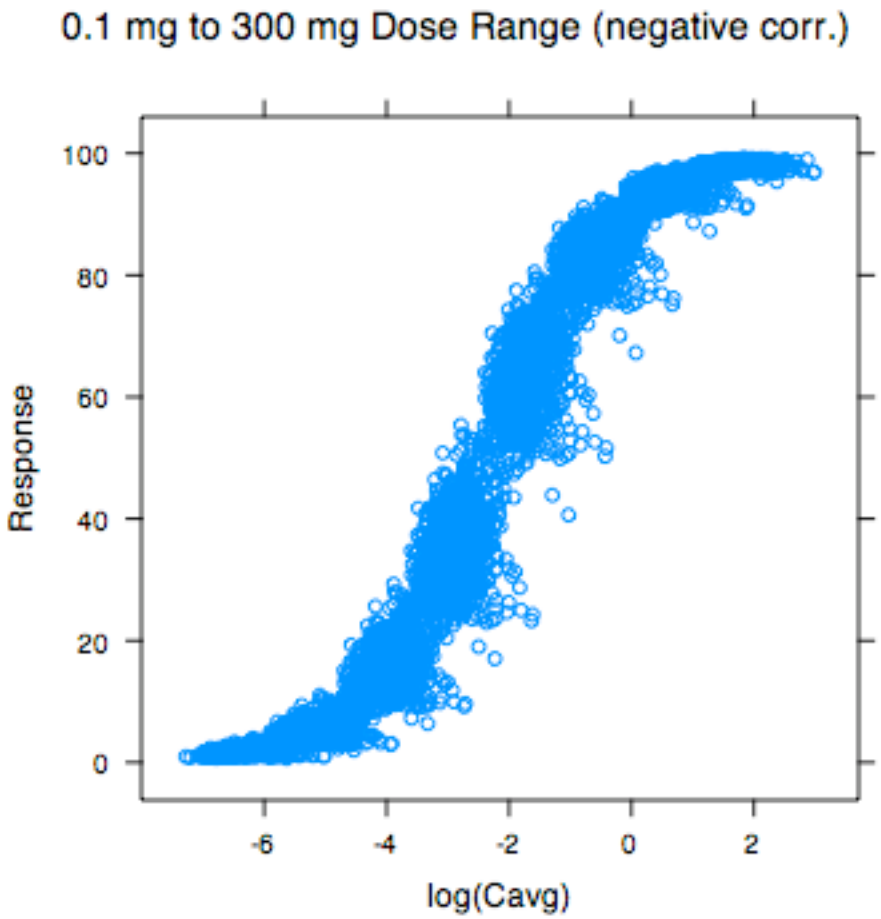
- One solution: Obtain within-individual E-R (e.g. crossover) analyzed with mixed-effects modeling

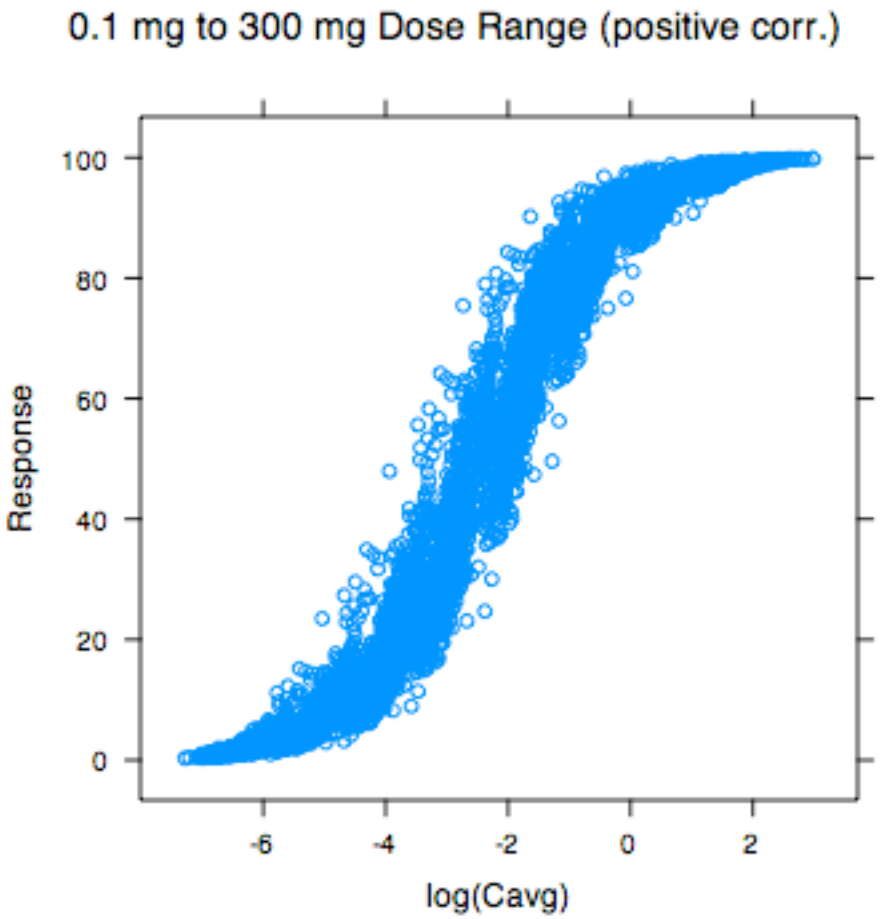




Exposure-Response in MTD-Type PoC

- Another solution: Population E-R with broad dose-range



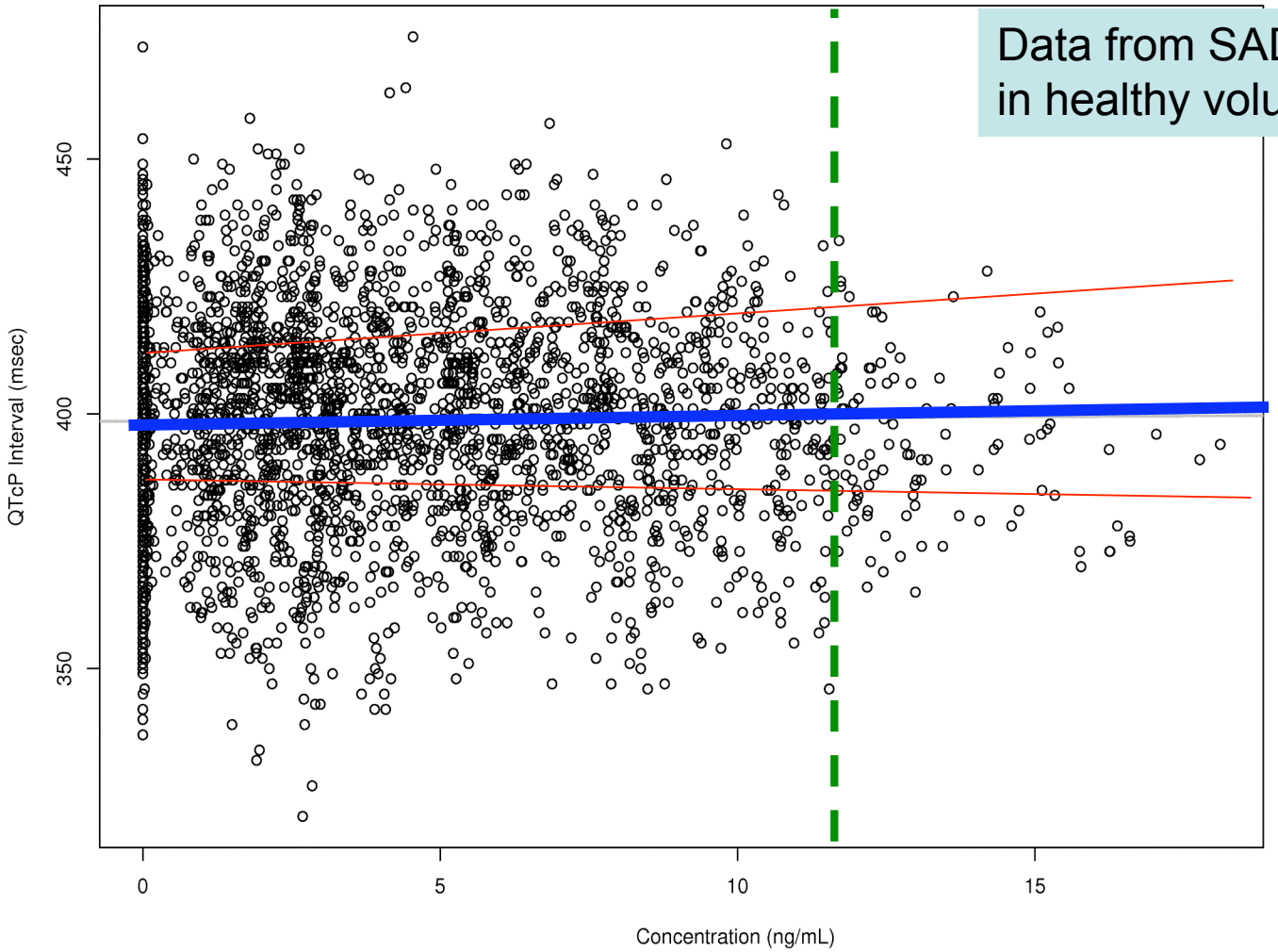


PK-PD in Planning and Design of PoC Trials

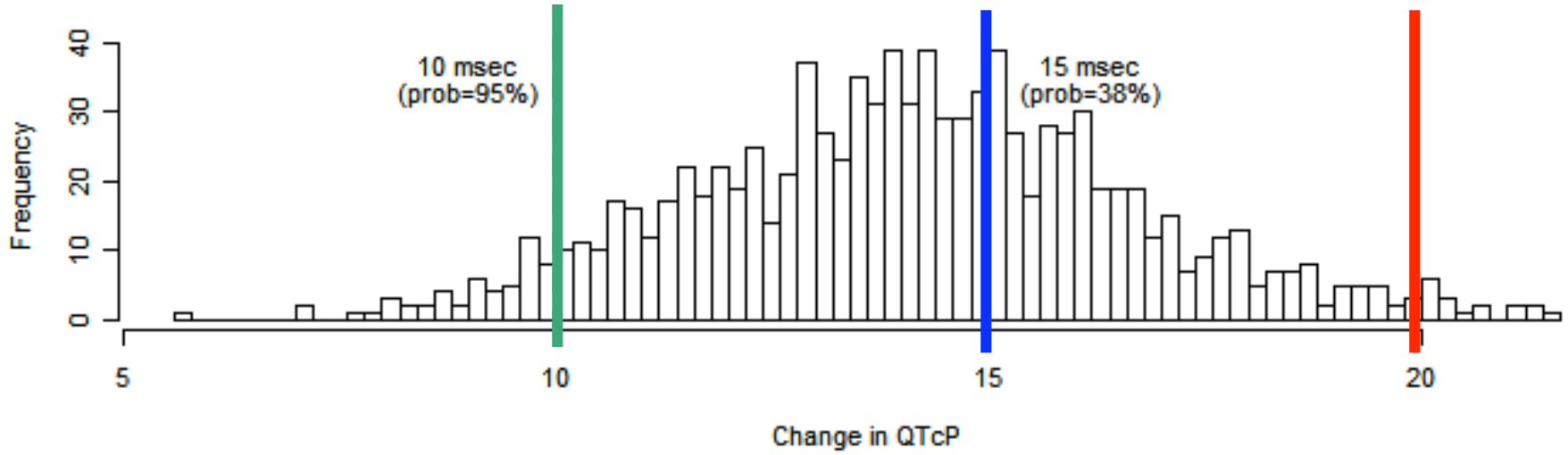
- Use prior information, when available

  - Phase I PK, tolerability, biomarkers
  - Pre-clinical estimates of effective concentrations, relative potency
  - Competitor data
  - Therapeutic area knowledge

Toxicity E-R to Inform PoC Dose Selection



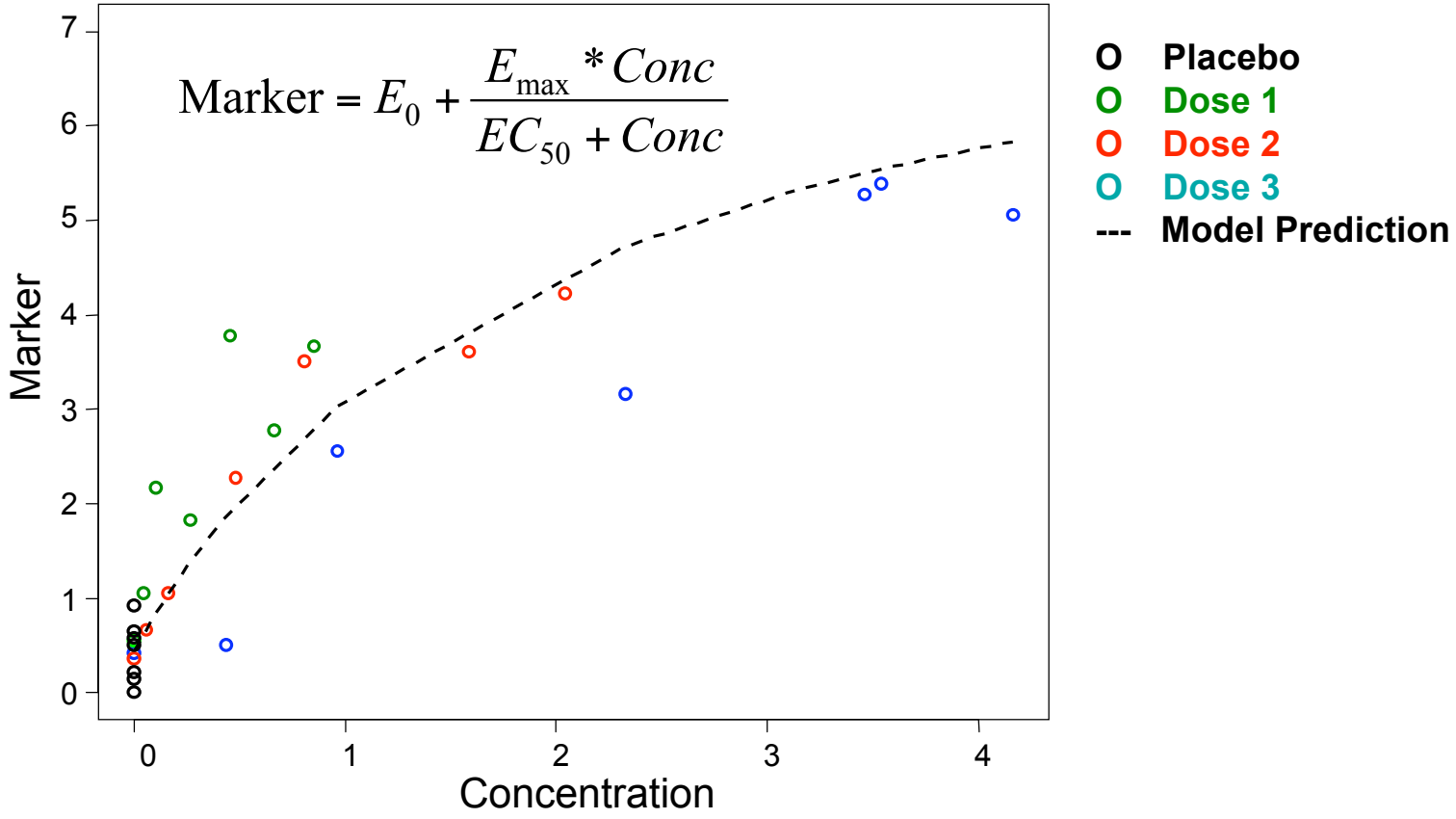
Probability of QTc Prolongation



- Explore probability of QTc – related toxicity at various doses from Phase I data
- Project QTc prolongation at expected Cmax, given top dose and DDI
- Define dose-limit and early probability of compound viability

Modeling Biomarker Data: Phase I MD Study

- PK-PD relationship evident & quantifiable ('Emax' model)
- Establish target PoM
- Set doses for investigation in PoC = concentrations within apparent efficacious range

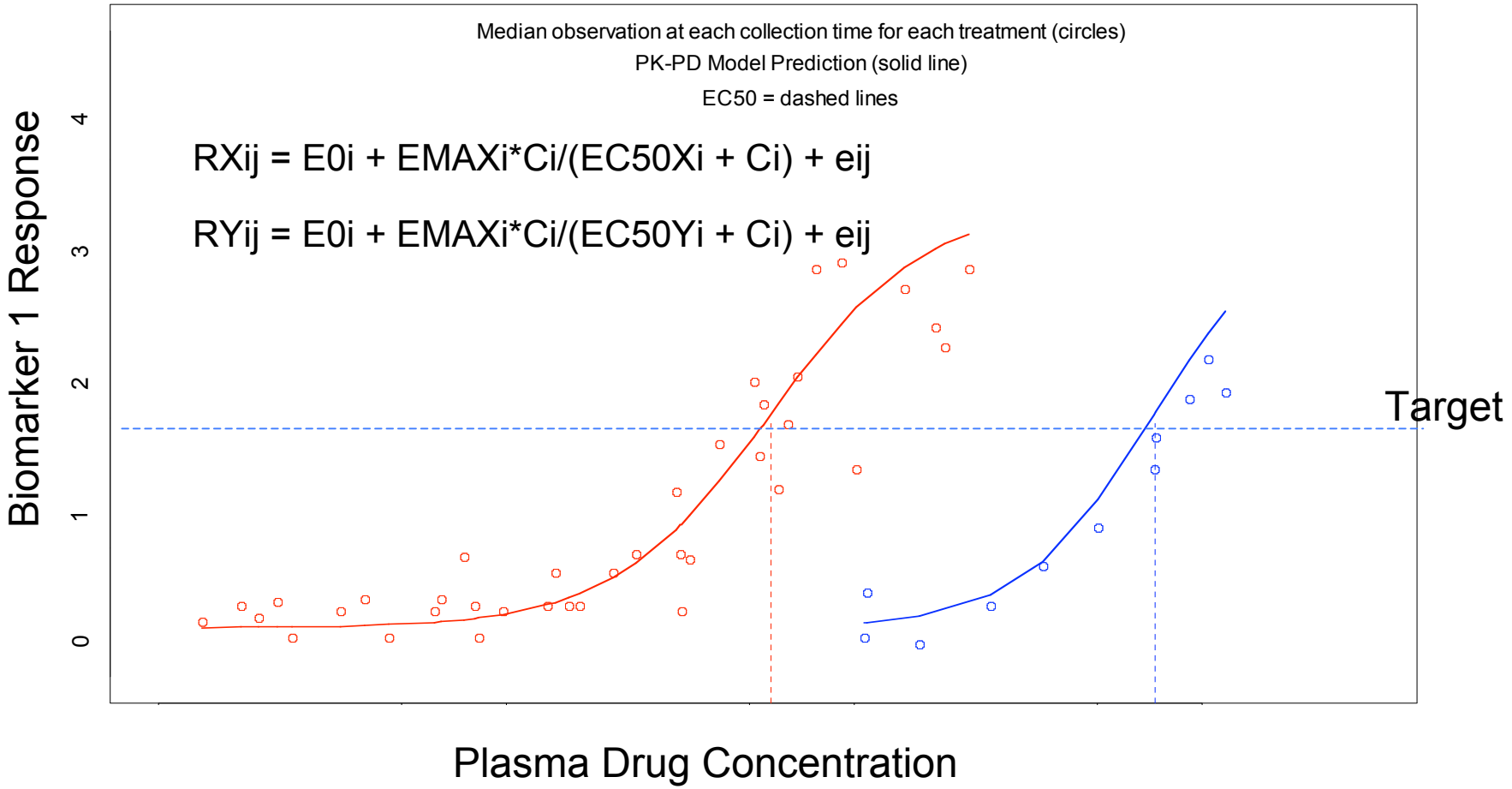


E-R Analysis of PoC Trials

- Example
  - Parallel groups: 4 active doses + placebo + active control (competing therapy)
  - Multiple Endpoints: biomarker 1 (efficacy), biomarker 2 (undesired), clinical outcome 1
  - PoC determination based on model-based posterior probability of reaching target response profile

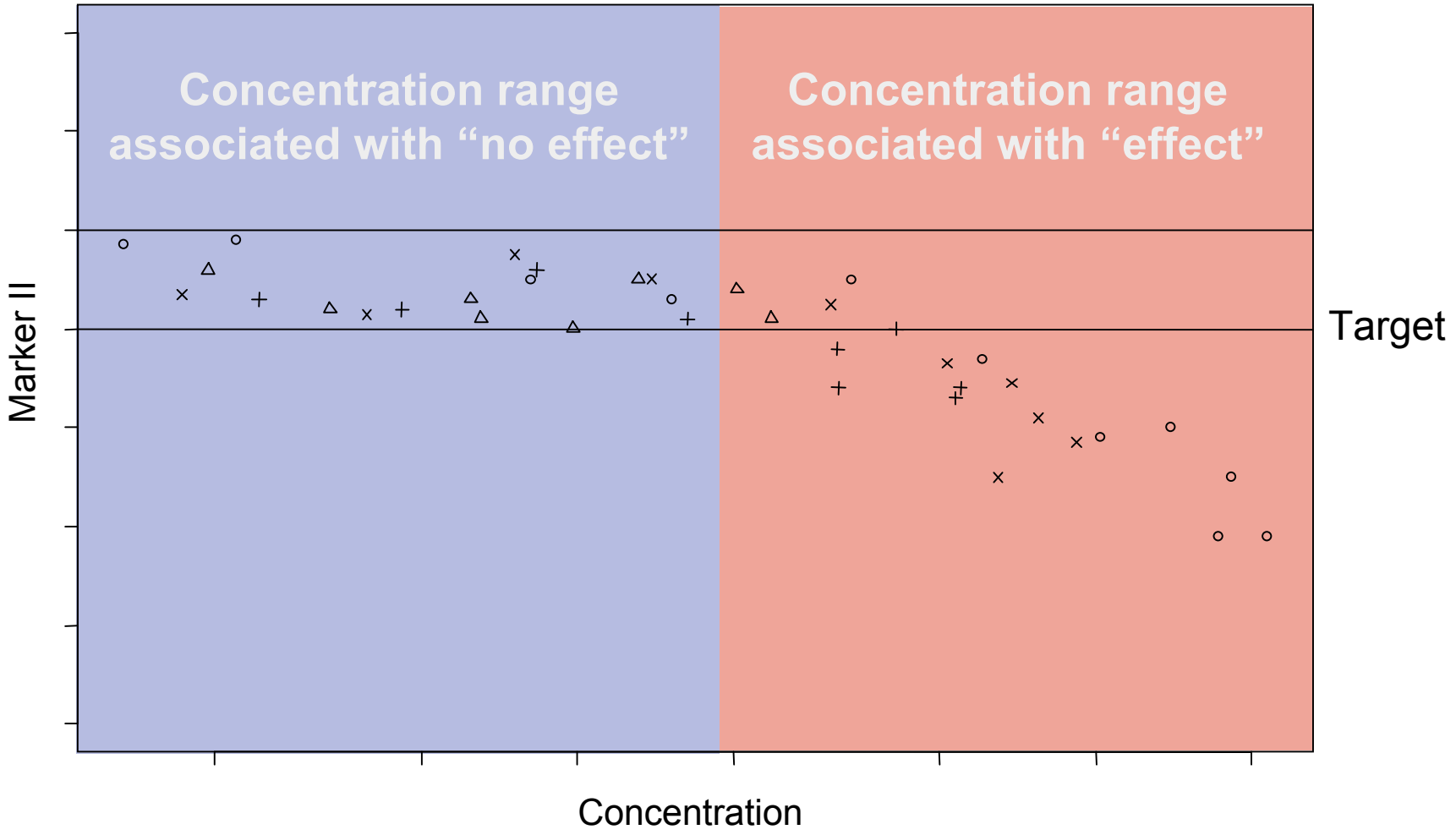
E-R Based PoC: Test & Active Comparator Response: Biomarker 1 (efficacy)

- **Drug X (red) was more potent than Comparator Y (blue)**
- **Relative potencies (EC_{50} of X vs. Y) very consistent across multiple response variables**

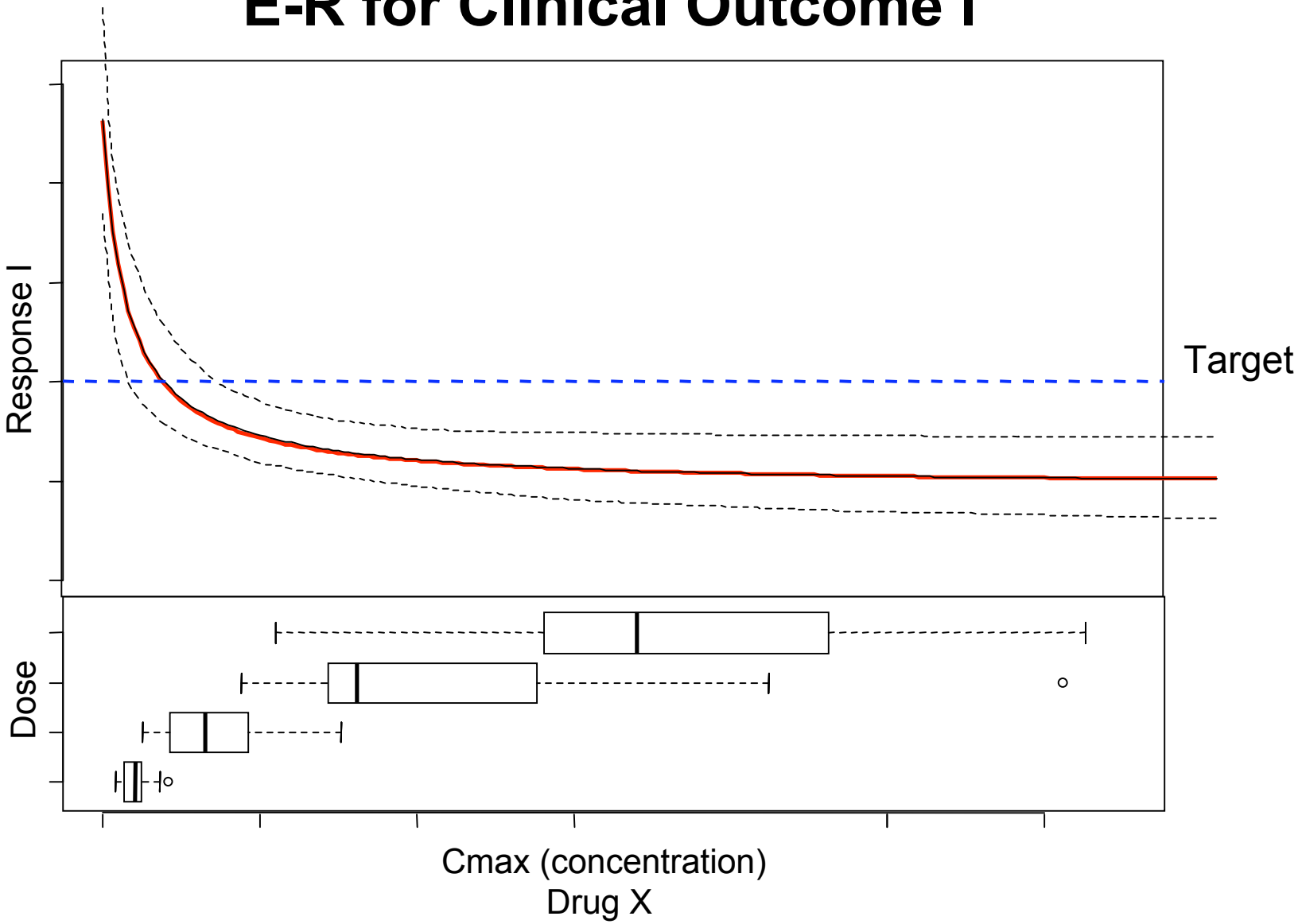


PoC: E-R for Biomarker 2 (undesired)

- Identified *Drug X* concentrations associated with BM II effect
- Consider doses that provide for target concentrations



E-R for Clinical Outcome I



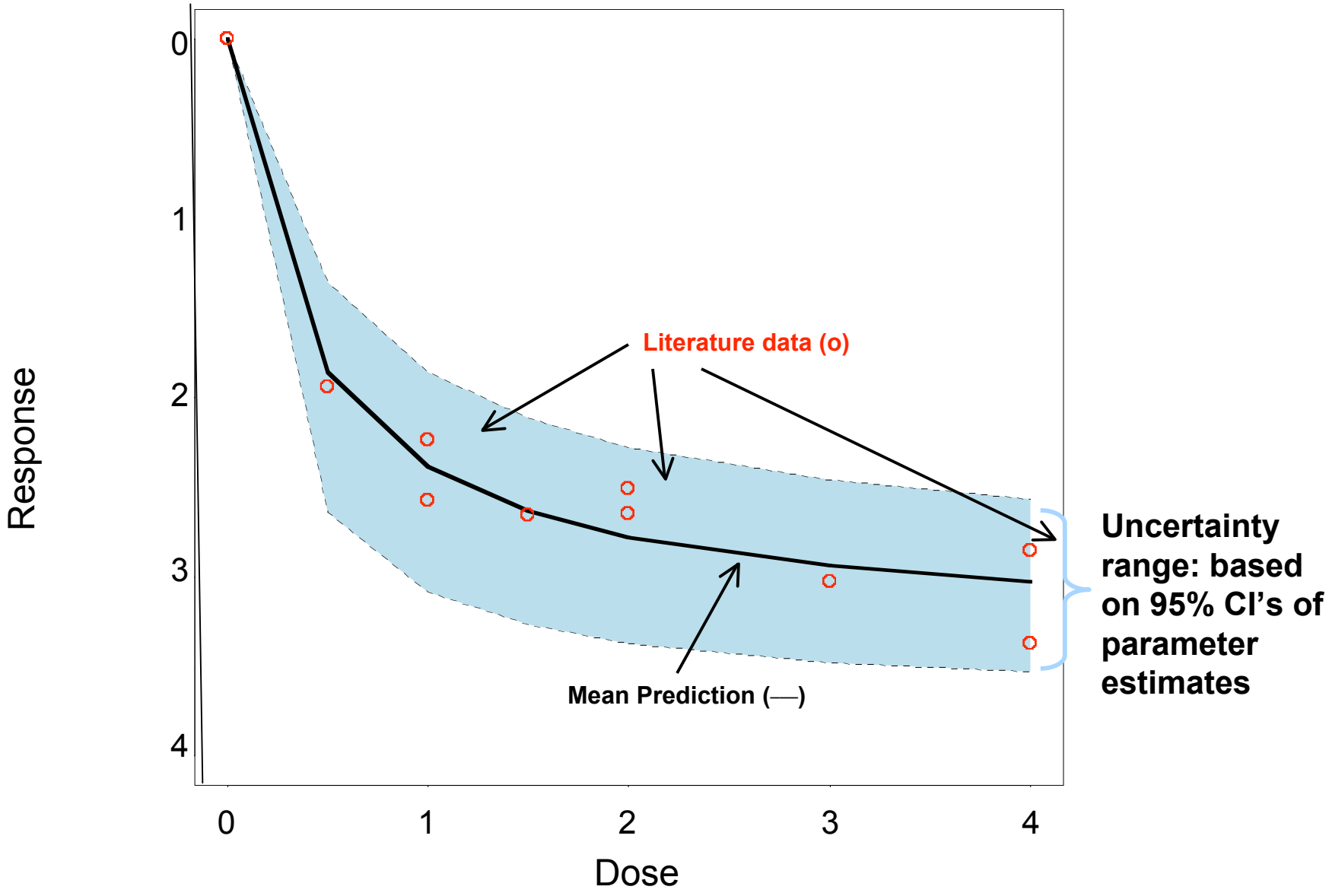
Building Knowledge for Phase 2b

- Drug X posterior probability distribution for target response meets PoC criterion, but which doses should go into Phase 2b, where primary endpoint will be an approval outcome measure?

- *Comparator Y* Dose-Response
  - Literature data
  - Model = Nonlinear 'Emax' model for mean relationship
  - Uncertainty range: Based on standard errors of parameter estimates

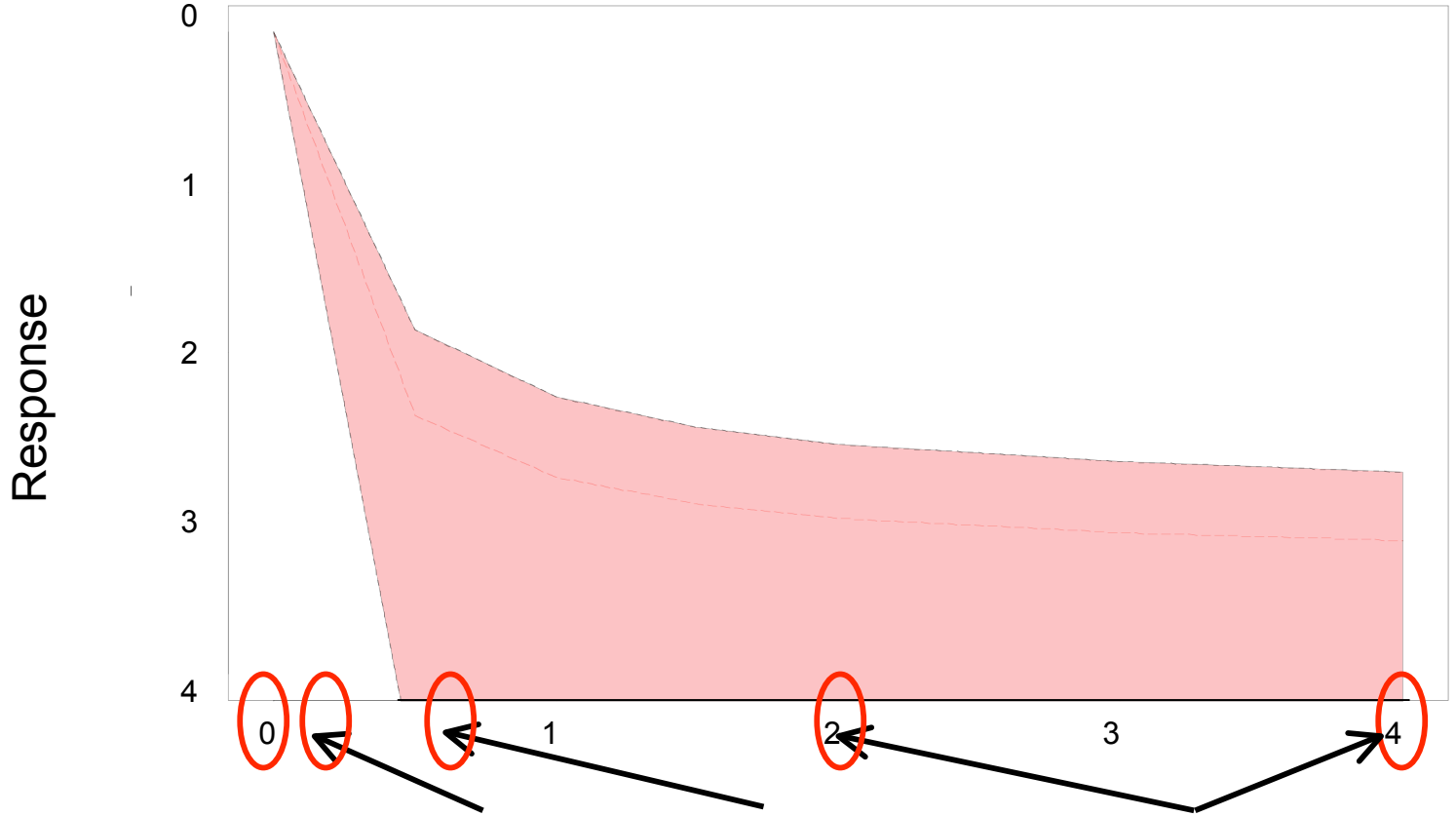
- Scaled for Approximate Dose-Response of *Drug X*
  - Based on biomarker relative EC_{50} of *Drug X* vs. *Comparator Y*
  - Accounted for PK differences
  - Additional variability for uncertainty in scaling ratios

Dose-Response Model for *Comparator Y*: 2b Response



Scaled Dose-Response for *Drug X*: Predicted 2b Response

- Select doses to further characterize (reduce uncertainty in) response surface



- Target doses ~ 50% (ED_{50}), 80% (ED_{80}) & max effects (E_{max})

Other Examples of E-R in Analgesic PoC Trials

- Dissociation of rescue drug effects from test treatment

- Model-based inferences with dropout (missing data)

Dissociating Treatment Effects from Rescue Dose Effects

- Chronic pain PoC design (PBO plus 4 dose levels)
- Acetaminophen rescue (500 mg) allowed as needed
- Reduction in pain intensity is primary endpoint
- Problem: How to interpret pain response in presence of rescue?

- Proposal: Analyze entire data set with model-based analysis using 2 simultaneous exposure-response relationships:
  - Study Drug E-R
  - Rescue E-R

Consideration

- Potential delay between plasma exposure and exposure at site of action (e.g.,CNS)
  - ➢ May be more pronounced with
    - with acute or 'prn' dosing
    - shorter $t_{1/2}$ and/or rapid Tmax

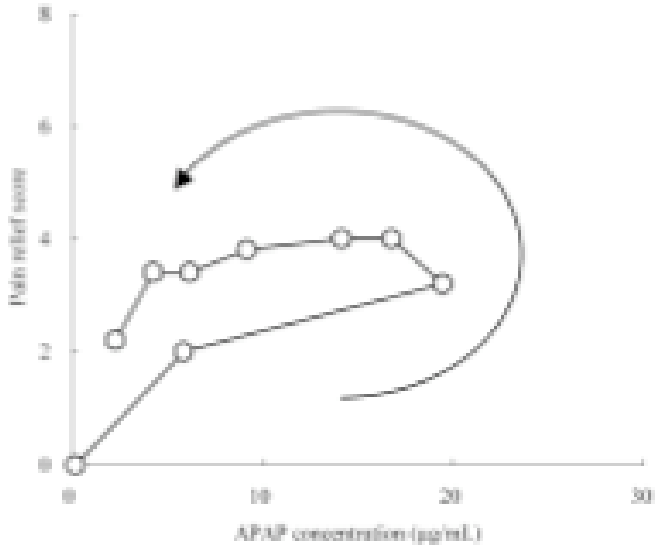


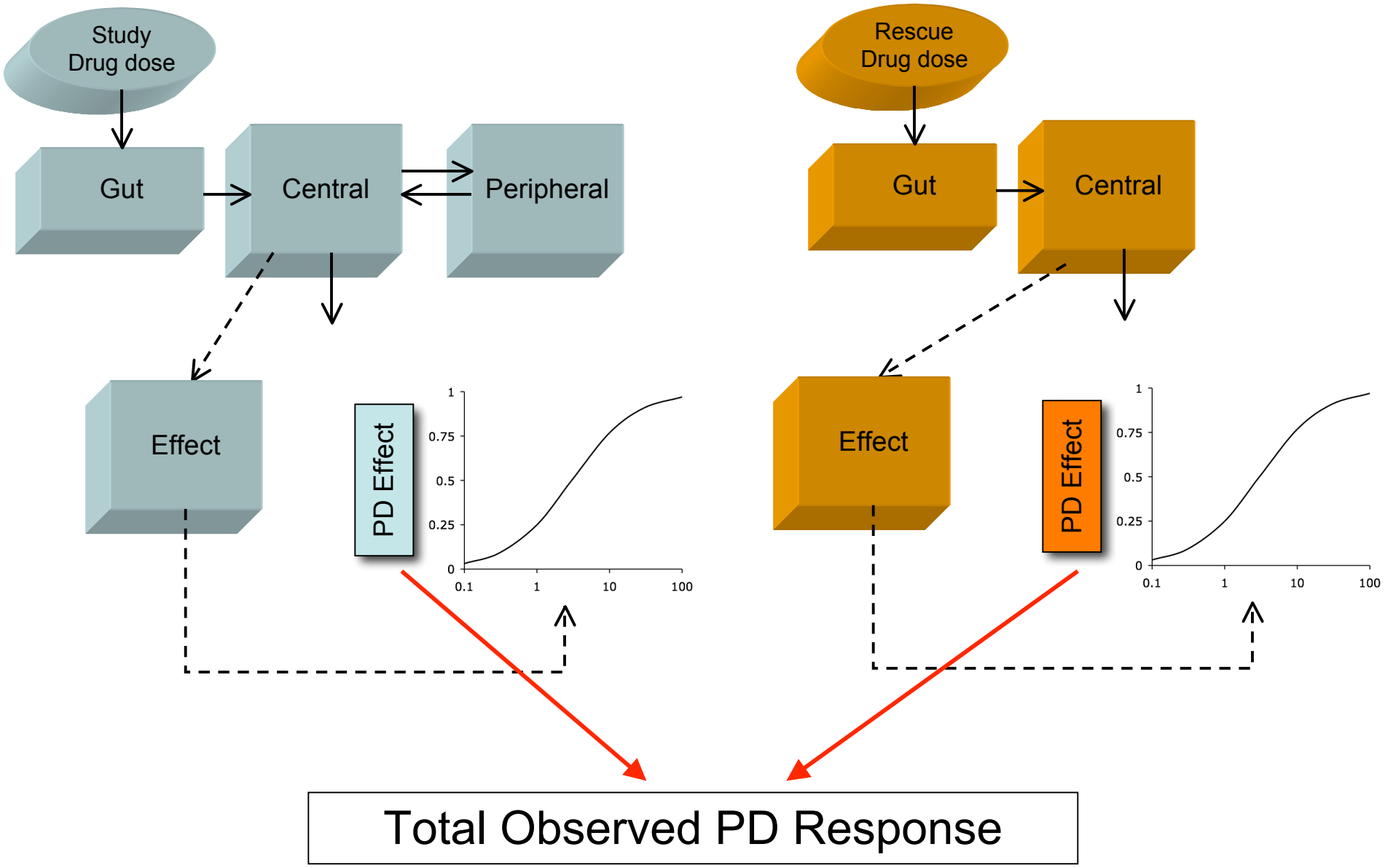
Fig. 4. Relationship between APAP Concentration and Pain Relief Score in Five Patients with Chronic Pain

Plots represent mean values.

Figure from: Shinoda S, Aoyama T, Aoyama Y, Tomioka S, Matsumoto Y, Ohe Y 2007. Pharmacokinetics/pharmacodynamics of acetaminophen analgesia in Japanese patients with chronic pain. Biol Pharm Bull 30(1):157-161

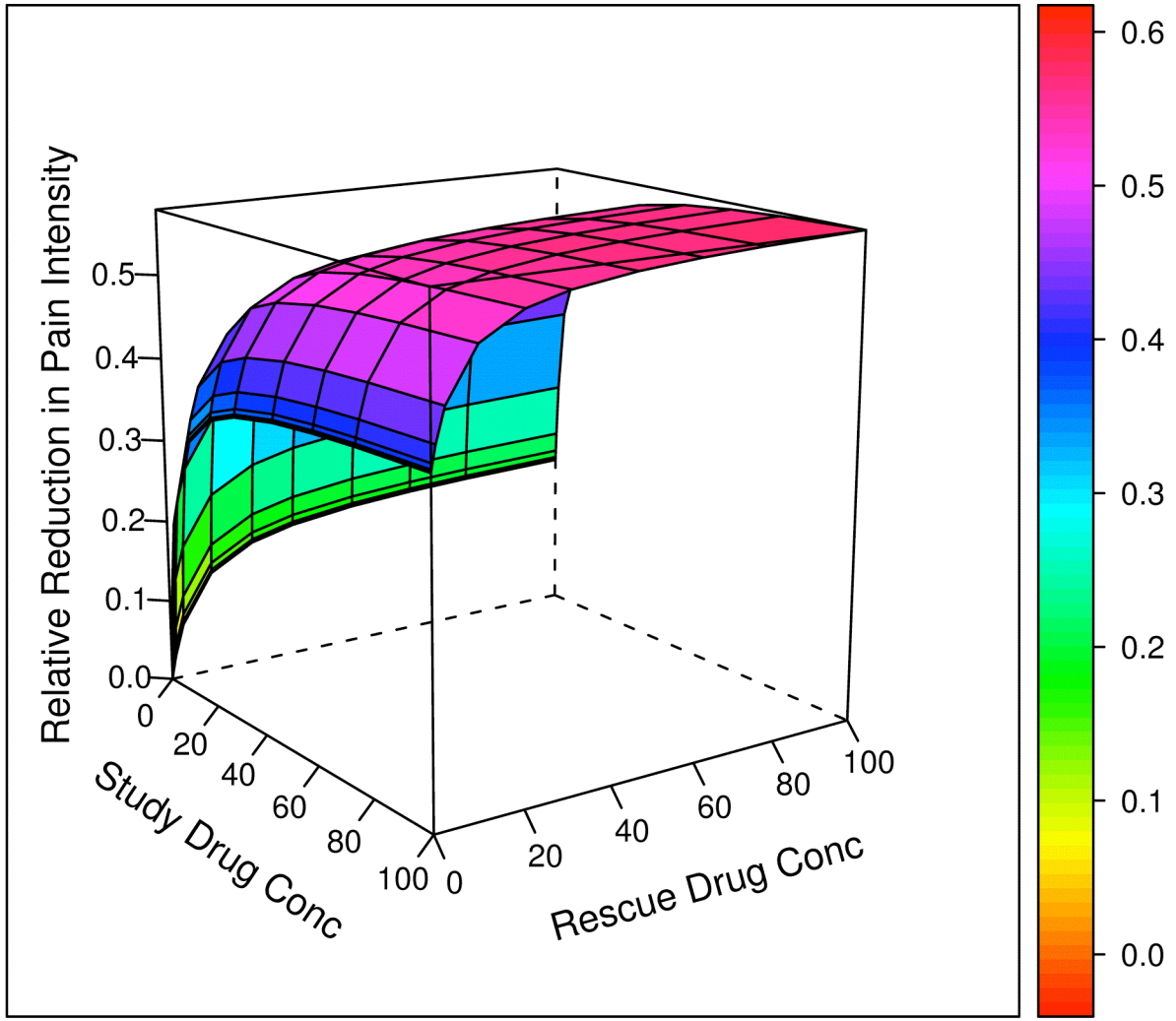
Also see: Staahl C, Upton R, Foster DJ, Christrup LL, Kristensen K, Hansen SH, Arendt-Nielsen L, Drewes AM. Pharmacokinetic-pharmacodynamic modeling of morphine and oxycodone concentrations and analgesic effect in a multimodal experimental pain model. J Clin Pharmacol. 2008 May;48(5):619-31.

Dual E-R Model Schematic



Individual Contributions to Total Response

- Integrated model of Study Drug and Rescue E-R
- Allows interpretation of individual and joint effects
- Success of this approach highly dependent on adequate Dose-Ranging design
- Results preliminary: Evaluation of performance through simulation ongoing



Model-Based Inferences in the Presence of Dropout

- Acute pain PoC study

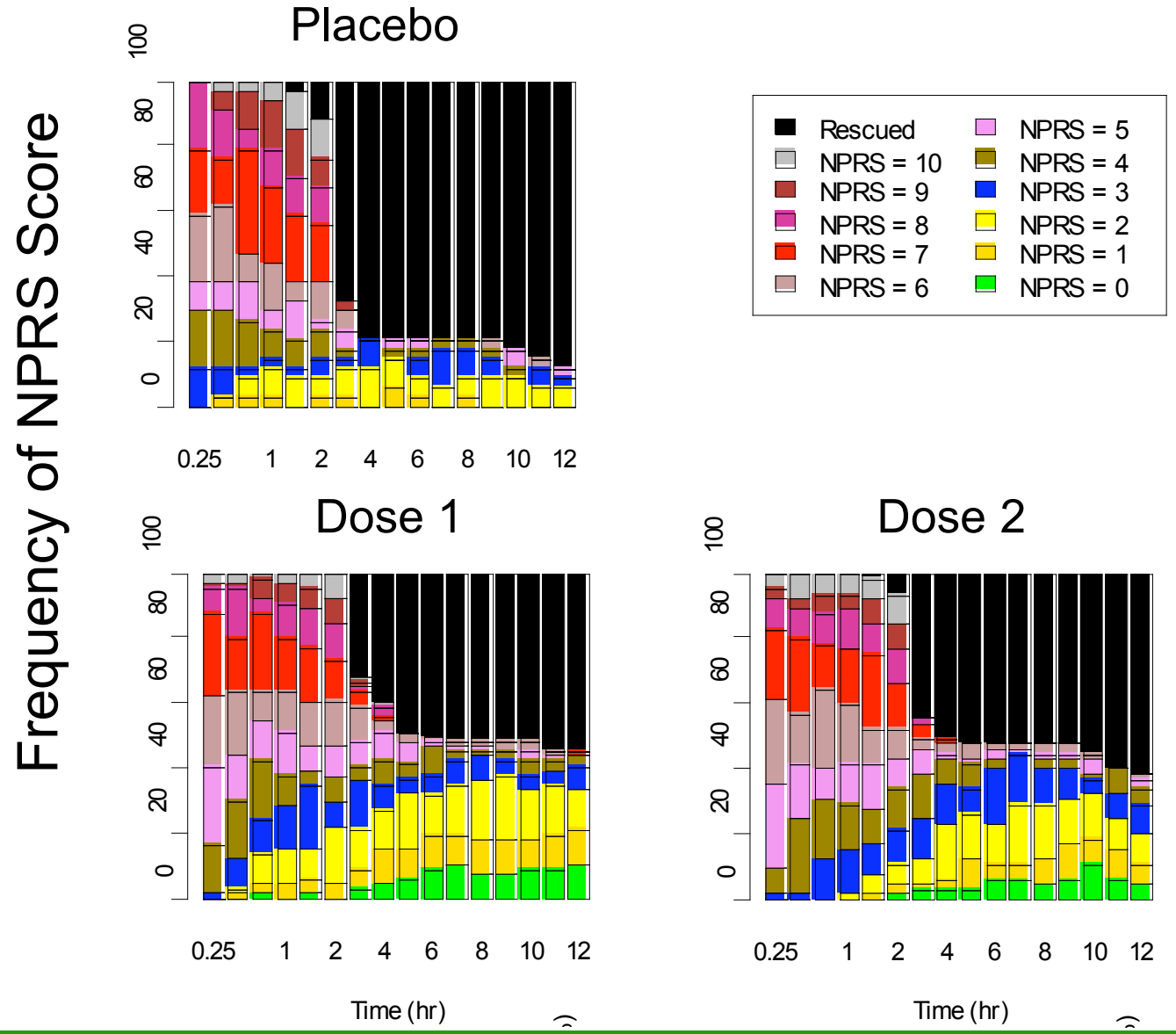
- Dropout after first rescue

- Population nonlinear-mixed effects exposure-response model developed from observed repeated-measures data (missing At random assumption)

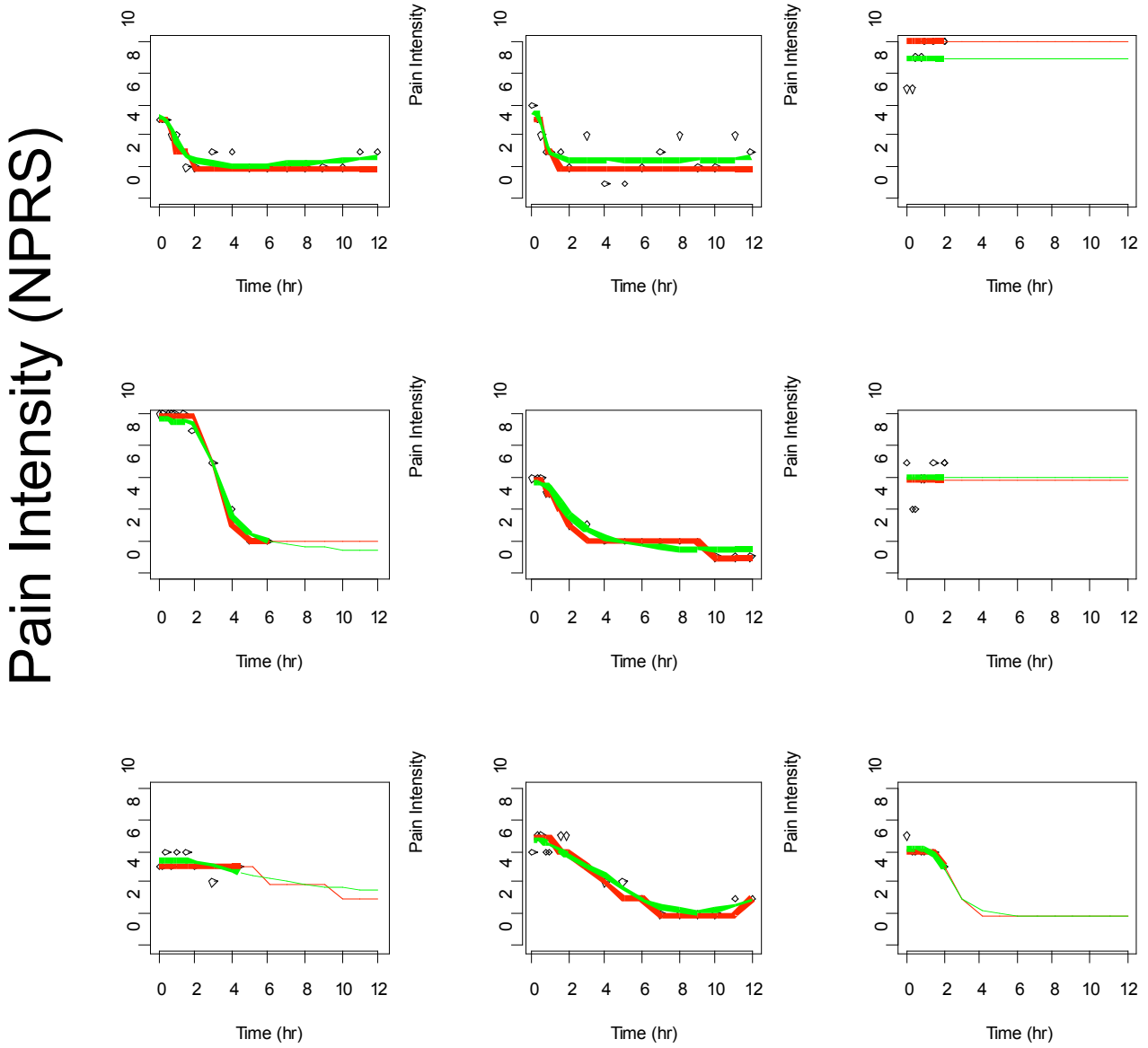
Approach first described in:

Sheiner LB. A new approach to the analysis of analgesic drug trials, illustrated with bromfenac data. Clin Pharmacol Ther. 1994 Sep;56(3):309-22.

Observed Data

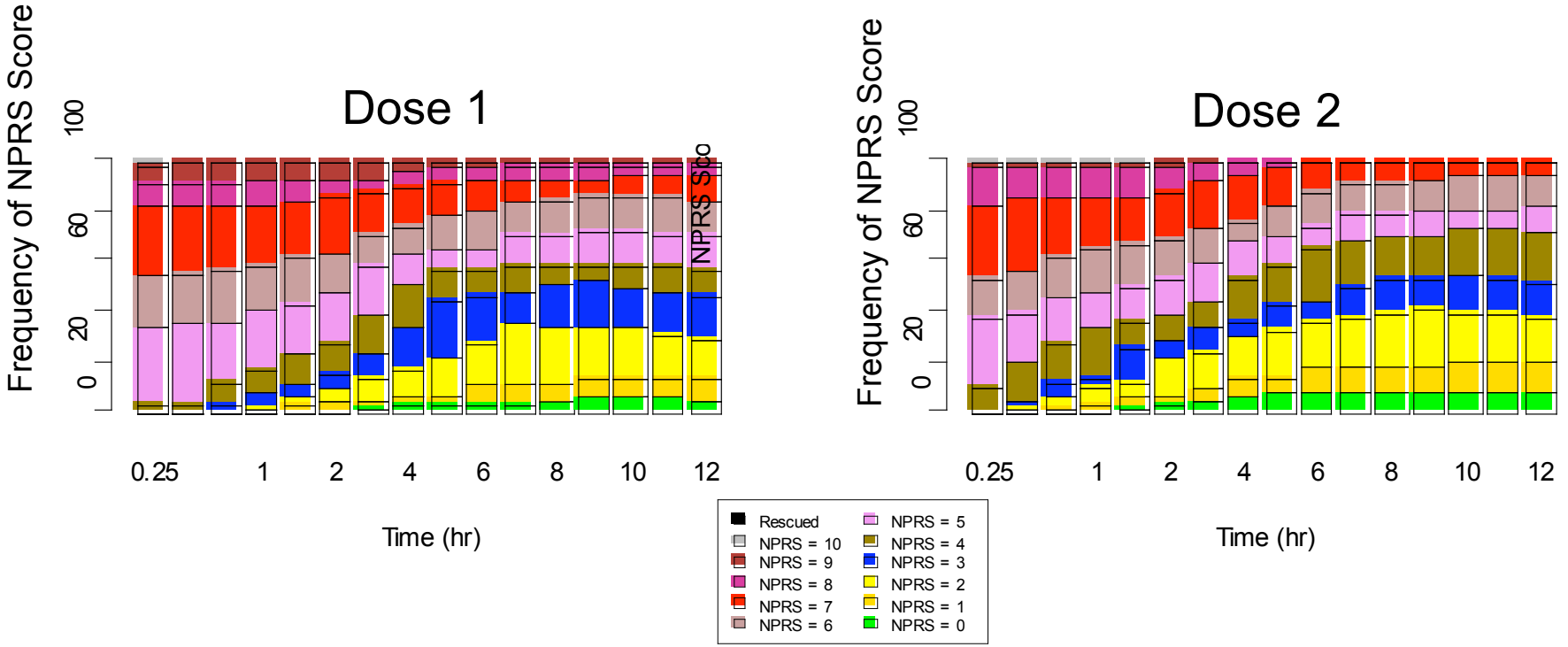


PD Response Time-Course



Model-Based Extrapolation

- Repeated-measures nonlinear mixed effects model used to extrapolate individual responses over time
- View simulated response time-course in the absence of dropout



Summary (1)

The utility of exposure-response in PoC trials depends on study design and PoC goals.

- MTD-Type PoC
  - E-R modeling of PoC data has minimal value; may be misleading
  - PK modeling still useful for understanding target population PK, reducing variability, or for explaining extreme outcomes
- Dose-Ranging PoC
  - E-R has high value for design, analysis and PoC determination
  - Comparative E-R relationships across multiple endpoints/active controls provides insight into probability of achieving target product profile
  - Advances knowledge building for future drug development phases
  - Basis for trial simulations to explore future designs

Summary (2)

- PK and E-R modeling and simulation:
  - are tools for knowledge-building and decision support in drug development
  - provide basis for trial simulations to explore and optimize trial design performance
  - are best supported by trial designs that explore individual E-R relationships
  - of multiple endpoints allows quantitative assessment of drug's multivariate response profile, supporting dose-selection decisions
  - may be useful in assessing test treatment response in presence of rescue dosing (preliminary)
  - may be useful for making inferences in the presence of dropout (for non-regulatory purposes)

Additional References

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FDA Presentations on Model-Based Drug Development

- http://www.fda.gov/oc/initiatives/criticalpath/presentations.html
- http://www.fda.gov/ohrms/dockets/ac/03/slides/3998s1.htm
- http://www.aapspharmaceutica.com/meetings/files/38/Booth.ppt

Acknowledgements

- Heidi Costa
- Leonid Gibiansky
- Bill Knebel
- Matthew Riggs
- Bill Gillespie

- Industry collaborators