Expanding Statistical Influence in Pharmacometrics: What it Means, Why it Matters, and How to Make it Work

Jim Rogers, PhD
Nov 18, 2023

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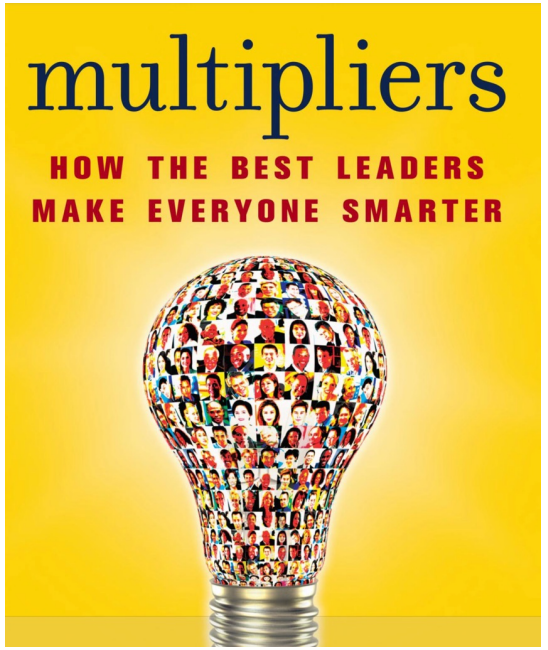
The Four “I”s of Dan Meyer

- **Initiative :** are you self-motivated?
- **Independence :** can you make skilled progress with minimal oversight?
- **Innovation :** are you changing how the game is played?
- **Influence :** can you expand your impact by working through others?



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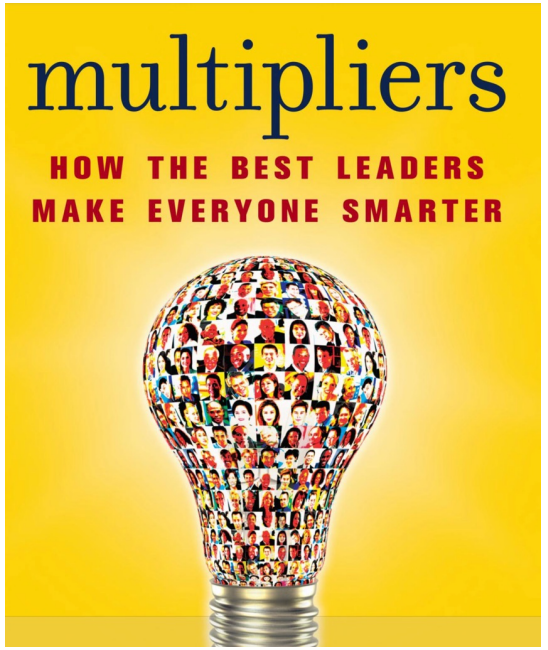

“The key to this business is personal relationships”

- Dicky Fox, *Jerry Maguire 1996*

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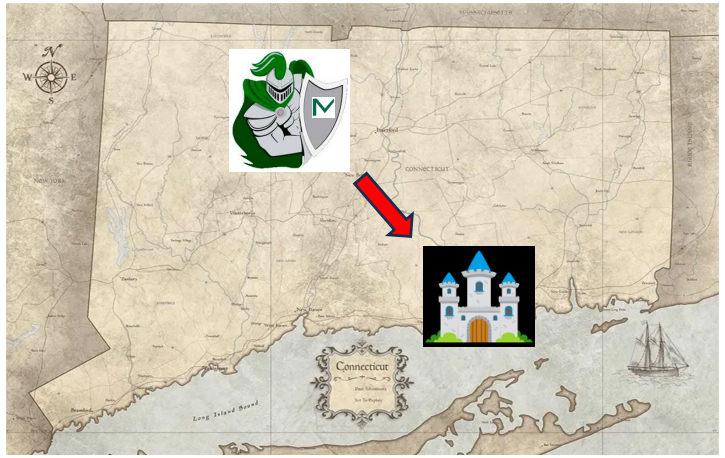
My Origin Story

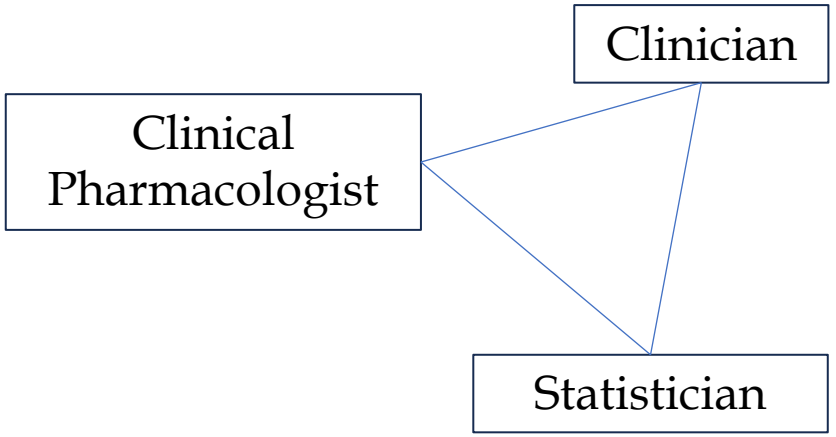
Once upon a time … (about 17 yrs ago)

In a castle on the peaceful shores of
New London,
The dashing young clinical statistician,
Sir James,
was working as part of
a mighty "triad" …

… then news came of strangers
approaching from the North …



… they were called,
"modelers"



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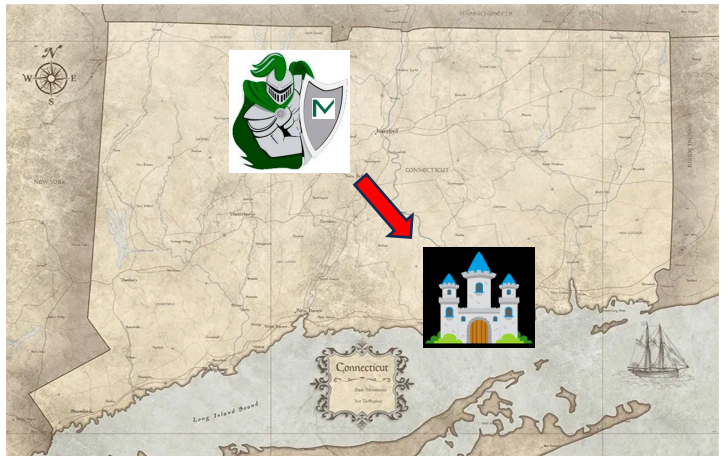
Clinician

Clinical Pharmacologist

Statistician

… then news came of strangers approaching from the North …



… they were called,
"modelers"

Wait, I thought
I was a modeler???

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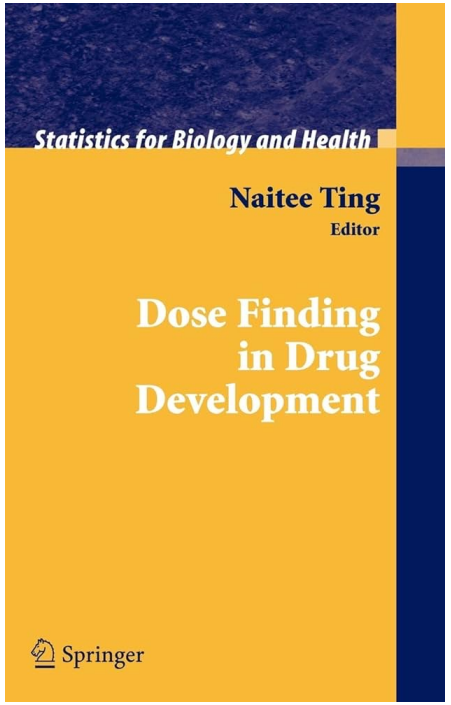
Dose-Response Analyses



Analysis of Clinical Dose–Response in Small-Molecule Drug Development: 2009–2014

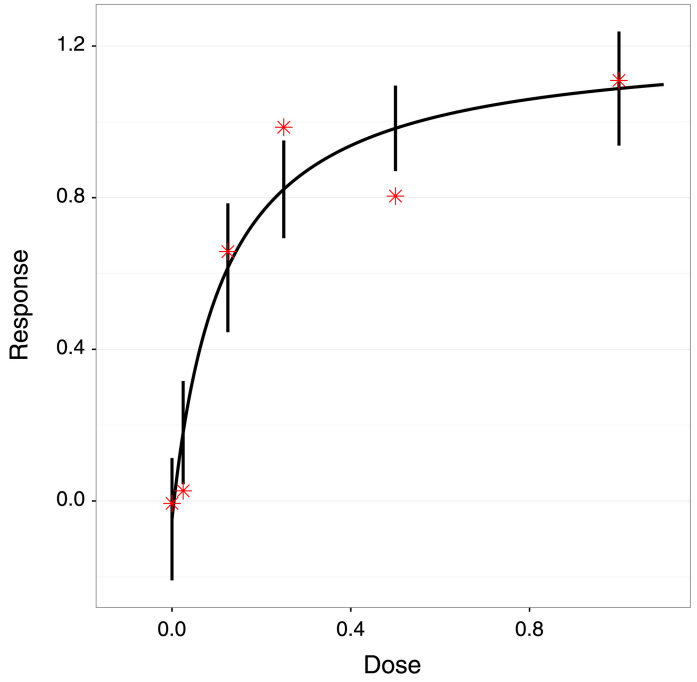
Neal Thomas & Dooti Roy

Pages 137-146 | Received 01 Jan 2016, Published online: 12 May 2017

Cite this article https://doi.org/10.1080/19466315.2016.1256229 Check for updates

BIOMETRICS 61, 738–748
September 2005

DOI: 10.1111/j.1541-0420.2005.00344.x



Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies

F. Bretz,[1,*] J. C. Pinheiro,[2] and M. Branson[1]

[1]Novartis Pharma AG, Lichtstrasse 35, Basel, Switzerland

[2]Novartis Pharmaceuticals, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

*email: frank.bretz@novartis.com

OFFICE OF CLINICAL PHARMACOLOGY
DIVISION OF PHARMACOMETRICS

Application	Request for Qualification of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty
Applicant	Janssen Pharmaceuticals and Novartis Pharmaceuticals
Application date	22 April, 2015
OCP Division	Division of Pharmacometrics
OCP Reviewer	Dinko Rekić, MSc(Pharm), Ph.D.
Concurring reviewers	Yaning Wang, Ph.D. Deputy Director, Division of Pharmacometrics Vikram Sinha, Ph.D. Director, Division of Pharmacometrics

OCP: Office of Clinical Pharmacology

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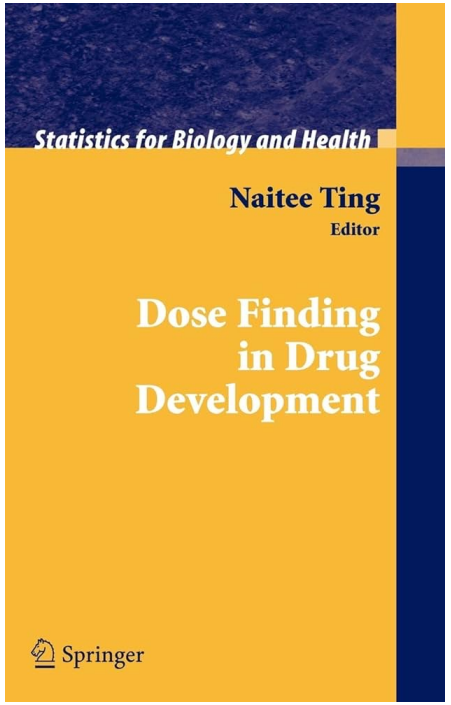
Dissenting Voices



6
Dose Response:
Pharmacokinetic–Pharmacodynamic
Approach

NICK HOLFORD

6.1.1 *How Dose Response and Exposure Response Differ*

A fundamental difference between dose response and exposure response arises because individuals differ in their responses when given the same dose. Exposure response methods explicitly recognize this and try to describe individual differences as well as the average dose–response relationship.

6.1.2 *Why Exposure Response is More Informative*

The exposure response approach is capable of describing and explaining the time course of response after a single dose or multiple doses. Unlike the usual dose

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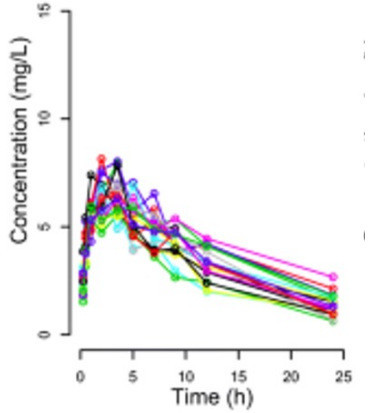
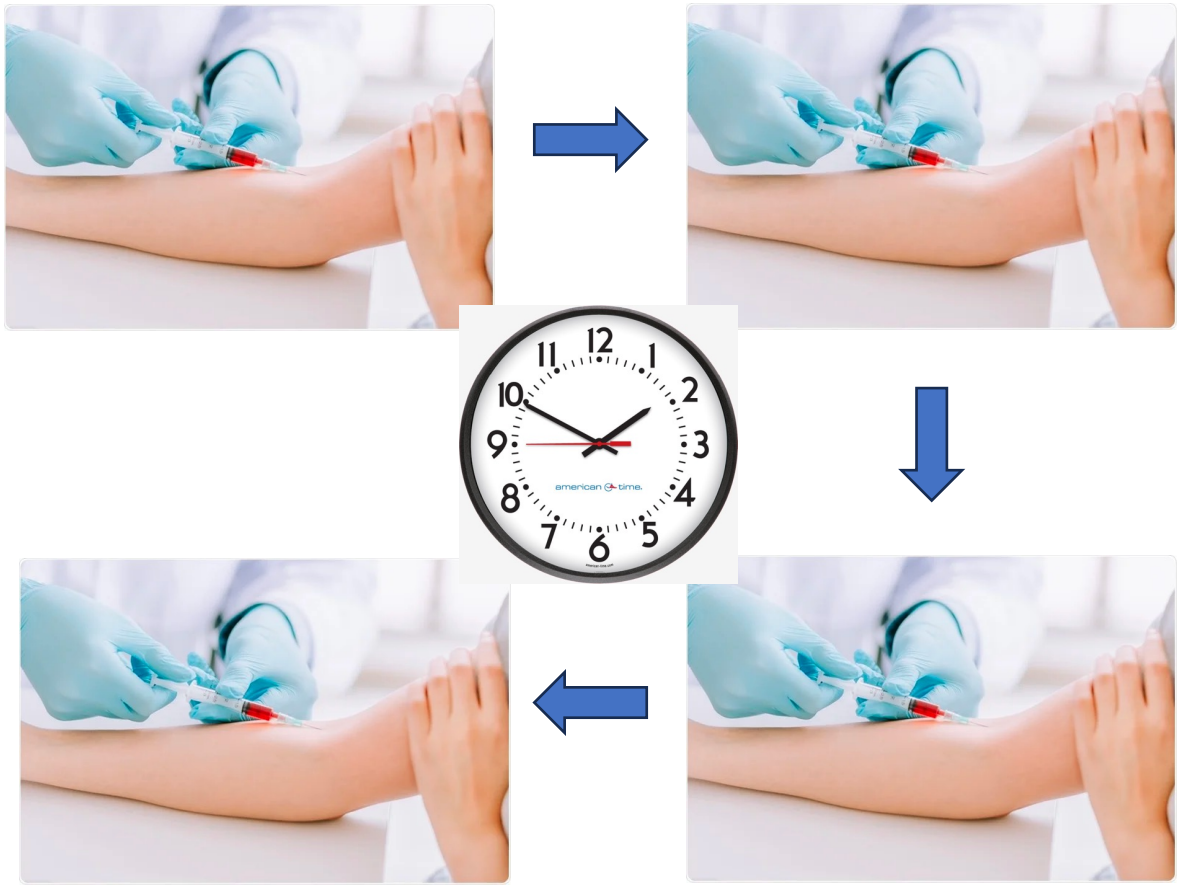
Dose Versus Exposure



Exposure versus time curves for multiple people who all took the same dose



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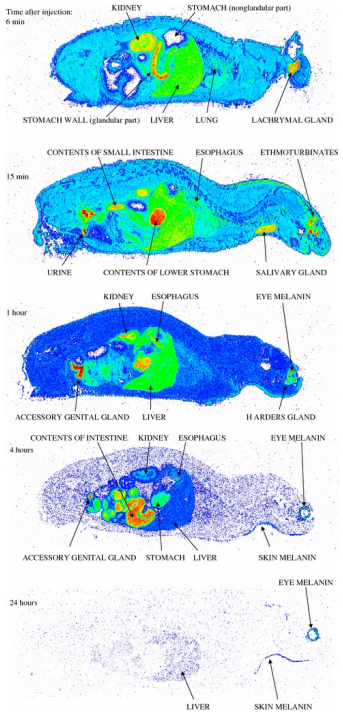
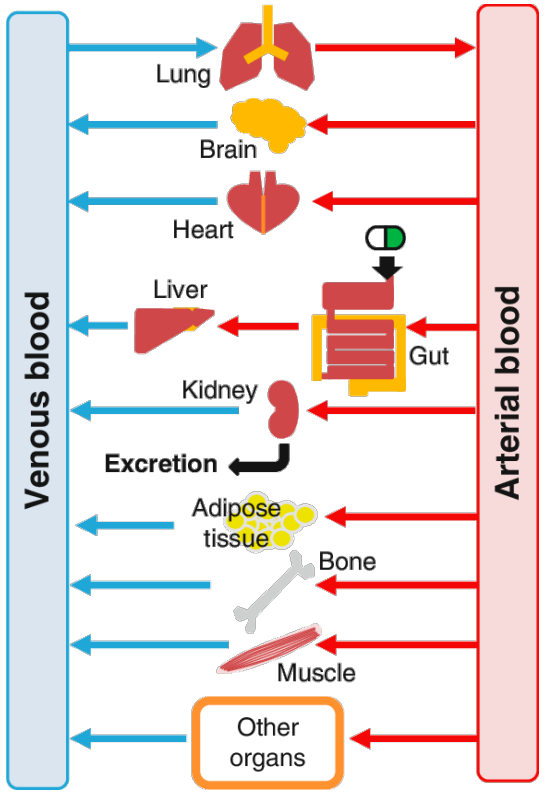
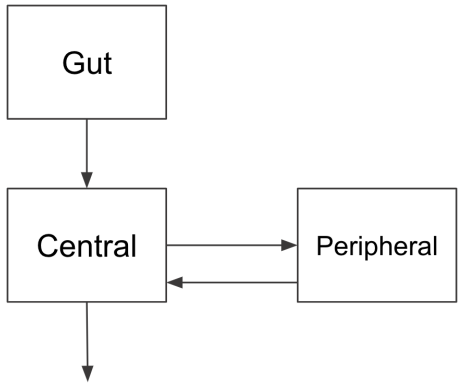
Pharmacokinetic Modeling Approaches

Physiologically-based Pharmacokinetics (PBPK)





"Semi-mechanistic" Pharmacokinetics



$$\frac{dA_1}{dt} = -k_a \times A_1$$

$$\frac{dA_2}{dt} = k_a \times A_1 - (k_{20} + k_{23}) \times A_2 + k_{32} \times A_3$$

$$\frac{dA_3}{dt} = k_{23} \times A_2 - k_{32} \times A_3$$

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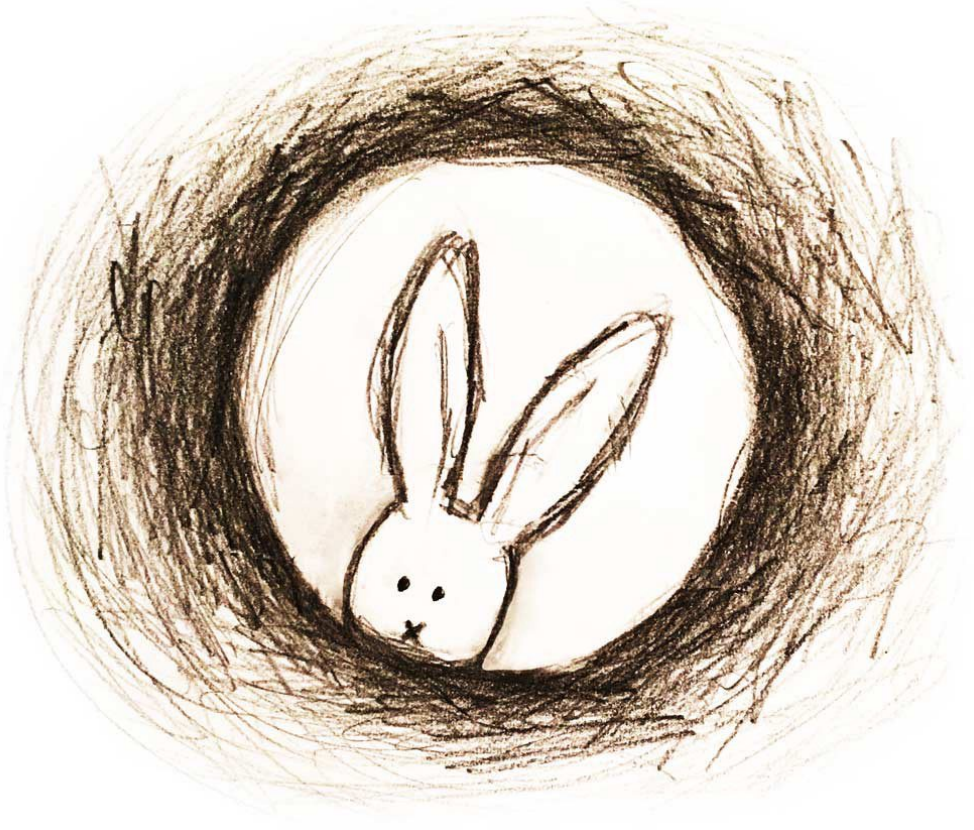
Are We Going Down a Rabbit Hole When We Don't Need To?



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Dose-Response is Simpler and Leverages Randomization …

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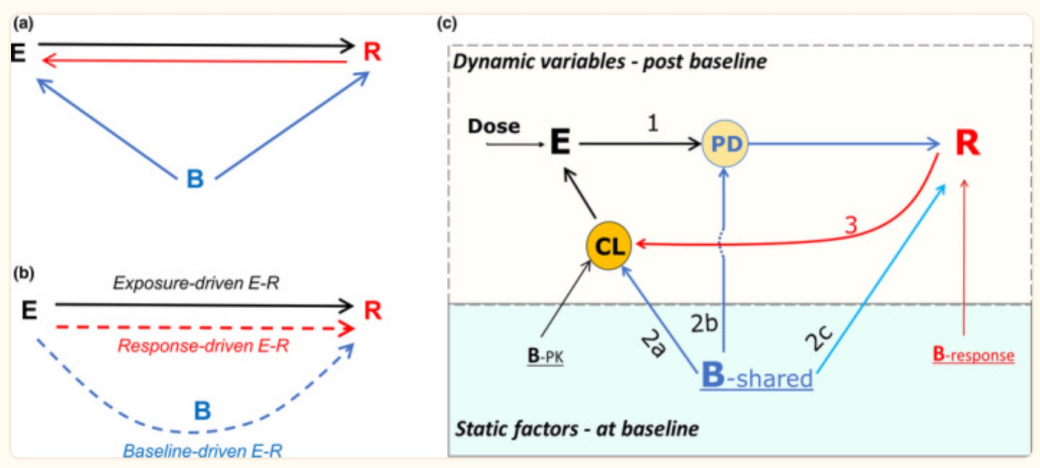
OCP: Office of Clinical Pharmacology

The main caveat of exposure-response modeling is that exposure in a subject is not randomized (some randomization is present because different doses result in different exposure ranges). Since exposures are not truly random, there is a possibility that a patient factor affecting drug exposure is also affecting drug response (independent of drug exposure). This phenomenon is commonly observed for large molecules with oncology indications where tumor burden can increase the elimination of drugs; however, this phenomenon is rare for small molecules (Yang et al. 2013.)

Clin Pharmacol Ther. 2020 Dec; 108(6): 1156–1170. PMCID: PMC7689749
Published online 2020 Aug 2. doi: 10.1002/cpt.1953 PMID: 32557643

Characterizing Exposure–Response Relationship for Therapeutic Monoclonal Antibodies in Immuno-Oncology and Beyond: Challenges, Perspectives, and Prospects

Haiqing Isaac Dai,[✉1,†] Yulia Vugmeyster,[1,†] and Naveen Mangal[1]



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… BUT …

~~The Right Dose~~ The Right Dose *For You*

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Application	Request for Qualification of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

4.1.1 The Utility of Concentration-Response Modeling

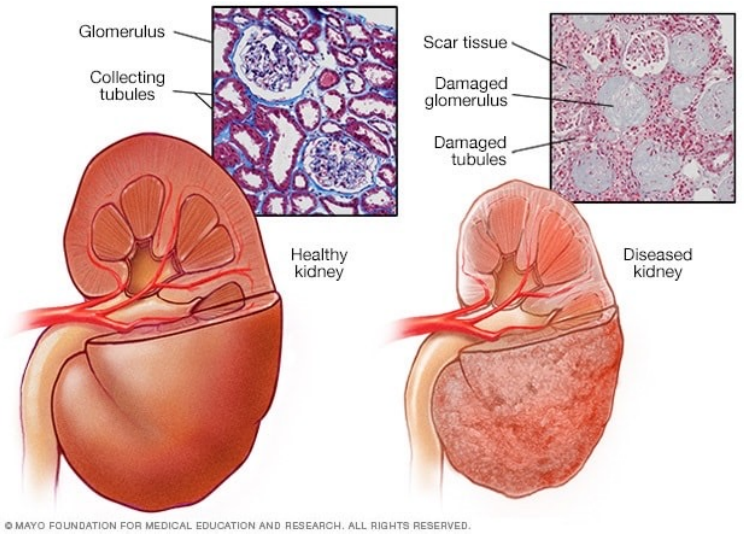
The MCP-Mod method focuses on analysis of dose-response; however, exposure-response analysis is a fundamental part of dose selection, as such it needs to be put in context of this application.

Dose-response analysis assumes that all subjects in one dose group are exposed to the same amount of drug. Due to between subject variability in drug absorption, distribution, metabolism, and elimination (ADME), subjects administered the same dose may have vastly different drug concentrations in blood. In addition to variability in drug exposure, there is variability in drug response.

Thus i, if we can identify what concentration results in a particular effect we can answer the question what dose will result in a particular concentration.

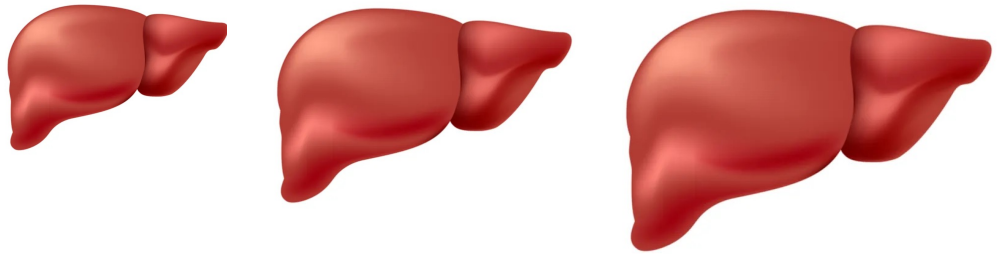
Exposure-response modeling can also inform the need for dose adjustment in specific populations that may have different drug exposure compared to the typical patient, e.g. due to renal or hepatic impairment. Without relating exposure to response, there is no way of determining the need to adjust dose due to difference in drug exposure.

Same dose regardless of kidney health?



Same dose regardless of age?

Same dose regardless of liver size?



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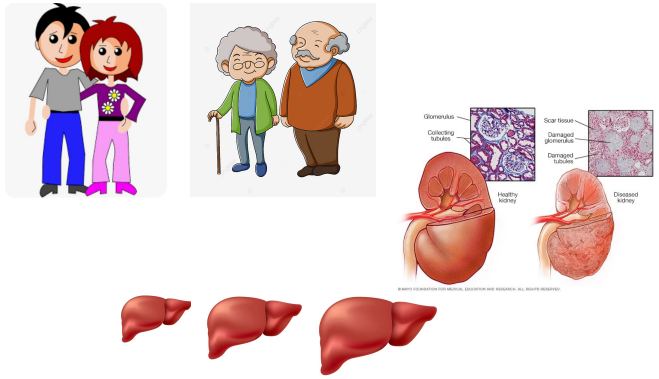
A Small Non-random (*) Sample of Clinical Pharmacology Questions

Dose differently in certain patient subroups?

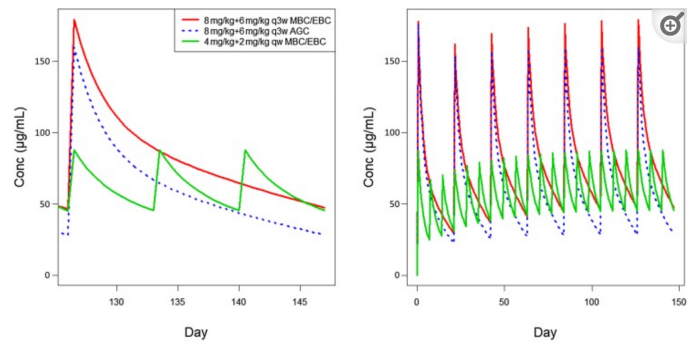


Dose 1x / day, 2x/day, 3x/day?
Risks & benefits of loading dose?

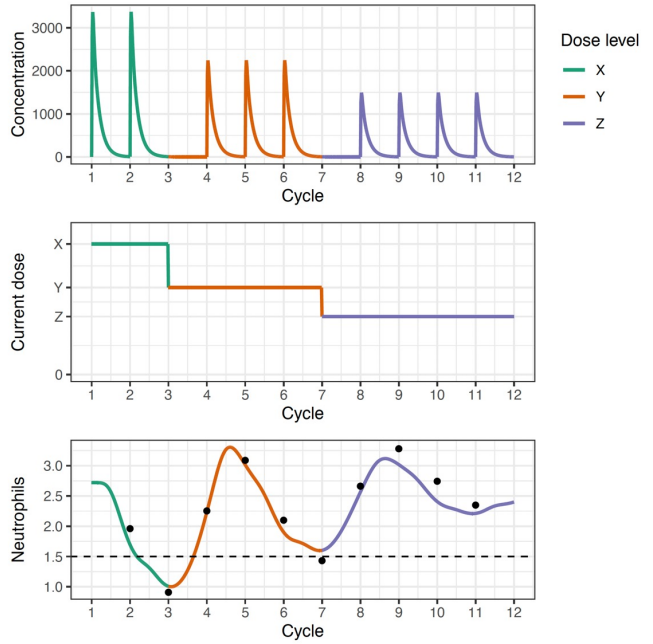
Cancer Chemother Pharmacol. 2019; 83(2): 329–340. Published online 2018 Nov 22. doi: 10.1007/s00280-018-3728-z

<< Prev Fig. 4 Next >>

Fig. 4



Rules for dose adjustment?



Empirical dose-response alone is not up to the task!
Randomized comparisons alone are not are not up to the task!

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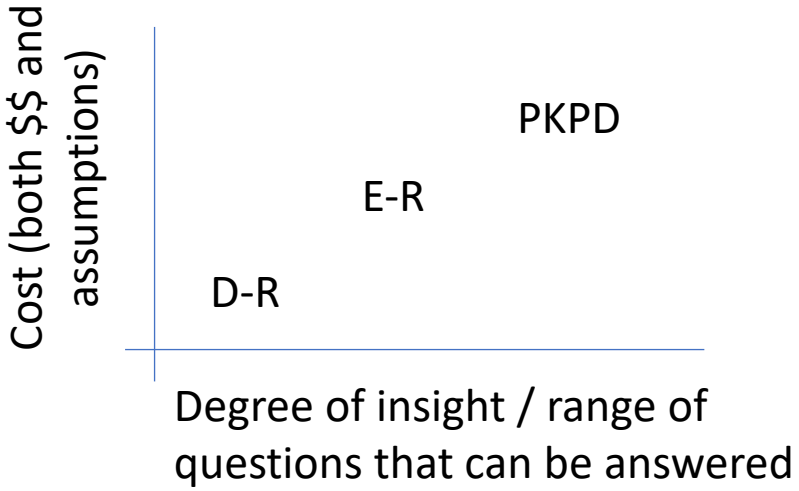
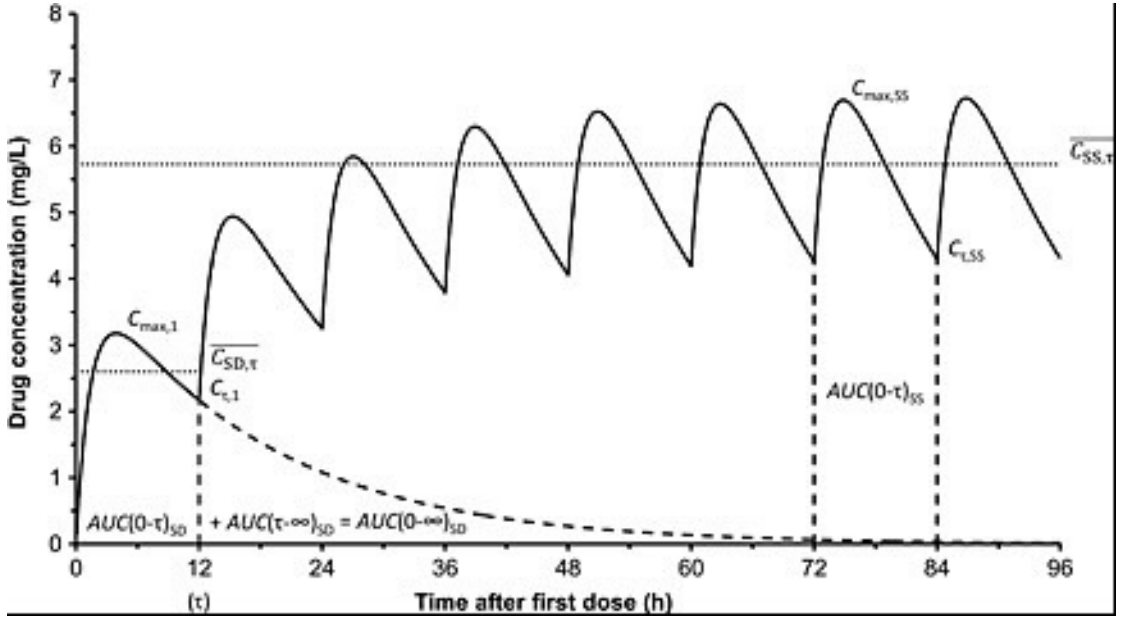
(*) Hand-selected from the subset of questions that I know something about. I am still learning!

Exposure Response (E-R) Approach

- **E-R approach**: first summarize the exposure versus time curves with "exposure metrics" that capture the essential features
- Contrast with **PKPD approach**: don't reduce the exposure versus time curve at all; rather, use it as a time-varying predictor





BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. **36**: 93–103 (2015)
Published online 21 January 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/bdd.1923

Proposal for defining the relevance of drug accumulation derived from single dose study data for modified release dosage forms

Christian Scheerans*, Roland Heinig, and Wolfgang Mueck
Clinical Pharmacology, Bayer Pharma AG, Research Center, Wuppertal, Germany

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A Slightly Deeper Dive on Intrinsic and Extrinsic Factors

- Next few slides will be based on analyses done to support a New Drug Application for Valemetostat for Adult T-cell Leukemia / Lymphoma
- I will only focus on the “exposure-response” aspect of these analyses to address the question of special dosing for subgroups. The full analysis also included population pharmacokinetic and pharmacodynamic analyses

Landmark and longitudinal exposure-response analyses for multiple efficacy and safety endpoints to justify the clinical dose of valemetostat for adult T-cell leukemia/lymphoma

Masato Fukae (1), Kyle Baron (2), James Rogers (2), Ramon Garcia (2), Masaya Tachibana (1), John Mondick (2), Takako Shimizu (1)
(1) Daiichi Sankyo Co., Ltd. Tokyo, Japan, (2) Metrum Research Group, Tariffville, CT, USA

Daiichi-Sankyo

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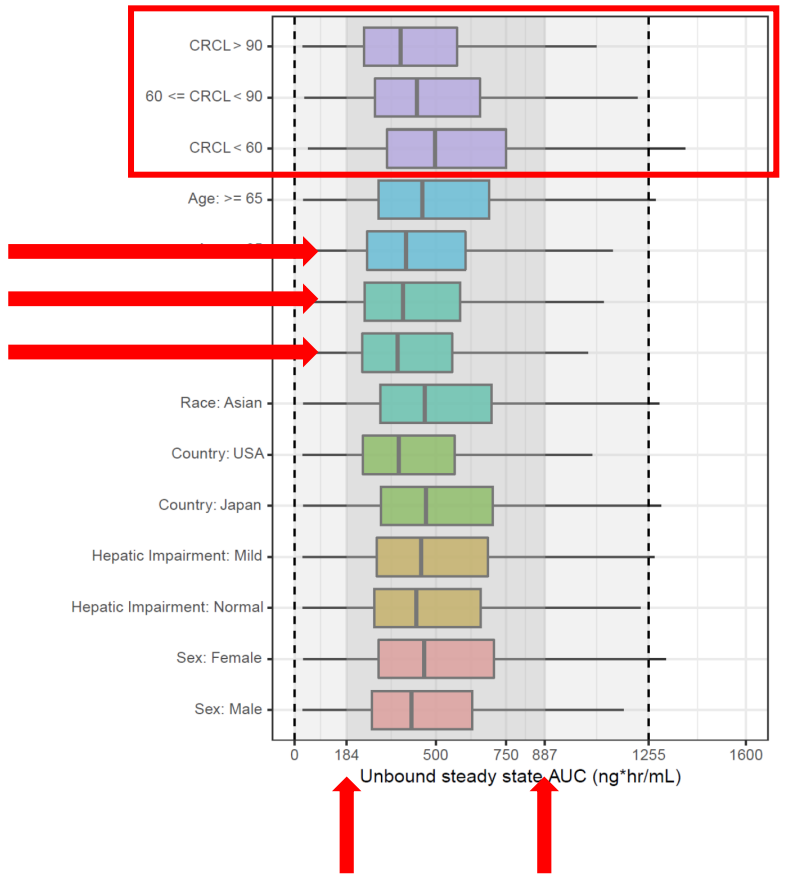
Let’s Begin at the End of The Story

”Boxplots” represent predicted population distributions for unbound drug exposure (steady-state AUC) if everyone is given a dose of 200 mg QD.



Implication (arguably) : no need to adjust dose in populations with mild renal impairment

(And similarly for other subgroups of interest)

Target exposure range resulting from exposure-response analyses
Next few slides will examine how these limits were derived

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How Target Exposure Range Was Determined.
Step 1: Elicit “Target Product Profile”

Satisfactory efficacy: probability of objective response of greater than 30% for typical patients

Acceptable safety: probability of dose reduction due to AE of less than 50% for 90% of patients

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Step 1: Elicit “Target Product Profile”

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Defining Target Exposure Range, Step 2: Identify Data and Fit E-R Models

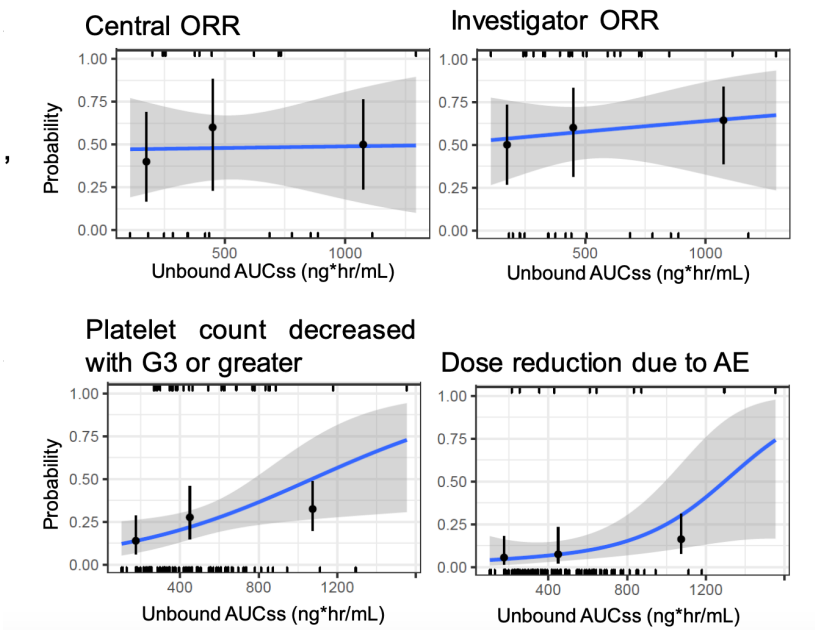
Landmark Exposure-Response Analyses

- The analysis was conducted using data from Studies DS3201-A-J101 and DS3201-A-J201 with non-Hodgkin's lymphoma (NHL), including ATL. Patients with ATL were included for efficacy endpoints and the whole population of NHL were analyzed for safety with wider dose range (**Table 1**).

Table 1 Summary of dataset assessed in the landmark exposure-response analyses by endpoint

Endpoint	Population	N	Dose (mg)	Note
ORR by central assessment	ATL	25	200 mg	Efficacy
ORR by investigator	ATL	39	150-200 mg	Efficacy
Anemia (Grade >=3)	NHL	102	150-300 mg	Safety
Neutrophil count decreased (Grade >=3)	NHL	102	150-300 mg	Safety
Platelet count decreased (Grade >=3)	NHL	102	150-300 mg	Safety
Dose reduction due to AEs	NHL	102	150-300 mg	Safety
Dose interruption due to AEs	NHL	102	150-300 mg	Safety
Any AEs with Grade >=3	NHL	102	150-300 mg	Safety

Fig. 1 Observed exposure-response relationship for selected endpoints. Solid blue lines and gray areas represent smoothing curves and the 95% confidence intervals, respectively.



Logistic regression models relating efficacy and safety outcomes to exposure and covariates

$$\text{logit}(p) = \alpha_0 + \beta_E E + \boldsymbol{X}^T \boldsymbol{\alpha}_x + \boldsymbol{X}^T \boldsymbol{\beta}_x E$$

- p is the probability of having an event
- E is a standardized exposure metric
- X is a standardized covariate matrix

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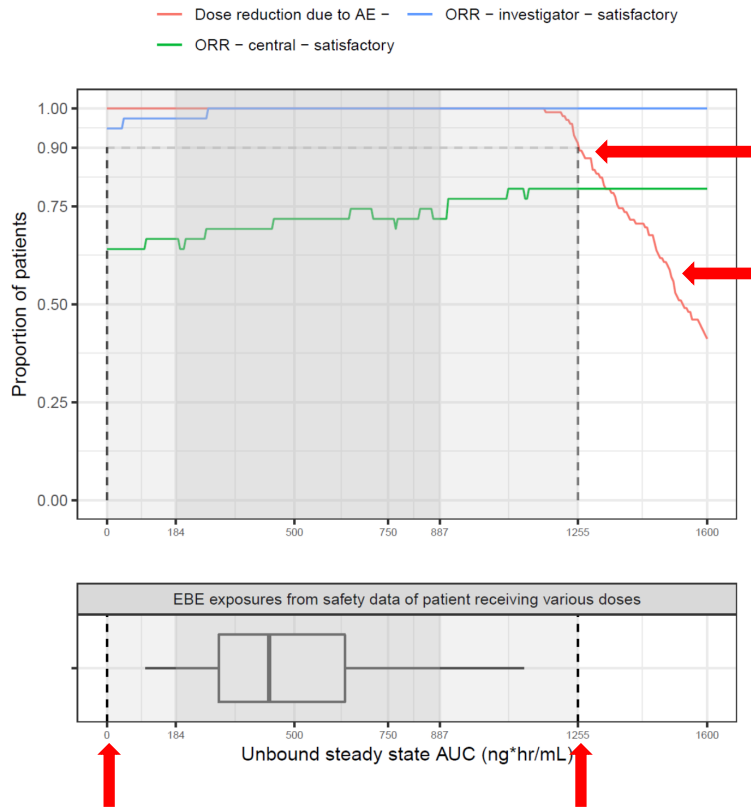
Defining Target Exposure Range, Step 3: Solve For Exposure Limits:



Horizontal line defined by TPP for safety

Red line determined by population simulation with E-R Models + empirical covariate distribution

Technically, models implied lower limit of target exposure range = 0; we modified based on region of direct empirical support

Vertical line obtained by numerically solving for upper limit of target range

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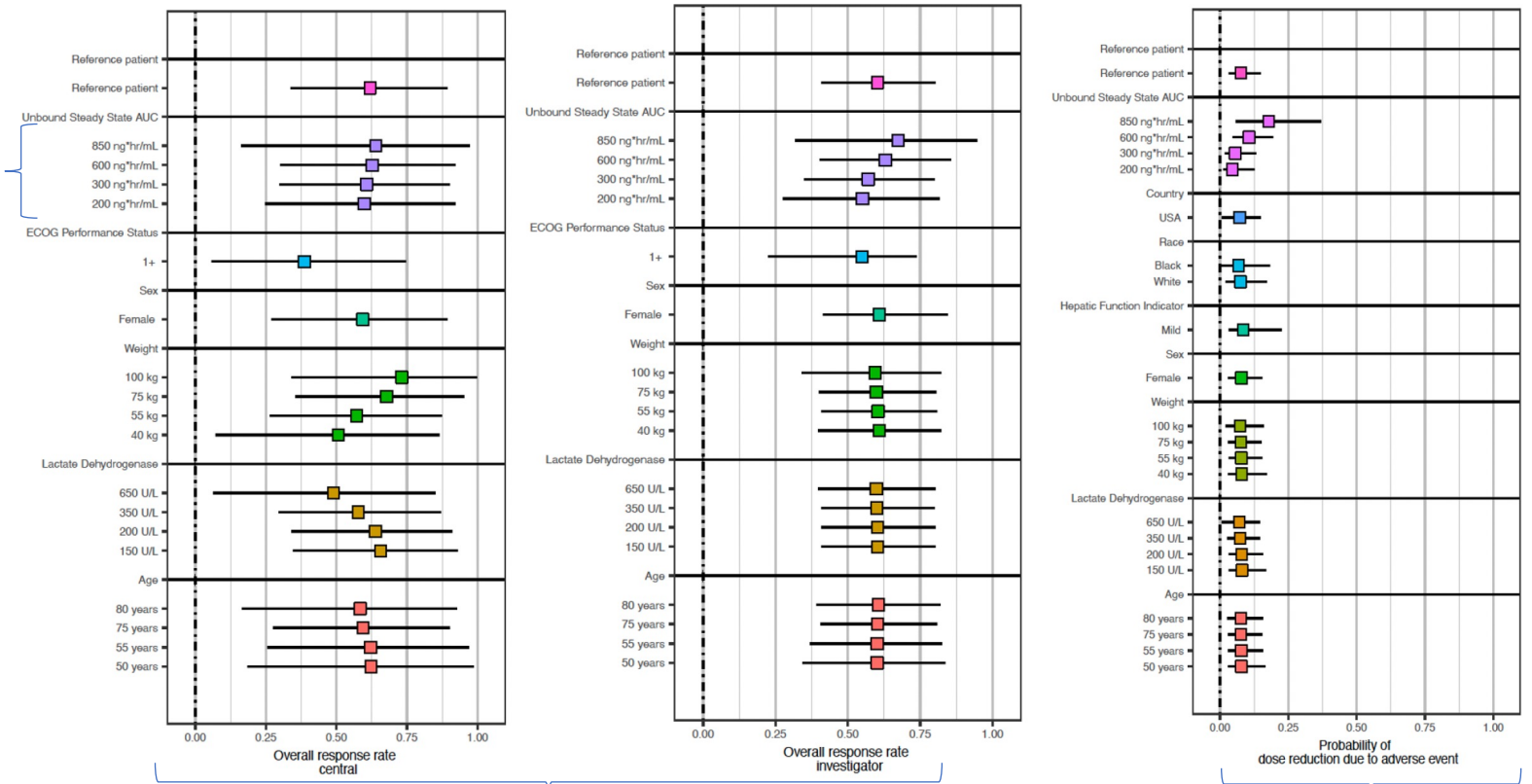
Defining Target Exposure Range, Step 4: Same Limits for Everyone?

This is the "exposure" variable (not randomized)



Efficacy

Safety

Implication of "no covariate effects"in E-R : it is therefore reasonable to use the same target exposure range for everyone

Technical note: We used Spike and Slab priors in logistic regression to estimate all these covariate effects

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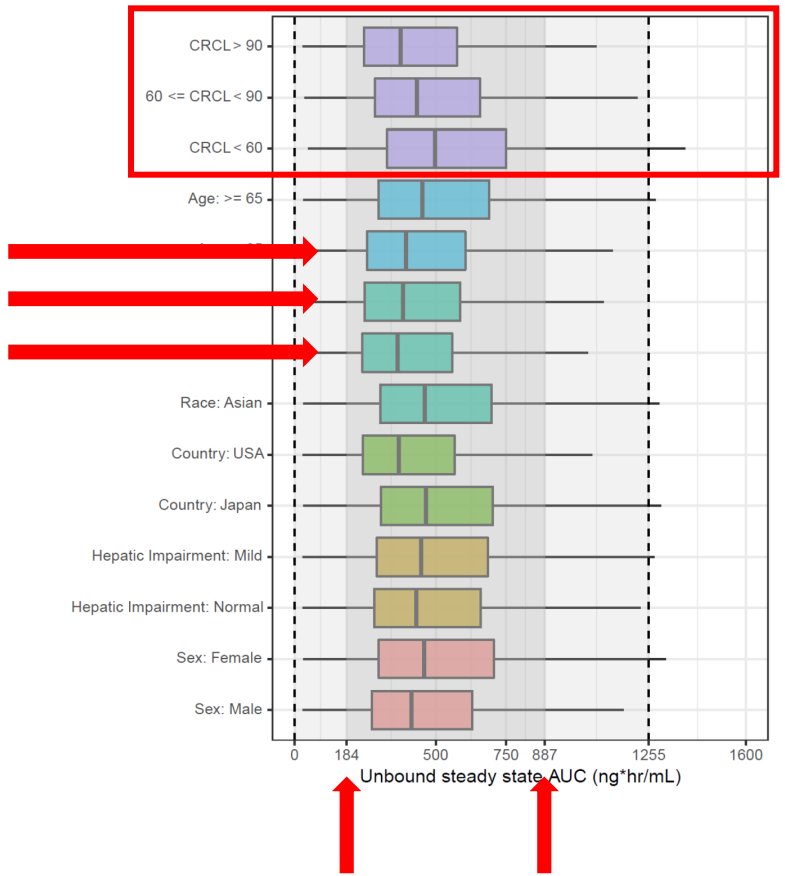
Now We Can End at the End of The Story

”Boxplots” represent predicted population distributions for unbound drug exposure (steady-state AUC) if everyone is given a dose of 200 mg QD.



Implication (arguably) : no need to adjust dose in populations with mild renal impairment

(And similarly for other subgroups of interest)

… what about our uncertainty in those population percentiles? (left as an exercise for the reader)

Target exposure range resulting from exposure-response analyses

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Regulatory & Organizational Factors

2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

2.7.2.3 Comparison and Analyses of Results Across Studies

- Population PK analyses, such as results based on sparse sampling across studies that address interindividual variations in the pharmacokinetics or pharmacodynamics of the active drug substances that may be due to extrinsic or intrinsic factors.
- Dose-response or concentration-response relationships. This discussion should highlight evidence to support the selection of dosages and dose intervals studied in the important clinical trials. In addition, information that supports the dosage instructions in the proposed labeling should be discussed in section 2.7.3.4.

- Primary contributions come from Sponsor Clin Pharm & Pharmacometrics groups
- Primary review responsibility lies with Office of Clinical Pharmacology & Division of Pharmacometrics

2.7.3 SUMMARY OF CLINICAL EFFICACY

2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

This section should provide an integrated summary and analysis of all data that pertain to the dose-response or blood level-response relationships of effectiveness (including dose-blood level relationships) and thus have contributed to dose selection and choice of dose interval. Relevant data from nonclinical studies may be referenced, and relevant data from pharmacokinetic studies, other clinical pharmacology studies, and controlled and uncontrolled clinical studies should be summarized to illustrate these dose-response or blood level-response relationships. For PK and PD studies from which data have been summarized in section 2.7.2.2, it may be appropriate to draw on those data in this summary while cross-referencing the summaries in section 2.7.2.2, without repeating those summaries.

- Primary quant sci contributions come from Biostat groups
- Primary review responsibility lies with Office of Biostatistics

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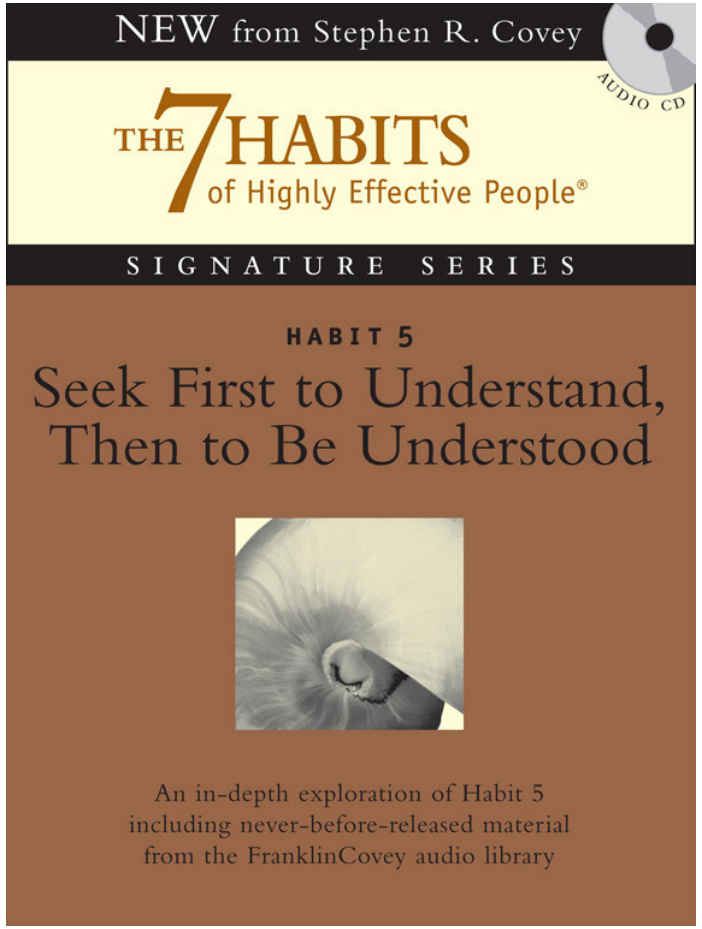
Now That We Understand, Let's Offer Some (Respectful, Intelligent) Critique



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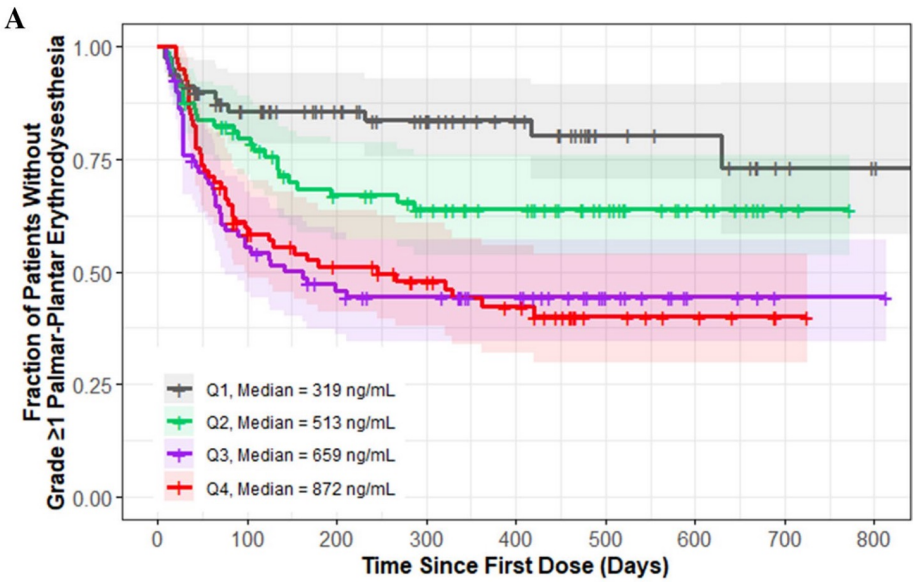
Self-inflicted Confounding in Exposure-Response

Fig. 5 Kaplan–Meier Plot for Grade ≥ 1 palmar-plantar erythrodysesthesia (**A**) and Grade ≥ 3 diarrhea (**B**) by average cabozantinib exposure quartiles. Shaded regions represent 95% confidence intervals for each exposure quartile (Q#) of CAVG0T, the predicted average cabozantinib concentration from time zero to the event or censoring



The (incorrect, but common) reasoning being applied here:

- Dose, and therefore exposure, can change a lot over time prior to an adverse event
- Seems wise to use an exposure metric that is sensitive to that entire dose history

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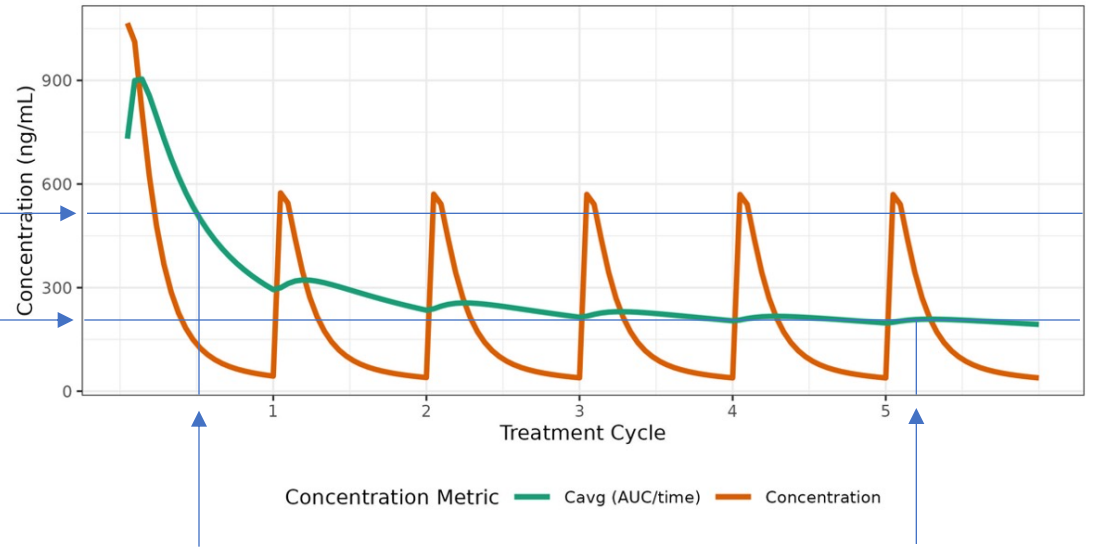
Understanding Average Concentration Up to an Event Time ($CAVG_{0-T}$)

Example PK profile when there is a ”loading dose” :

$CAVG_{0-T}$ for Patient 1

$CAVG_{0-T}$ for Patient 2



Adverse event time for Patient 1

Adverse event time for Patient 2

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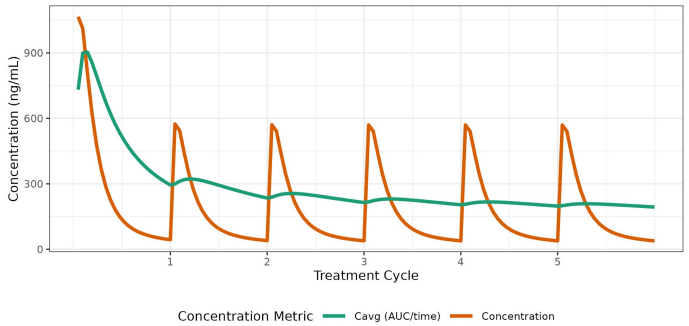
Creating Exposure-Response Associations Out of Thin Air



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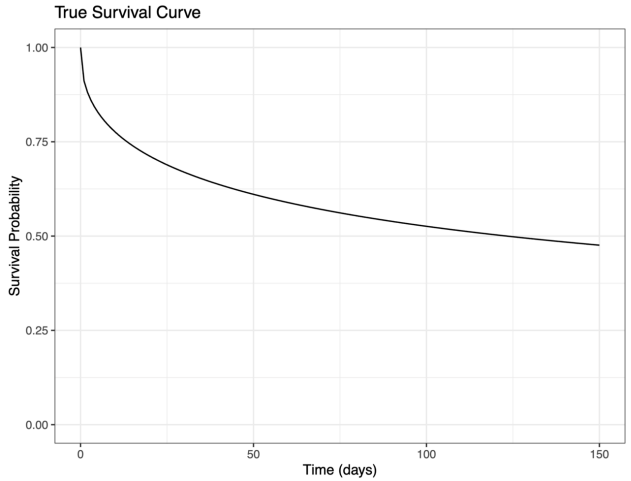

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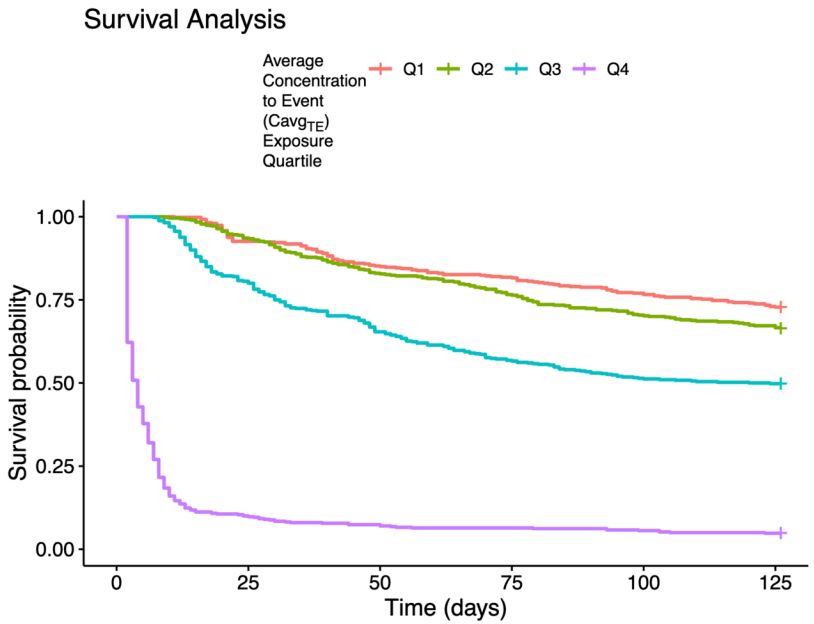

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How Can We Reduce the Likelihood of Bad Causal Thinking?

Estimands (in the ICH E9 addendum sense)

Directed Acyclic Graphs (DAGs)

Target Trial Emulation

Pearl's "do-Calculus"

Neyman-Rubin Potential Outcomes Framework (*)

- dating to Jerzy Neyman in 1923. Happy 100th Birthday PO Notation!

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A Thought Exercise to Ensure Sound Thinking With Observational Data

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

Miguel A. Hernán* and James M. Robins

Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

Abstract

Go to: ▸

Ideally, questions about comparative effectiveness or safety would be answered using an appropriately designed and conducted randomized experiment. When we cannot conduct a randomized experiment, we analyze observational data. Causal inference from large observational databases (big data) can be viewed as an attempt to emulate a randomized experiment—the target experiment or target trial—that would answer the question of interest. When the goal is to guide decisions among several strategies, causal analyses of observational data need to be evaluated with respect to how well they emulate a particular target trial. We outline a framework for comparative effectiveness research using big data that makes the target trial explicit. This framework channels counterfactual theory for comparing the effects of sustained treatment strategies, organizes analytic approaches, provides a structured process for the criticism of observational studies, and helps avoid common methodologic pitfalls.

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A Sea-Change in Thinking About Quantitative Evidence

A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks

Miguel A. Hernán, John Hsu, and Brian Healy

For much of the recent history of science, learning from data was the academic realm of statistics,[1,2] but in the early 20th century, the founders of modern statistics made a momentous decision about what could and could not be learned from data: They proclaimed that statistics could be applied to make causal inferences when using data from randomized experiments, but not when using nonexperimental (observational) data.[3,4,5] This decision classified an entire class of scientific questions in the health and social sciences as not amenable to formal quantitative inference.

Not surprisingly, many scientists ignored the statisticians' decree and continued to use observational data to study the unintended harms of medical treatments, health effects of lifestyle activities, or social impact of educational policies. Unfortunately, these scientists' causal questions often were mismatched with their statistical training.

e.g. pharmacometricians

We now have a historic opportunity to redefine data analysis in such a way that it naturally accommodates a science-wide framework for causal inference from observational data. A recent influx of data analysts, many not formally trained in statistical theory, bring a fresh attitude that does not a priori exclude causal questions. This new wave of data analysts refer to themselves as data scientists and to their activities as data science, a term popularized by technology companies and embraced by academic institutions.

Yes please!

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An Improving Regulatory & Organizational Landscape

Clinical Pharmacology & Therapeutics

State of the Art

Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development

P A Milligan, M J Brown, B Marchant, S W Martin, P H van der Graaf, N Benson, G Nucci, D J Nichols, R A Boyd, J W Mandema, S Krishnaswami, S Zwillich, D Gruben, R J Anziano, T C Stock, R L Lalonde

First published: 14 March 2013 | https://doi.org/10.1038/clpt.2013.54 | Citations: 76

Clinical Pharmacology & Therapeutics

Perspective | Open Access

Model Informed Drug Development: Collaboration Through A Common Framework

Richard J. Anziano, Peter A. Milligan

First published: 28 October 2020 | https://doi.org/10.1002/cpt.2066 | Citations: 4

SECTIONS PDF TOOLS SHARE

Model-informed drug development (MIDD) utilizes the knowledge extracted from relevant data to improve the efficiency of decision making within the pharmaceutical industry. The MIDD framework creates overlap between the quantitative disciplines, including statistics and pharmacometrics, with many opportunities for collaboration. MIDD necessitates effective alignment in the thoughts and deeds of statisticians and pharmacometricians, which is not a sector norm. The challenge of greater collaboration must be met in order for MIDD to realize its potential.

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Goals of the MIDD Paired Meeting Program

The MIDD Paired Meeting Program fulfills a performance goal agreed to under the seventh iteration of the Prescription Drug User Fee Act (PDUFA VII), included as part of the FDA Reauthorization Act of 2023.

The MIDD Paired Meeting Program is designed to:

- Provide an opportunity for drug developers and FDA to discuss the application of MIDD approaches to the development and regulatory evaluation of medical products in development, and
- Provide advice about how particular MIDD approaches can be used in a specific drug development program

ICH harmonisation for better health

Final Concept Paper

M15: Model-Informed Drug Development General Principles Guideline

2 November 2022

Endorsed by the Management Committee on 10 November 2022

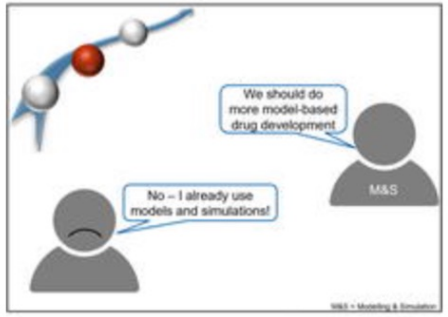
Type of Harmonisation Action Proposed

A new, overarching guideline on General Principles for Model-Informed Drug Development (MIDD) to broadly cover general principles and good practices for use of MIDD in regulatory submissions.

Statement of the Perceived Problem

Many regulatory authorities expect to receive, and currently accept model-based analyses as part of dossier submissions. However, the lack of common documentation standards, model assessment expectations and understanding of concepts/principles hinders assessment of quality of the data used, the robustness of the analysis, vis-à-vis the modelling impact and credibility with respect to its intended applications. As a result, the level of integration of MIDD into regulatory decision making can vary between regulatory authorities, from application to application, and within authorities for the same or similar submissions.

An Improving Landscape in Professional Societies



SxP Statistics & Pharmacometrics

ISoP | ASA SPECIAL INTEREST GROUP

https://sxpsig.github.io/

ASA Biopharmaceutical Section

Current BIOP Working Groups

- Alzheimer's Disease
- Cell & Gene Therapy
- Centralized Statistical Monitoring and Quality Tolerance Limits
- Estimands in Oncology
- Nonclinical Biostatistics
- Pediatric Drug Development
- Real World Evidence Scientific Working Group
- Re-Randomization
- Safety Scientific Working Group
- Statistics and Pharmacometrics Special Interest Group
- Software Engineering Working Group
- Statistical Methods in Oncology
- Health Technology Assessment Scientific Working Group

Statistical Innovation in Healthcare: Celebrating the Past 40 Years and Looking Toward the Future - Special issue for the 2021 Regulatory-Industry Statistics Workshop

The Role of Statistical Thinking in Biopharmaceutical Research

Frank Bretz & Joel B. Greenhouse

Pages 458-467 | Received 19 Dec 2021, Accepted 19 May 2023, Published online: 24 Jul 2023

"The second dialogue happened more than 15 years ago, at a time when pharmacometricians started to add a new dimension to drug development by promoting a broader use of model-based analyses. The reaction from junior and senior statisticians throughout the pharmaceutical community was, repeatedly, "No - I already use models and simulations." The disconnect here was a problem of communication. Whereas our pharmacometrics colleagues had much broader classes of models in mind, many statisticians, at least at that time, were thinking in terms of analysis-of-covariance models or, at best, mixed-model repeated measures analyses, and were using simulations primarily for power and sample size calculations."

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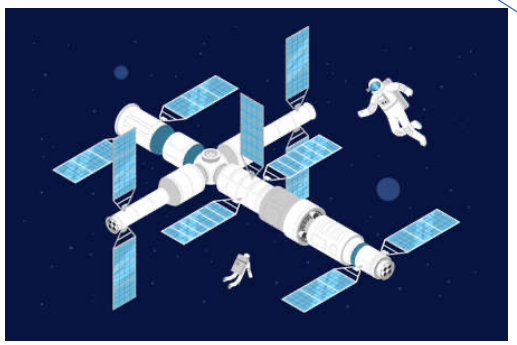
We Need Quantitative Scientists for the Full Voyage!

Analysis Plan



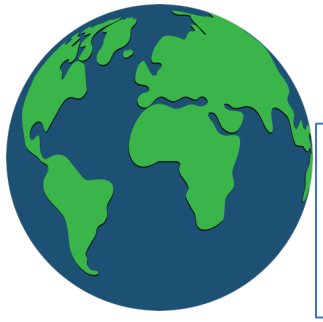
Objectives, Formalization of Questions, Scope of Work

Code, Results (TFL)

Elicitation

I have learned enormously from pharmacometricians about the "take off and landing"

Interpretation



Vague inchoate questions and evidential needs + some data that might be useful

Discussion, Conclusions, Decisions

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Thank You!
jimr@metrumrg.com

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What is a Good Dose Adjustment Rule for Patients with Low Platelets?

Fig. 4 Observed platelet count data after administration of valemetostat by exposure level

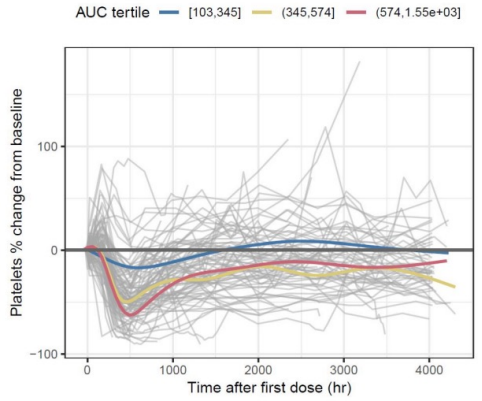


Fig. 5 Schematic representation of the longitudinal exposure-response model for platelet count decreased

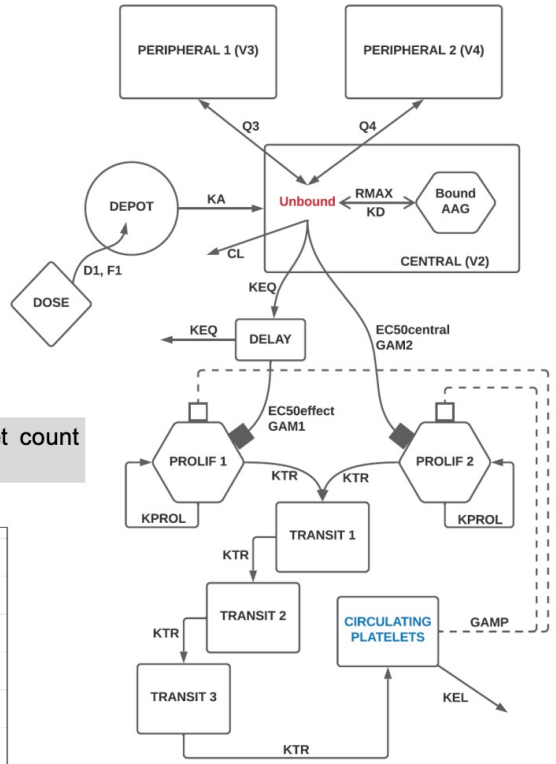
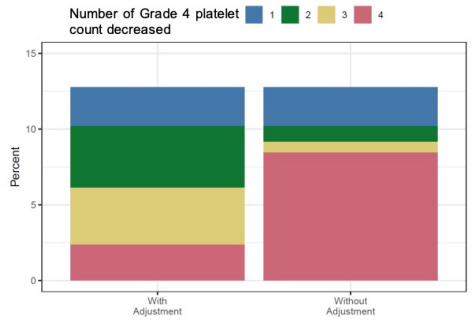


Fig. 6 Predicted frequency of Grade 4 platelet count decreased with or without dose adjustment



PKPD model for platelets

- Each arrow in the diagram corresponds to a differential equation
- Data consist of
  - Dosing events over time
  - Concentrations of unbound drug in plasma over time
  - Platelet counts over time
  - All three data components collected on different schedules
- Used to evaluate rules for dose adjustments based on platelet levels: when should we adjust and by how much
- To use statistical terminology, this is a dynamic treatment regimen (DTR) … but DTR research and PKPD research don't (yet) intersect much (?)

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How My Ph.D. in Stats Did and Didn't Prepare Me to be Influential

- What I did learn:
  - How to think rigorously about the nature of statistical confirmation
  - **This was enough to get me a seat at the table, and I am grateful**
- What I didn't learn:
  - How to think rigorously about non-randomized comparisons
  - How to think rigorously about extrapolation
  - How to make holistic scientific arguments
  - **What I learned was "enough", but how can we train the next generation to do "more than enough"?**

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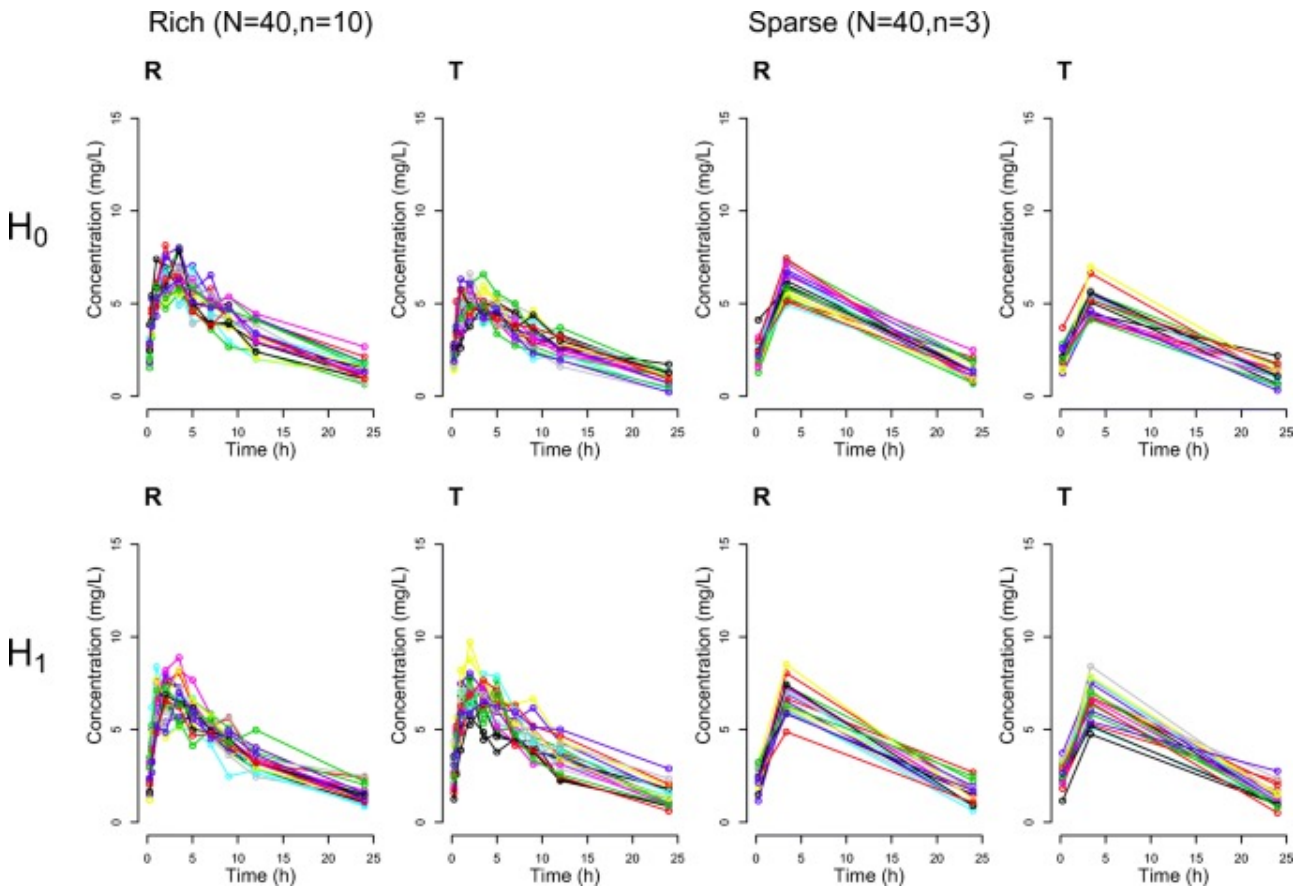
Evidence Integration

Rich / dense data from relatively small and homogeneous population in early development

We can get non-model-based estimates of exposure metrics for these subjects



Sparse data from relatively large and heterogeneous population in late development

Non-model-based estimates of exposure metrics will be bad here; use nonlinear mixed effects modeling to get predicted values instead

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Statistical Science
2014, Vol. 29, No. 4, 579–595
DOI: 10.1214/14-STS486

External Validity: From Do-Calculus to Transportability Across Populations

Judea Pearl and Elias Bareinboim

Science is about generalization, and generalization requires that conclusions obtained in the laboratory be transported and applied elsewhere, in an environment that differs in many aspects from that of the laboratory.

Clearly, if the target environment is arbitrary, or drastically different from the study environment nothing can be transferred and scientific progress will come to a standstill. However, the fact that most studies are conducted with the intention of applying the results elsewhere means that we usually deem the target environment sufficiently similar to the study environment to justify the transport of experimental results or their ramifications.

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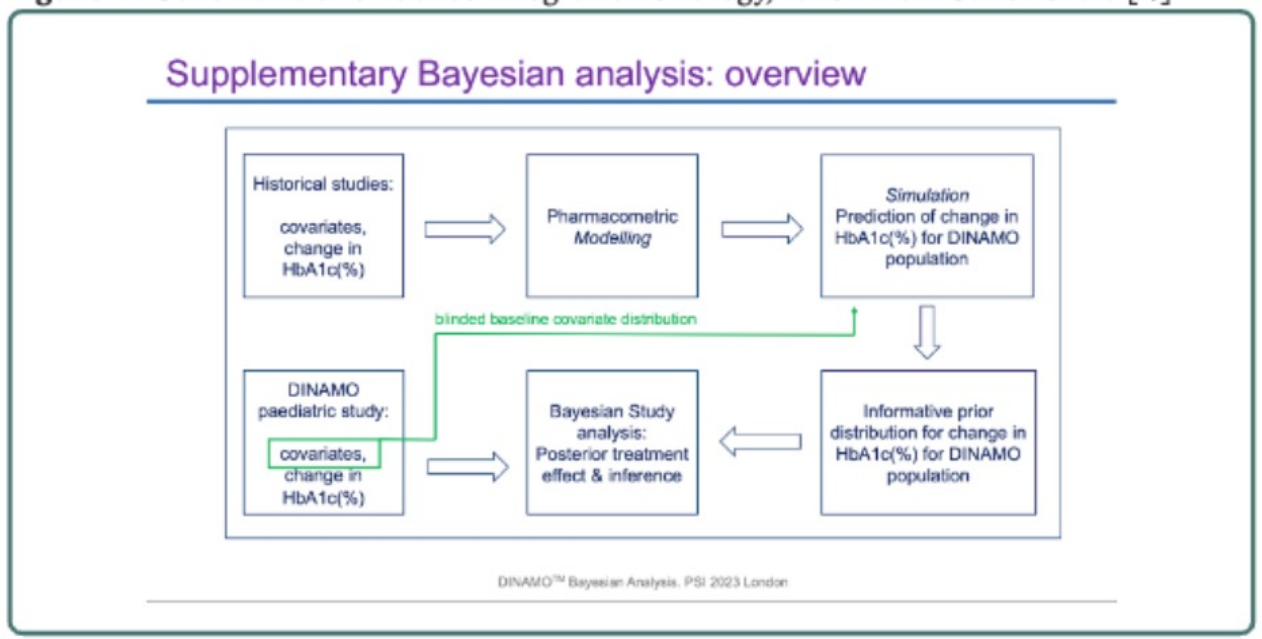
Figure 1: Schematic of evidence integration strategy, taken from Sailer et al. [4]



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Extrapolation and Why It Matters

Bayesian Borrowing in the DINAMO Pediatric Study using Informative Priors Derived from Model-based Extrapolation

Curtis Johnston[1], Matthew Wiens[1], James Rogers[1], Alejandro Pérez-Pitarch[2], Oliver Sailer[2], Igor Tartakovsky[2], Valerie Nock[2]
[1]*Metrum Research Group, Tariffville, CT, USA,* [2]*Boehringer Ingelheim Pharma GmbH & Co KG*

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Boehringer Ingelheim

Results

Figure 3: Accuracy of placebo-corrected HbA1c predictions for empagliflozin.

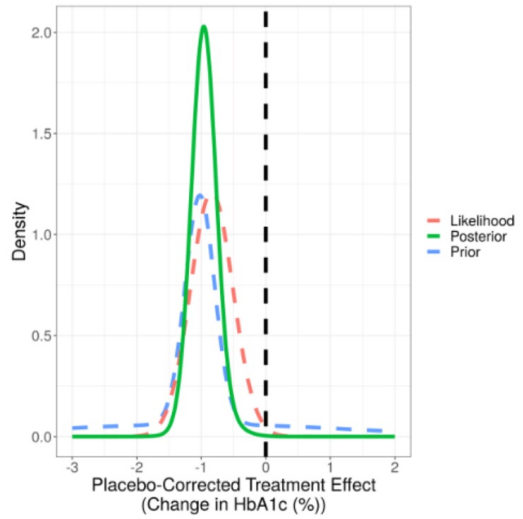


Figure 4: The density of the **prior** for the placebo-corrected treatment effect for the two normal components and the mixture.

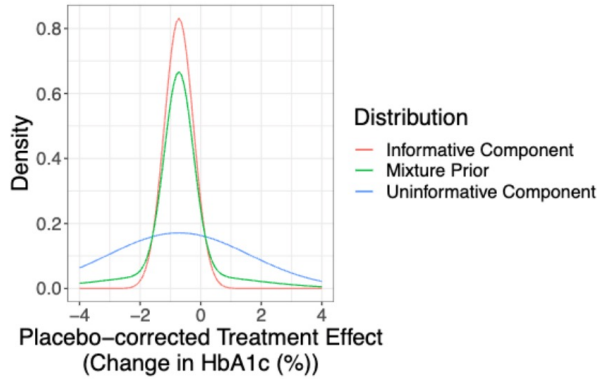
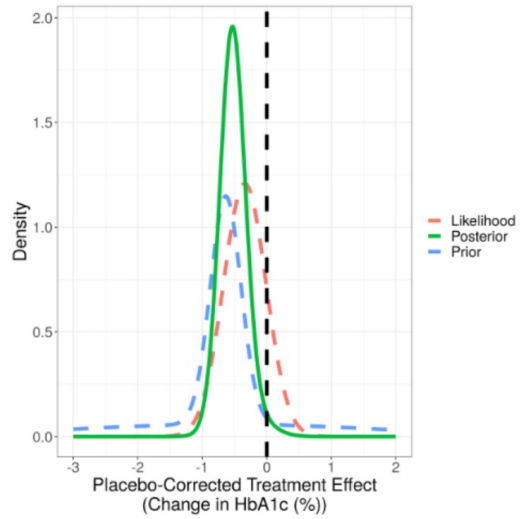


Figure 5: Accuracy of placebo-corrected HbA1c predictions for linagliptin.



Priors were centered at means of predictive distributions based on pediatric covariates + extrapolation from adult model. Why is or isn't that valid?

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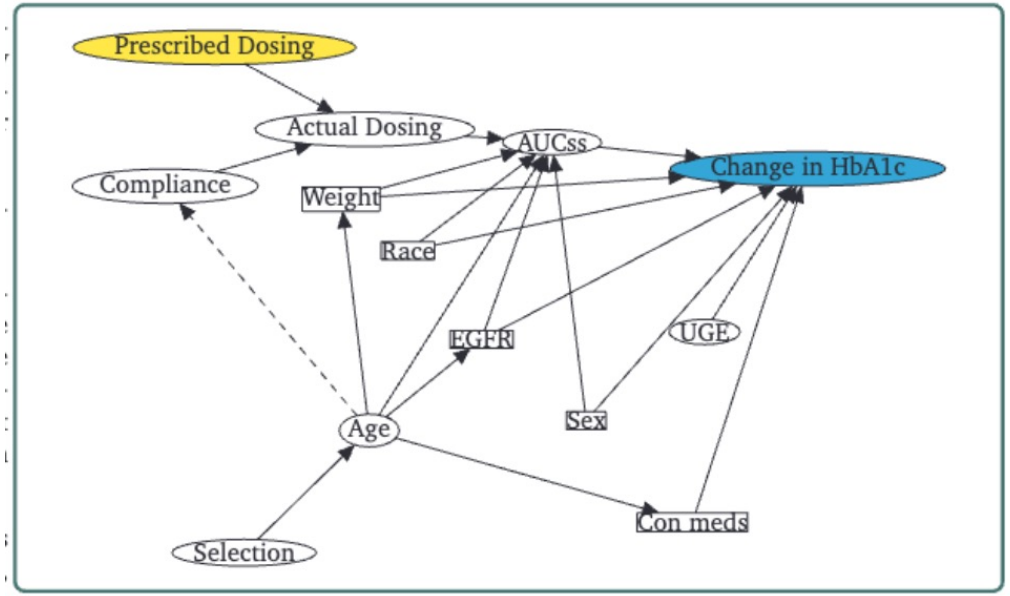
Extrapolation and Why It Matters

Figure 2: A causal selection graph for pediatric predictions.

This selection graph was developed retrospectively as one element of formal justification for the transportability between adult and pediatric populations. Per the criteria of Pearl and Bareinboim [6], such a selection graph may be formally analyzed to identify conditions for conditional exchangeability of evidence, i.e. conditions under which similarity is expected between adults and pediatrics.



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