

FDA/UMD CERSI pJIA Drug Development Workshop - October 2, 2019

Use of Exposure-Response Information in Pediatric Drug Development

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Acknowledgements



Metrum Research Group Scientists

Academic and Industry Collaborators

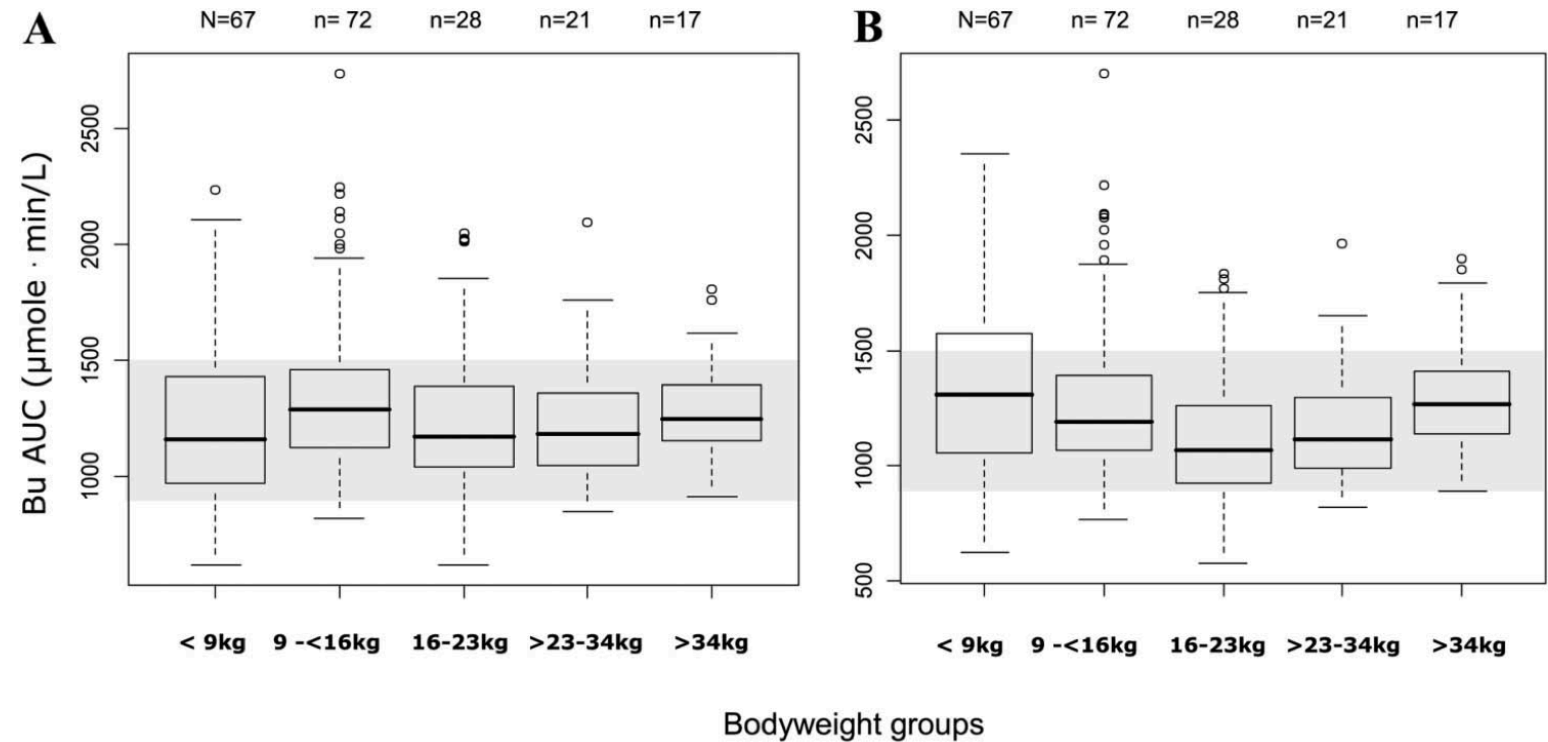
FDA-UMD CERSI Workshop
Organizers, Panelists and
Participants

Pediatric Trial Participants



Exposure Matching is Not the Topic of Discussion

FIGURE 5. Comparison of dosing strategy between model-based and EU labeled dosing. A, Bu AUC distribution using approved EU labeling dosing. B, Bu AUC distribution using model-based dosing.



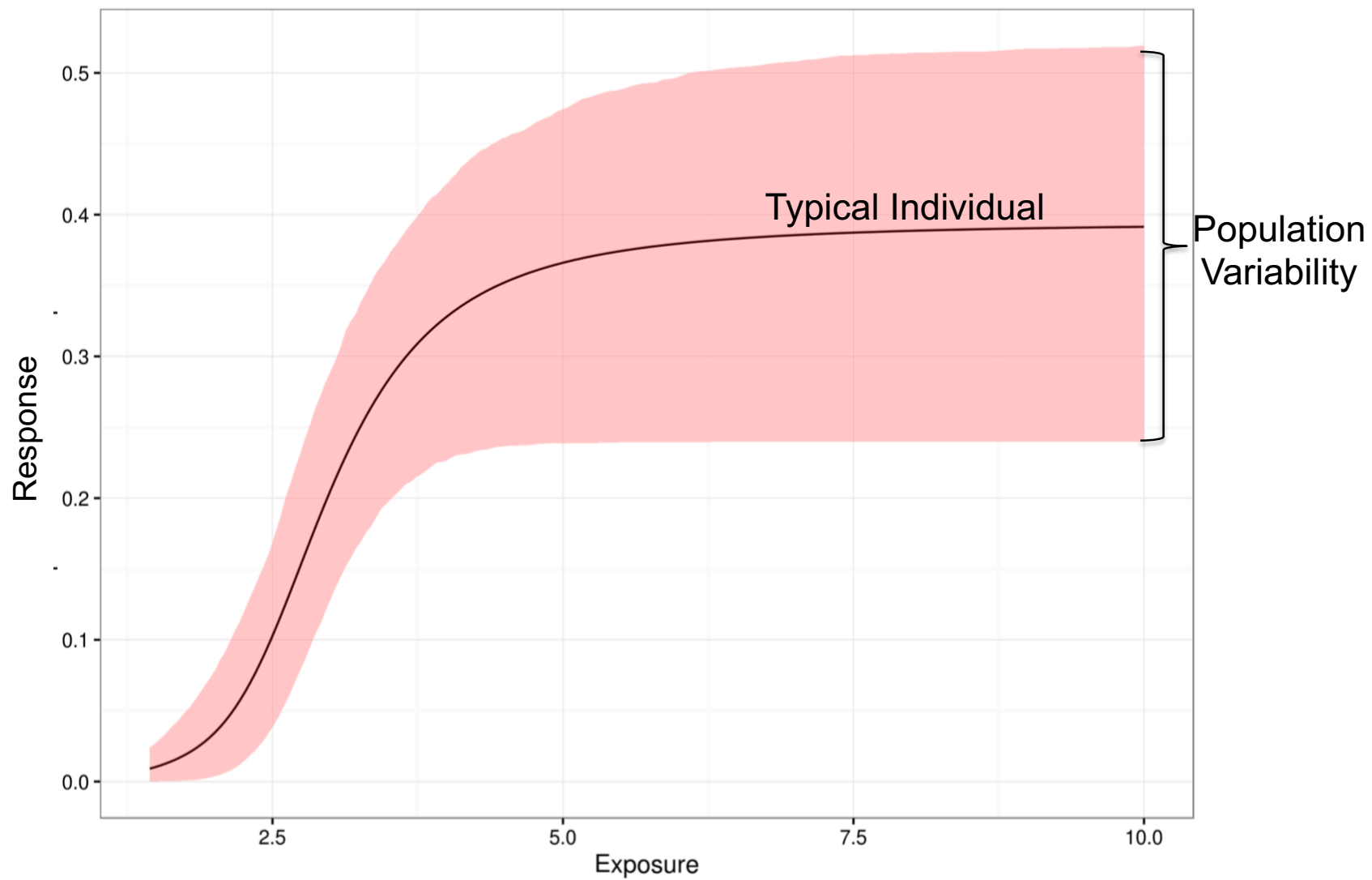
Paci et al. Pharmacokinetic Behavior and Appraisal of Intravenous Busulfan Dosing in Infants and Older Children: The Results of a Population Pharmacokinetic Study From a Large Pediatric Cohort Undergoing Hematopoietic Stem-Cell Transplantation. *Ther Drug Monit* 2012;34:198–208.

Guidance for Industry

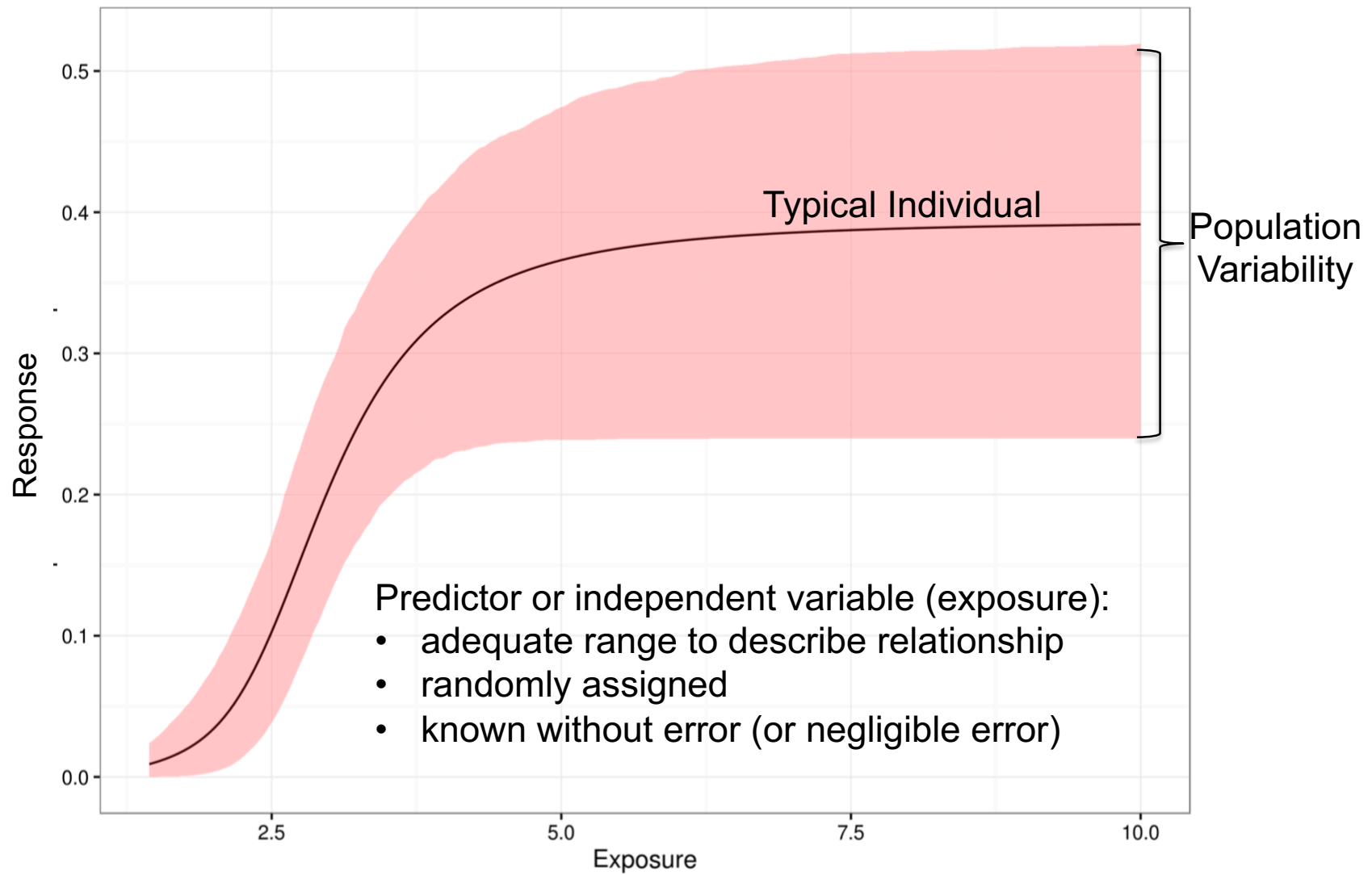
Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

- “A dose-response study is one kind of adequate and well-controlled trial that can provide primary clinical evidence of effectiveness.”
- “Exposure-response information can support the primary evidence of safety and/or efficacy.”
- “In general, the more critical a role that exposure-response information is to play in the establishment of efficacy, the more critical it is that it be derived from an **adequate and well controlled study** (see 21 CFR 314.126), whatever endpoints are studied.”

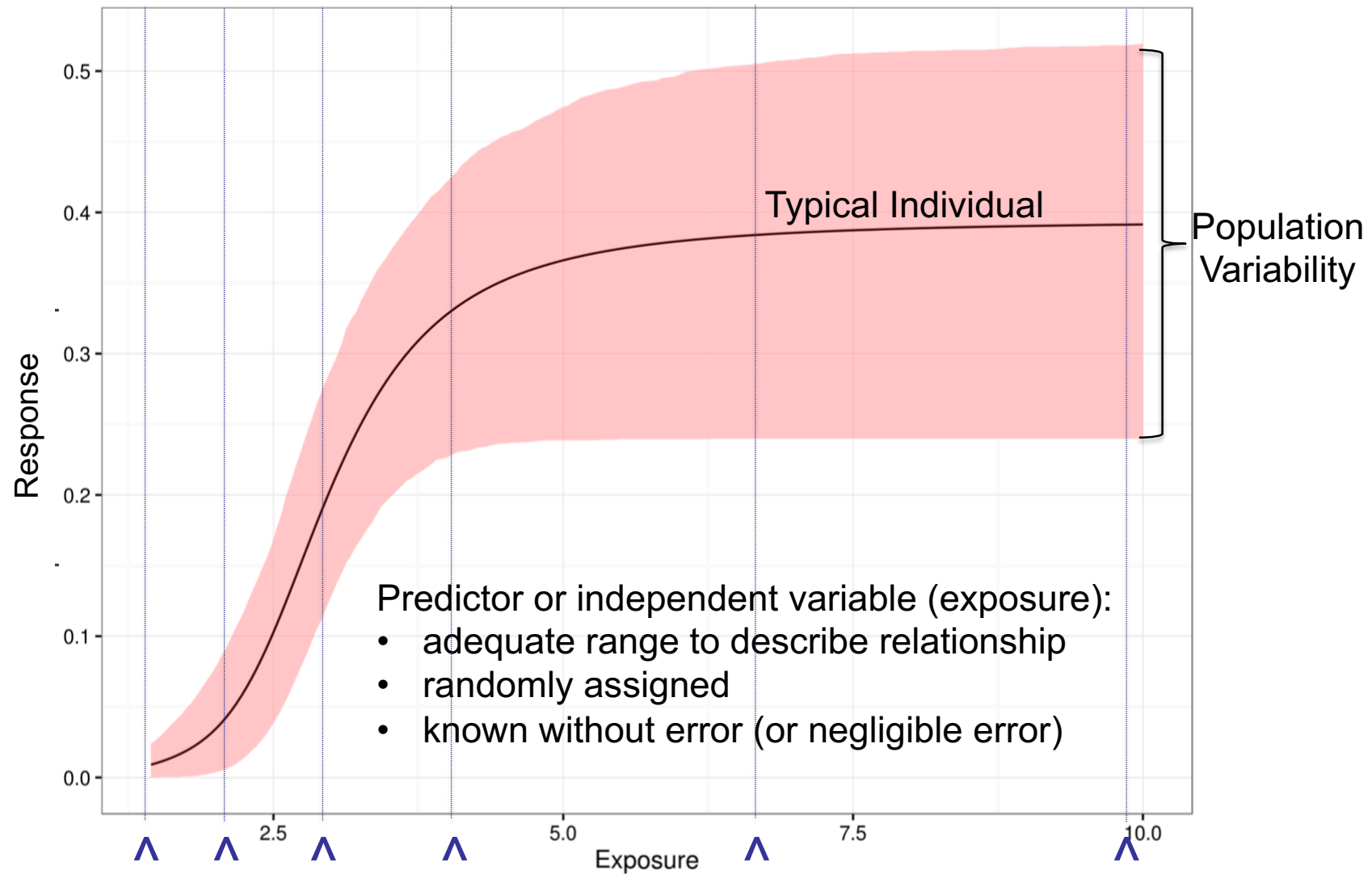
Hypothetical True Exposure-Response Relationship



Ideal E-R Study Design Characteristics

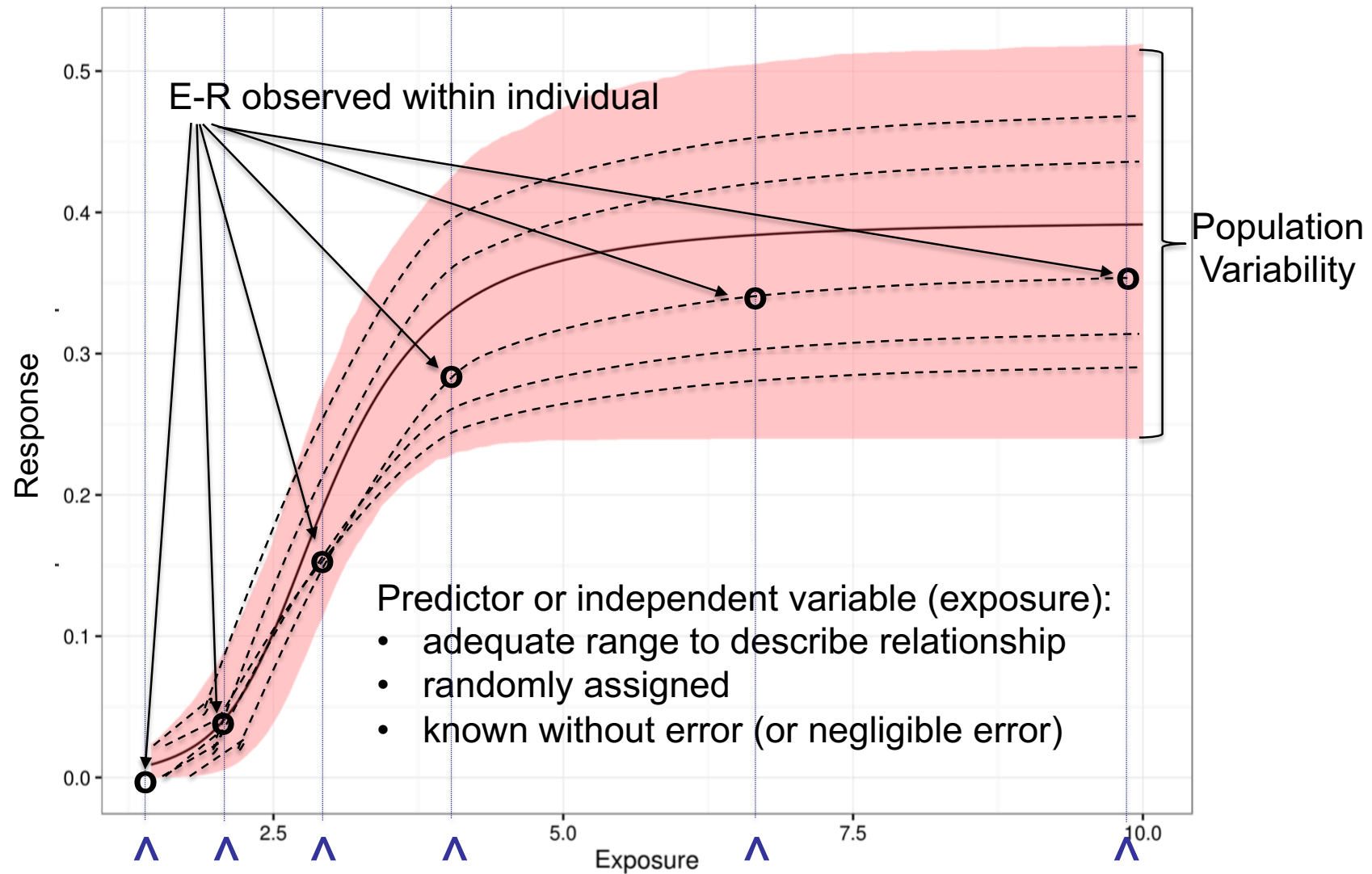


Ideal E-R Study Design Characteristics



Design-driven range in predictor (e.g. randomized to dose or exposure) is key.

Ideal E-R Study Design Characteristics: Individual E-R



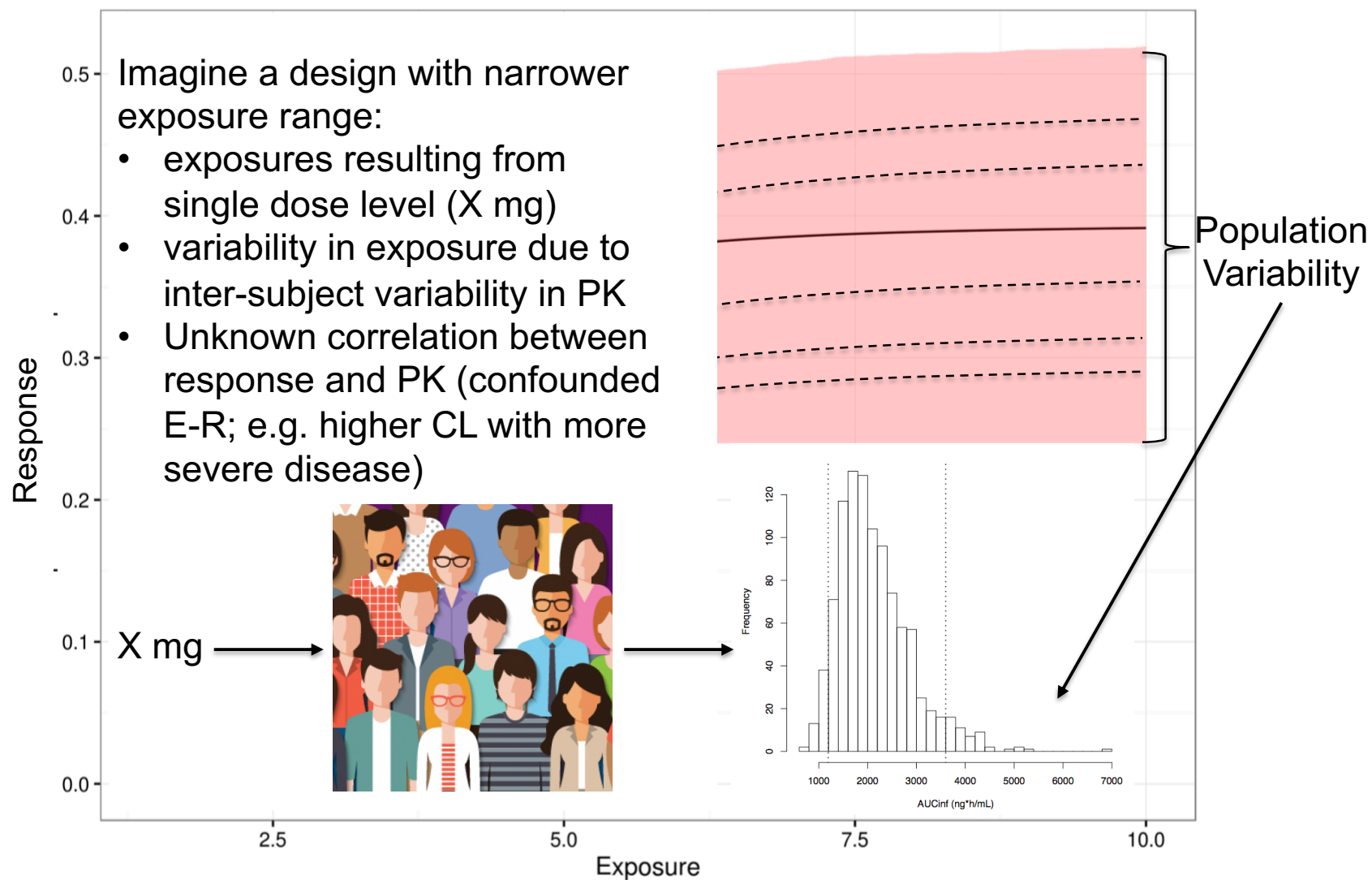
Design-driven range in predictor (e.g. randomized to dose or exposure) is key.

RA and pJIA Trial Designs: Adequate for E-R?

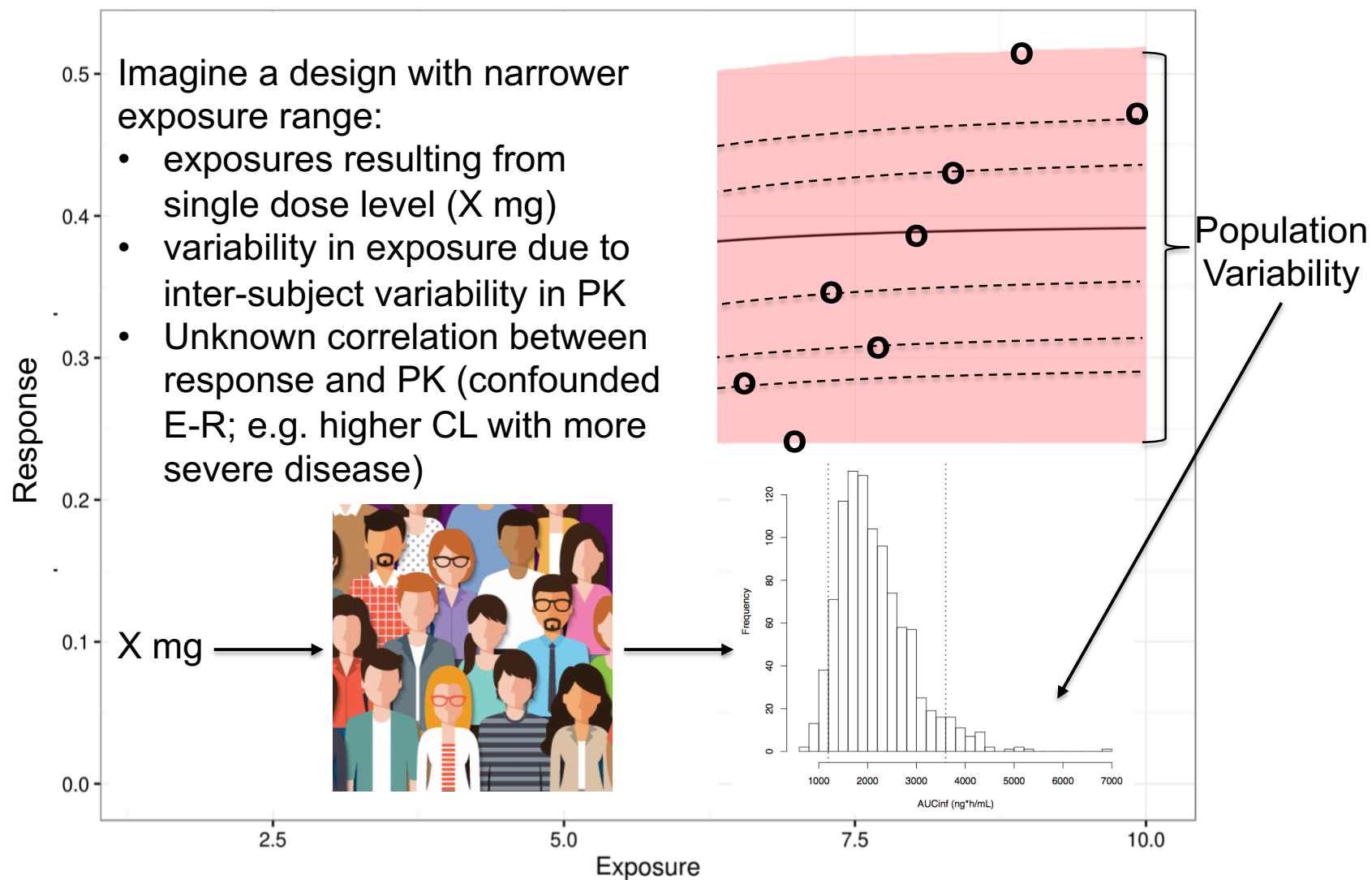
	Adult trials	Doses in pivotal RA	Pediatric trial	Dose in pivotal PJIA
Adalimumab	DB, PC	2 doses	RW	1 BSA based dose
Golimumab SC	DB, PC	2 doses	RW	1 BSA based dose
Infliximab	DB, PC	3 doses	DB, PC	1 WGT based dose
Etanercept	DB, PC	3 doses	RW	1 WGT based dose
Abatacept IV	DB, PC	3 doses	RW	1 WGT based dose
Tocilizumab	DB, PC	2 doses	RW	2 WGT based doses

Slide courtesy of Renu Singh. FDA/UMD CERSI pJIA Drug Development Workshop - October 2, 2019

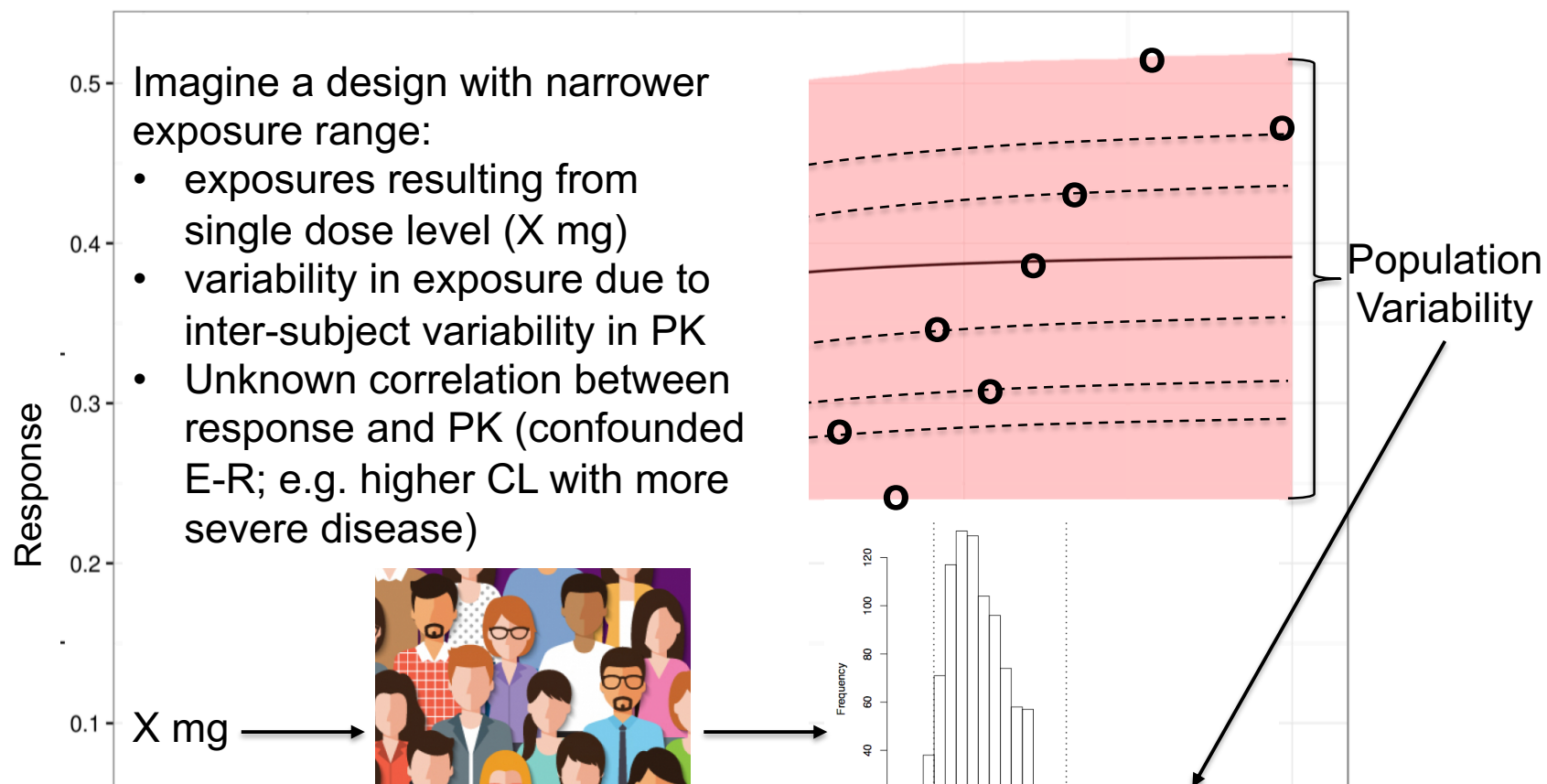
Observed (not Design-Driven) Population E-R



Observed (not Design-Driven) Population E-R



Observed (not Design-Driven) Population E-R



Predictor or independent variable (exposure):

- inadequate range to describe relationship
- not randomly assigned – actually an outcome
- known with some error

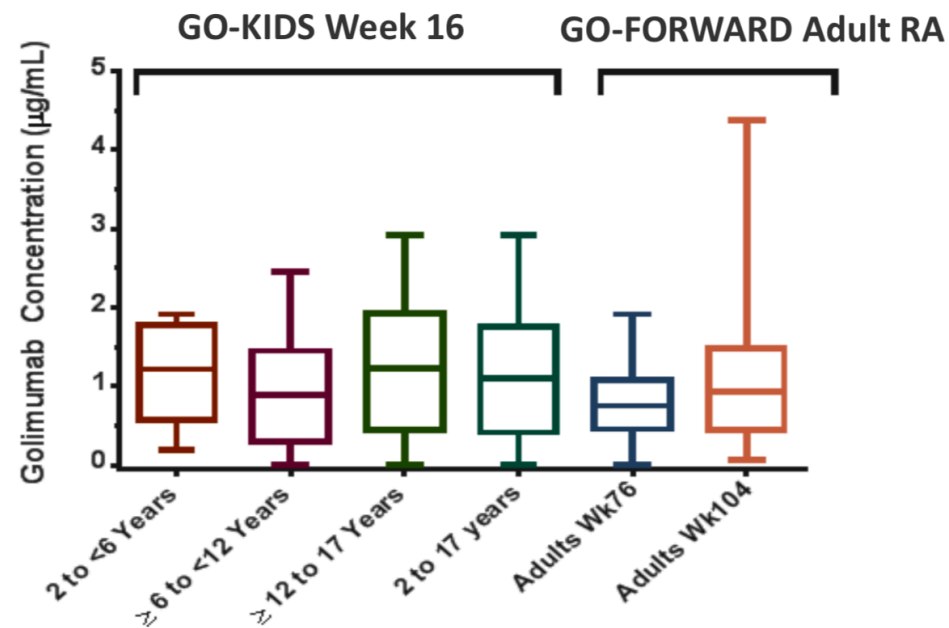
Exposure in Pediatric and Adult Populations

PK/PD - Dosing

Single Dose Level

- Dosing with GLM 30 mg/m² every 4 weeks resulted in GLM levels similar or higher compared to adults with RA
- Immunogenicity
 - Did not affect GLM levels with exception of patients with high titers of ADA
 - Did not affect efficacy unless titers were >1:1000 (n=6)
- There is no identified mechanistic basis for prolonged PD effect in anti-TNF agents

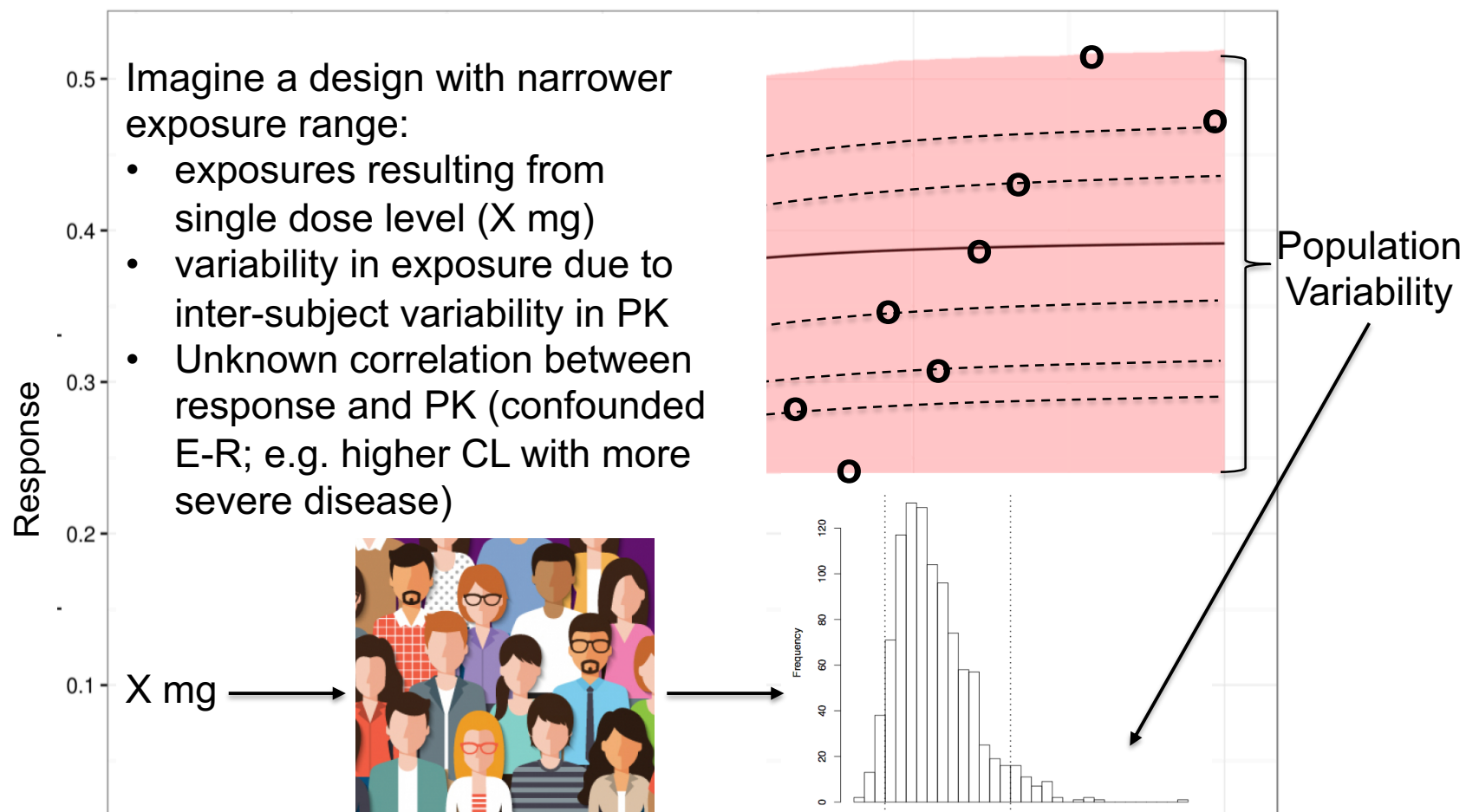
Exposures sufficient to saturate target



Bioanalysis with the same PK assay (MSD)

- Week 16 GO-KIDS SC golimumab 30 mg/m² + MTX Q4W
- Week 76 & 104 GO-FORWARD SC golimumab 50 mg + MTX Q4W

Observed (not Design-Driven) Population E-R



Is the apparent exposure-response relationship confounded by disease severity?

Strong Interest in Understanding Causal E-R Relationships

The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

The Journal of Clinical Pharmacology
53(2) 160-166
© The Author(s) 2012
DOI: 10.1177/0091270012445206

Jun Yang, PhD¹, Hong Zhao, PhD¹, Christine Garnett, PharmD¹,
Atiqur Rahman, PhD¹, Jogarao V. Gobburu, PhD¹, William Pierce, PharmD²,
Genevieve Schechter, MD², Jeffery Summers, MD², Patricia Keegan, MD²,
Brian Booth, PhD¹, and Yaning Wang, PhD¹

2012

Exposure-Response Relationship of T-DM1: Insight Into Dose Optimization for Patients With HER2-Positive Metastatic Breast Cancer

J Wang¹, P Song¹, S Schrieber¹, Q Liu¹, Q Xu², G Blumenthal³, L Amiri Kordestani³, P Cortazar³,
A Ibrahim³, R Justice³, Y Wang¹, S Tang², B Booth¹, N Mehrotra¹ and A Rahman¹

2015

CCR Perspectives in Drug Approval

Clinical
Cancer
Research

FDA Approval Summary: Ramucirumab for Gastric Cancer

Sandra J. Casak¹, Ibilola Fashoyin-Aje¹, Steven J. Lemery¹, Lillian Zhang², Runyan Jin²,
Hongshan Li², Liang Zhao², Hong Zhao², Hui Zhang³, Huanyu Chen³, Kun He³,
Michele Dougherty⁴, Rachel Novak⁴, Sarah Kennett⁴, Sachia Khasar¹, Whitney Helms¹,
Patricia Keegan¹, and Richard Pazdur³

2015

Concern About Confounded Causal Inference is Not New

Pitfalls in Retrospective Analysis in Search of Concentration-Effect Relationships

Carl Peck, Tom Ludden

Leiden University, The Netherlands, and CDER, FDA, USA

1994

Intention-to-treat analysis and the goals of clinical trials

Lewis B. Sheiner, MD, and Donald B. Rubin, PhD^a
San Francisco, Calif. and Cambridge, Mass.

1995

Diagnostics for confounding in PK/PD models for oxcarbazepine

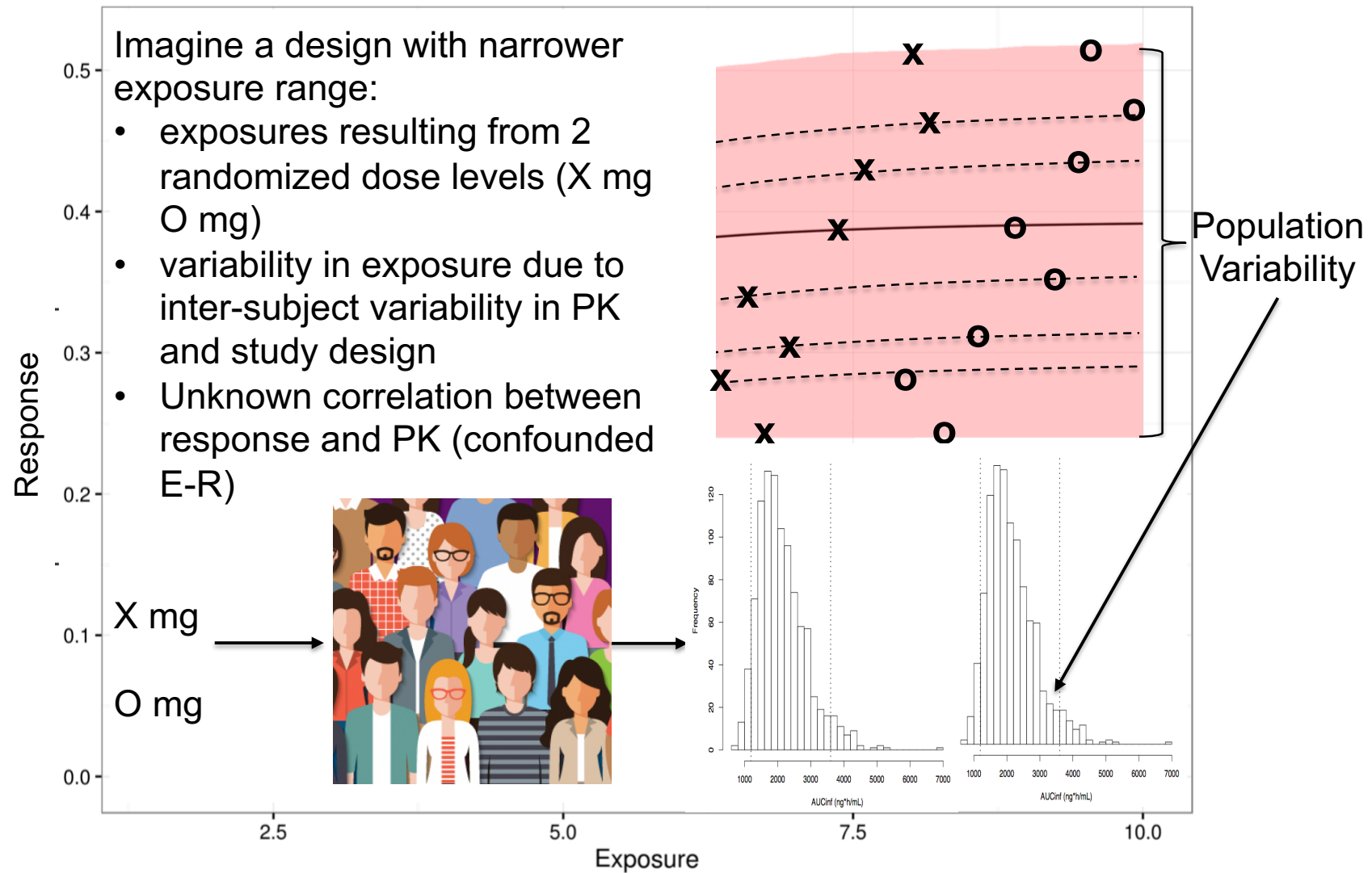
Jerry R. Nedelman^{1,*†}, Donald B. Rubin² and Lewis B. Sheiner^{3,✕}

2007

Possible Solutions to Confounded Exposure-Response

- Case matching or model-based adjustment for confounding
 - Not practical for small sample size
- Randomize exposure across population through randomized dose range
 - Broad range needed for accurate inferences, may not be practical
 - 2 doses may be diagnostic for confounded E-R
 - MCPMOD approach may be useful
- Within-individual exposure-response designs
- Make inferences from randomized dose-response designs (avoid E-R)
- Use biomarkers or mechanistic understanding to guide dose selection

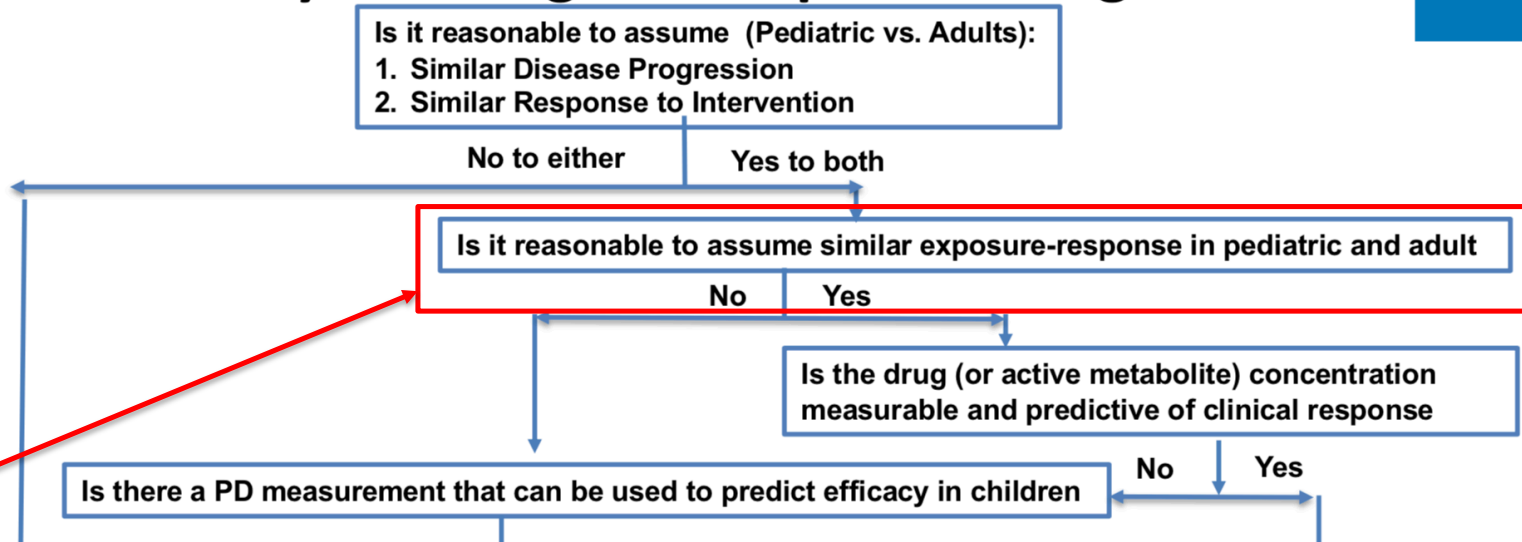
Possible Diagnostic for Confounded Population E-R



E-R in Pediatric Drug Development: Where Do We Go From Here?

- Acknowledge that adequate and well controlled exposure-response studies are very difficult and probably impractical in pediatric development programs.
- Understand that apparent exposure-response relationships resulting from inadequate designs lead to misguided inferences.
- Adapt decision-making in this context.

Pediatric Study Planning & Extrapolation Algorithm



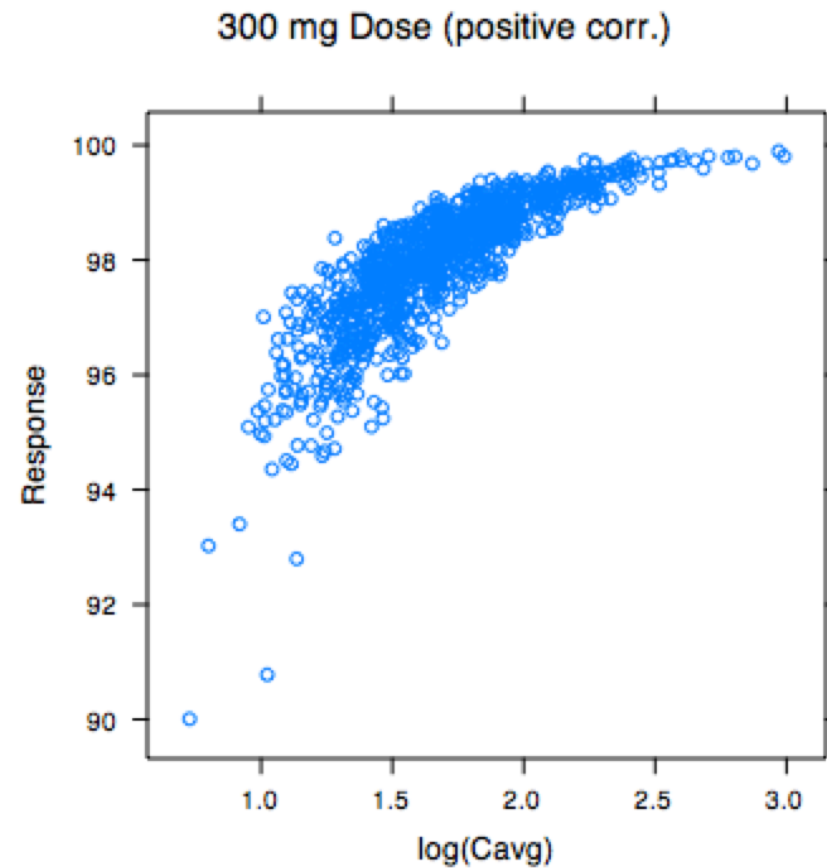
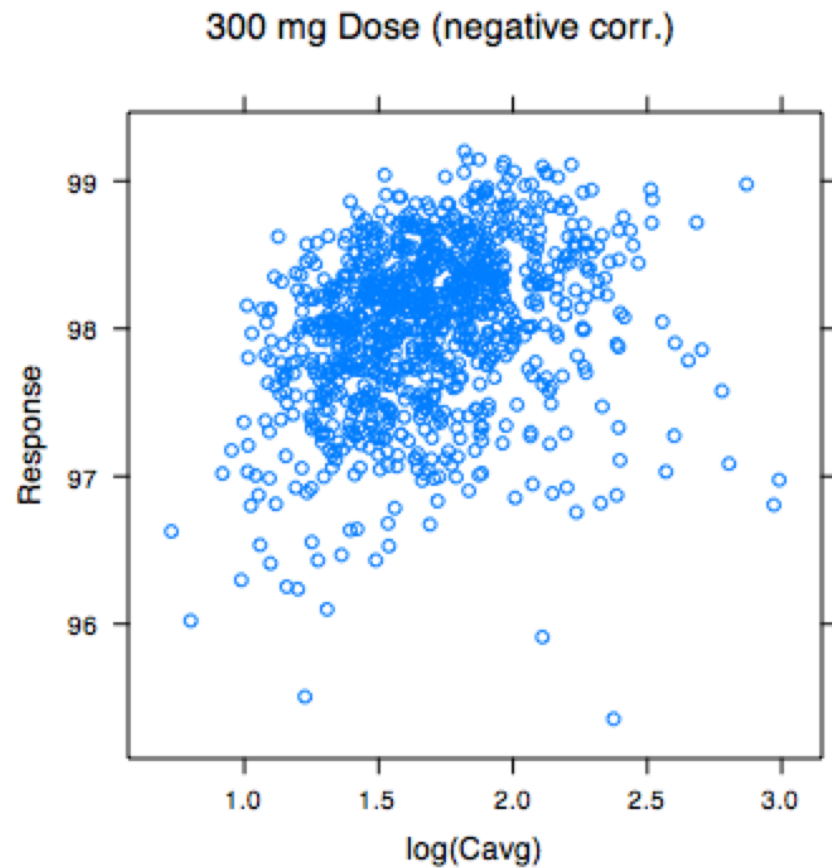
- Is this step necessary for extrapolation?
- Are we really learning what we think we are learning?
- Or, are we simply demonstrating similarity of disease-exposure relationship?

Related References

- Casak et al. FDA Approval Summary: Ramucirumab for Gastric Cancer. *Clin Cancer Res.* 2015; 21(15): 3372-6.
- Gruber S and van der Laan MJ. Consistent causal effect estimation under dual misspecification and implications for confounder selection procedures. *Stat Meth Med Res.* 2015; 24(6): 1003-8.
- Nedelman JR, Rubin DB, and Sheiner LB. Diagnostics for confounding in PK/PD models for oxcarbazepine. *Stat Med.* 2007; 26:290-308.
- Peck C and Ludden T. Pitfalls in Retrospective Analysis in Search of Concentration-Effect Relationships. PAGE 3 (1994) Abstr 867 [www.page-meeting.org/?abstract=867]
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- Wang J et al. Exposure-Response Relationship of T-DM1: Insight into Dose Optimization for Patients with HER2-Positive Metastatic Breast Cancer. *Clin Pharmacol Ther.* 2015; 95(5)
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Population Exposure-Response w/ Single Dose Level

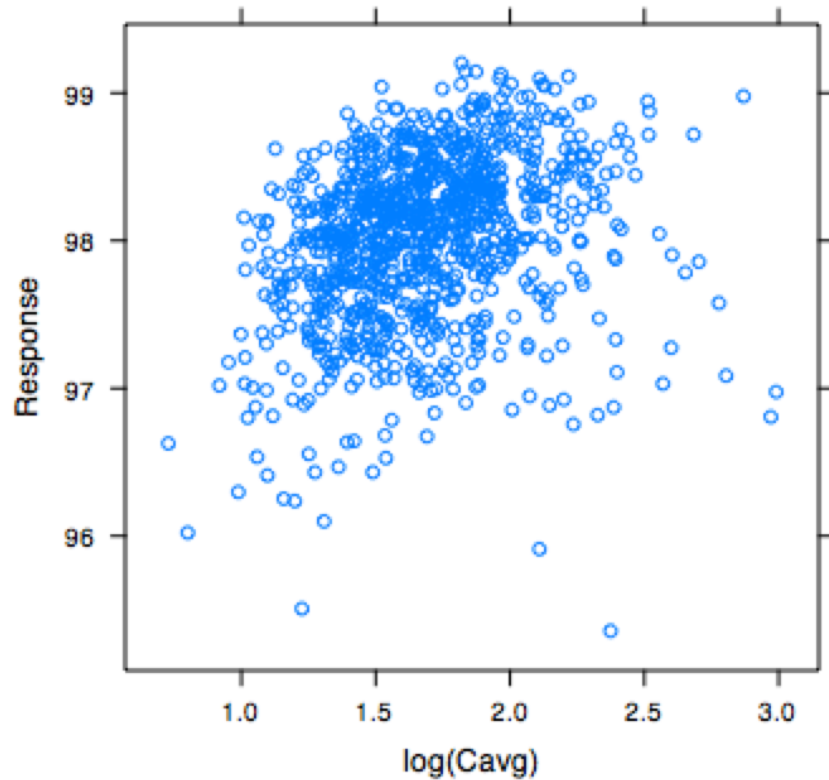
- Resulting exposure-response relationships are misleading



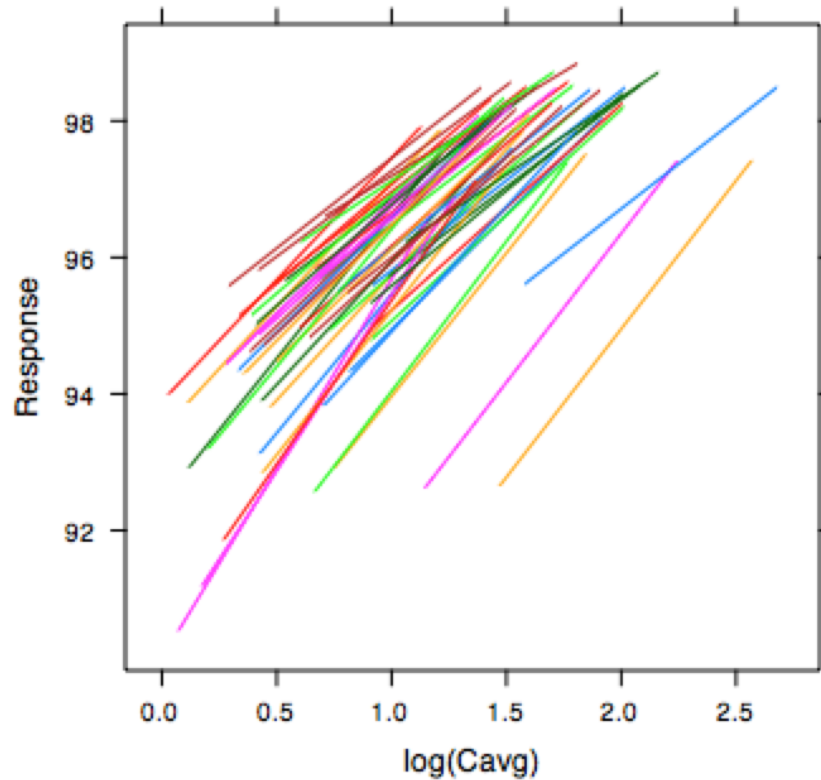
Population Exposure-Response w/ Single Dose Level

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

300 mg Dose (negative corr.)



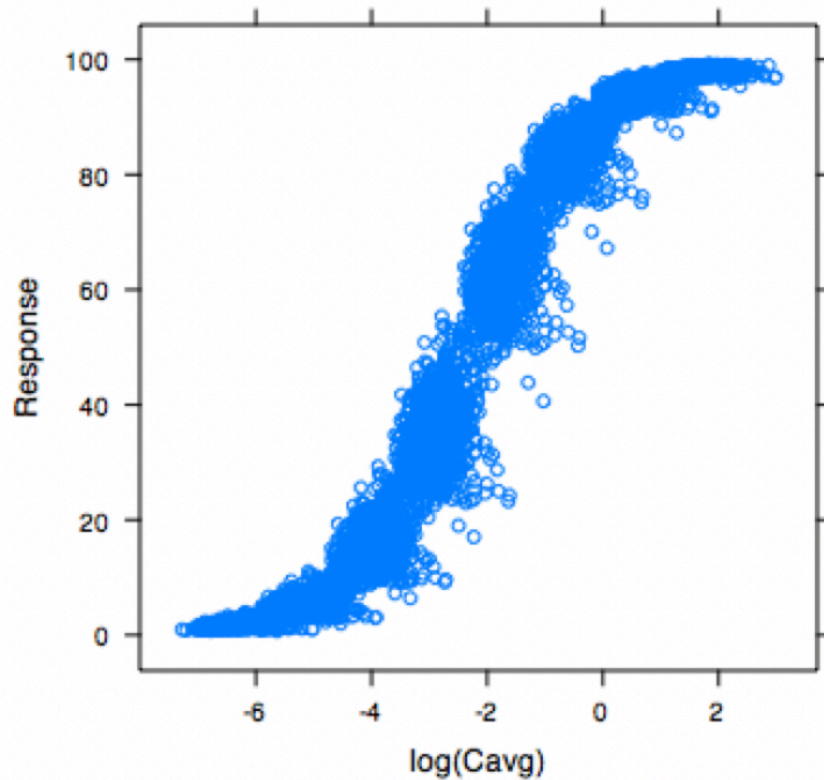
100 mg to 300 mg Dose Range (negative corr.)



Population Exposure-Response w/ Single Dose Level

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

0.1 mg to 300 mg Dose Range (negative corr.)



0.1 mg to 300 mg Dose Range (positive corr.)

