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

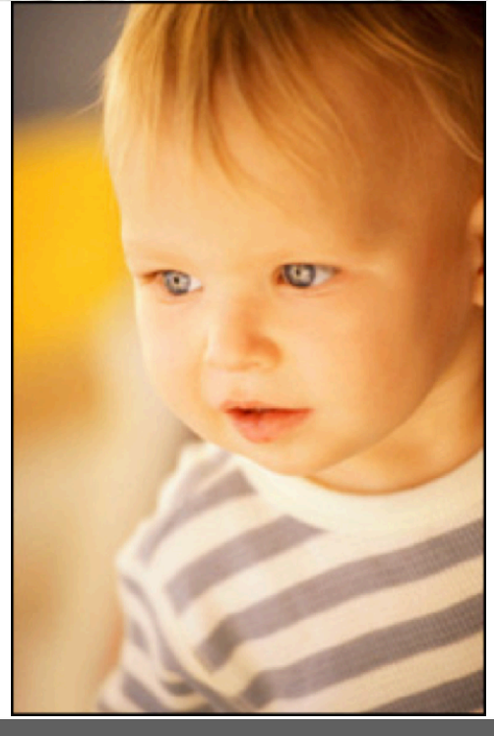
Use of Exposure-Response Information in Pediatric Drug Development

Marc R. Gastonguay, Ph.D.

CEO, Metrum Research Group

METRUM
RESEARCH GROUP

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

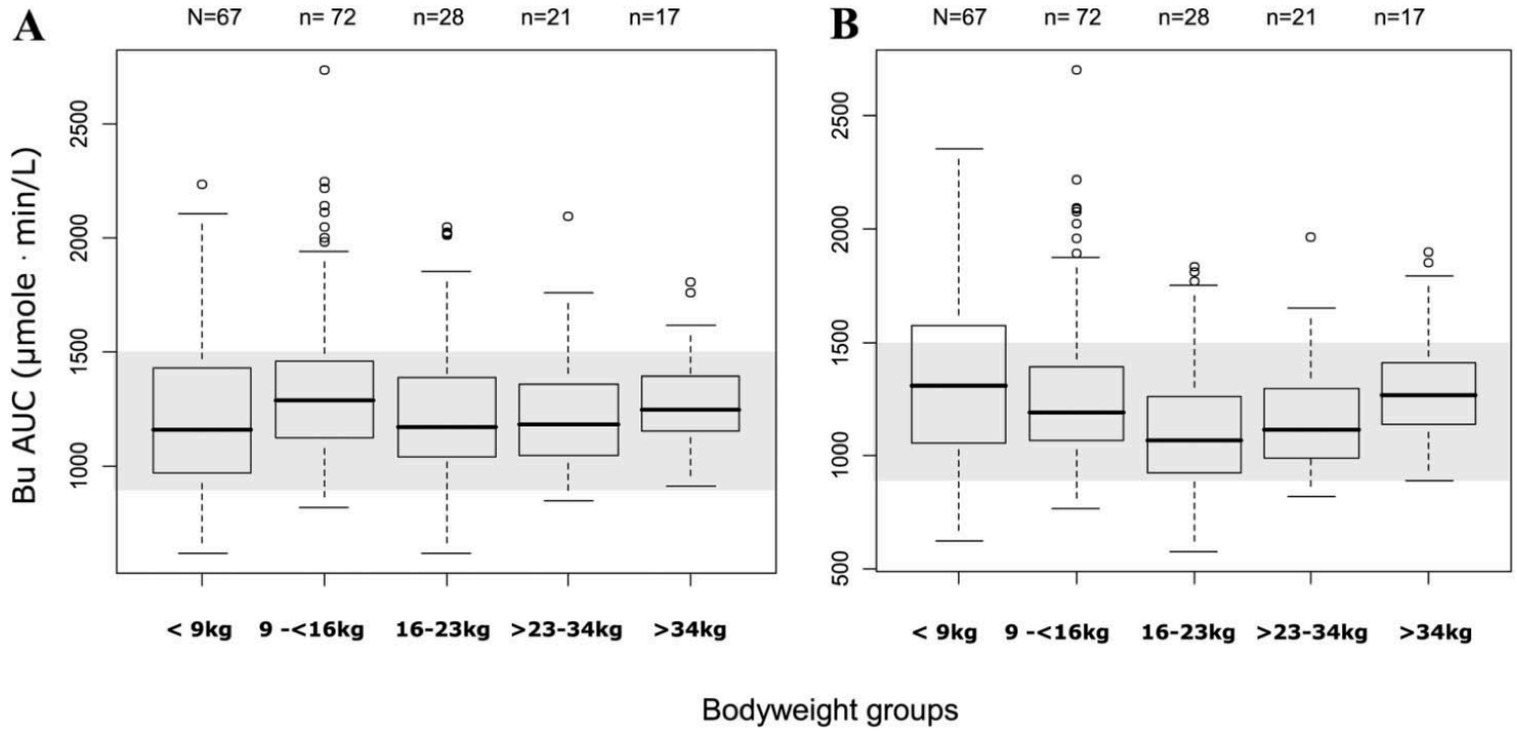


FIGURE 5. Comparison of dosing strategy between model-based and EU labeled dosing. A, Bu AUC distribution using approved EU labeling dosing. B, Bu AUC distribution using model-based dosing.

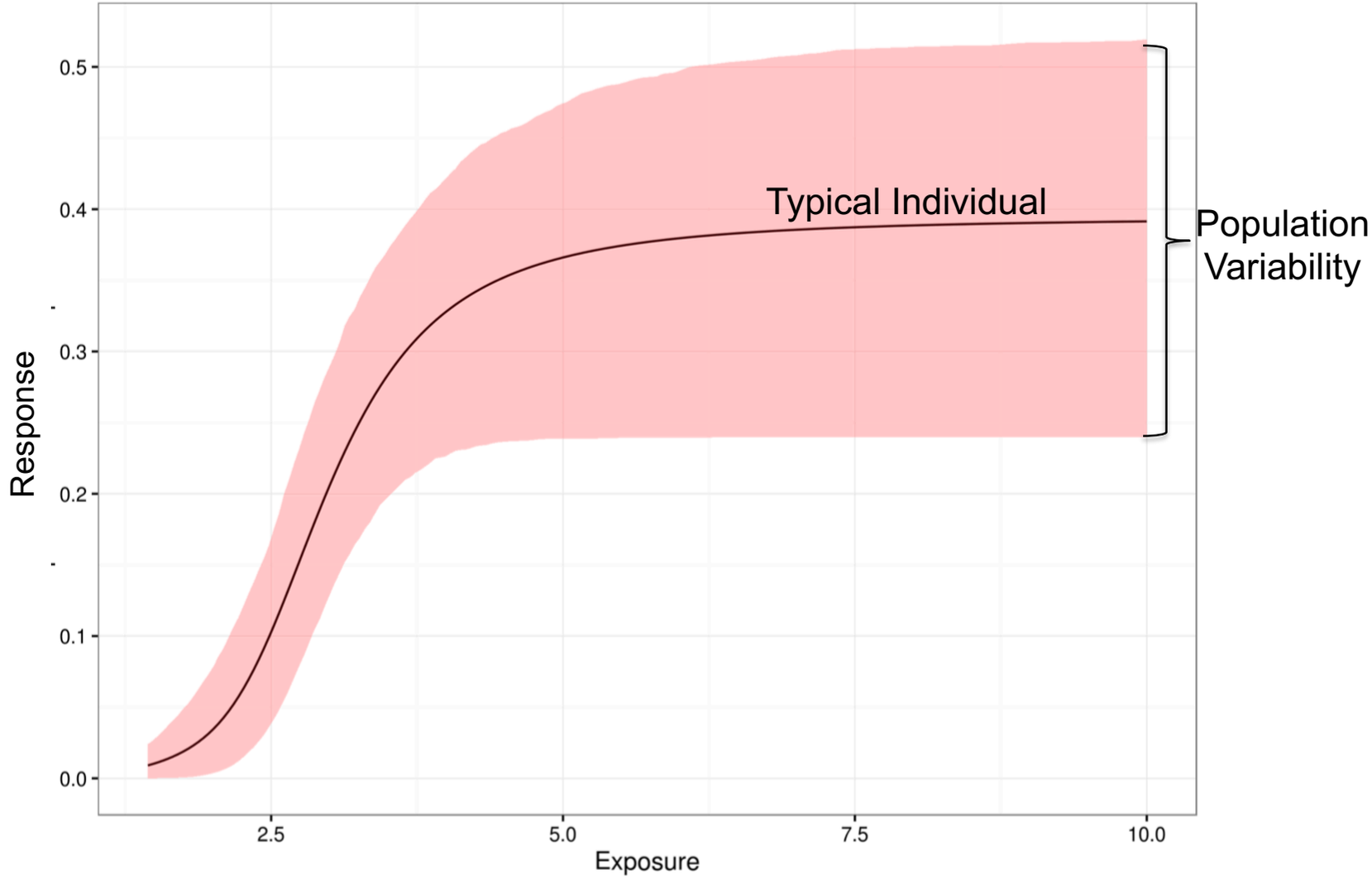
Paci et al. Pharmacokinetic Behavior and Appraisal of Intravenous Busulfan Dosing in Infants and Older Children: The Results of a Population Pharmacokinetic Study From a Large Pediatric Cohort Undergoing Hematopoietic Stem-Cell Transplantation. Ther Drug Monit 2012;34:198–208.

Guidance for Industry

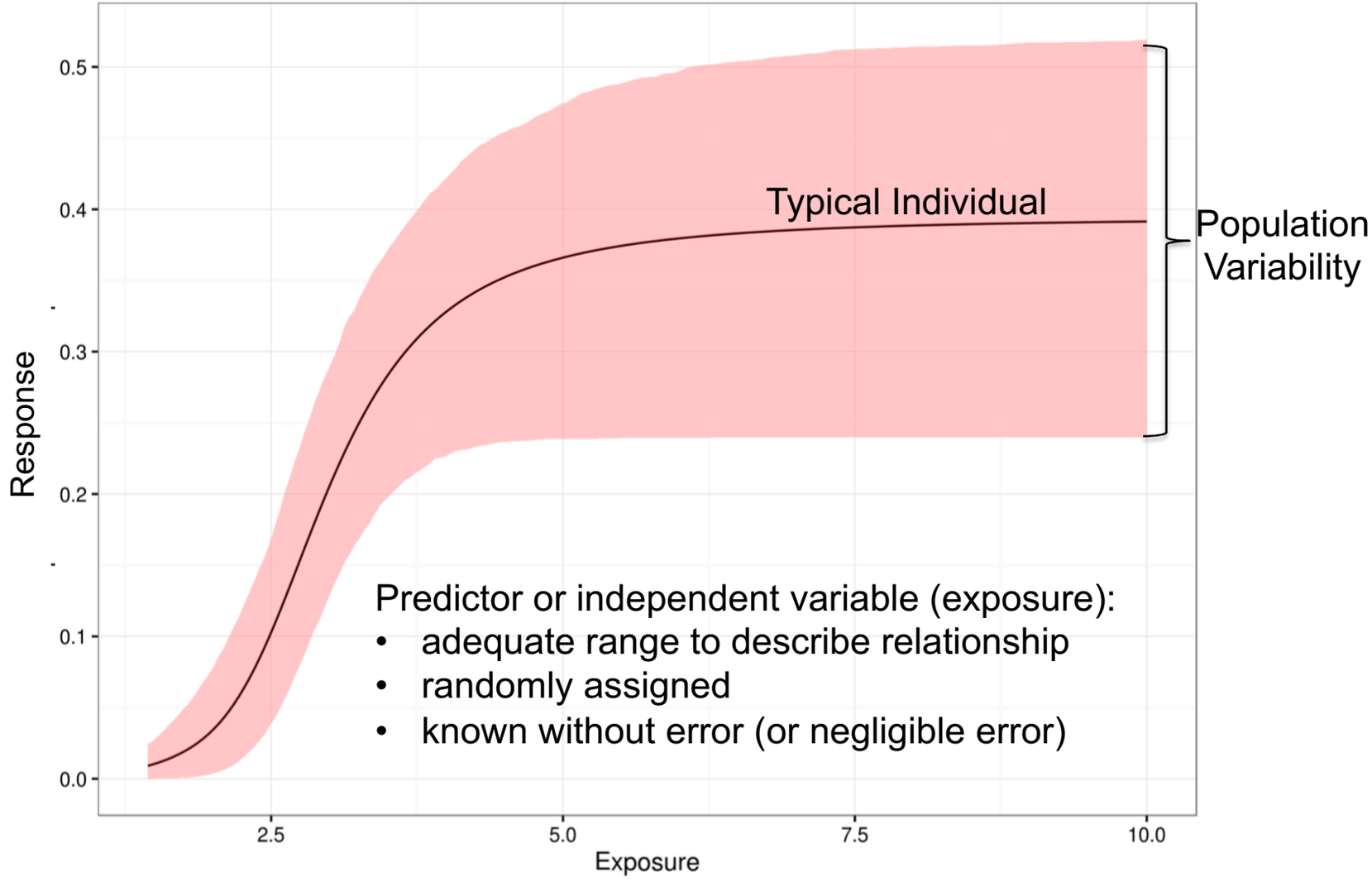
Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

- "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."

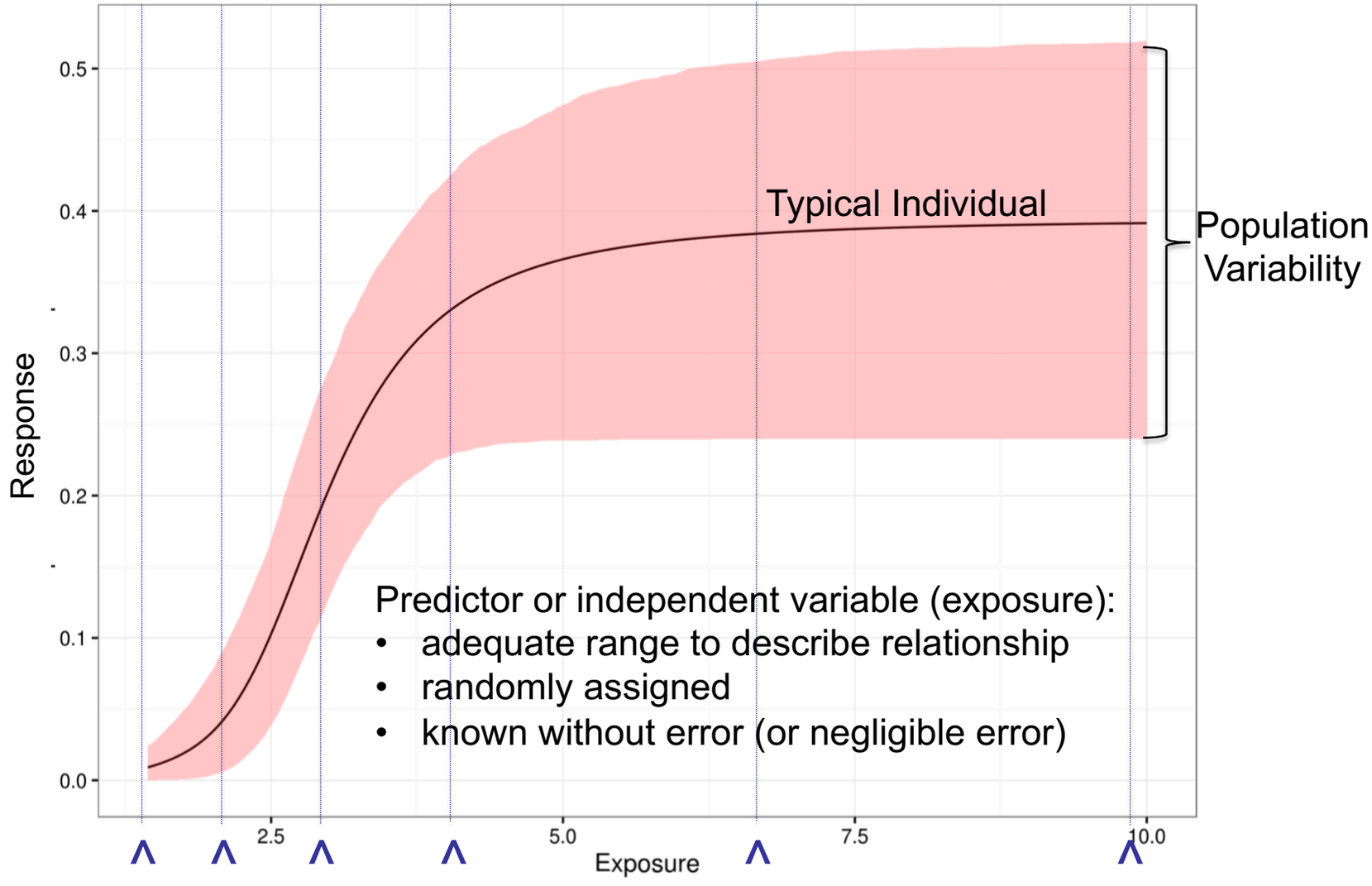
Hypothetical True Exposure-Response Relationship



Ideal E-R Study Design Characteristics

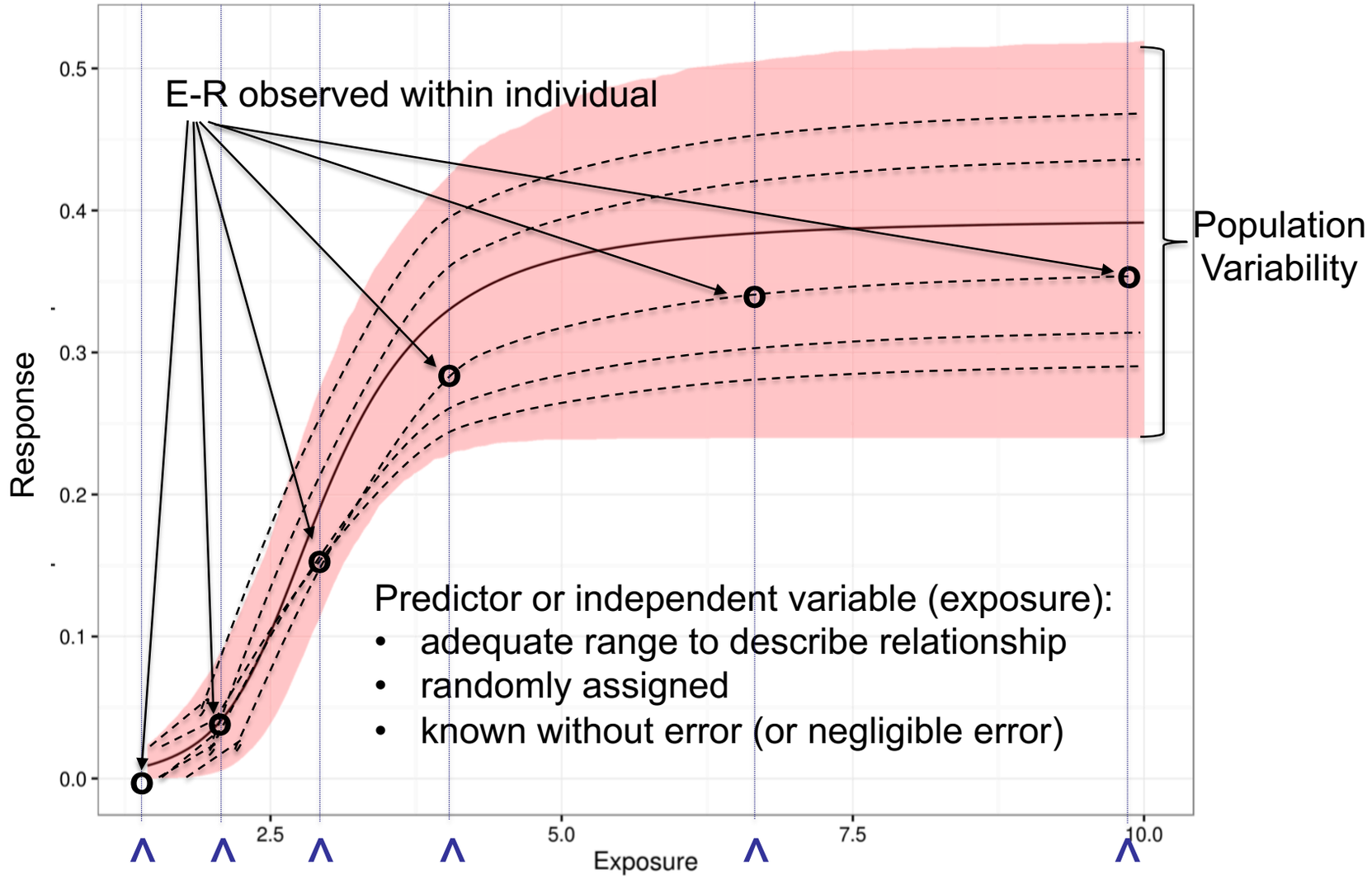


Ideal E-R Study Design Characteristics



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

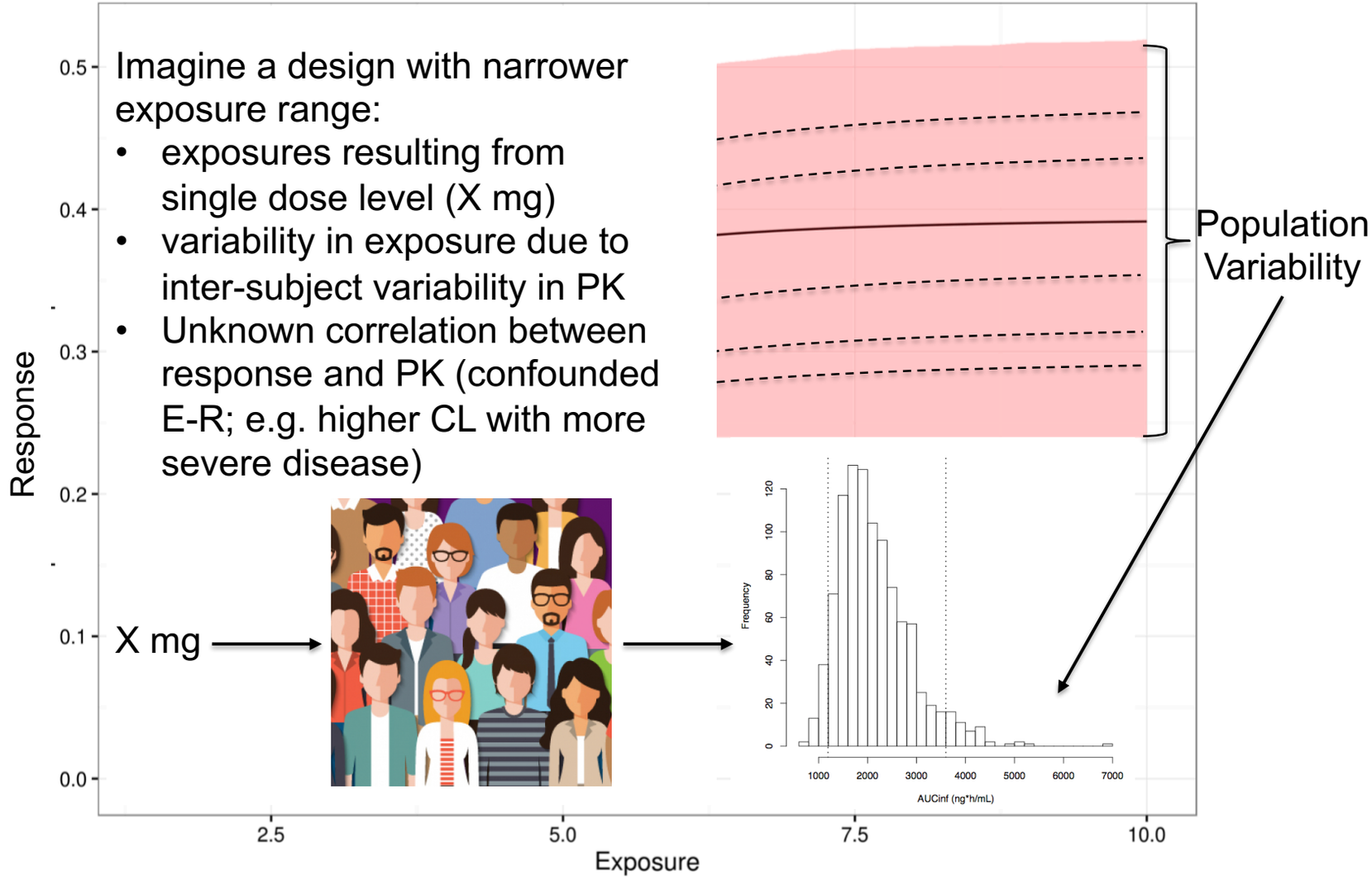
Slide courtesy of Renu Singh. FDA/UMD CERSI pJIA Drug Development Workshop - October 2, 2019

5

Observed (not Design-Driven) Population E-R

Imagine a design with narrower exposure range:

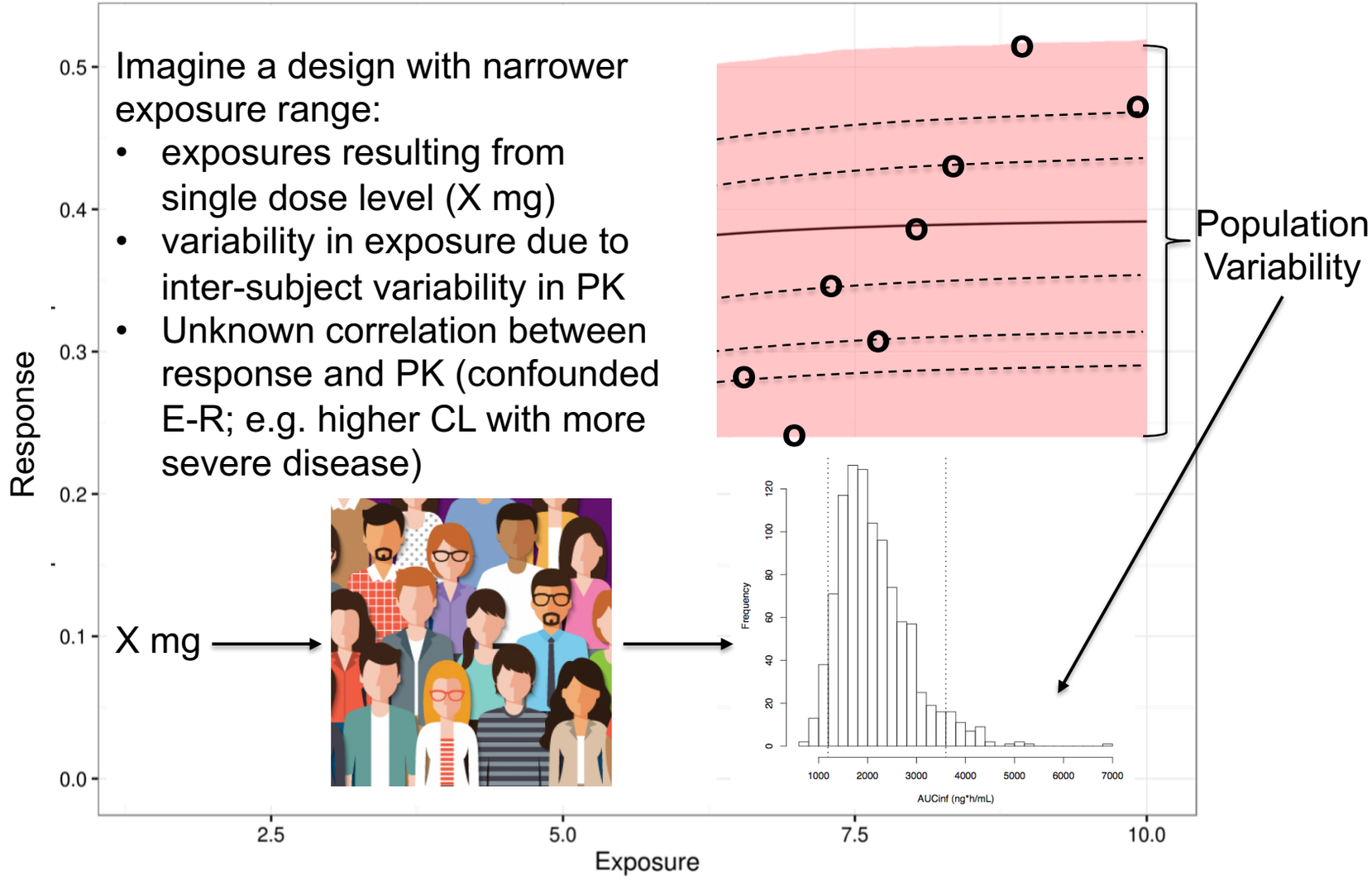
- exposures resulting from single dose level (X mg)
- variability in exposure due to inter-subject variability in PK
- Unknown correlation between response and PK (confounded E-R; e.g. higher CL with more severe disease)



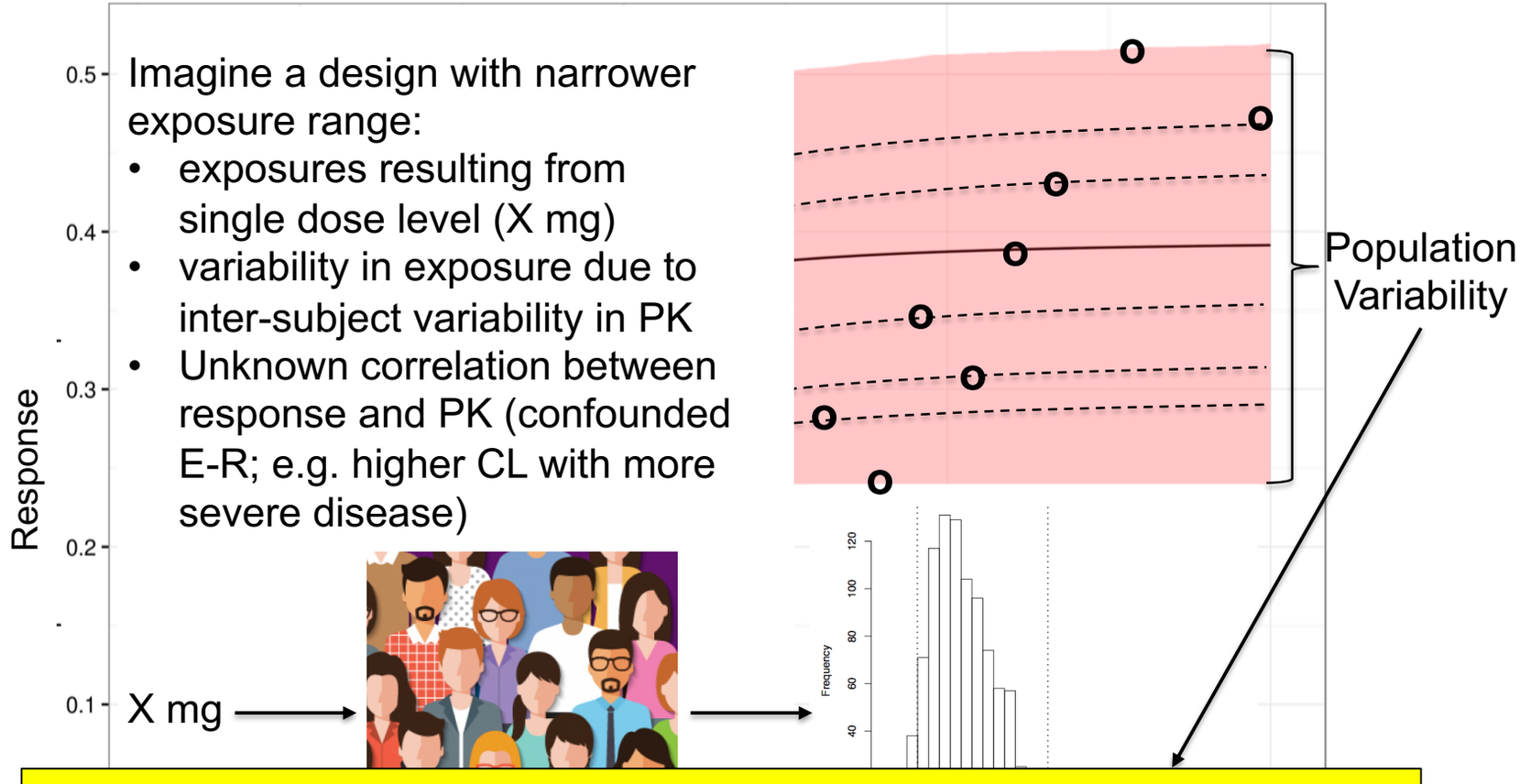
Observed (not Design-Driven) Population E-R

Imagine a design with narrower exposure range:

- exposures resulting from single dose level (X mg)
- variability in exposure due to inter-subject variability in PK
- Unknown correlation between response and PK (confounded E-R; e.g. higher CL with more severe disease)



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

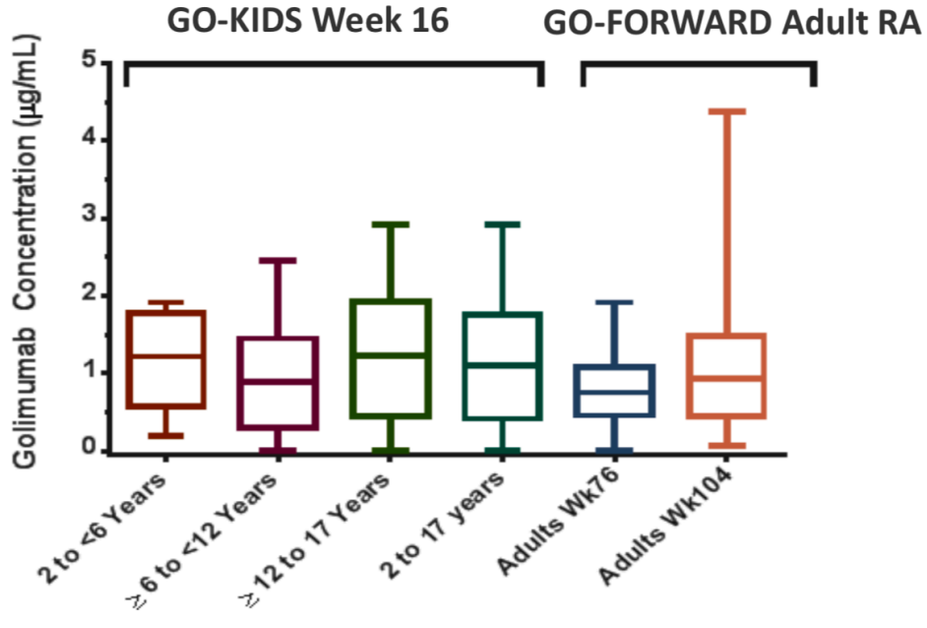
Exposure in Pediatric and Adult Populations

PK/PD - Dosing

Single Dose Level

- Dosing with GLM 30 mg/m^2 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)

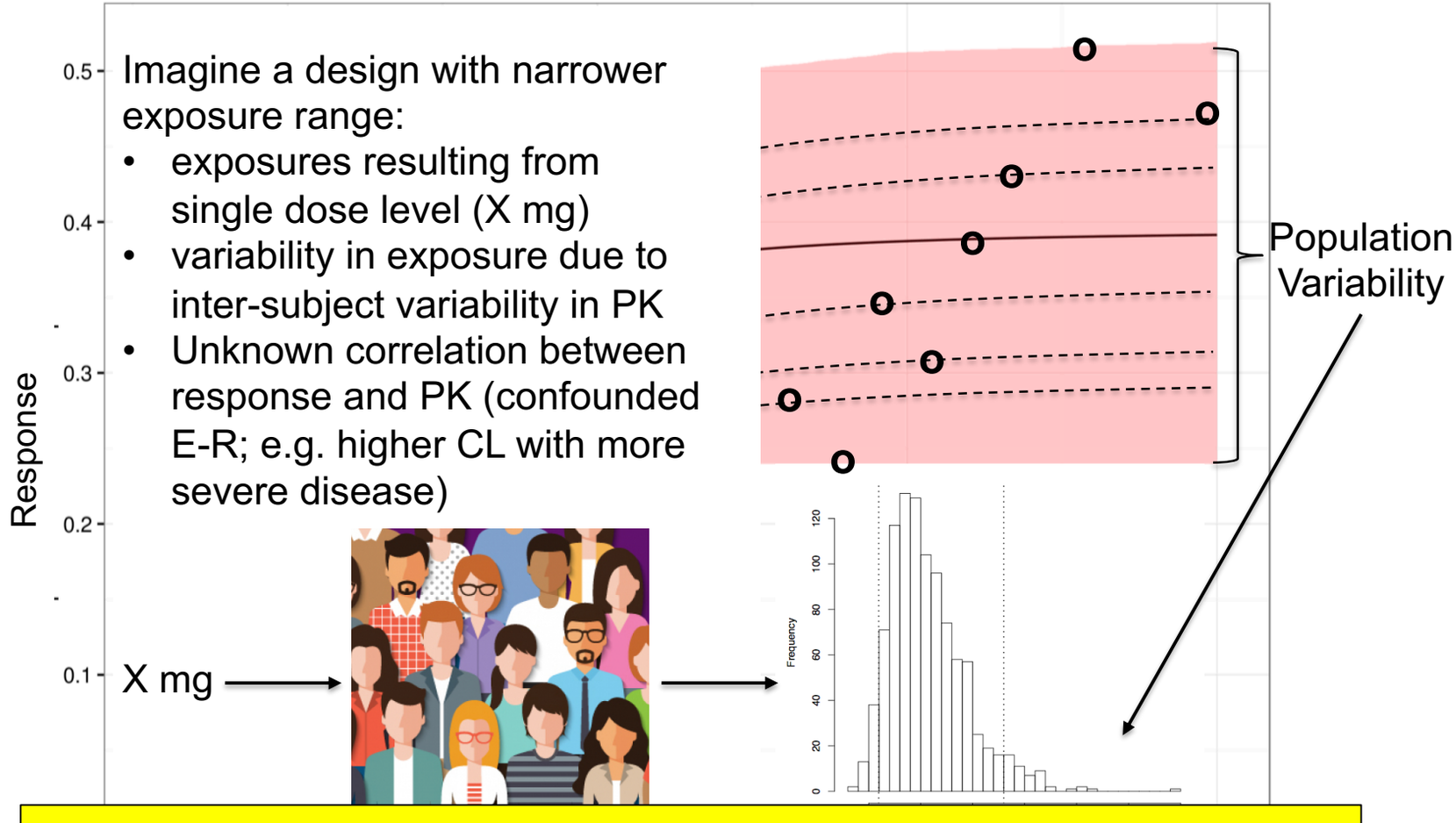
- Week 16 GO-KIDS SC golimumab 30 mg/m^2 + MTX Q4W
- Week 76 & 104 GO-FORWARD SC golimumab 50 mg + MTX Q4W

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

Observed (not Design-Driven) Population E-R

Imagine a design with narrower exposure range:

- exposures resulting from single dose level (X mg)
- variability in exposure due to inter-subject variability in PK
- Unknown correlation between response and PK (confounded E-R; e.g. higher CL with more severe disease)



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, PhD[1], Hong Zhao, PhD[1], Christine Garnett, PharmD[1], Atiqur Rahman, PhD[1], Jogarao V. Gobburu, PhD[1], William Pierce, PharmD[2], Genevieve Schechter, MD[2], Jeffery Summers, MD[2], Patricia Keegan, MD[2], Brian Booth, PhD[1], and Yaning Wang, PhD[1]

2012

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

J Wang[1], P Song[1], S Schrieber[1], Q Liu[1], Q Xu[2], G Blumenthal[3], L Amiri Kordestani[3], P Cortazar[3], A Ibrahim[3], R Justice[3], Y Wang[1], S Tang[2], B Booth[1], N Mehrotra[1] and A Rahman[1]

2015

CCR Perspectives in Drug Approval

Clinical Cancer Research

FDA Approval Summary: Ramucirumab for Gastric Cancer

Sandra J. Casak[1], Ibilola Fashoyin-Aje[1], Steven J. Lemery[1], Lillian Zhang[2], Runyan Jin[2], Hongshan Li[2], Liang Zhao[2], Hong Zhao[2], Hui Zhang[3], Huanyu Chen[3], Kun He[3], Michele Dougherty[4], Rachel Novak[4], Sarah Kennett[4], Sachia Khasar[1], Whitney Helms[1], Patricia Keegan[1], and Richard Pazdur[3]

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. Rubin[2] 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

Imagine a design with narrower exposure range:

- exposures resulting from 2 randomized dose levels (X mg O mg)
- variability in exposure due to inter-subject variability in PK and study design
- Unknown correlation between response and PK (confounded E-R)

X mg

O mg

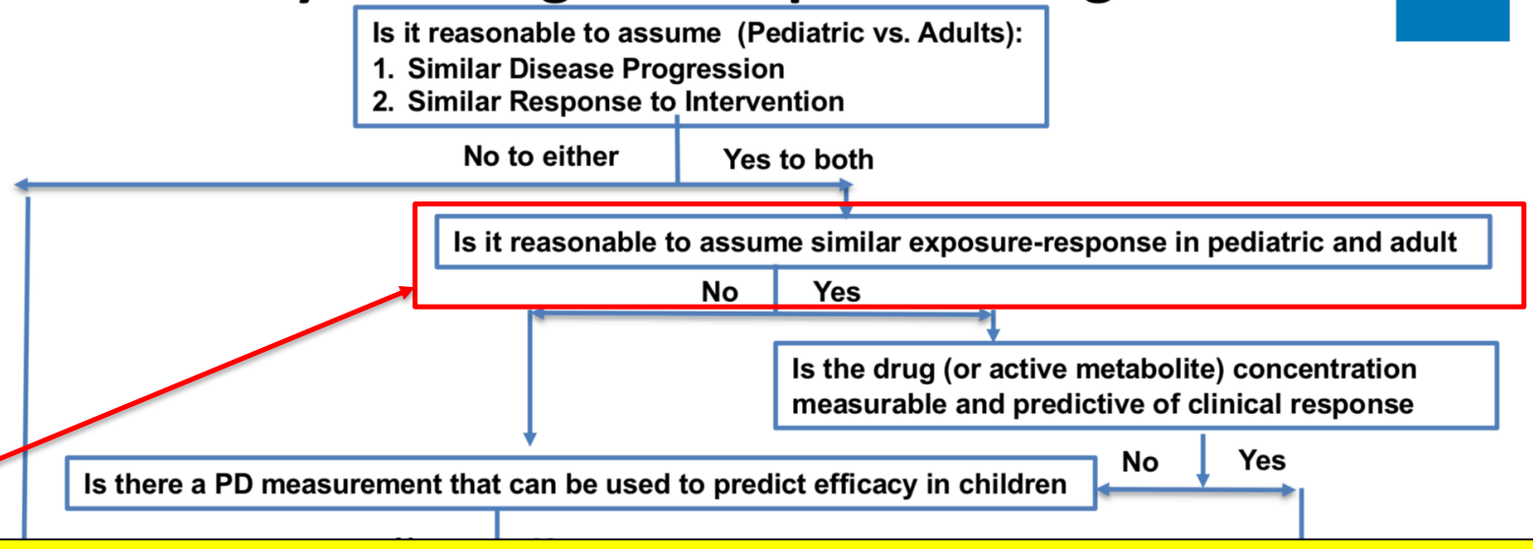
E-R in Pediatric Drug Development: Where Do We Go From Here?

- 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



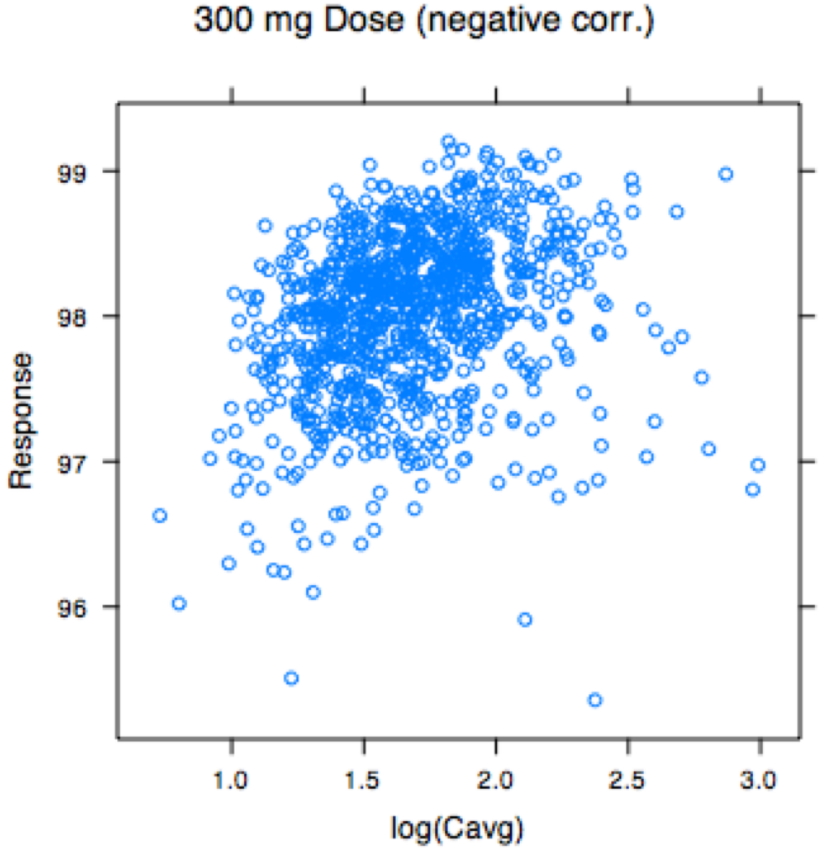
- Is this step necessary for extrapolation?
- Are we really learning what we think we are learning?
- Or, are we simply demonstrating similarity of disease-exposure relationship?

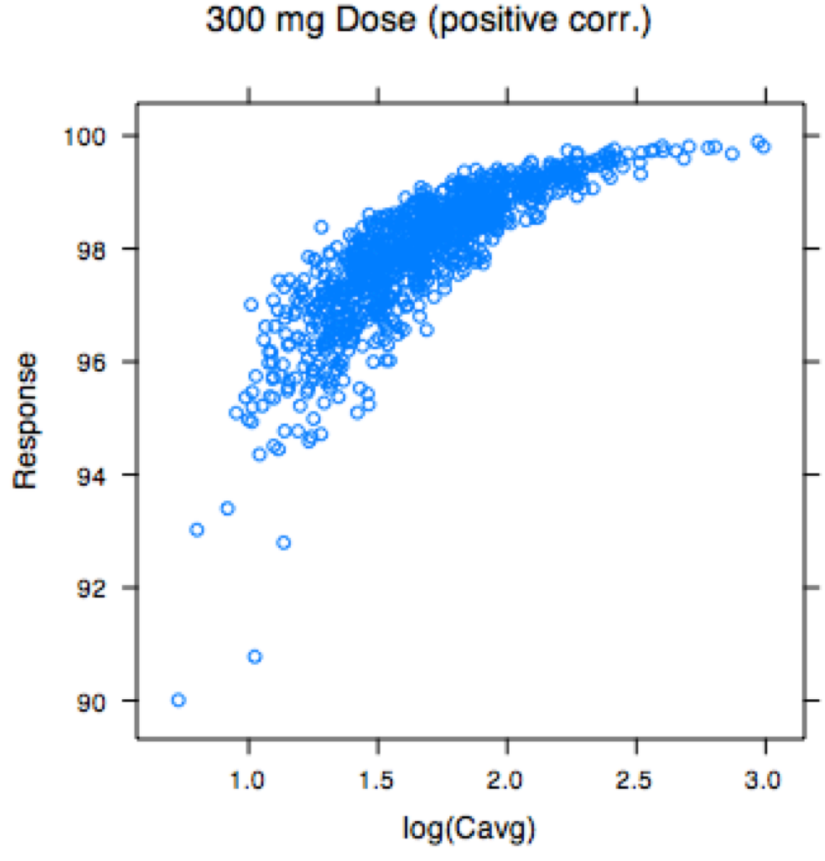
Related References

- 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]
- Petersen ML and van der Laan MJ. Causal Models and Learning from Data: Integrating Causal Modeling and Statistical Estimation. *Epidemiology.* 2014; 25(3): 418-425.
- Sheiner LB and Rubin DB. Intention-to-treat analysis and goals of clinical trials. *Clin Pharm Ther.* 1995; 57: 6-15.
- 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)
- Yang JY et al. The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making. *J Clin Pharmacol.* 2012; 53(2): 160-6.

Population Exposure-Response w/ Single Dose Level

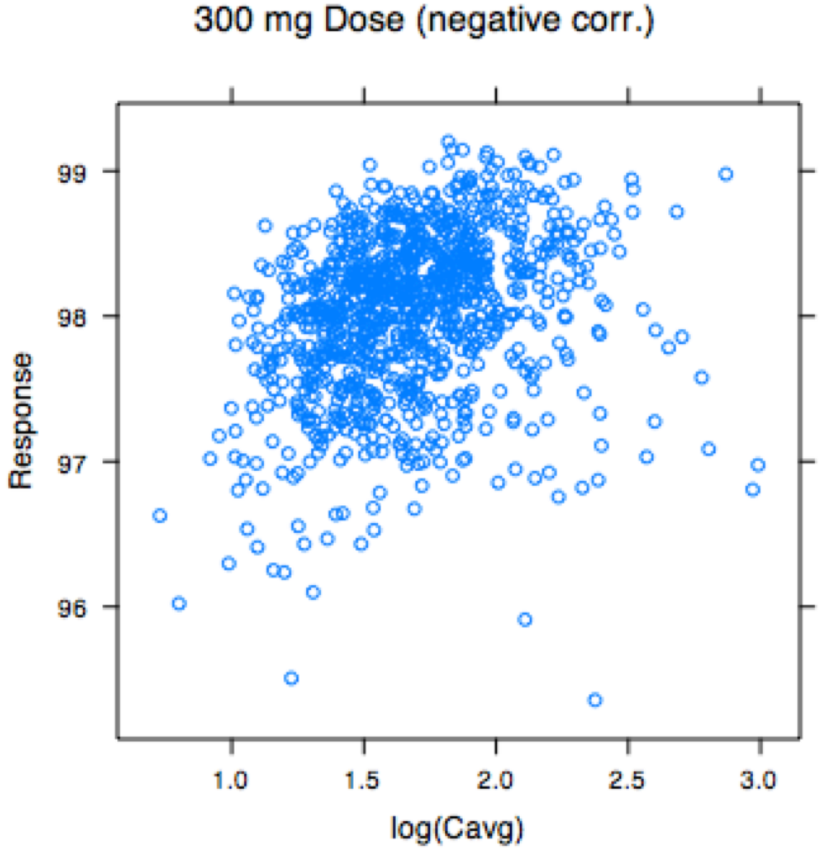
- Resulting exposure-response relationships are misleading

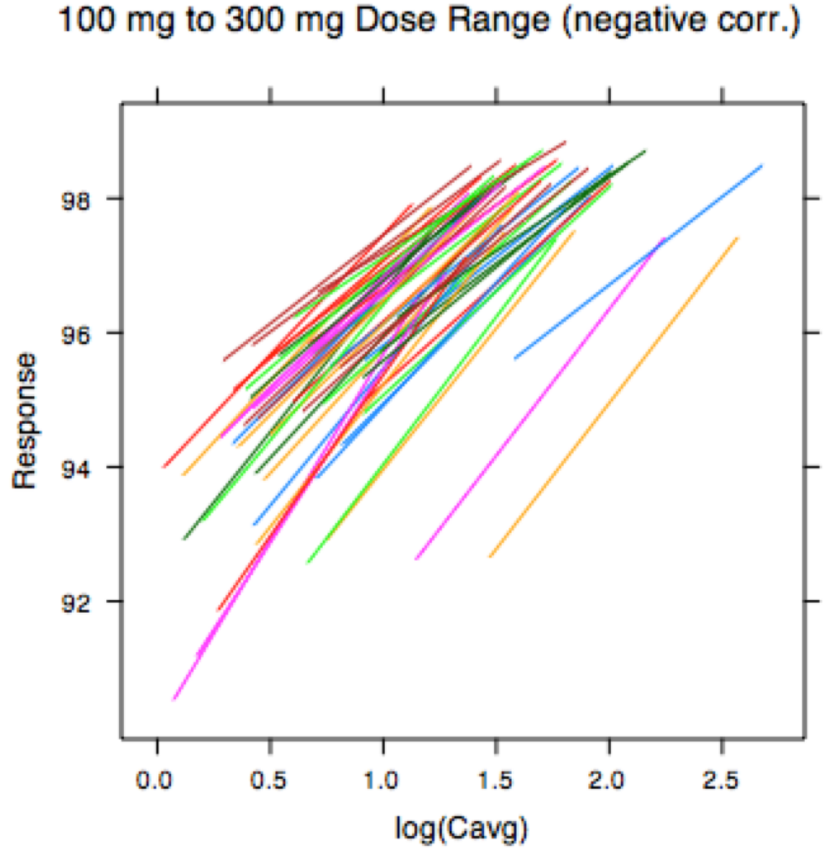




Population Exposure-Response w/ Single Dose Level

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





Population Exposure-Response w/ Single Dose Level

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