ACCP Annual Meeting 2020
SYM 17: Innovative Approaches in the Use of Exposure-Response in Therapeutic Proteins to Support Pediatric Extrapolation

The Use of Exposure-Response With Therapeutic Proteins in Pediatric Drug Development

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Exposure Matching is Not the Topic of Discussion Today

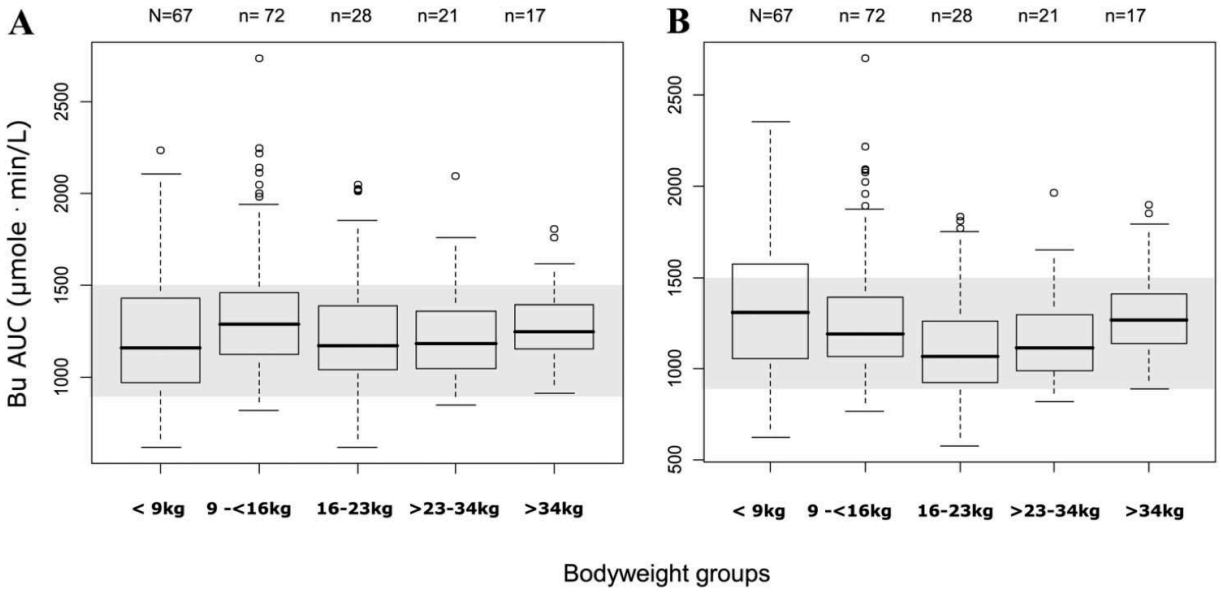


FIGURE 5. Comparison of dosing strategy between model-based and EU labeled dosing. A, Bu AUC distribution using approved EU labeling dosing. B, Bu AUC distribution using model-based dosing.

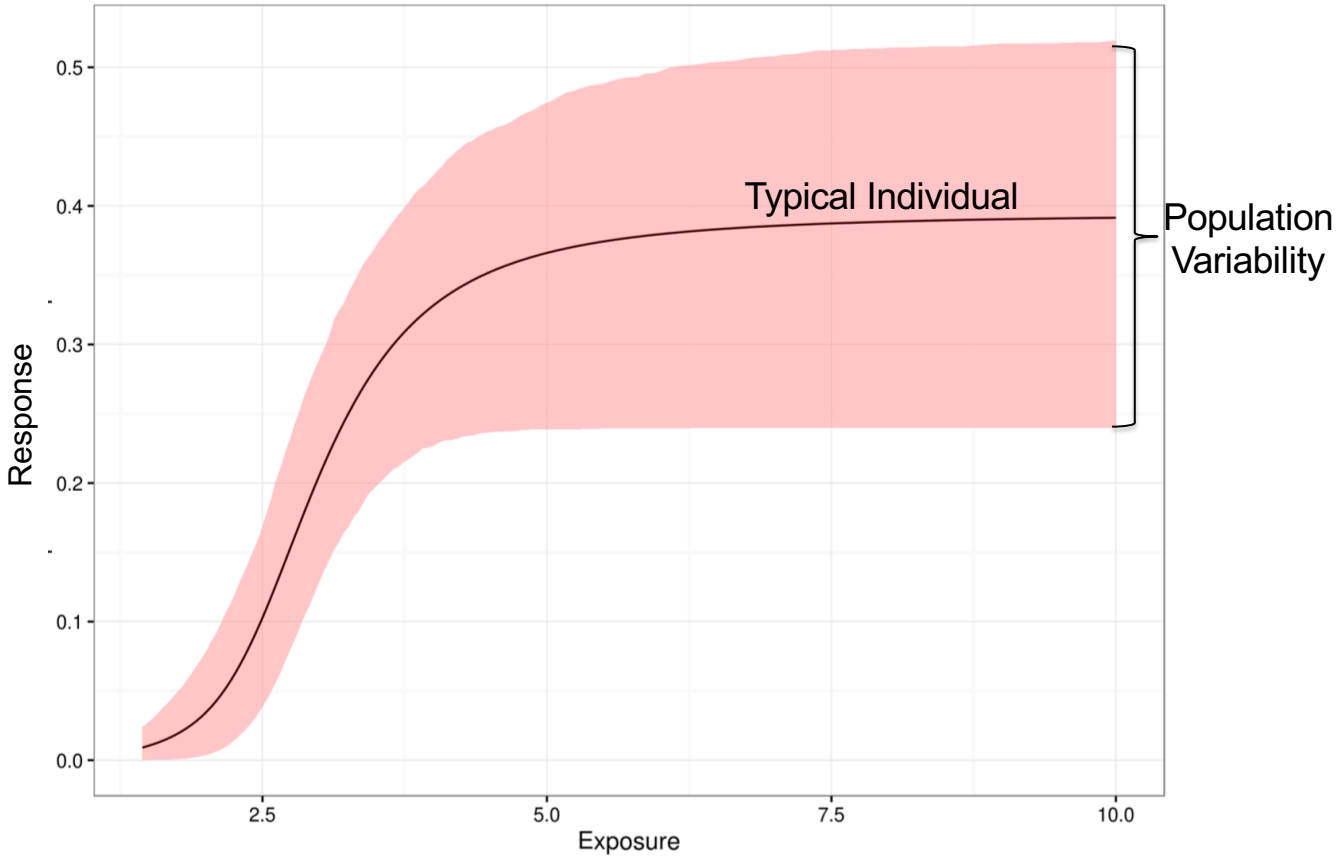
Paci et al. Pharmacokinetic Behavior and Appraisal of Intravenous Busulfan Dosing in Infants and Older Children: The Results of a Population Pharmacokinetic Study From a Large Pediatric Cohort Undergoing Hematopoietic Stem-Cell Transplantation. Ther Drug Monit 2012;34:198–208.

Guidance for Industry

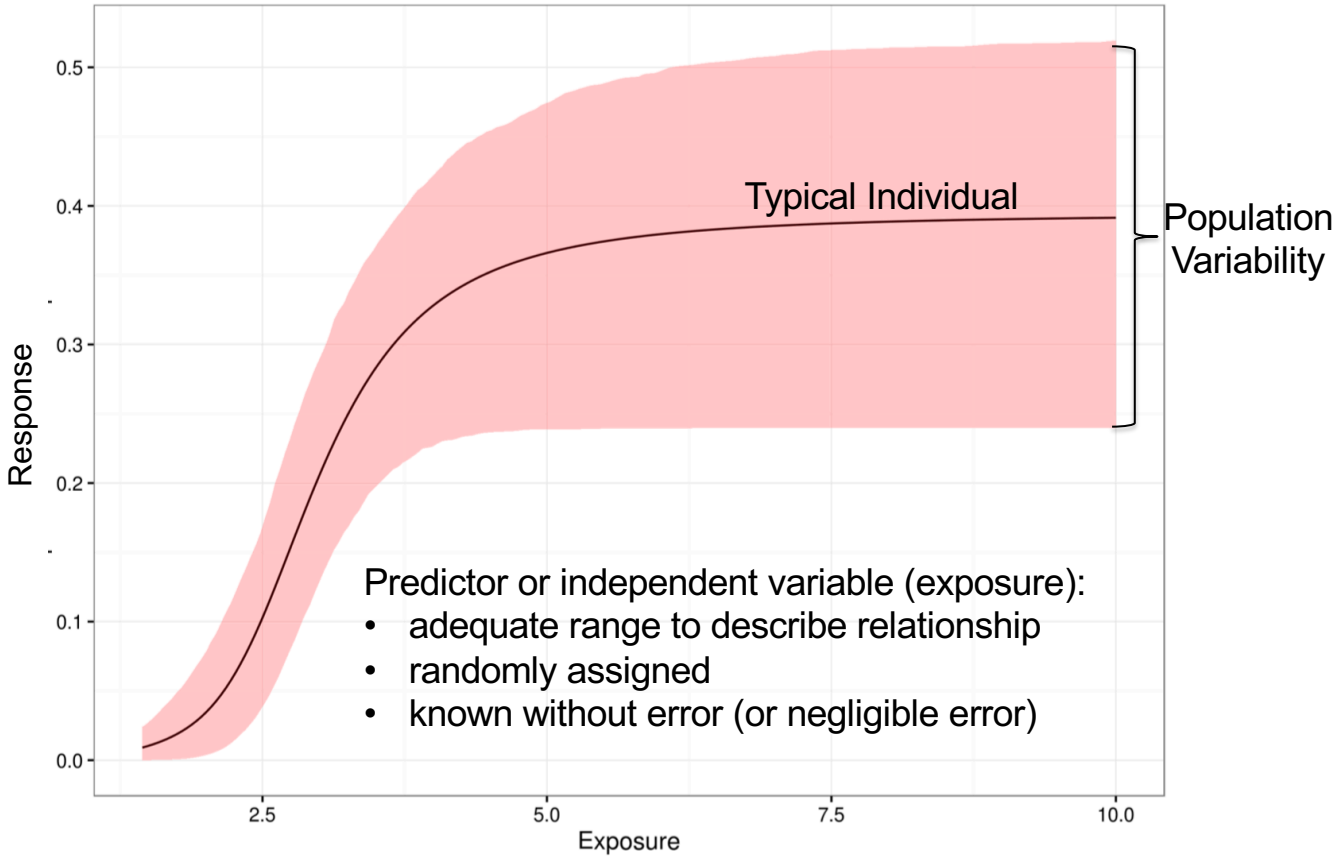
Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

- "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."

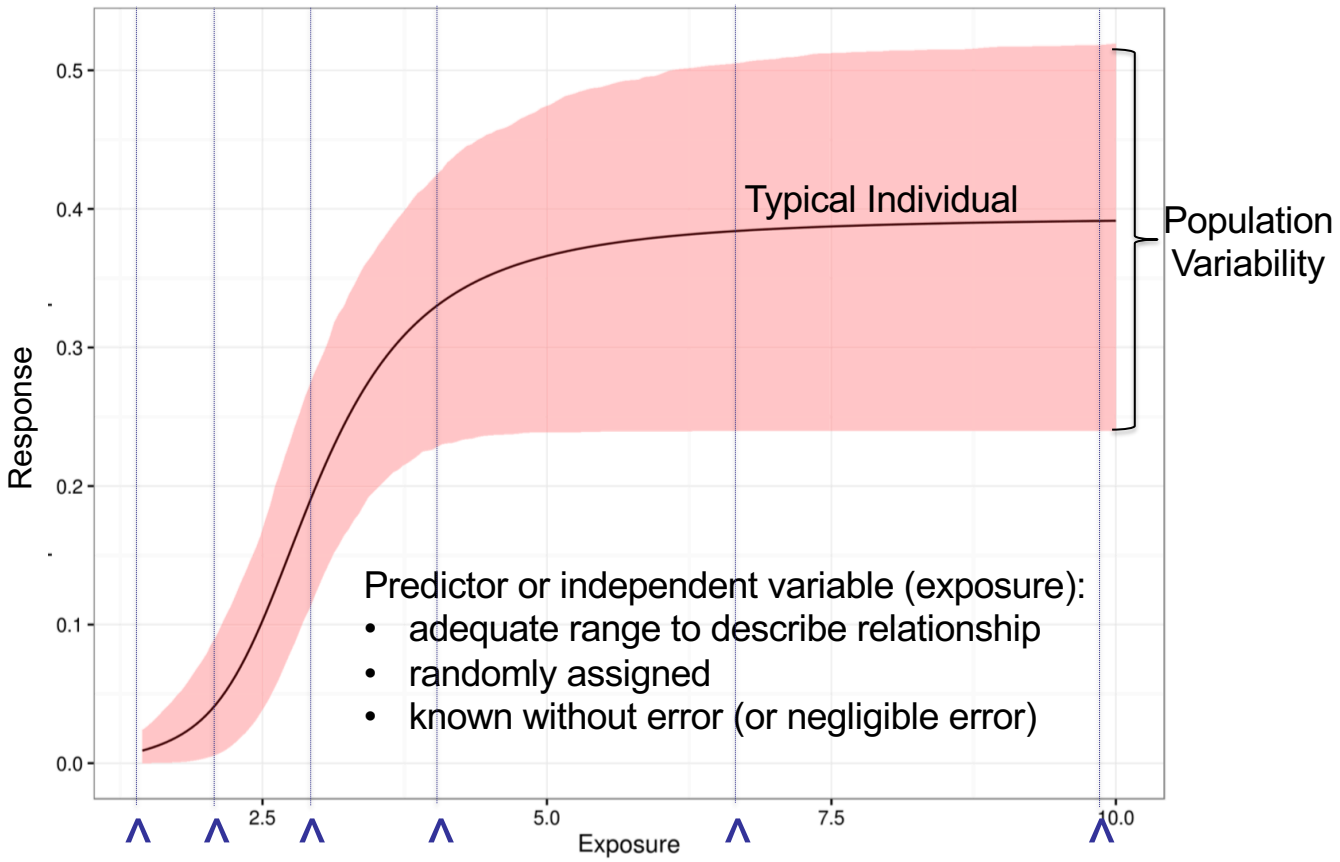
Hypothetical True Exposure-Response Relationship



Ideal E-R Study Design Characteristics

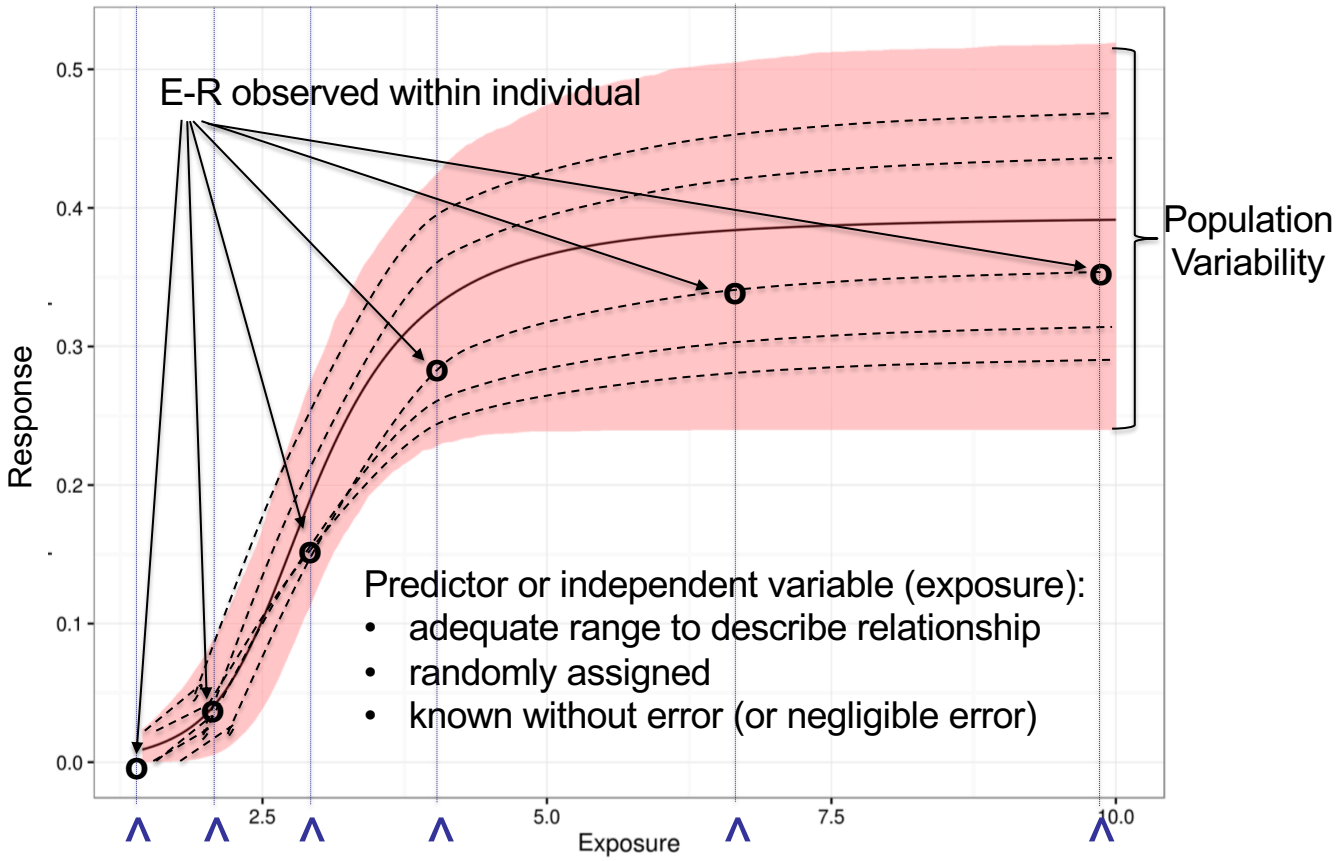


Ideal E-R Study Design Characteristics



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

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



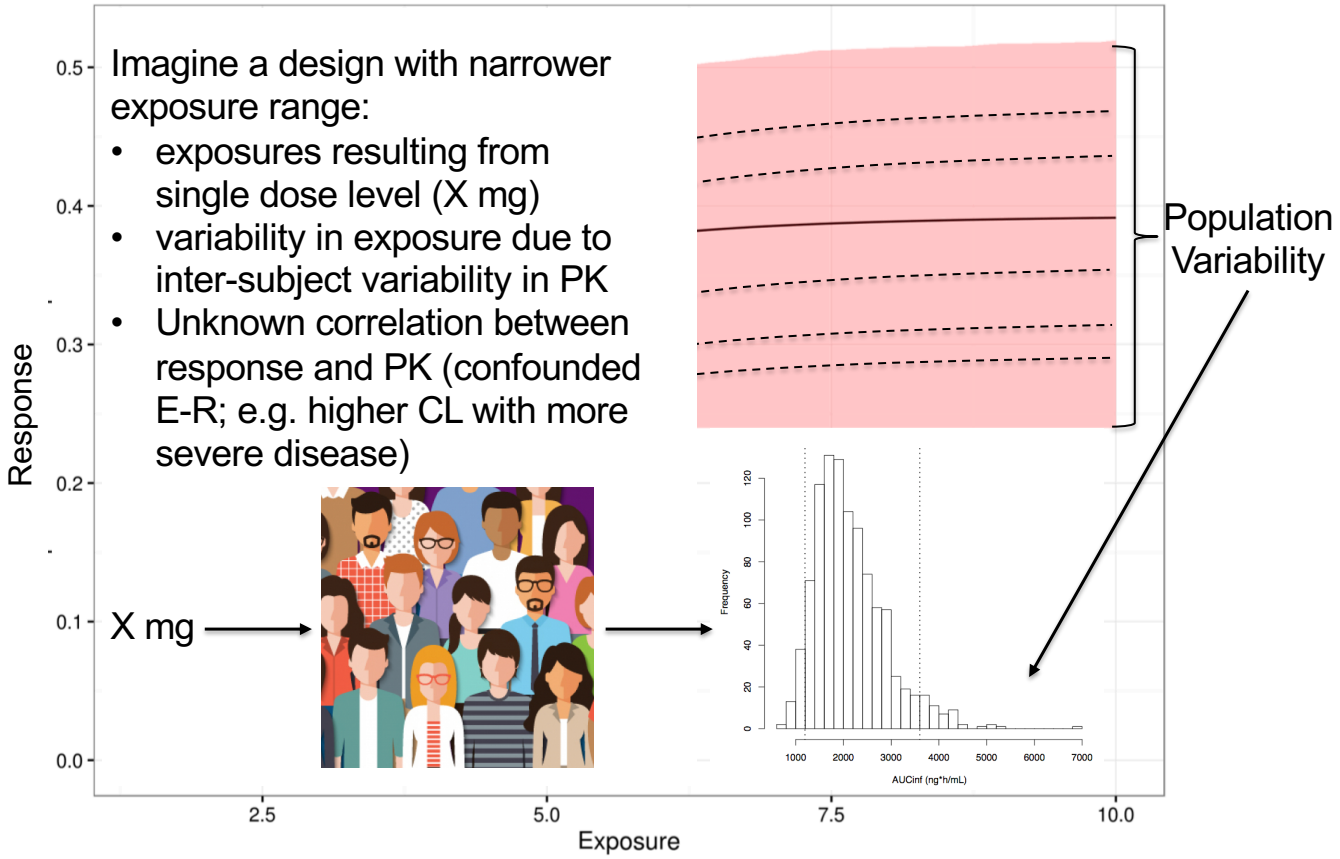
Design-driven range in predictor (e.g. randomized to dose or exposure) is key.

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



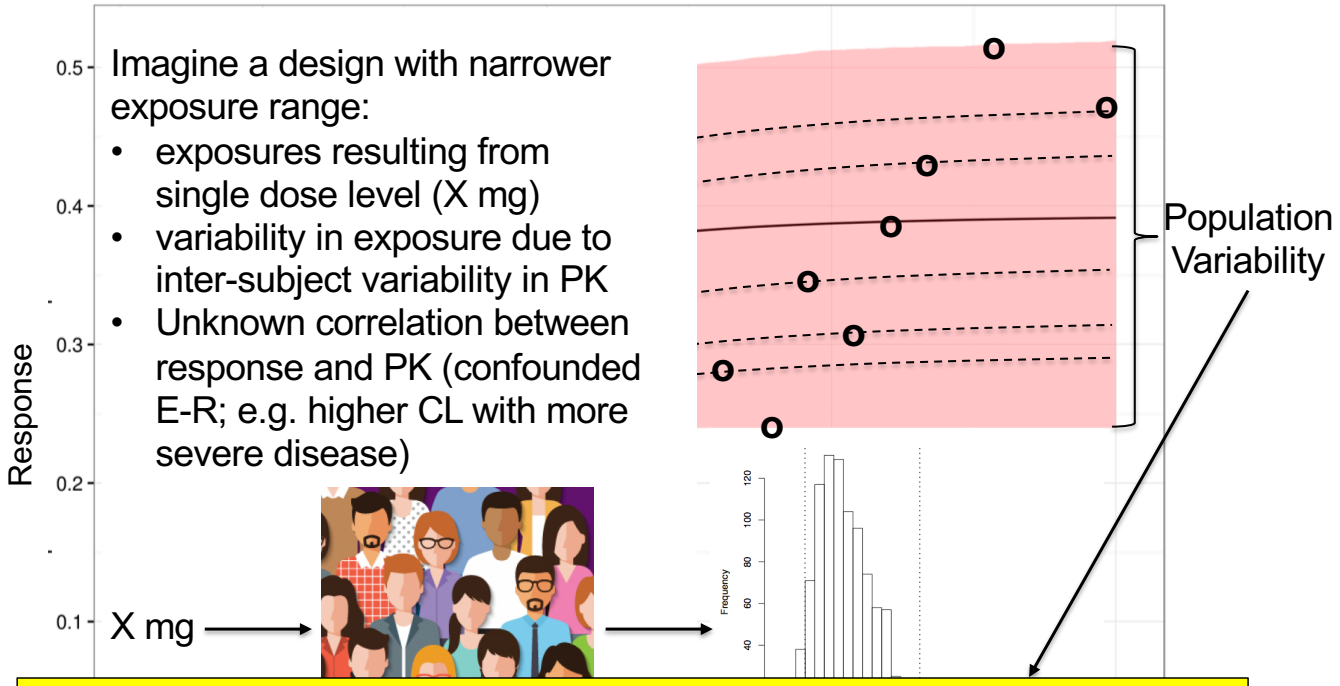
Observed (not Design-Driven) Population E-R

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)

X mg →

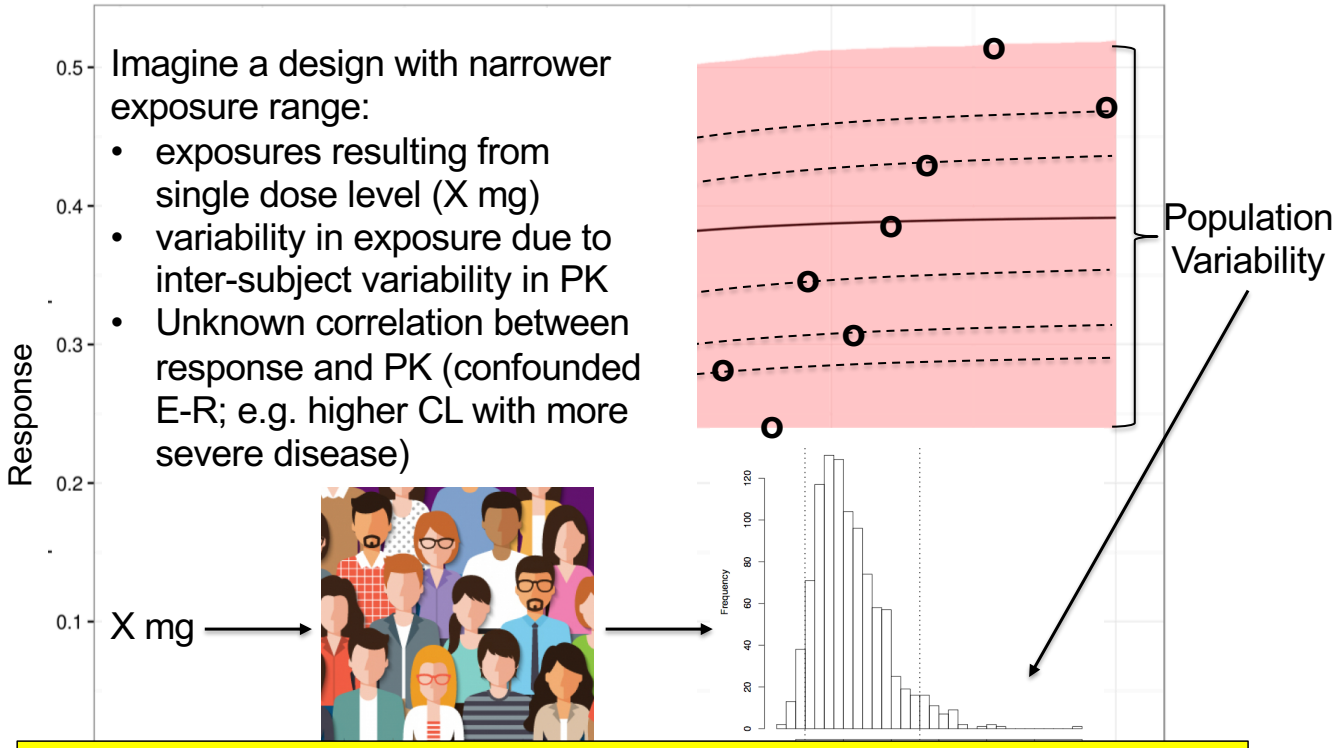
Observed (not Design-Driven) Population E-R



Predictor or independent variable (exposure):

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

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, 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[5]

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

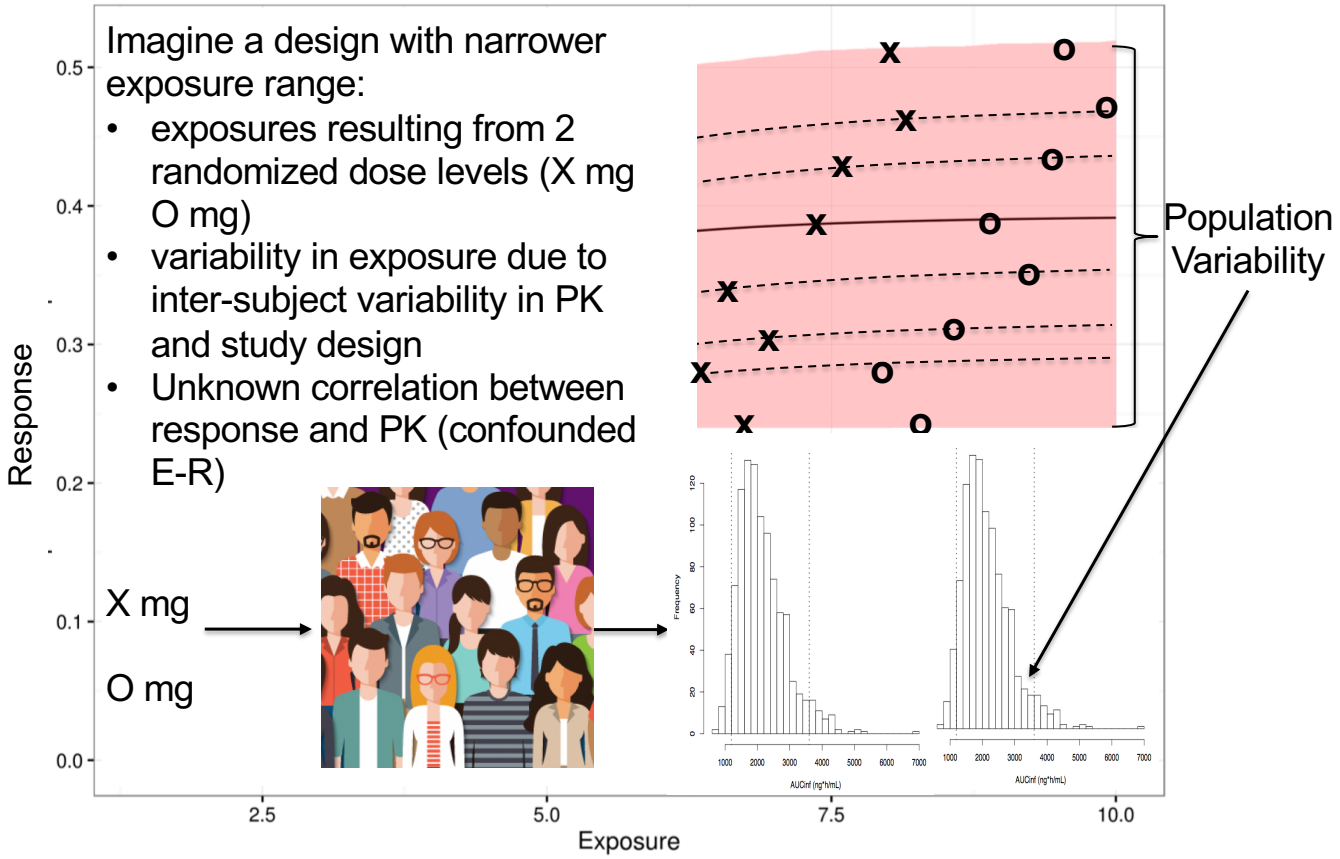
Jerry R. Nedelman[1,*,†], Donald B. Rubin[2] and Lewis B. Sheiner[3,✠]

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
- **Most of these solutions are impractical in pediatric clinical trials – rely on thorough E-R design and analysis in adults**

Possible Diagnostic for Confounded Population E-R



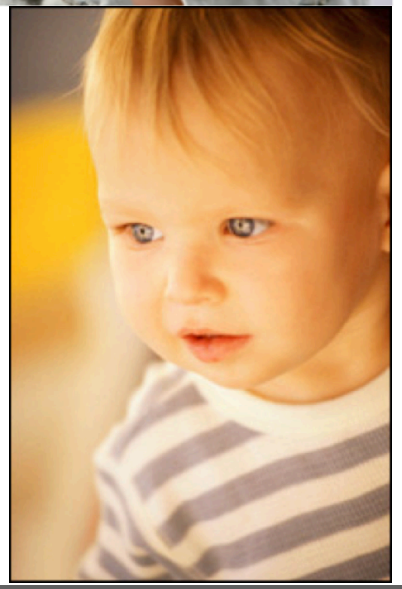
E-R in Pediatric Drug Development with Therapeutic Proteins: Where Do We Go From Here?

- 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.

Acknowledgements



Metrum Research Group Team

Academic, Industry, Government, Non-Profit Scientists

Pediatric Trial Participants and Families

Related References

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