METRUM RESEARCH GROUP

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2016 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop
Moving Pharmacometrics and Statistics Beyond a Marriage of Convenience - Improving Discipline Synergy and Drug Development Decision Making
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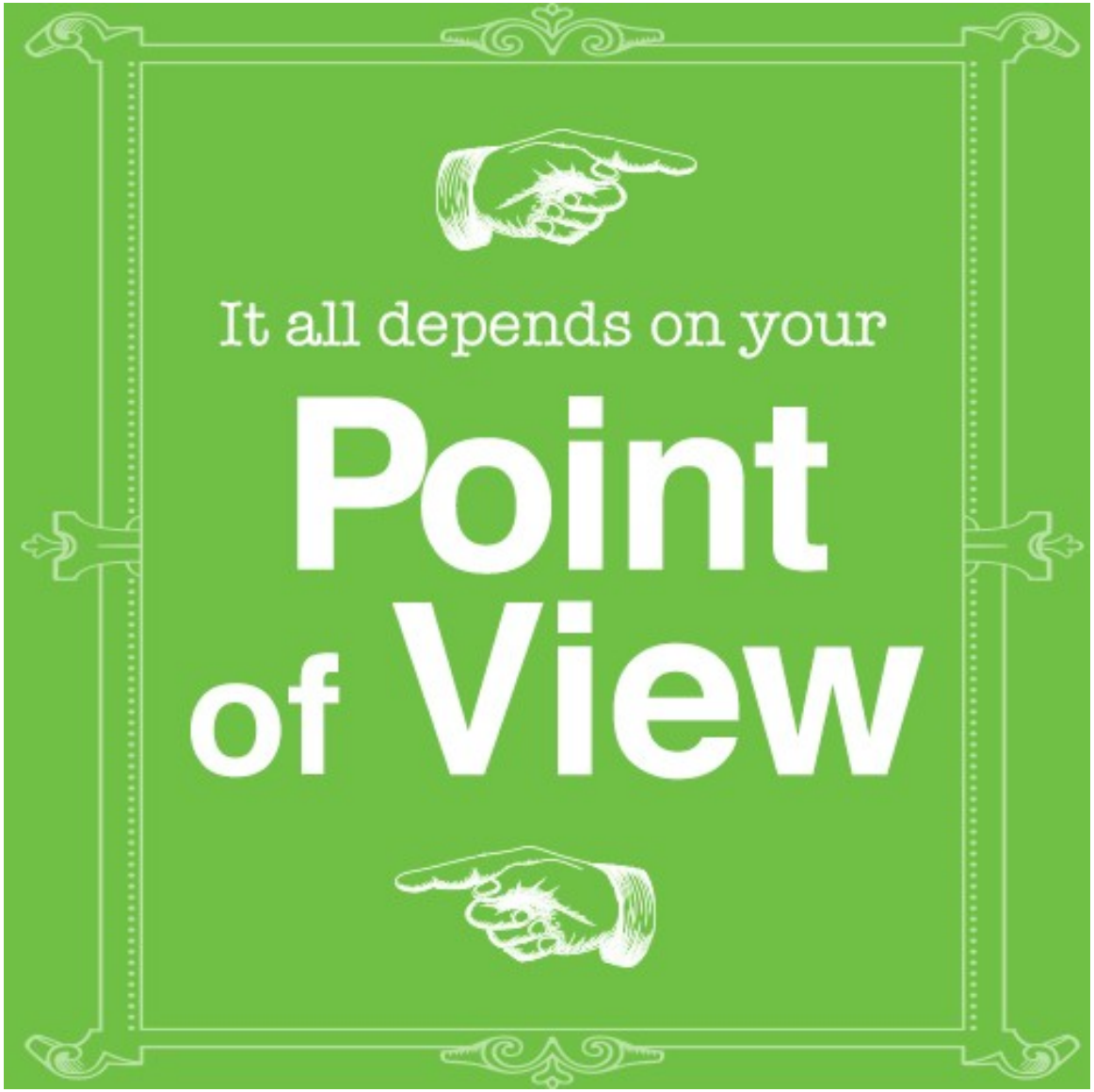
An Industry Perspective on Statistics and Pharmacometrics

Marc R. Gastonguay, Ph.D.

CEO
Metrum Research Group
metrumrg.com

Scientific Director
Metrum Institute
metruminstitute.org

My Perspective



To Consider

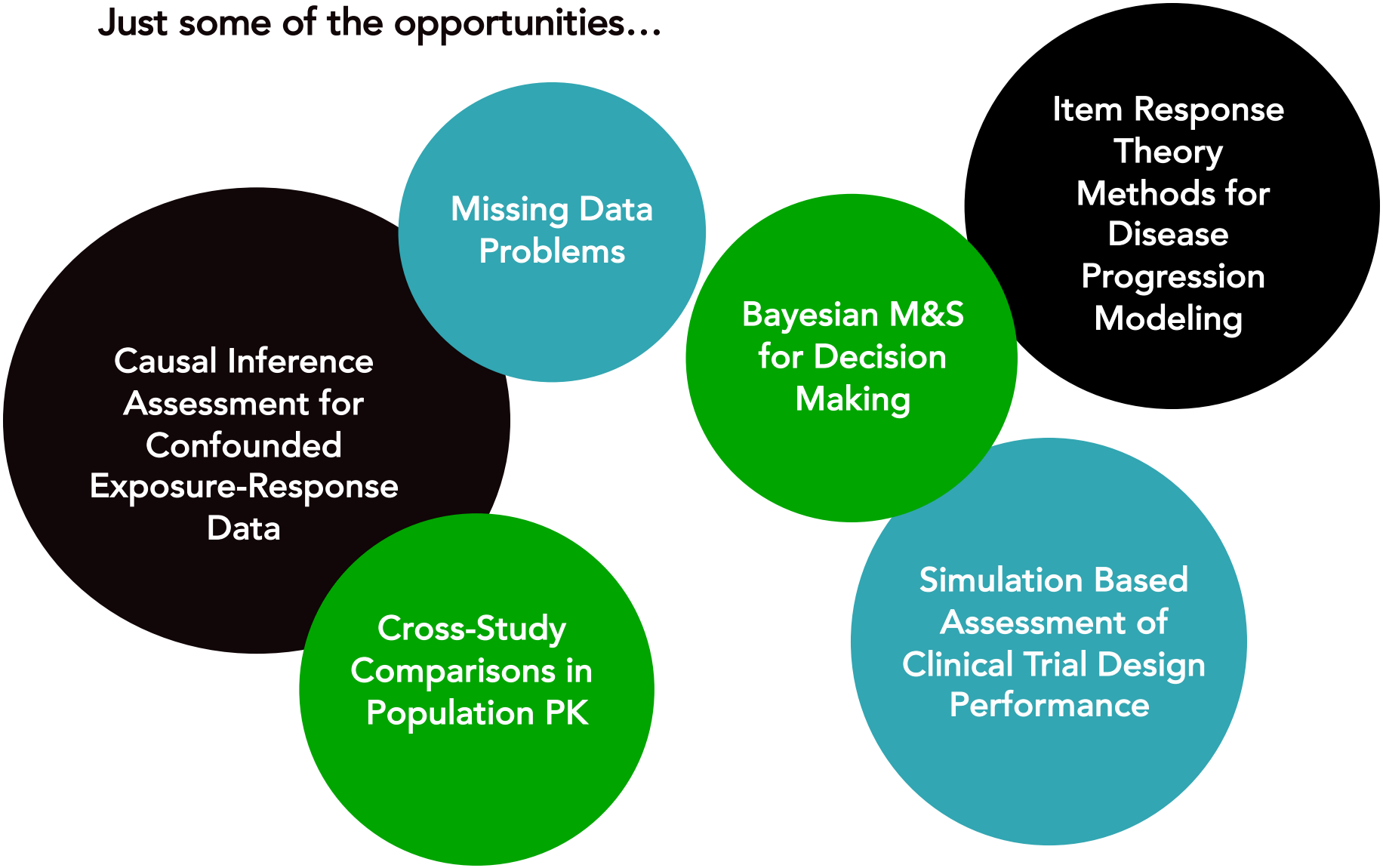
- What are the perceived hurdles to overcome for successful implementation of pharmacometrics - statistics collaborations?

- How does the organizational decision-making process impact collaboration across disciplines?

- What are the key principles or characteristics that drive strong synergy between statistics and pharmacometrics in drug development decision making?

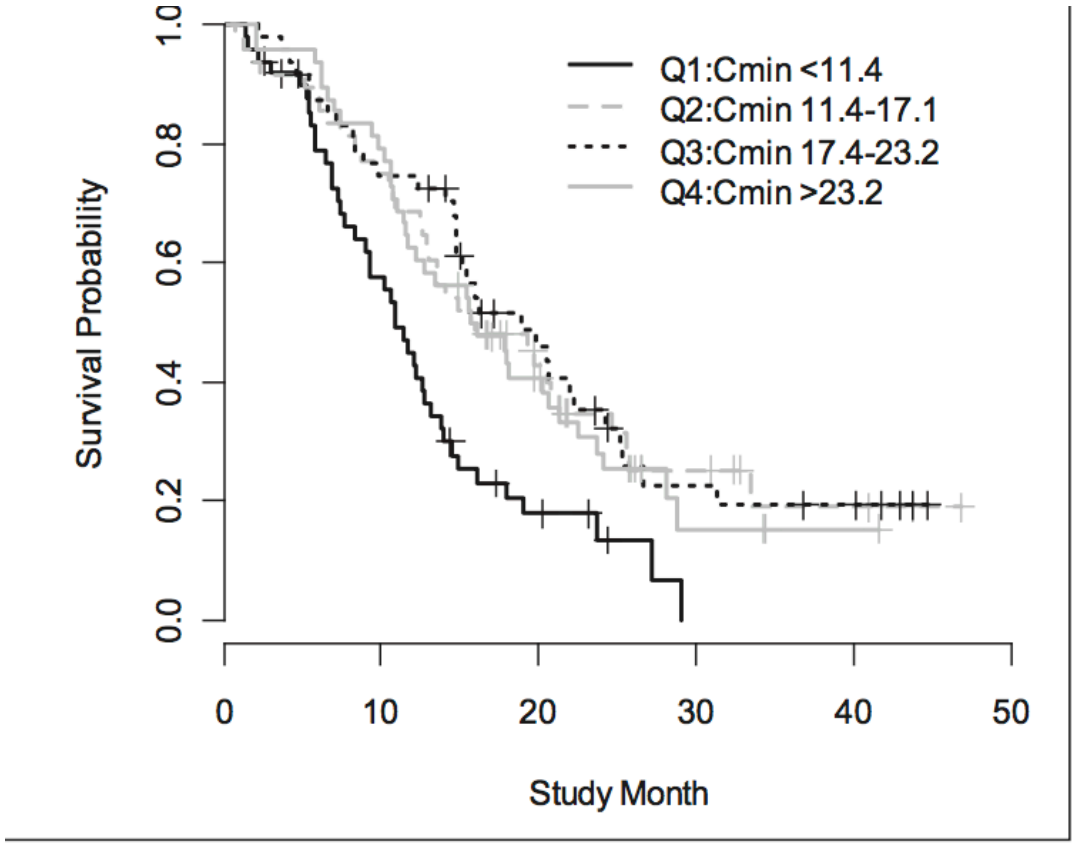
Statistics / Pharmacometrics Collaboration

Just some of the opportunities…



Confounded Exposure-Response

Causal Inference Assessment for Confounded Exposure-Response Data



Yang, Jun and Zhao, Hong and Garnett, Christine and Rahman, Atiqur and Gobburu, Jogarao V and Pierce, William and Schechter, Genevieve and Summers, Jeffery and Keegan, Patricia and Booth, Brian and Wang, Yaning. The combination of exposure-response and case-control analyses in regulatory decision making. J Clin Pharmacol. 2013. 53 (2), 160-6.

Diagnosing the Problem

Causal Inference Assessment for Confounded Exposure-Response Data

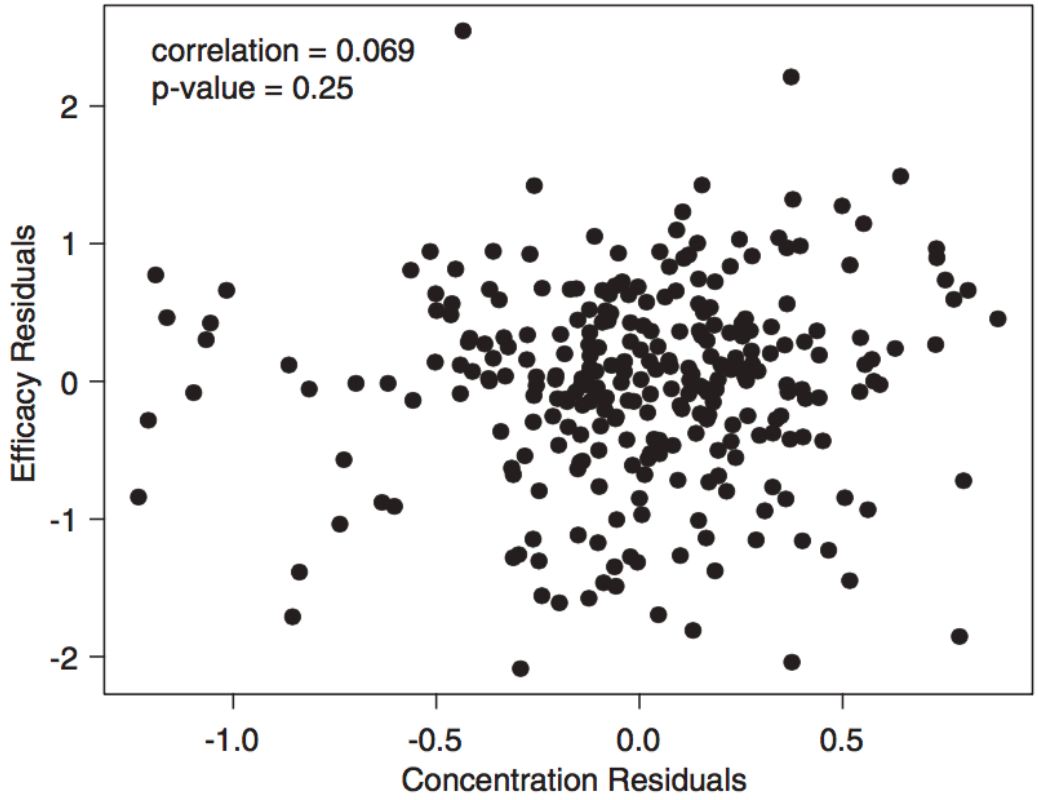


Figure 3. Correlation analysis of residuals, Study A.

Nedelman, Jerry R and Rubin, Donald B and Sheiner, Lewis B. Diagnostics for confounding in PK/PD models for oxcarbazepine. Stat Med. 2007, 26(2), 290-308.

Inconsistent Awareness of the Key Issues

Causal Inference Assessment for Confounded Exposure-Response Data

Comparison of Exposure-Response Analyses

COMPANY A	COMPANY B
Analyst: pharmacometrician	Analyst: statistician
Traditional model-based E-R	First identified imbalance across Q
Suggested dose adjustment in low Q	Recognized potential bias in E-R

Missing Data: Inconsistent Data Analysis Approaches

- **Assessment of expected efficacy at new dose**
- **25% dropout in Phase 2a trial**

Statistics	Pharmacometrics
D-R model based on landmark data	Repeated measures PK-PD model
Completers only	NLME model and simulation
New dose efficacy is favorable	New dose efficacy insufficient

Interesting Team Dynamics

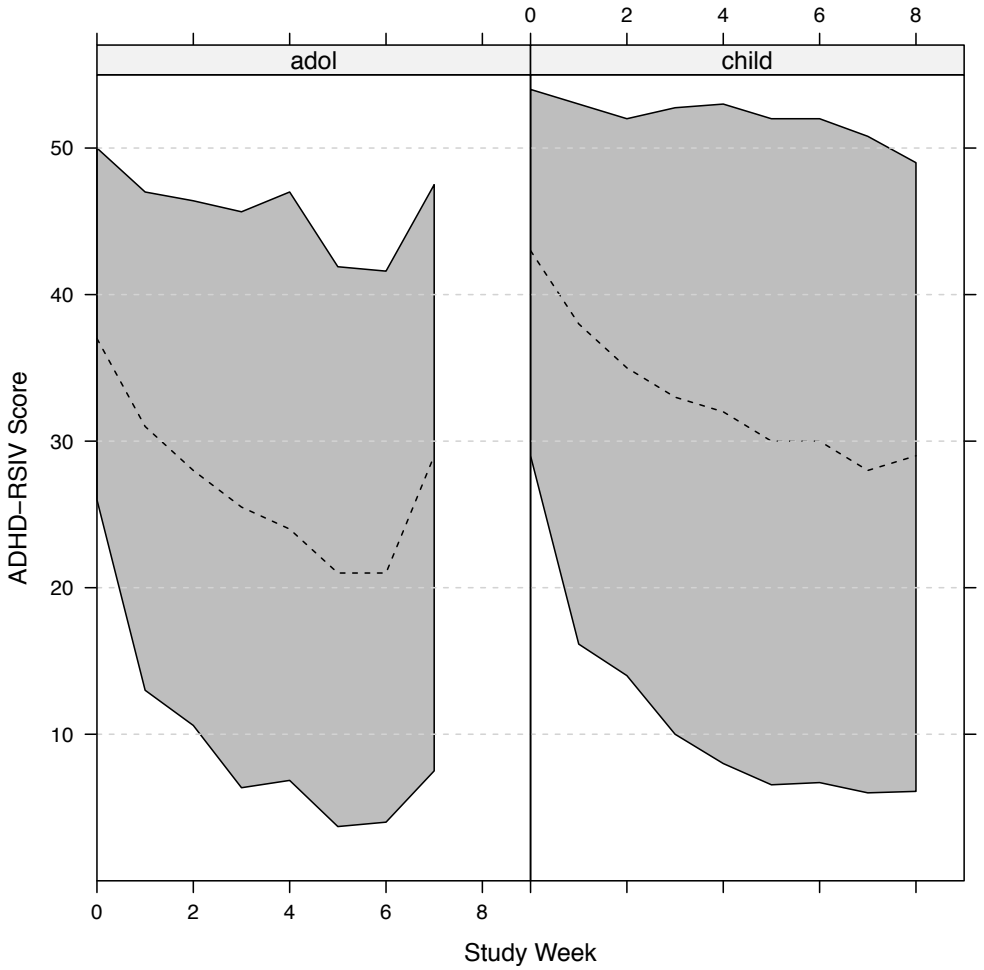
Missing Data Problems

How were analyses perceived by dev. team?

Statistics	Pharmacometrics
Looks great!	Must be something wrong
Immediate acceptance	Scrutiny & criticism of model
Let's move ahead	Your analysis is not needed

Successful Collaboration on ADHD Trial Simulation

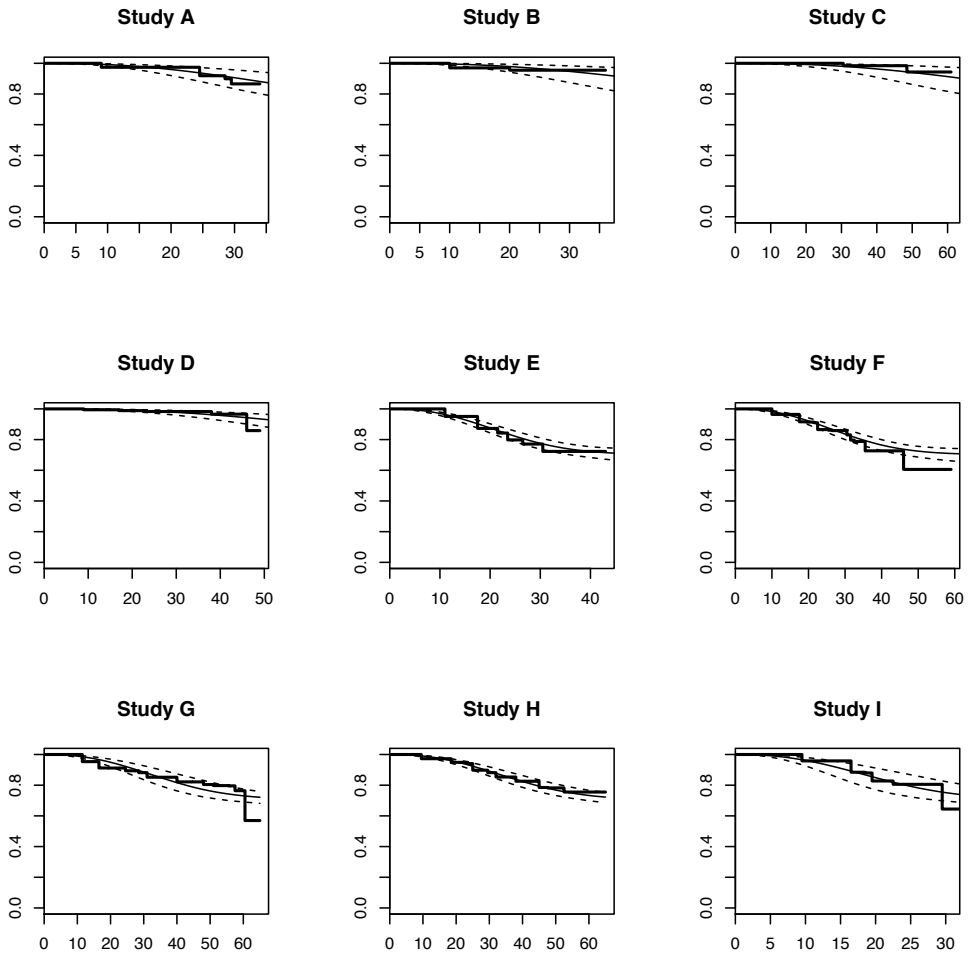
Simulation Based Assessment of Clinical Trial Design Performance



Knebel, William and Rogers, Jim, Polhamus, Dan, Ermer, James and Gastonguay, Marc R. Modeling and simulation of the exposure-response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD. J Pharmacokinet Pharmacodyn. 2015 42 (1) 45-65.

ADHD Trial Dropout Model Checking

Simulation Based Assessment of Clinical Trial Design Performance



ADHD Trial Dropout Model

- **Trial simulations guided actual design**
- **Success: Efficacy trial and reg. approval**

Simulation Results:

Method	Probability of Success	Treatment Effect[a]	SD of Change from Baseline	Effect Size[c]
MMRM	98%	-7.9 [-12, -3.4][b]	10.4 [0.14, 11.8]	-0.76 [-1.2, -0.31]
ANCOVA	97%	-7.6 [-11, -3.2][b]	11.8 [10.0, 13.5]	-0.64 [-1.0, -0.26]

a = difference between placebo and active at Visit 13
b = median [95% CI]
c = calculated as Treatment Effect/SD of Change from Baseline

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How Not to Collaborate