

Quantitative Assessment of Assumptions to Support Extrapolation of Efficacy in Pediatrics: FDA-U Maryland CERSI Cosponsored Workshop.
FDA White Oak Campus. June 1, 2016

The Role of Simulation in Assessing Extrapolation Assumptions

Marc R. Gastonguay, Ph.D.

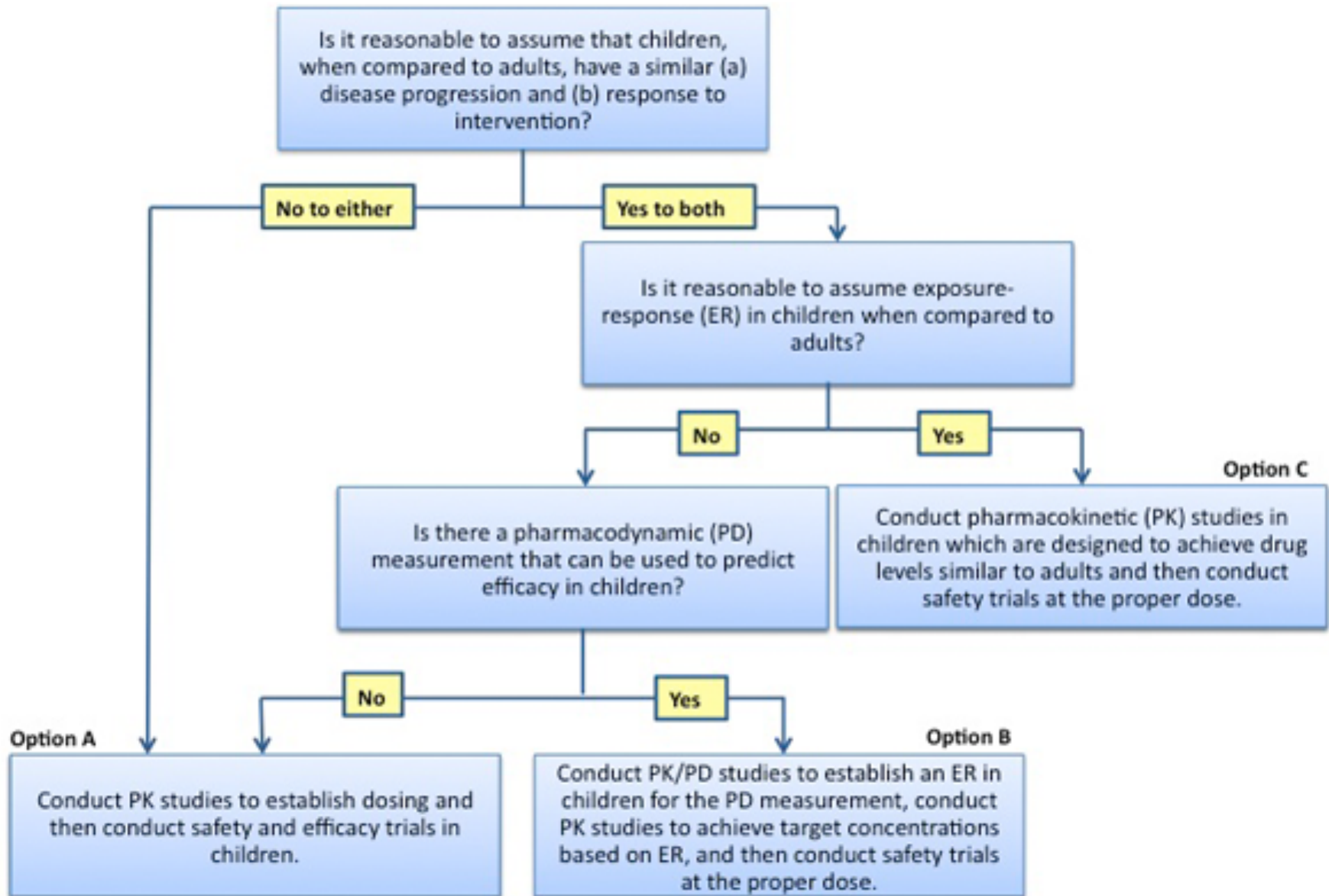
CEO, Metrum Research Group
Scientific Director, Metrum Institute



Relevant Points for Discussion

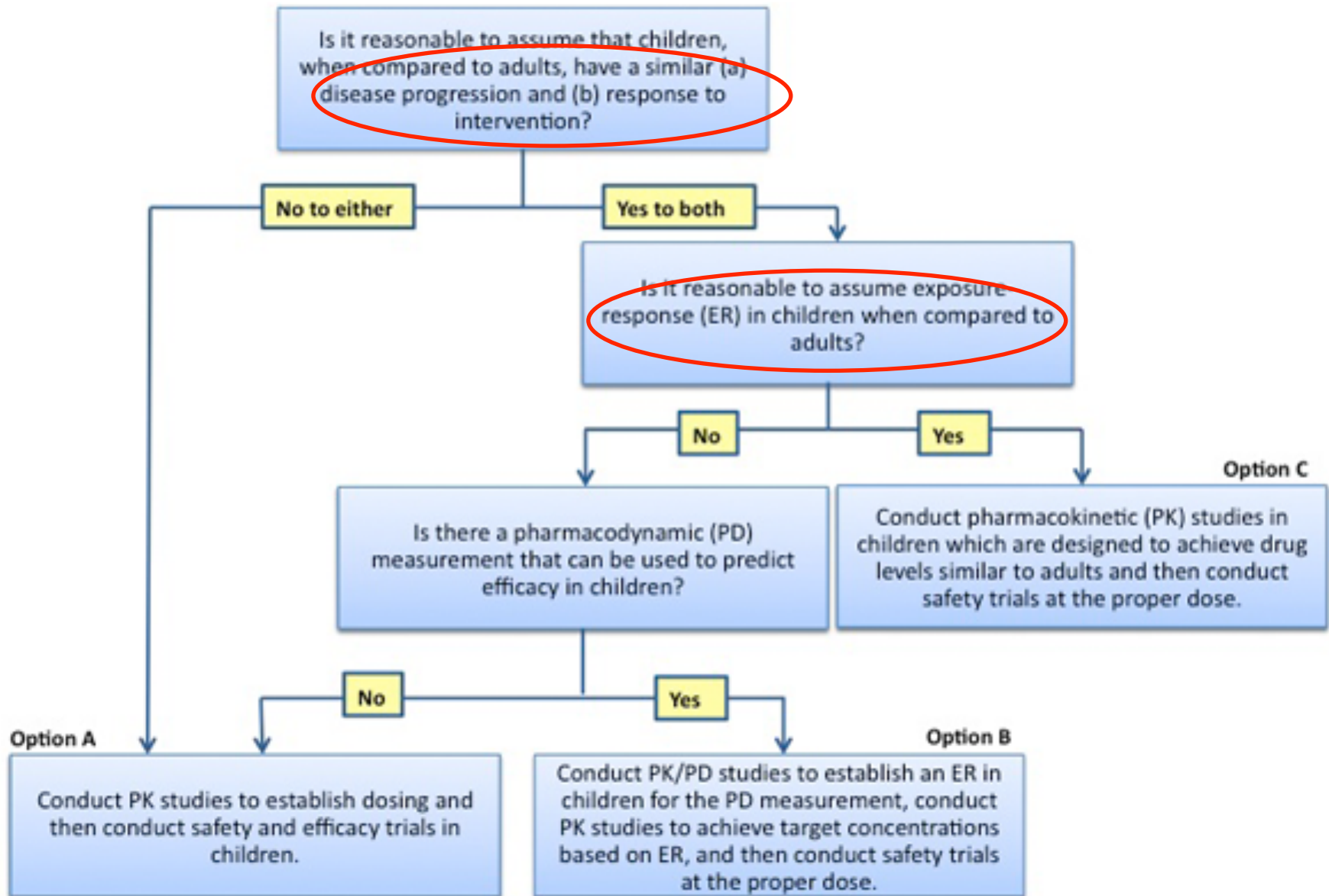
- What is the added value of quantitative approaches in reinforcing the total body of evidence to support extrapolation?
- How can we best design adult drug development programs to obtain the necessary information that will help us evaluate assumptions for extrapolation and also inform the path of extrapolation?

Figure 1: FDA Pediatric Study Decision Tree



<http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106614.htm>

Figure 1: FDA Pediatric Study Decision Tree

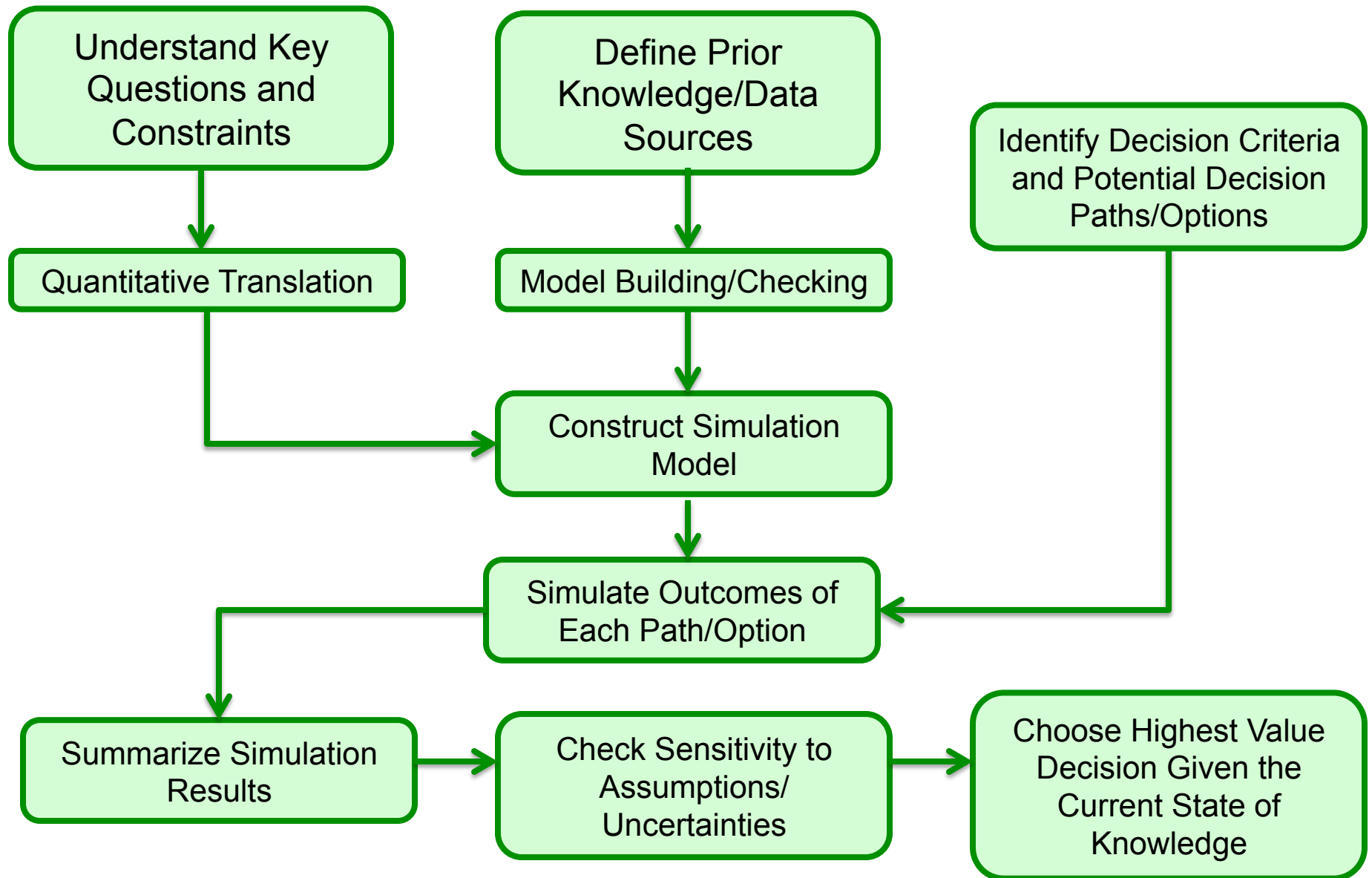


<http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106614.htm>

The Challenge to Sanity

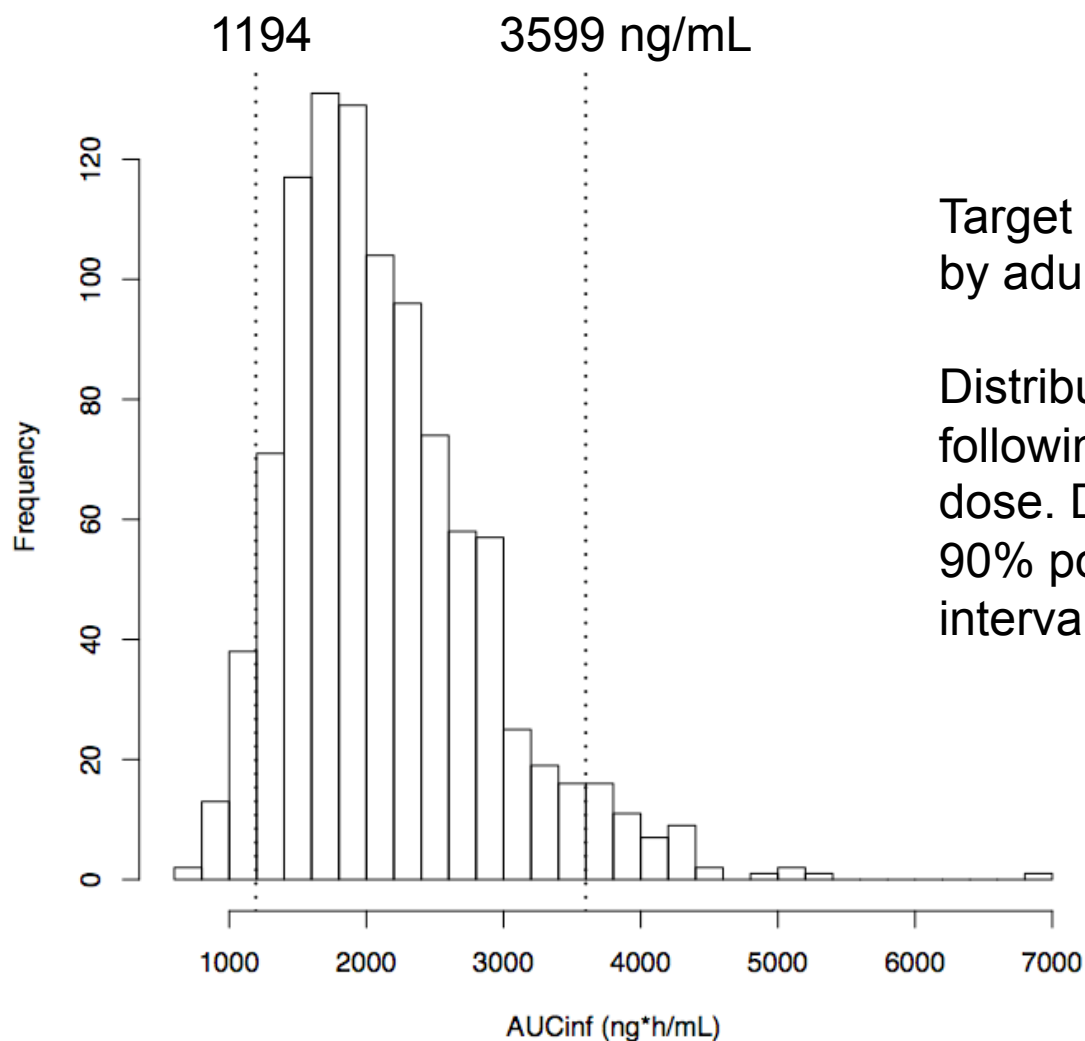
- How can I judge if the adult or pediatric disease are similar if I don't understand the adult disease progression?
 - How should this (disease progression) be defined and/or quantified?
- What are reasonable criteria for assessing “similarity” of disease?
 - Do criteria change with the disease? How? Why?
- The same questions apply to similarity of drug response
- How can simulation be used to assess these assumptions, quantitatively?

Simulation Based Decision-Making Process Flow



Define Metric(s) for Comparison and Decision Criteria

An Example Under Full Extrapolation Assumptions



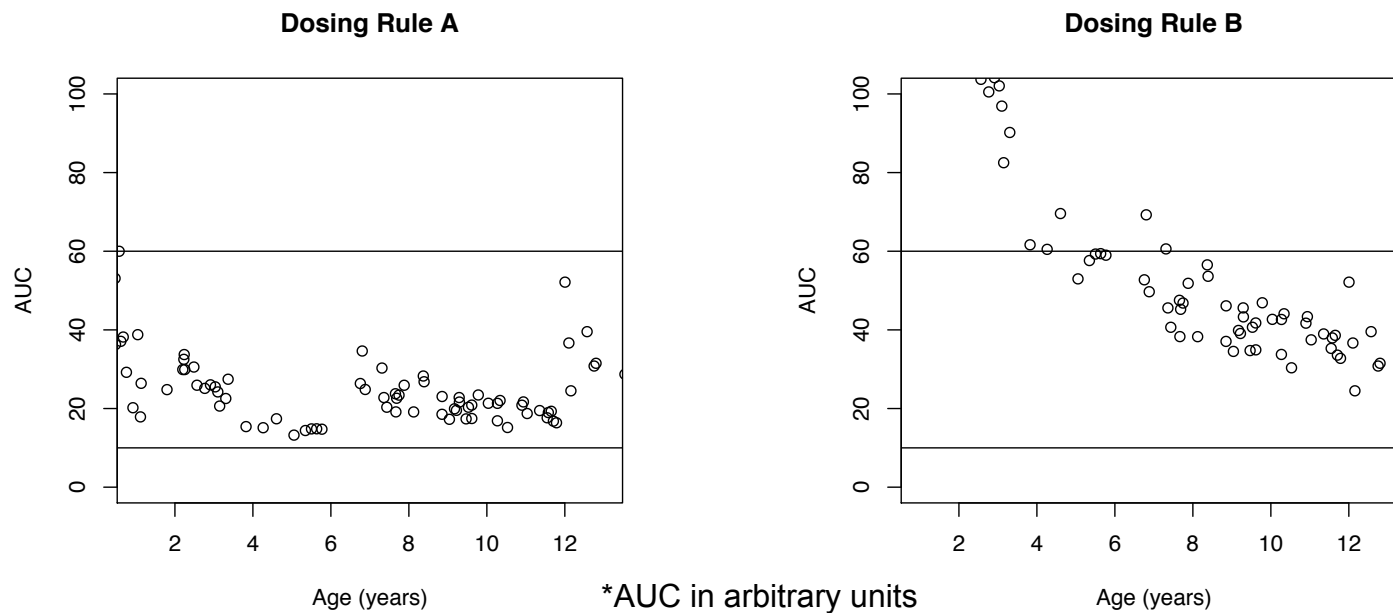
Target exposure range defined by adult data

Distribution of Adult AUC_{inf} following a single 60 mg PSE dose. Dotted lines represent the 90% population prediction interval.

Gastonguay et al. Evaluation of the Performance of Pediatric OTC Monograph Dosing Guidance for Pseudoephedrine via Population Pharmacokinetic Modeling and Simulation. CP&T. Suppl. 2011

Simulation to Assess Performance Across Age/Weight Range

- Visual inspection
- Quantify % individuals within target range
- Across age/weight ranges



More Quantitative Decision Criteria

Decision: Select dosing rule that achieves decision criteria, given practical constraints.

Percent of Pediatric Subjects with AUC_{inf} Below and Above Target Exposure Bounds Following Monograph Dosing by Age. 95% CI based on 1000 simulated trials with 1821 subjects/trial (amplified from CDC age-weight database).

Age Group (yr)	Below Target			Above Target			Dose (mg)
	Median	95% CI		Median	95% CI		
		2.5 th	97.5 th		2.5 th	97.5 th	
2	18.20	12.300	25.10	0.000	0	0.535	15
3	31.20	22.900	40.00	0.000	0	0.000	15
4	46.60	37.400	54.60	0.000	0	0.000	15
5	59.80	51.700	69.00	0.000	0	0.000	15
6	2.21	0.552	4.97	1.660	0	3.870	30
7	4.44	1.670	8.33	0.556	0	2.220	30
8	9.39	4.970	14.90	0.000	0	1.100	30
9	16.80	10.800	22.70	0.000	0	0.541	30
10	26.90	20.300	34.60	0.000	0	0.549	30
11	37.70	30.600	44.80	0.000	0	0.000	30

Gastonguay et al. Evaluation of the Performance of Pediatric OTC Monograph Dosing Guidance for Pseudoephedrine via Population Pharmacokinetic Modeling and Simulation. CP&T. Suppl. 2011

What Are the Metrics and Criteria for Assumption Checking?

- How do we arrive at a decision of similarity or non-similarity of disease progression, intervention response, exposure-response?

“Whoever best describes the problem is the one most likely to solve it”

– Dan Roam

Quantitative Specification of Decision Criteria

AT LEAST 90%
OF PATIENTS

effect size of + 3 points

average response
rate of 85%

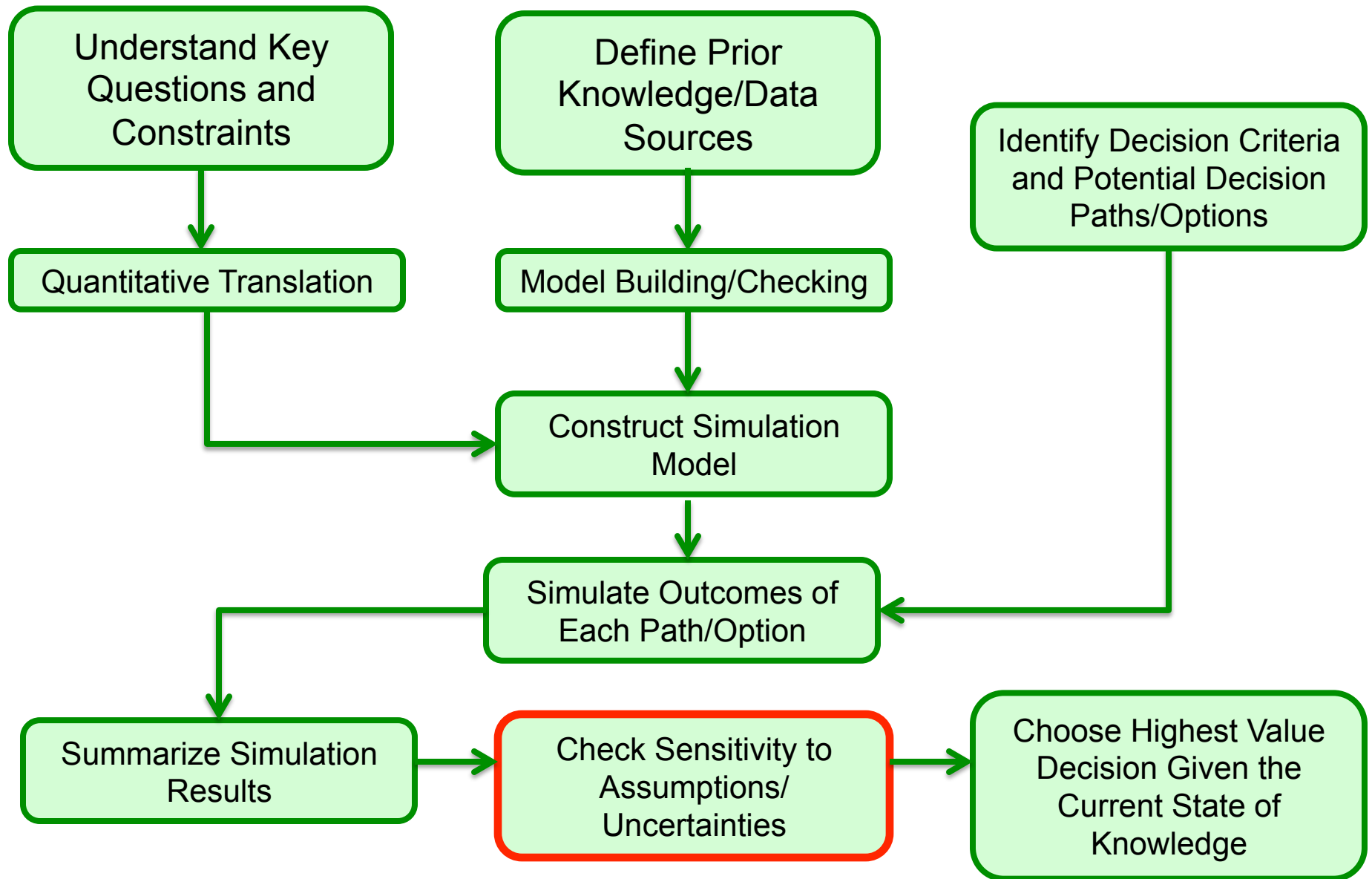
no more
than 10
msec

less Than 12%
Incidence Rate

15% BETTER THAN
COMPETITOR

LESS THAN OR EQUAL TO 5 MMHG

Simulation Based Decision-Making Process Flow



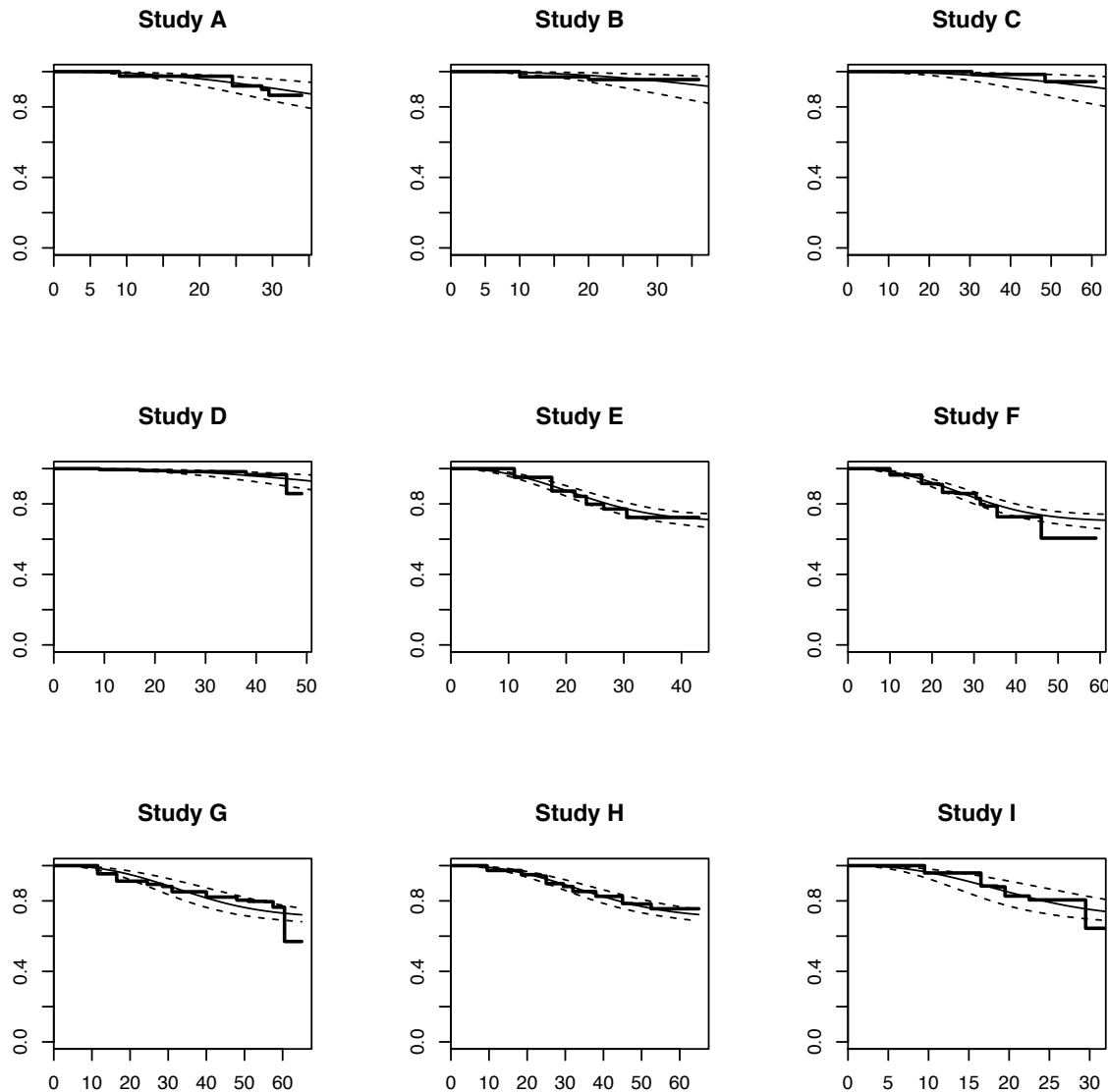
Simulation-Based Assumption Checking

- Scenario 1: Sufficient data are available to quantitatively check assumptions using simulation
- Scenario 2: Assumptions rely on extrapolation to new conditions where data are insufficient for quantitative checking

Simulation-Based Assumption Checking

- Scenario 1: Sufficient data are available to quantitatively check assumptions using simulation
- Scenario 2: Assumptions rely on extrapolation to new conditions where data are insufficient for quantitative checking

Model and Assumption Checking: Dropout



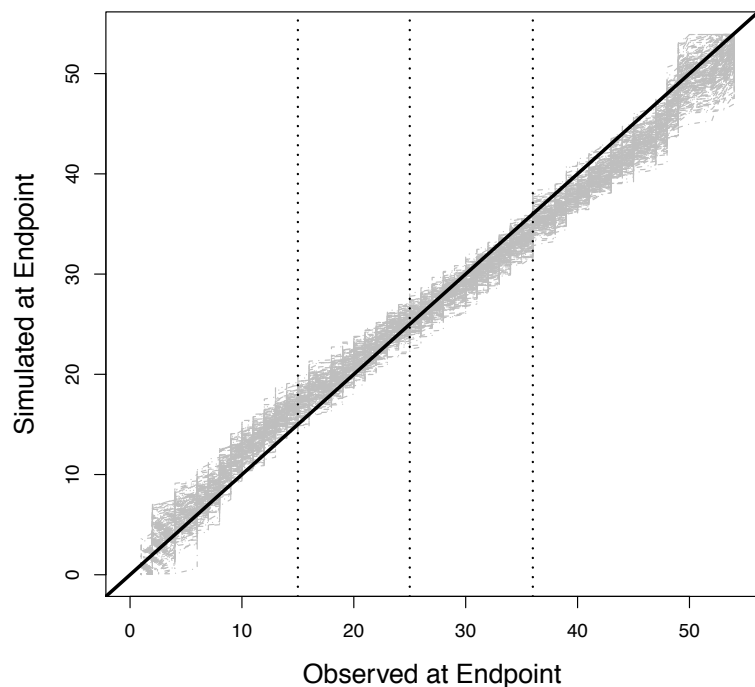
Distribution of simulated dropout times within each individual are compared to the actual observed dropout times from the model building dataset. Simulations were performed using the final time to event dropout model. Kaplan-Meier survival curves (thick black line) for each study demonstrate the observed distribution of dropout times.

Modeling and simulation of the exposure-response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD. Knebel W, Rogers J, Polhamus D, Ermer J, Gastonguay MR. *J Pharmacokinet Pharmacodyn.* 2015 Feb;42(1):45-65.

Model and Assumption Checking – Endpoint

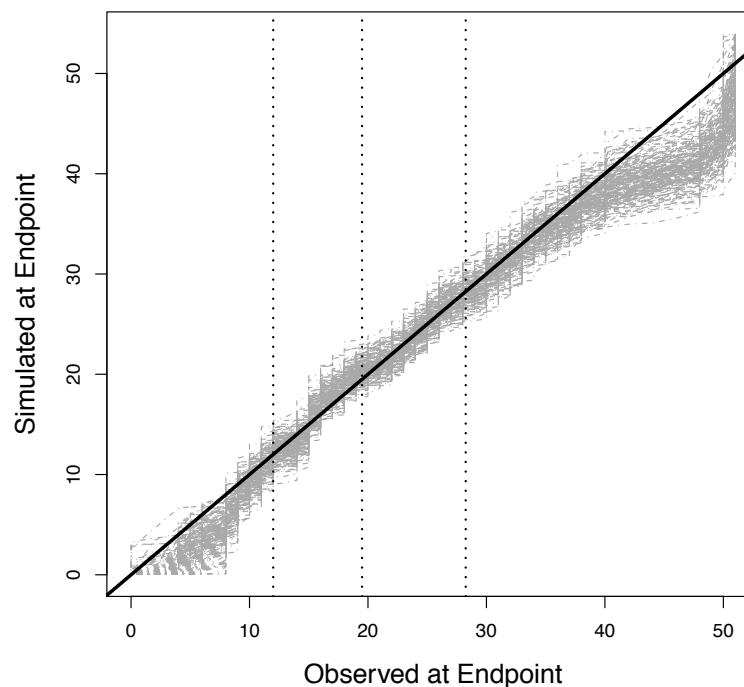
Placebo

adolescents



Exposure-response

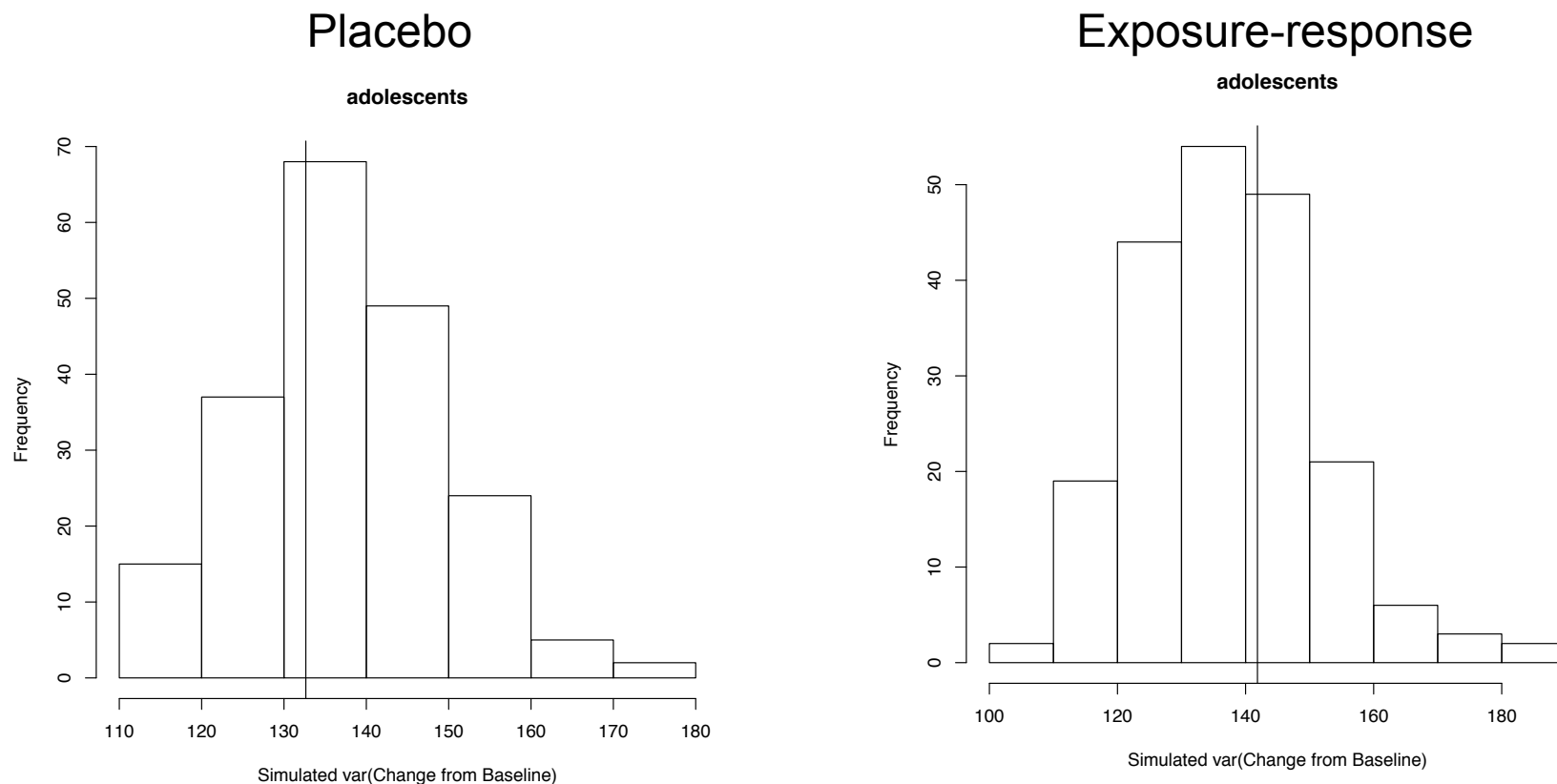
adolescents



Distributions of simulated ADHD RS-IV score at endpoint within each individual are compared to the actual observed distribution of baseline values for adolescents from the model building datasets. Simulations were performed using the final placebo model and exposure-response models with correction for dropouts.

Modeling and simulation of the exposure-response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD. Knebel W, Rogers J, Polhamus D, Ermer J, Gastonguay MR. J Pharmacokinet Pharmacodyn. 2015 Feb;42(1):45-65.

Model Checking – Variance in Change from Baseline



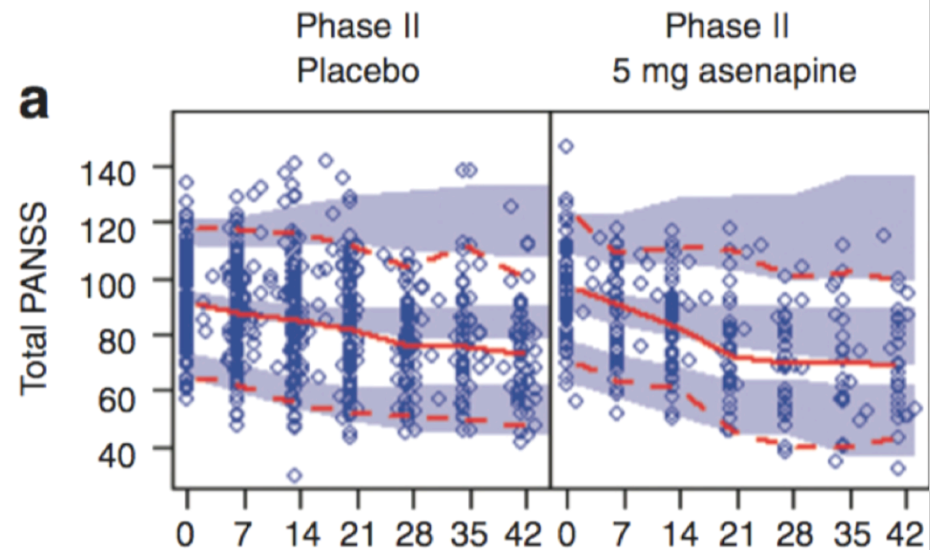
Distributions of variance in change from baseline to endpoint in ADHD RS-IV score in simulated individuals are compared to the actual observed variance in change from baseline to endpoint for adolescents from the model building datasets. Simulations were performed using the final placebo model and exposure-response models with correction for dropouts.

Modeling and simulation of the exposure-response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD. Knebel W, Rogers J, Polhamus D, Ermer J, Gastonguay MR. J Pharmacokinet Pharmacodyn. 2015 Feb;42(1):45-65.

Simulation-Based Checking of Similar Disease Progression

Assessing similarity of disease progression...

Is simulation in panel **a** quantitatively different from observed data?



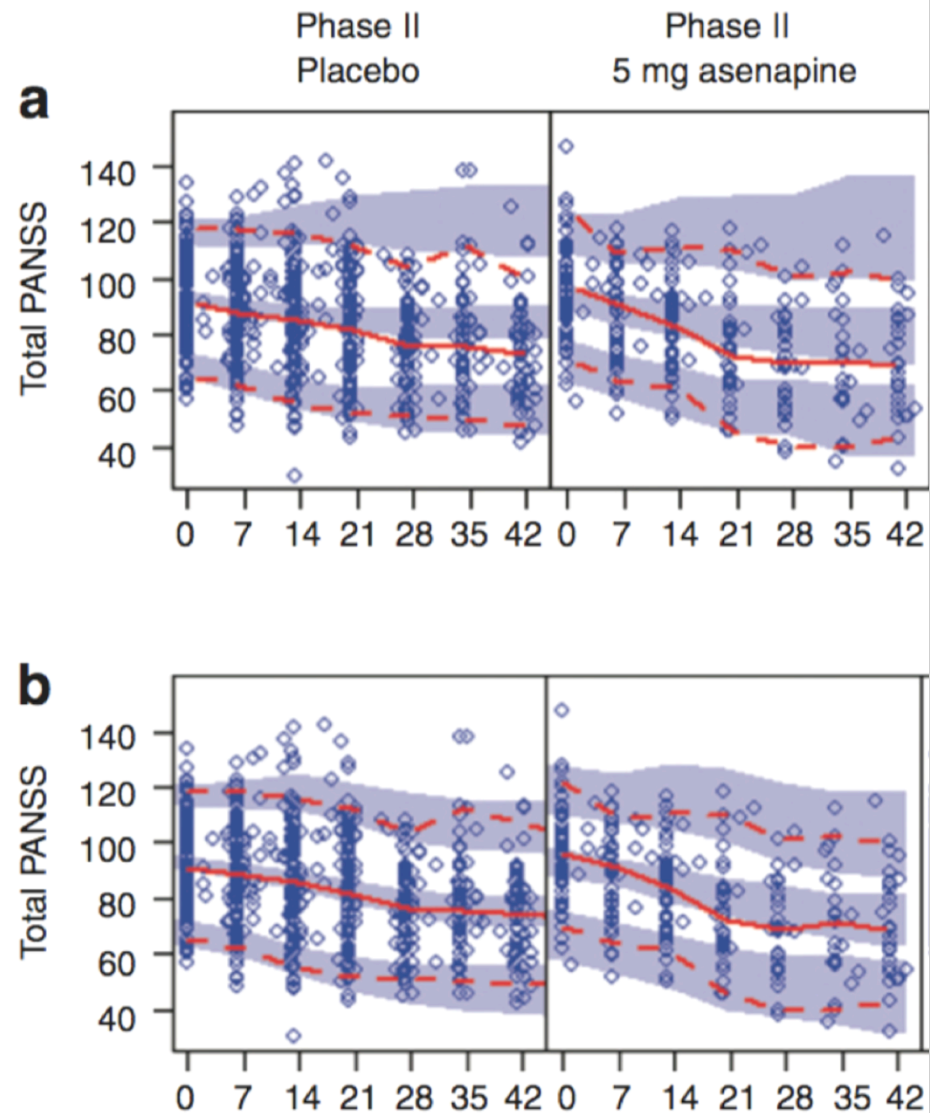
Friberg LE, de Greef R, Kerbusch T, Karlsson MO. Modeling and simulation of the time course of asenapine exposure response and dropout patterns in acute schizophrenia. *Clin Pharmacol Ther.* 2009 Jul;86(1):84-91.

Simulation-Based Checking of Similar Disease Progression

Assessing similarity of disease progression...

Is simulation in panel **a** quantitatively different from observed data?

Would results in panel **b** provide evidence of similarity? Why or Why not?



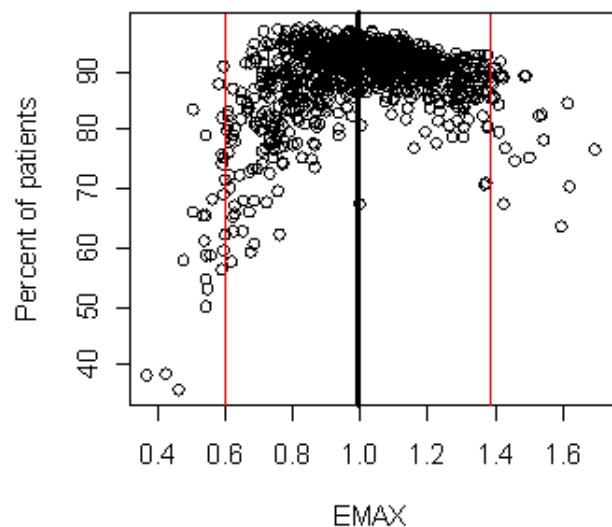
Friberg LE, de Greef R, Kerbusch T, Karlsson MO. Modeling and simulation of the time course of asenapine exposure response and dropout patterns in acute schizophrenia. *Clin Pharmacol Ther.* 2009 Jul;86(1):84-91.

Simulation-Based Assumption Checking

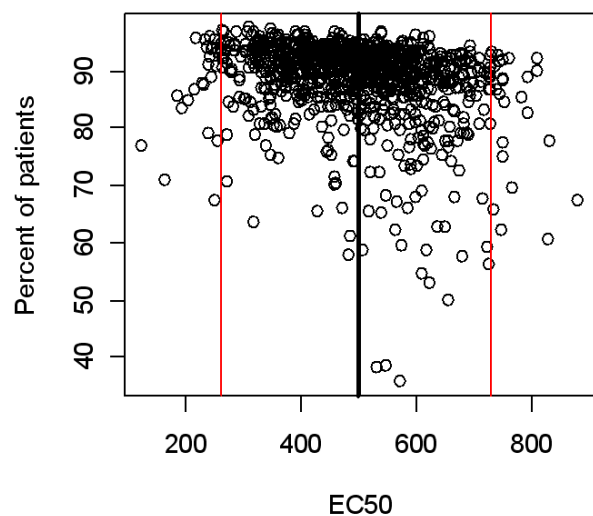
- Scenario 1: Sufficient data are available to quantitatively check assumptions using simulation
- Scenario 2: Assumptions rely on extrapolation to new conditions where data are insufficient for quantitative checking

Similarity of Exposure Response – No Reference Data

Effect within 0.25 - 1.25



Effect within 0.25 - 1.25

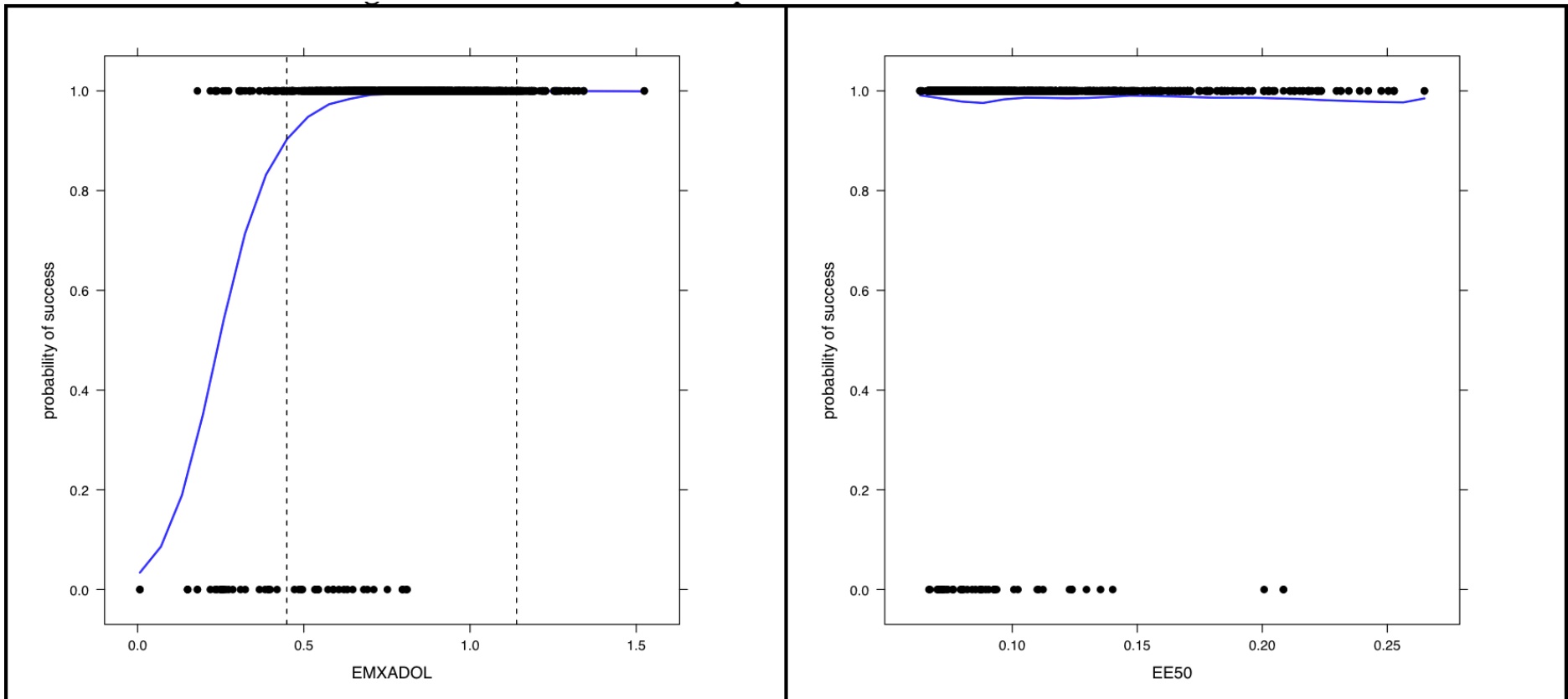


- No test data set available. What can be done?
- Assess sensitivity of decision/conclusion to uncertainties about extrapolation assumptions.

Hypothetical Q: Will 80% of patients land within target trough effect range at this dose?

- Conclusions depend on the value of EMAX.
- Uncertainty in extrapolation assumptions about EC50 is less important than assumptions about in EMAX

What Is the Probability of a Successful Pediatric Efficacy Trial?



- Are conclusions independent of uncertainties in extrapolation assumptions?

Other Suggestions for Checking Extrapolation Assumptions

- Qualitative understanding of biology/pharmacology
 - Similarity of disease (subtypes based on aetiology, pathophysiology, clinical manifestation, progression (indicators)).
 - Similarity of medicine disposition & effect (mode of action, PK, PD).
 - Similarity and applicability of clinical efficacy and safety endpoints.
- Quantitative evidence
 - Disease progression: Simulation with disease models to characterize differences between groups.
 - PK and PD: using existing data, modeling and simulation to investigate the relationship between PK/PD, age and other important covariates.
 - Clinical response: quantitative synthesis of all existing data to predict the degree of similarity in clinical response

Adapted from: Concept paper on extrapolation of efficacy and safety in medicine development. EMA. 19 March 2013. Final.

TABLE 1 Summary of Approaches to Use of Extrapolation of Efficacy From Adult Population to Pediatric Population

Extrapolation of Efficacy From Adult Data	Assumptions Made to Extrapolate Efficacy	Purposes of Pediatric Studies	Supportive Evidence Requested From Pediatric Studies	Products for Which WRs Issued, <i>n/N</i> (%)	New or Expanded Pediatric Indication Achieved, <i>n/N</i> (%)
No extrapolation	Disease/condition and/or response to intervention are not similar.	Demonstration of efficacy and assessment of safety.	Two adequate, well-controlled, efficacy and safety trials plus pharmacokinetic data.	19/166 (11)	7/19 (37)
		For oncology products only, demonstration of response and assessment of safety.	For oncology products only, sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial extrapolation	Disease/condition and/or response to intervention are similar but there is some uncertainty about the strength of assumptions.	Confirmation of efficacy and assessment of safety.	Single, adequate, well-controlled, efficacy and safety trial plus pharmacokinetic data.	67/166 (40)	35/67 (52)
	Disease/condition and/or response to intervention are similar but there is less uncertainty about the strength of assumptions (or patient numbers are such that it would not be feasible to conduct a controlled or adequately powered study).	Confirmation of response and assessment of safety.	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus pharmacokinetic data.	20/166 (12)	15/20 (75)
		Single exposure-response trial (not powered for efficacy determination) plus pharmacokinetic and safety data, pharmacokinetic/pharmacodynamic and uncontrolled efficacy data plus safety data, or pharmacokinetic/pharmacodynamic data plus safety data.	26/166 (16)	19/26 (73)	
Complete extrapolation	Disease/condition and/or response to intervention are similar and there is a high degree of certainty about the strength of assumptions.	Exposure data to confirm age- appropriate dose and assessment of safety.	Pharmacokinetic and safety data.	10/166 (6)	9/10 (90)
	Disease/condition and/or response to intervention are similar and there is a high degree of certainty about the strength of assumptions. Dose assumed to be the same (eg, topical application).	Assessment of safety.	Safety data only.	14/166 (8)	6/14 (43)

TABLE 1 Summary of Approaches to Use of Extrapolation of Efficacy From Adult Population to Pediatric Population

Extrapolation of Efficacy From Adult Data	Assumptions Made to Extrapolate Efficacy	Purposes of Pediatric Studies	Supportive Evidence Requested From Pediatric Studies	Products for Which WRs Issued, <i>n/N</i> (%)	New or Expanded Pediatric Indication Achieved, <i>n/N</i> (%)
No extrapolation	Disease/condition and/or response to intervention are not similar.	Demonstration of efficacy and assessment of safety.	Two adequate, well-controlled, efficacy and safety trials plus pharmacokinetic data.	19/166 (11)	7/19 (37)
		For oncology products only, demonstration of response and assessment of safety.	For oncology products only, sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial extrapolation	Disease/condition and/or response to intervention are similar but	Confirmation of efficacy and assessment of safety	Single, adequate, well-controlled, efficacy and safety trial plus	67/166 (40)	35/67 (52)

Even within extrapolation categories, sources of evidence and requirements for new pediatric studies vary.

What are the metrics/criteria driving this variability?

extrapolation	to intervention are similar and there is a high degree of certainty about the strength of assumptions.	age- appropriate dose and assessment of safety.			
	Disease/condition and/or response to intervention are similar and there is a high degree of certainty about the strength of assumptions. Dose assumed to be the same (eg, topical application).	Assessment of safety.	Safety data only.	14/166 (8)	6/14 (43)

TABLE 3 Changes in Approach to Extrapolation (*N* = 13)

Indication	Nature of Change
Analgesia	Initially FDA required independent proof of efficacy in pediatric population. After FDA workshop of experts in pediatric analgesia, FDA now accepts that, for opioids, nonsteroidal antiinflammatory drugs, acetaminophen, and local anesthetics, it is scientifically appropriate to extrapolate efficacy from adults to pediatric populations down to age 2–4 y. For analgesics with unknown mechanisms of action or novel analgesics for which pediatric relevance of the mechanism of action is unknown, adequate, well-controlled, efficacy studies and safety data are still necessary, after pharmacokinetic data are obtained to support dose selection.
Arrhythmia	FDA originally asked for a single, controlled, dose-response study, on the basis of continuity, and would have extrapolated between arrhythmias. Now less certainty about continuity between adult and pediatric populations and FDA would require 2 studies.
Detrusor instability secondary to neurologic impairment	FDA now grants waivers for patients ≤ 5 y of age. It used to request open-label studies with surrogate urodynamic end points. Since 2007, FDA has requested adequately controlled (including placebo), double-blind studies with clinical end points. FDA may not issue any more WRs for α -blockers for this indication, because 2 large, double-blind, placebo-controlled trials with clinically meaningful surrogate end points for tamsulosin and alfuzosin both yielded negative results.
GERD	FDA considers that the course of GERD in adults is not sufficiently similar to the course of pathologic gastroesophageal reflux in pediatric patients < 1 y of age to permit extrapolation of adult efficacy data to this pediatric age group. Approaches in this age group may change because no trials to date have demonstrated efficacy for the 1–11-mo-old population. FDA originally requested a separate efficacy study with neonates but now requires a pharmacokinetic/pharmacodynamic/safety study.
Heterozygous familial hypercholesterolemia	For first statin, FDA required 2 adequate, well-controlled trials. For subsequent statins, FDA required a single trial. Since review of several positive single studies, FDA has accepted open-label, uncontrolled, efficacy studies showing similar LDL-lowering effects in adult and pediatric populations.
Hypertension	Extrapolation was used to label enalapril for use down to age of 1 mo on the basis of consistent pharmacokinetic data across pediatric (2 mo to 16 y) and adult age groups and positive controlled, dose-response study results for patients 6–16 y of age. However, FDA changed this approach after receiving data on antihypertensive drugs that showed no efficacy in pediatric age groups despite similar pharmacokinetic characteristics for pediatric and adult populations. Antihypertensive drugs now receive pediatric labeling only for age groups for which efficacy is confirmed.
JIA	First WRs focused on pharmacokinetic and safety data and extrapolated efficacy from the adult population in a traditional manner. Now FDA requests independent confirmation of efficacy in the pediatric population, except in certain cases where the drug is in a class with established efficacy in the pediatric population. Also, different considerations apply for symptom-modifying treatments, compared with disease-modifying therapies. In general, a single, adequate, well-controlled, pediatric trial is requested on the basis of the similarity between JIA and adult rheumatoid arthritis. For symptom-modifying treatments, FDA encourages inclusion of children with all 7 subtypes of JIA, ¹⁵ because children with all subtypes will be treated. In contrast, for disease-modifying drugs, efficacy is extrapolated from adult rheumatoid arthritis to the polyarticular subtype of JIA, because this subtype most resembles rheumatoid arthritis. Separate studies would be requested for the other subtypes.

TABLE 3 Changes in Approach to Extrapolation (N = 13)

Indication	Nature of Change
Analgesia	Initially FDA required independent proof of efficacy in pediatric population. After FDA workshop of experts in pediatric analgesia, FDA now accepts that, for opioids, nonsteroidal antiinflammatory drugs, acetaminophen, and local anesthetics, it is scientifically appropriate to extrapolate efficacy from adults to pediatric populations down to age 2–4 y. For analgesics with unknown mechanisms of action or novel analgesics for which pediatric relevance of the mechanism of action is unknown, adequate, well-controlled, efficacy studies and safety data are still necessary, after pharmacokinetic data are obtained to support dose selection.
Arrhythmia	FDA originally asked for a single, controlled, dose-response study, on the basis of continuity, and would have extrapolated between arrhythmias. Now less certainty about continuity between adult and pediatric populations and FDA would require 2 studies.
Detrusor instability secondary to neuro	FDA now grants waivers for patients ≤5 y of age. It used to request open-label studies with surrogate urodynamic end points. Since 2007, FDA has requested adequately controlled (including placebo), double-blind studies with clinical end points. FDA
GERD	
Hetero	
hyp	
Hyper	
JIA	First WRs focused on pharmacokinetic and safety data and extrapolated efficacy from the adult population in a traditional manner. Now FDA requests independent confirmation of efficacy in the pediatric population, except in certain cases where the drug is in a class with established efficacy in the pediatric population. Also, different considerations apply for symptom-modifying treatments, compared with disease-modifying therapies. In general, a single, adequate, well-controlled, pediatric trial is requested on the basis of the similarity between JIA and adult rheumatoid arthritis. For symptom-modifying treatments, FDA encourages inclusion of children with all 7 subtypes of JIA, ¹⁵ because children with all subtypes will be treated. In contrast, for disease-modifying drugs, efficacy is extrapolated from adult rheumatoid arthritis to the polyarticular subtype of JIA, because this subtype most resembles rheumatoid arthritis. Separate studies would be requested for the other subtypes.

Extrapolation approaches differ across disease areas, and have evolved within disease areas.

What metrics or decision criteria drive these differences?

Gaps in the Strategy for Assessing Extrapolation Assumptions

- Disease Progression

- Which endpoints are relevant and comparable?
- Sufficient duration of disease progression in adult and pediatric populations

- Exposure-Response

- Sufficient characterization of randomized dose or exposure-response in adult development program
- Challenges of dose-ranging studies with relevant PD or efficacy endpoints in pediatric populations

- Decision Criteria

- How similar is similar enough?
- How different can disease progression or exposure-response be before it is a clinically meaningful difference?

Summary

- Simulation-based quantitative assessment of extrapolation assumptions:
 - May be useful to identify cases or conditions when adult and pediatric populations are not similar
 - Is likely insufficient to confirm similarity between adult and pediatric populations, without other sources of evidence
 - Should be supplemented with qualitative evidence based on biological understanding
- **NEEDED:** Disease-area specific guidance on metrics and decision criteria (or points to consider) when assessing similarity of disease progression, intervention response, and exposure-response

Thank You



FDA-UMD CERSI Workshop
Panel and Organizers

Metrum Research Group
Scientists

Industry Collaborators

Pediatric trial participants

