METRUM
RESEARCH GROUP

ASCPT 2016 Workshop: Lessons Learned from Failed Pediatric Trials
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Guanfacine for ADHD in Adolescents: Utility of Clinical Trial Simulation

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Acknowledgements and Support

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- Contributors

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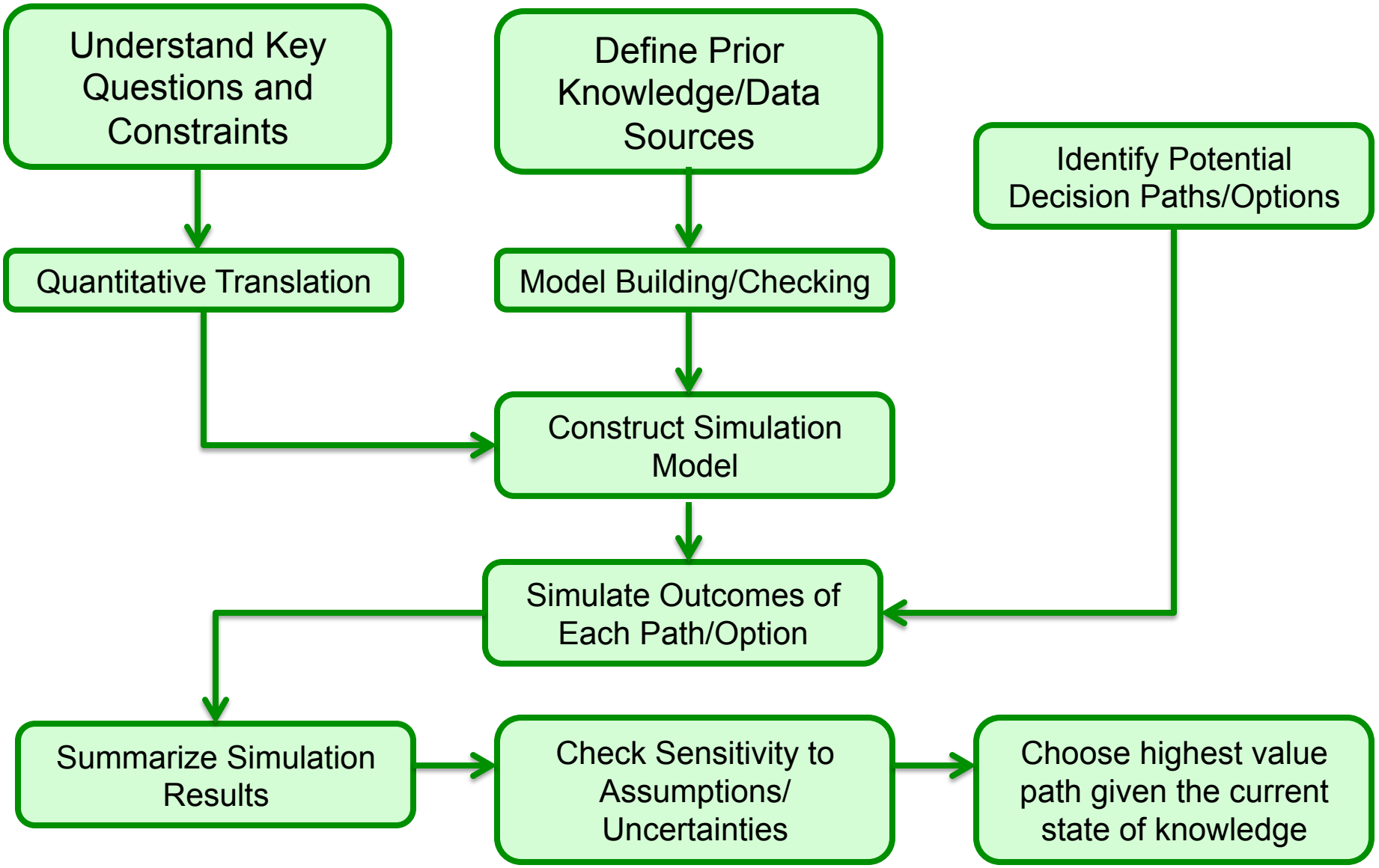
  MetrumRG: Bill Knebel, Marc Gastonguay, Jim Rogers and Dan Polhamus

Learning Objectives

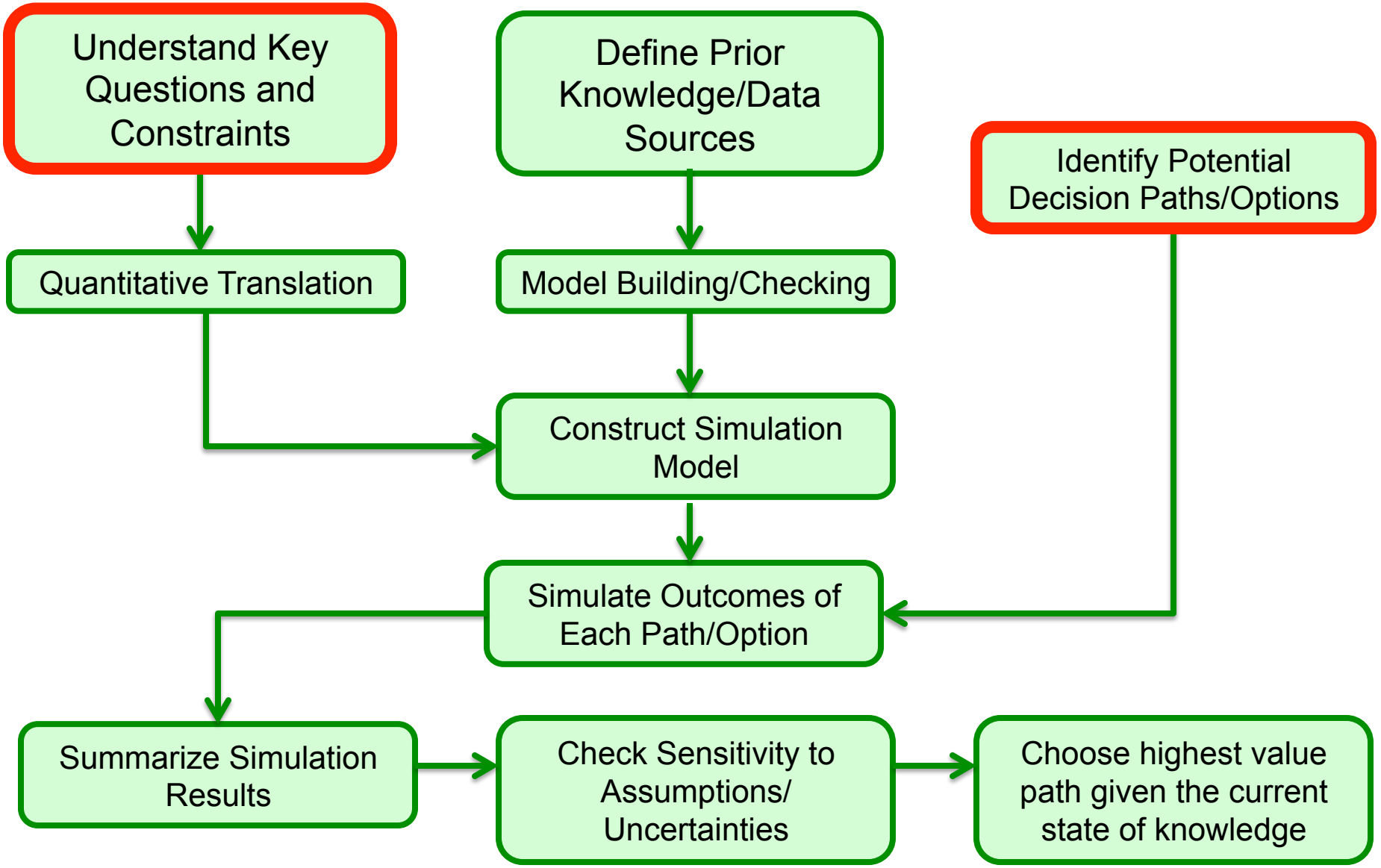
- Present an example of how clinical trial simulation can be used to optimize key design features of a new pediatric study

- Discuss application of clinical trial simulation to inform pediatric trials including accounting for potential differences in adult and pediatric disease manifestations

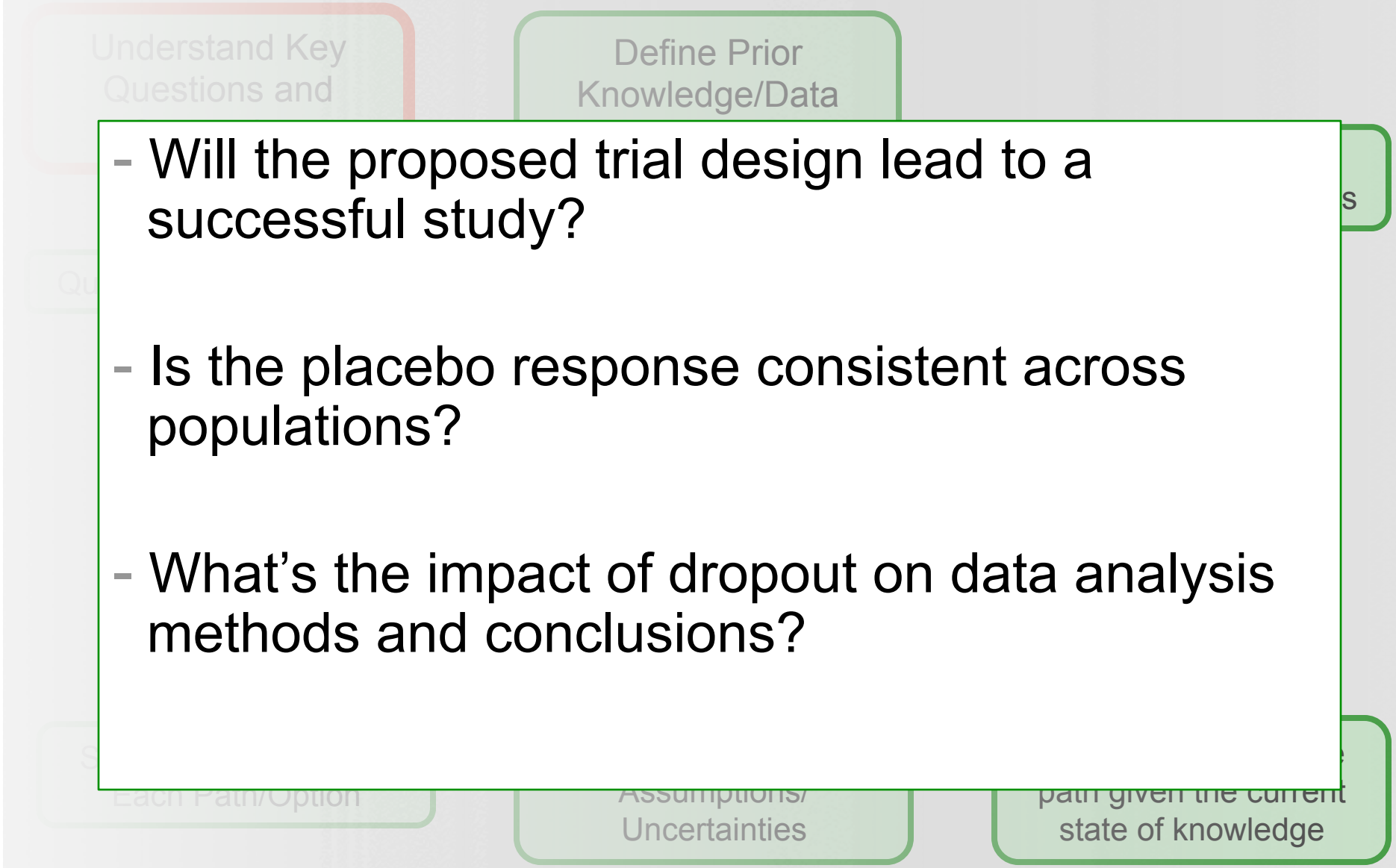
Simulation Based Decision-Making Process Flow



Simulation Based Decision-Making Process Flow

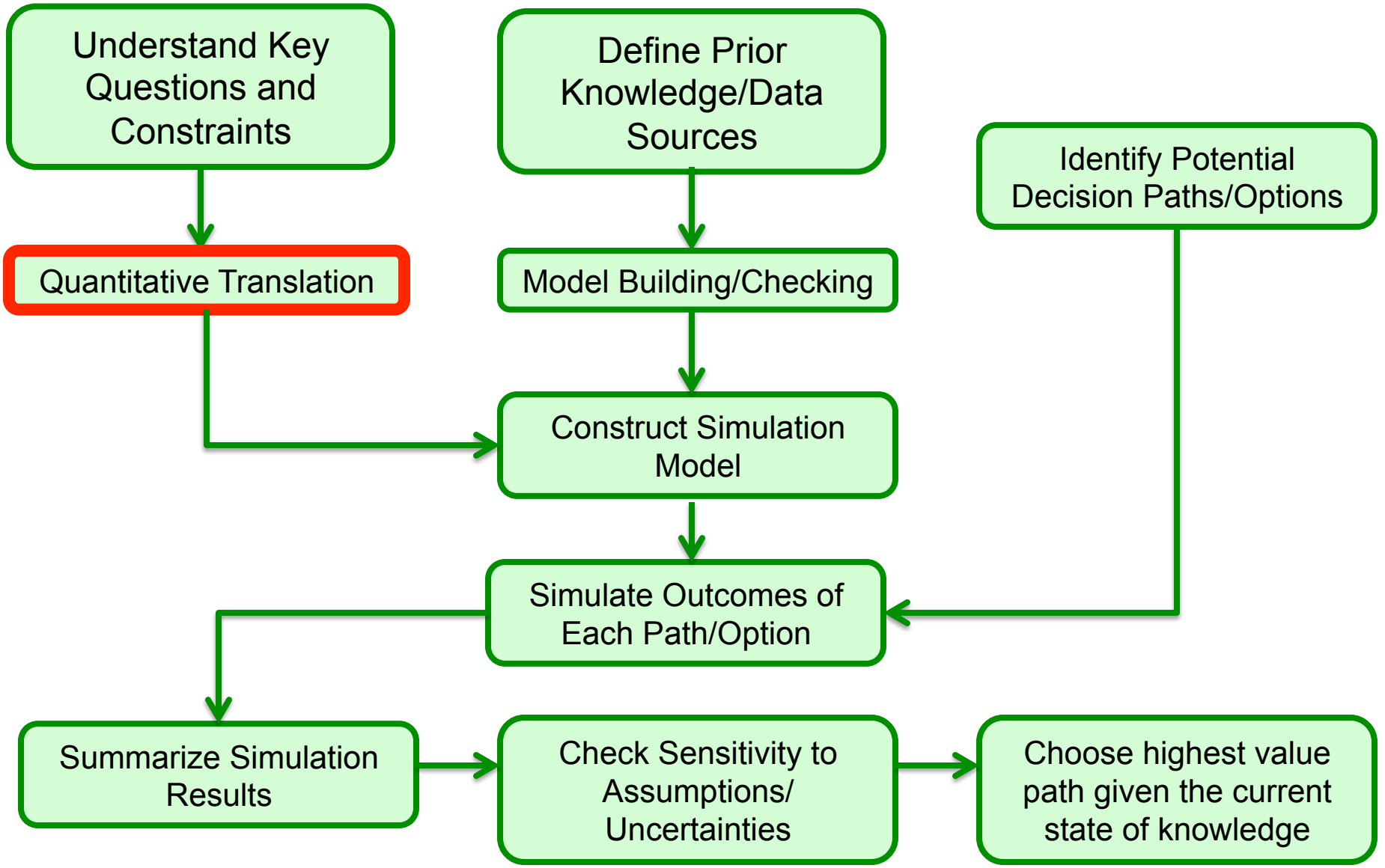


Simulation Based Decision-Making Process Flow



- Will the proposed trial design lead to a successful study?
- Is the placebo response consistent across populations?
- What's the impact of dropout on data analysis methods and conclusions?

Simulation Based Decision-Making Process Flow

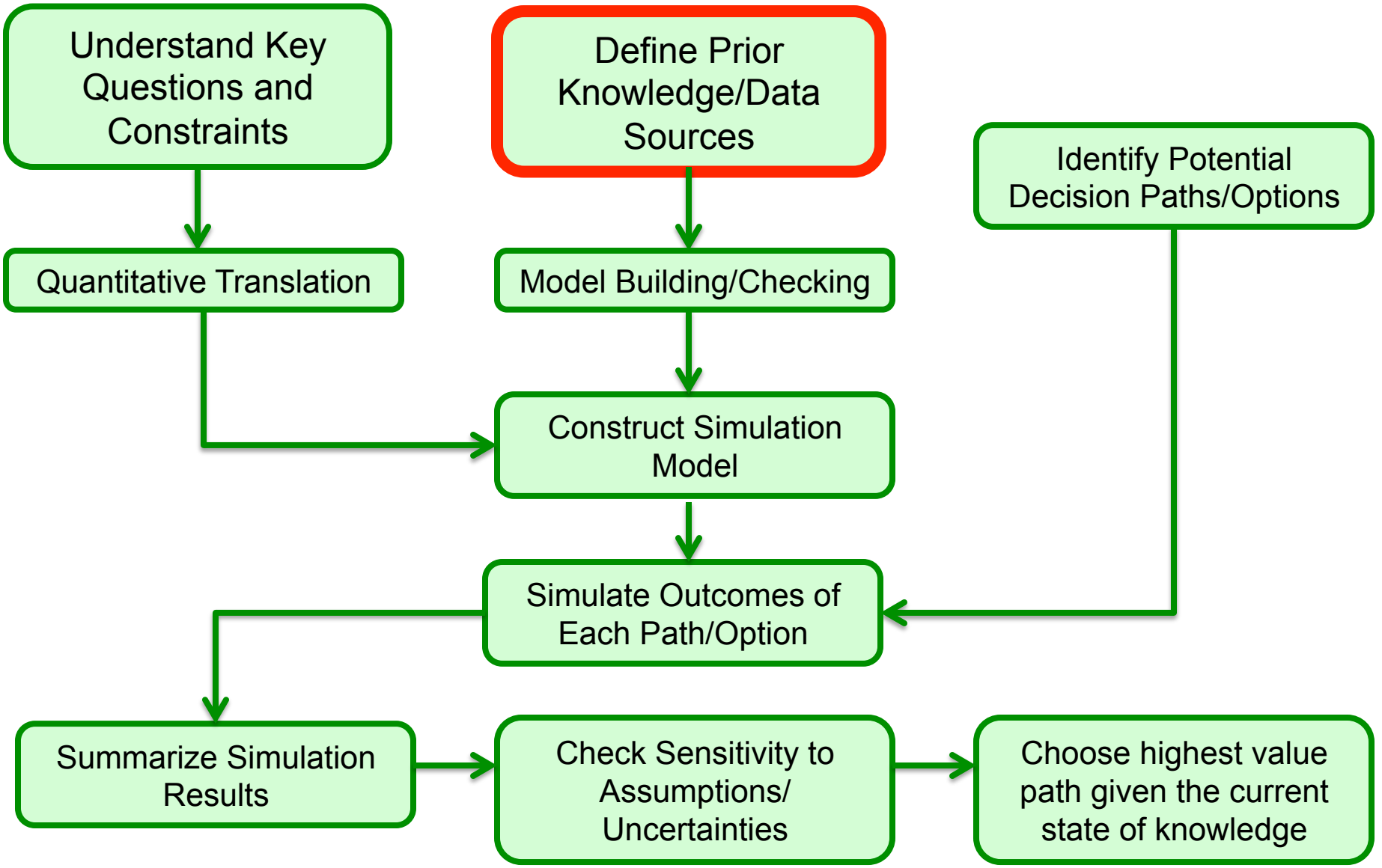


Simulation Based Decision-Making Process Flow

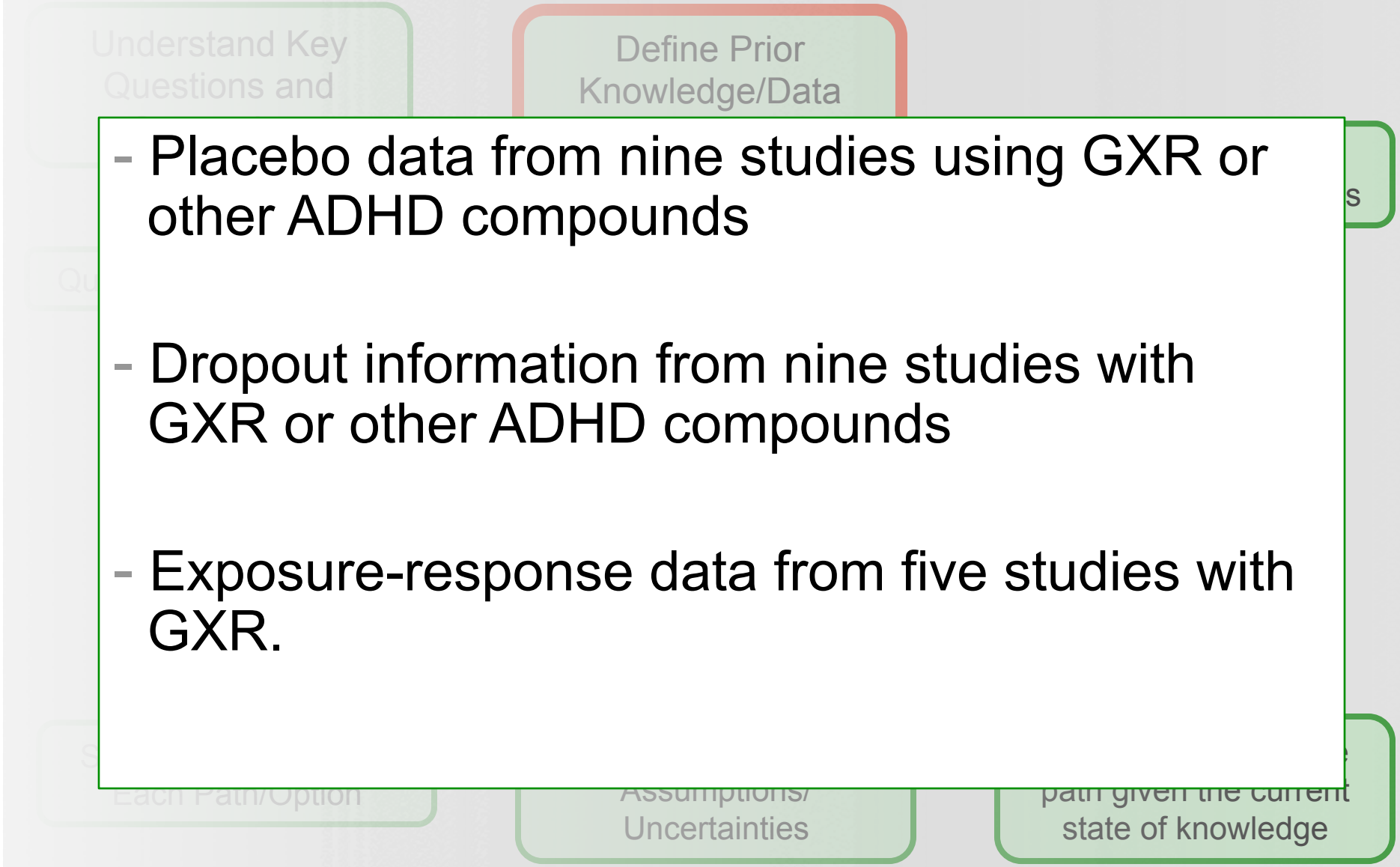
- Under a dose-optimization/titration trial design, what is the probability that guanfacine extended release (GXR) will beat placebo ($p < 0.05$) on the ADHD RS-IV score at week 13?

- Are conclusions dependent on analysis methods (LOCF/ANCOVA vs. MMRM) data analysis methods, given missing data due to expected dropout rate

Simulation Based Decision-Making Process Flow

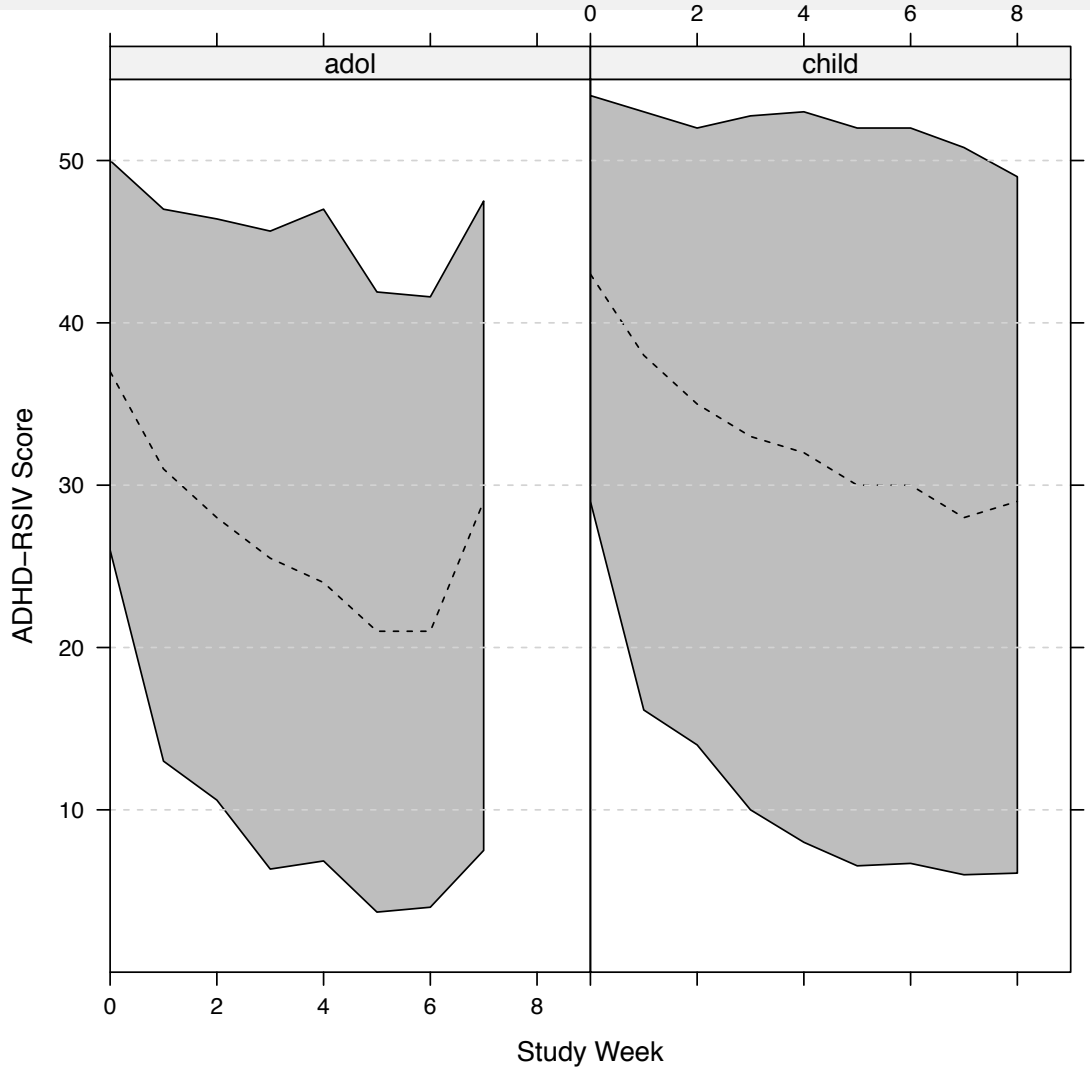


Simulation Based Decision-Making Process Flow



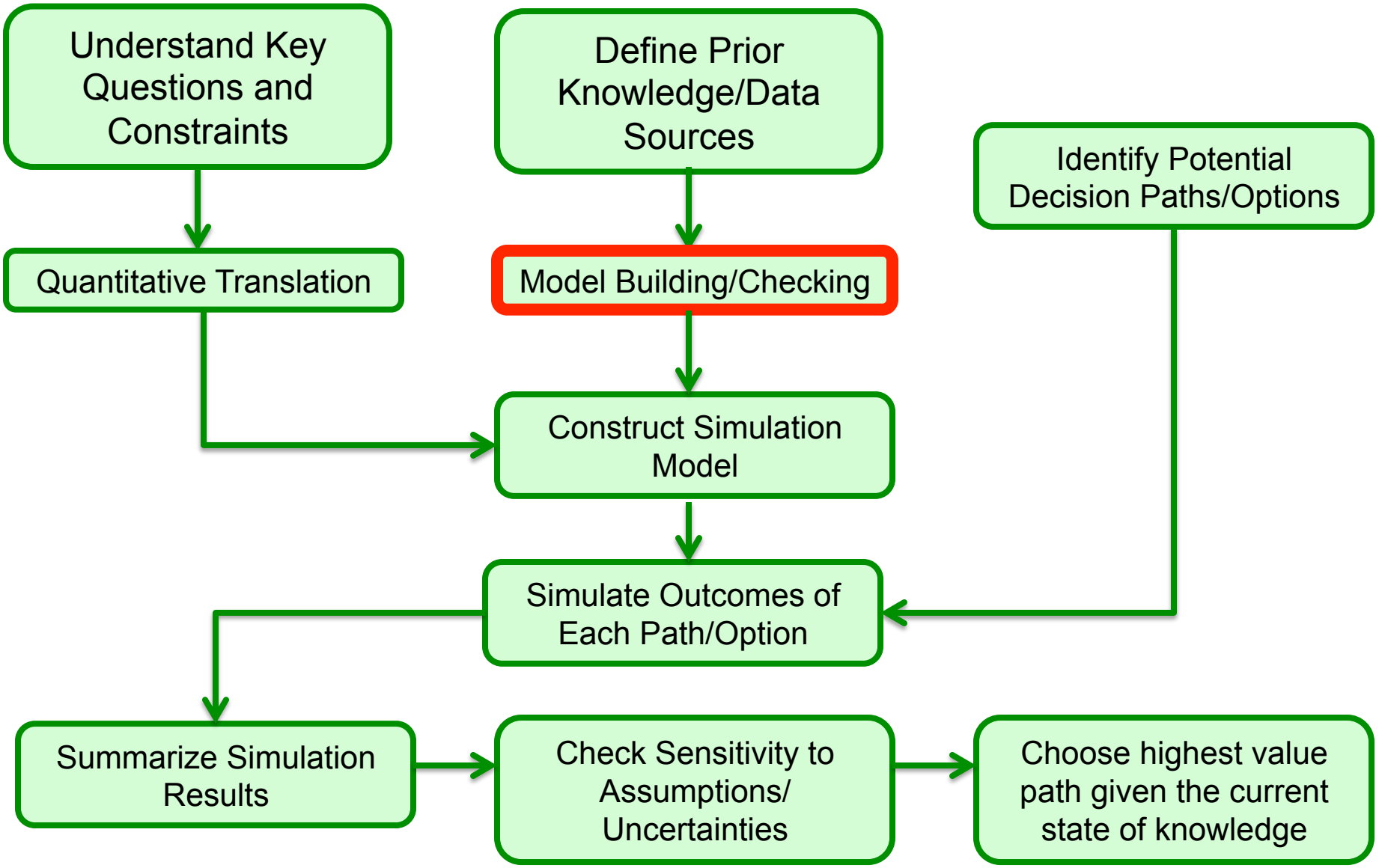
- Placebo data from nine studies using GXR or other ADHD compounds
- Dropout information from nine studies with GXR or other ADHD compounds
- Exposure-response data from five studies with GXR.

Prior Knowledge

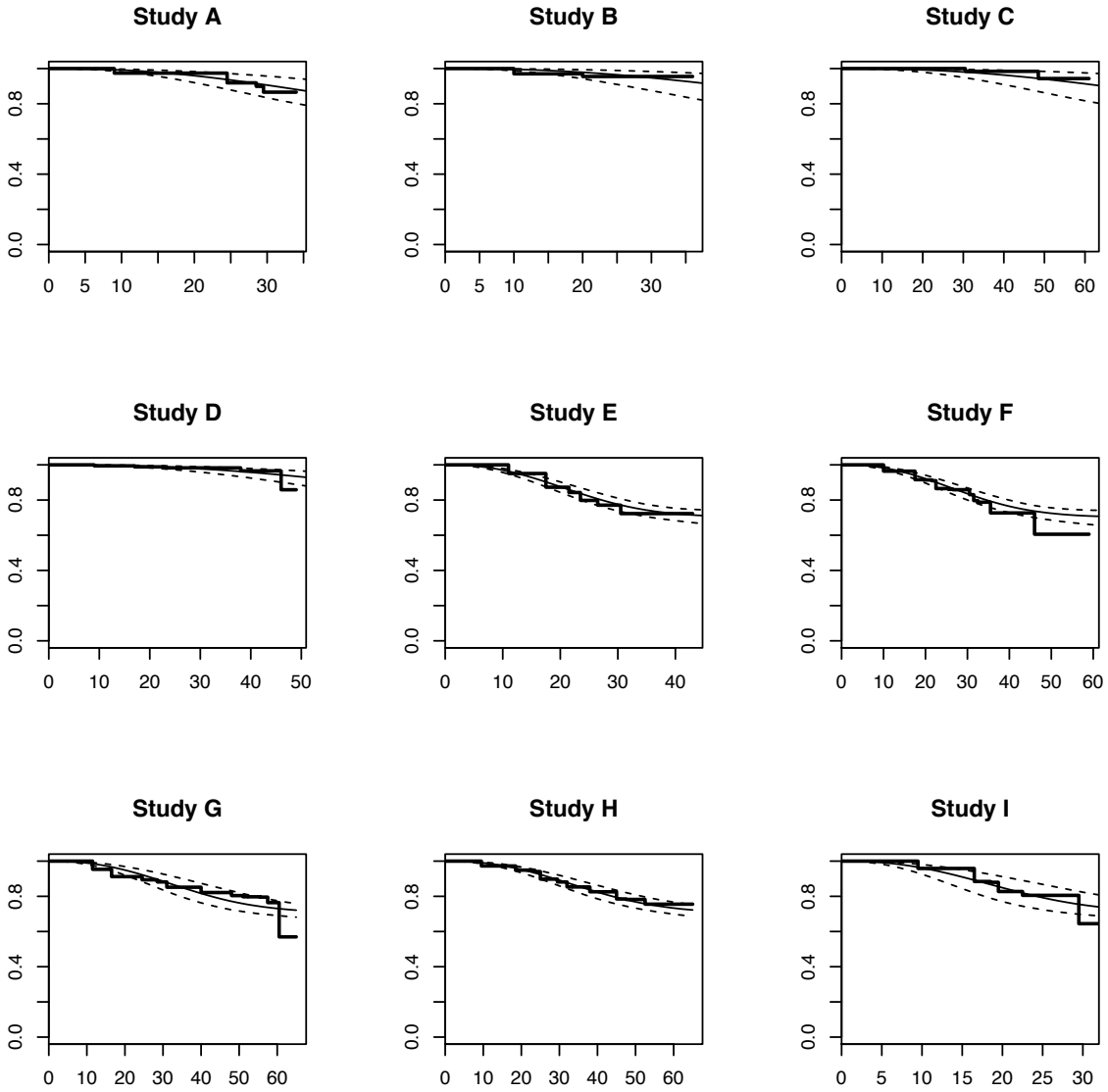


ADHD RS-IV score vs time in weeks for placebo patients. Median (dotted lines) with 5th and 95th percentiles (grey polygon)

Simulation Based Decision-Making Process Flow

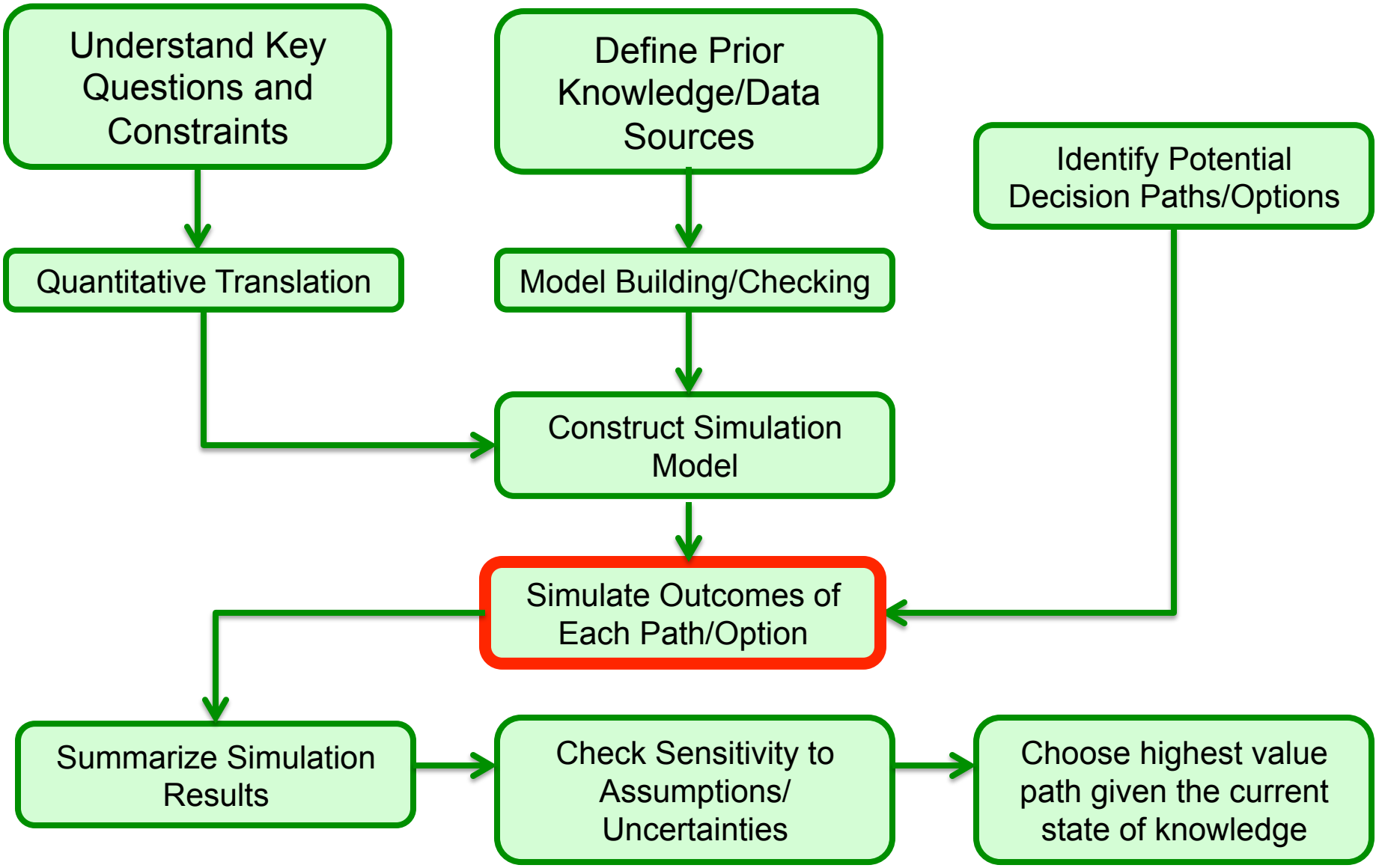


Model Checking: Dropout



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-Meir survival curves (thick black line) for each study demonstrate the observed distribution of dropout times.

Simulation Based Decision-Making Process Flow



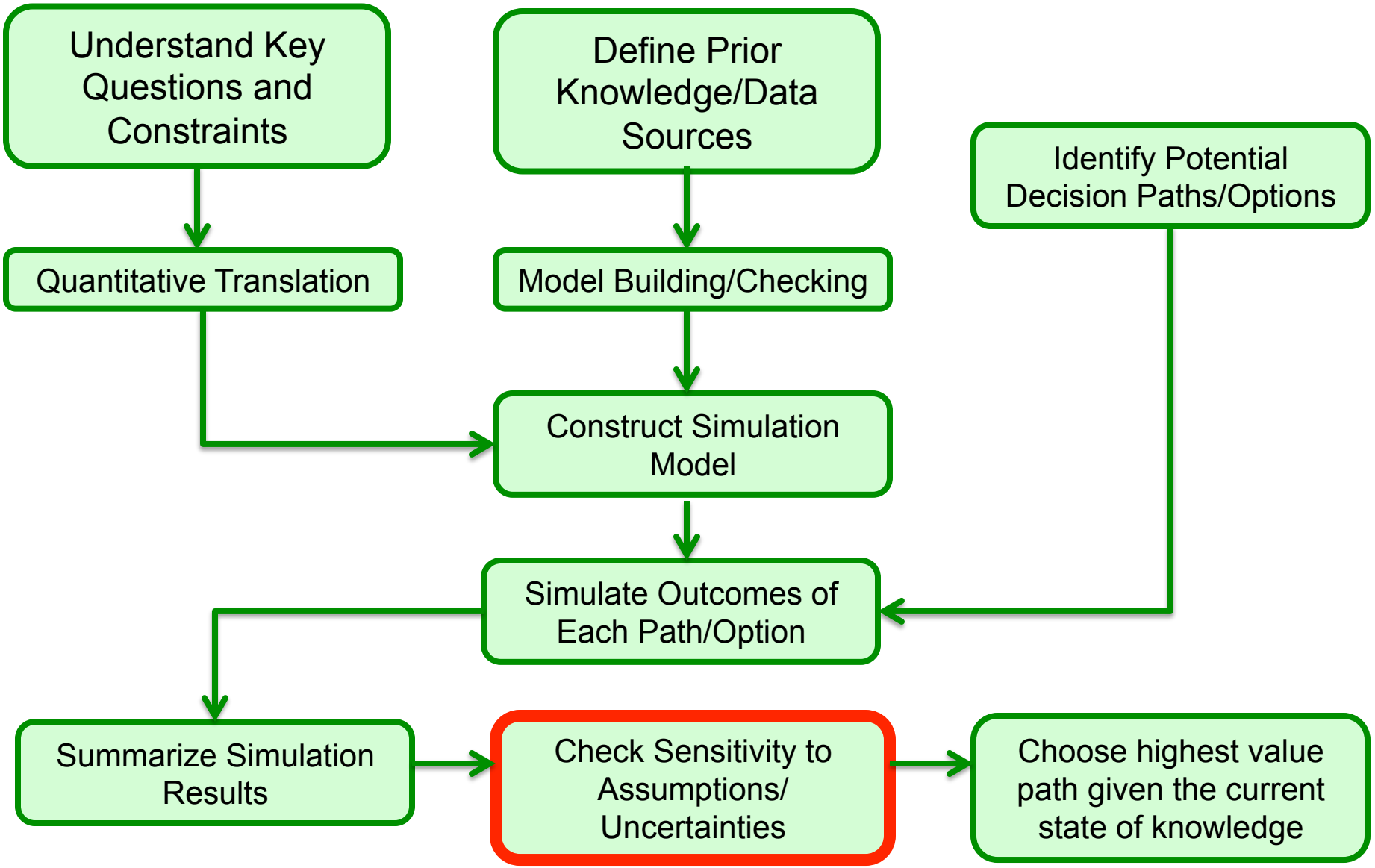
Simulation Results

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]

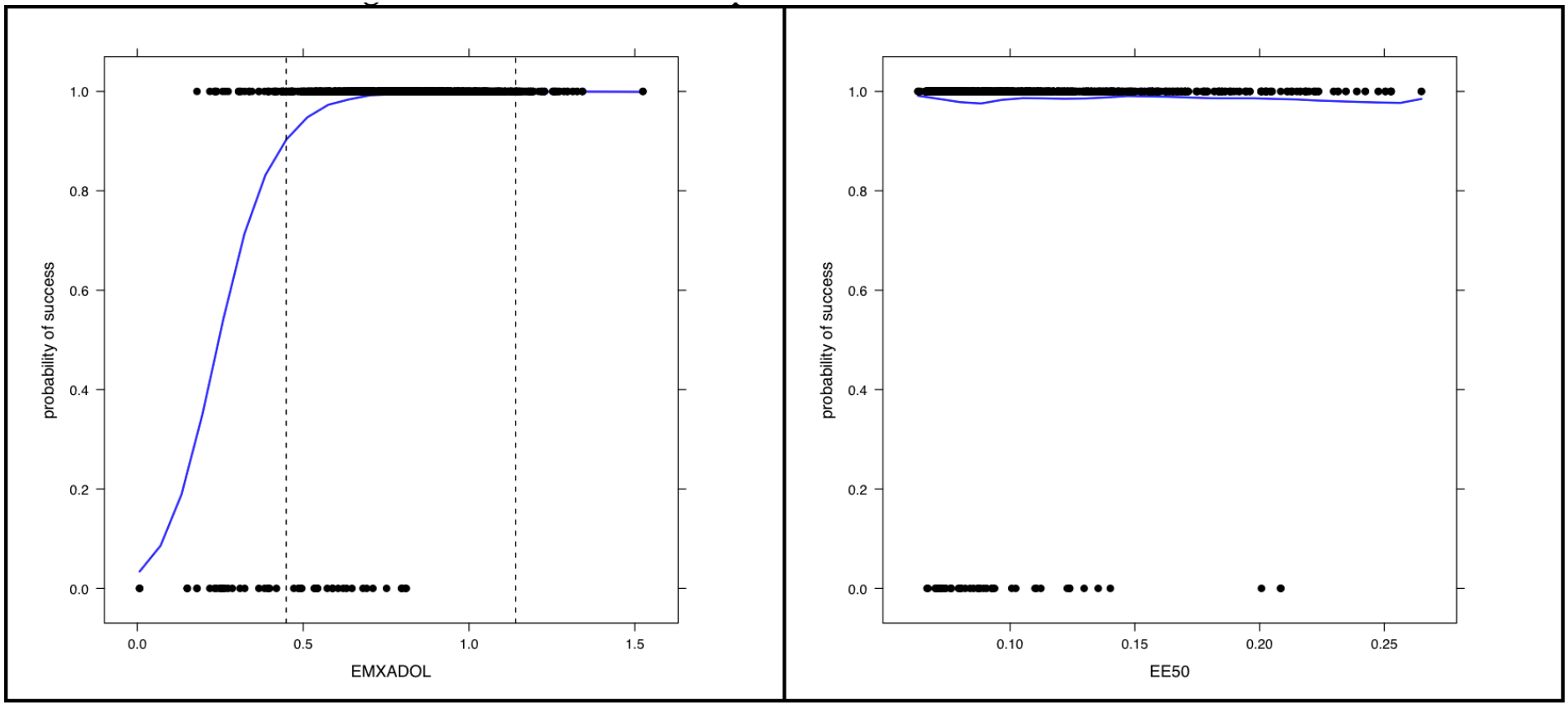
a = difference between placebo and active at Visit 13
b = median [95% CI]
c = calculated as Treatment Effect/SD of Change from Baseline

- Treatment effect was consistent with historical data
- Both analysis methods provided similar results

Simulation Based Decision-Making Process Flow



Sensitivity Analysis



- Conclusions independent of uncertainties in simulation model parameters

Successful Trial and Approval

Mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for INTUNIV® compared to placebo in both AM and PM dosing groups of INTUNIV® (see Table 6).

Table 6: Flexible-Dose studies

Study (Age Range)		Treatment Group		
		Placebo	Intuniv® 1mg – 4mg	
			AM	PM
3[a] (6 – 17 years)	Mean Baseline (SD)	37.7 (7.75)	37.6 (8.13)	37.0 (7.65)
	LS Mean Change from Baseline (SE)	-15.9 (0.96)	-20.3 (0.97)	-21.2 (0.97)
	LS Mean Difference from Placebo (95% CI)	--	-4.5[b] (-7.5, -1.4)	-5.3[b] (-8.3, -2.3)
4 (6 – 12 years)	Mean Baseline (SD)	42.9 (6.21)	41.7 (6.39)	41.6 (6.66)
	LS Mean Change from Baseline (SE)	-10.6 (1.20)	-20.0 (1.23)	-20.4 (1.19)
	LS Mean Difference from Placebo	--	-9.4[b] (-12.8, -6.0)	-9.8[b] (-13.1, -6.4)

UNTUNIV Prescribing Information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022037s009lbl.pdf

Thank You

Modeling and simulation of the exposure–response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD

William Knebel, Jim Rogers, Dan Polhamus, James Ermer & Marc R. Gastonguay

Journal of Pharmacokinetics and Pharmacodynamics

ISSN 1567-567X

J Pharmacokinet Pharmacodyn
DOI 10.1007/s10928-014-9397-6

Backup

Models

- The time course of ADHD RS-IV total scores were best described by an inverse Bateman function (placebo data) and an Emax model (GXR exposure-response data).

$$
\begin{aligned}
EFF_{plcb} &= \theta_{scale} \cdot \frac{k_{forp}}{k_{elp} - k_{forp}} \cdot (e^{-k_{forp} \cdot TIME} - e^{-k_{kelp} \cdot TIME}) \\
E_{max} &= E_{max,ss} \cdot (1 - e^{\frac{-0.693}{T_{ss}} \cdot TIME}) \\
EFF_{guan} &= \frac{E_{max} \cdot DKG}{EE_{50} + DKG} \\
\text{ADHD RS-IV} &= S_0 \cdot (1 - EFF_{plcb}) \cdot (1 - EFF_{guan})
\end{aligned}
\tag{1}
$$

Models

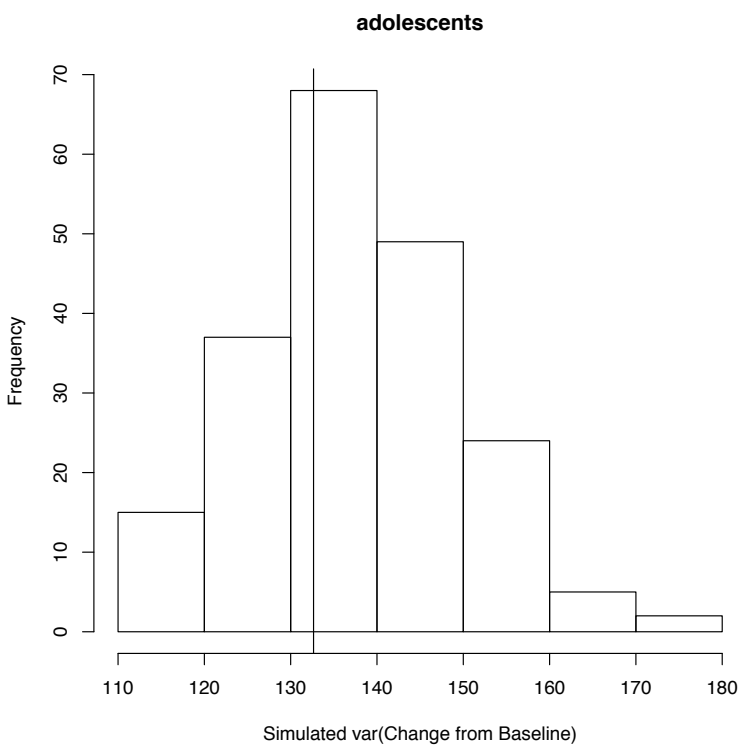
- The distribution of dropout times was best described using a ”cure” model where the maximum percentage of non-dropout patients was an estimated parameter .

$$
\begin{aligned}
S_1(t) &= \pi + (1-\pi)S(t) \\
t_{ij} &\sim \textit{Weibull}(r, \mu_i) \\
\mu_i &= e^{(\nu_0 + \nu_i^{\textit{study}})}
\end{aligned}
\tag{2}
$$

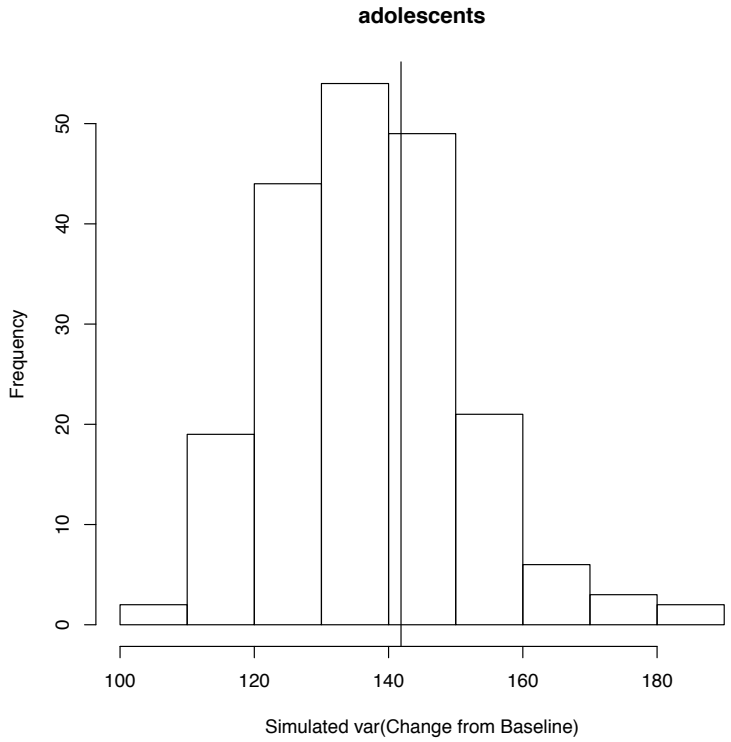
- $S(t)$ denotes the survival function in the patients and π is the fraction of patients that will not experience dropout
- Weibull distribution for subject *j* in study *i* was described by a shape parameter (r), a scale parameter (μ_i), and a random study effect ($\nu_i^{\text{study}} \sim N(\nu_0, \sigma^2)$) on the scale parameter

Model Checking – Variance in Change from Baseline

Placebo



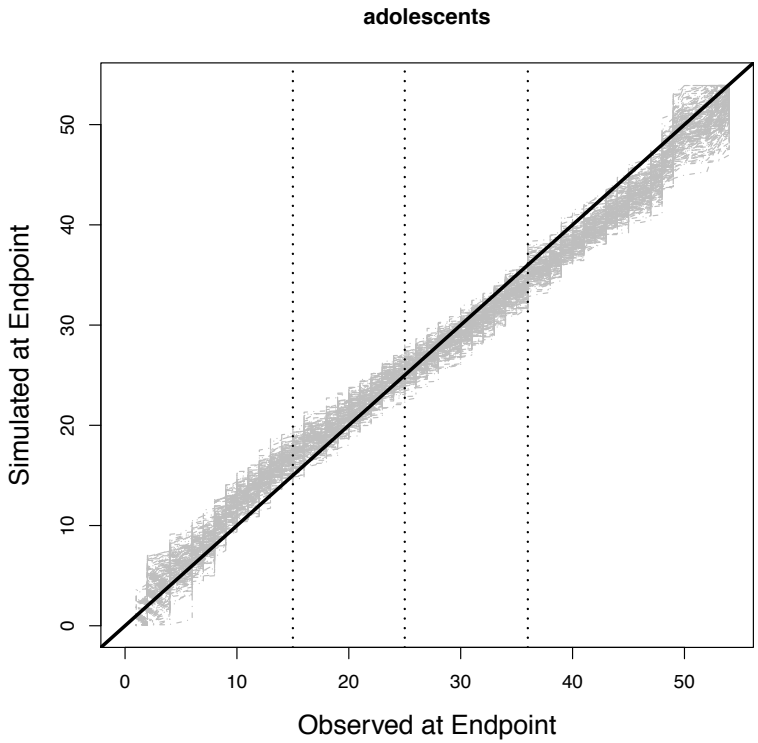
Exposure-response



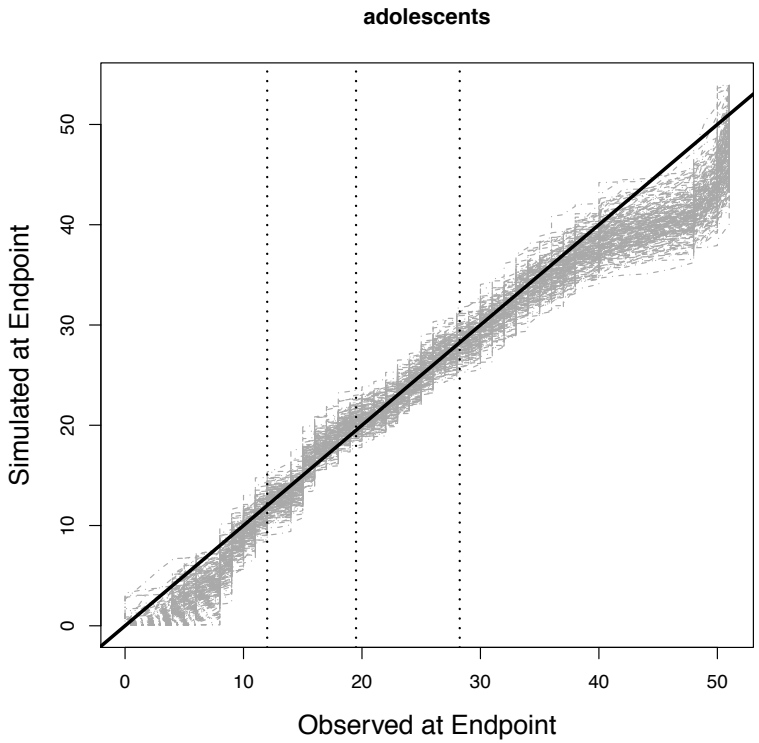
Distributions of variance in change from baseline to endpoint in ADHD RS-IV score in simulated individuals are compared to the actual observed variance in change from baseline to endpoint for adolescents from the model building datasets. Simulations were performed using the final placebo model and exposure-response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

Model Checking – Endpoint

Placebo



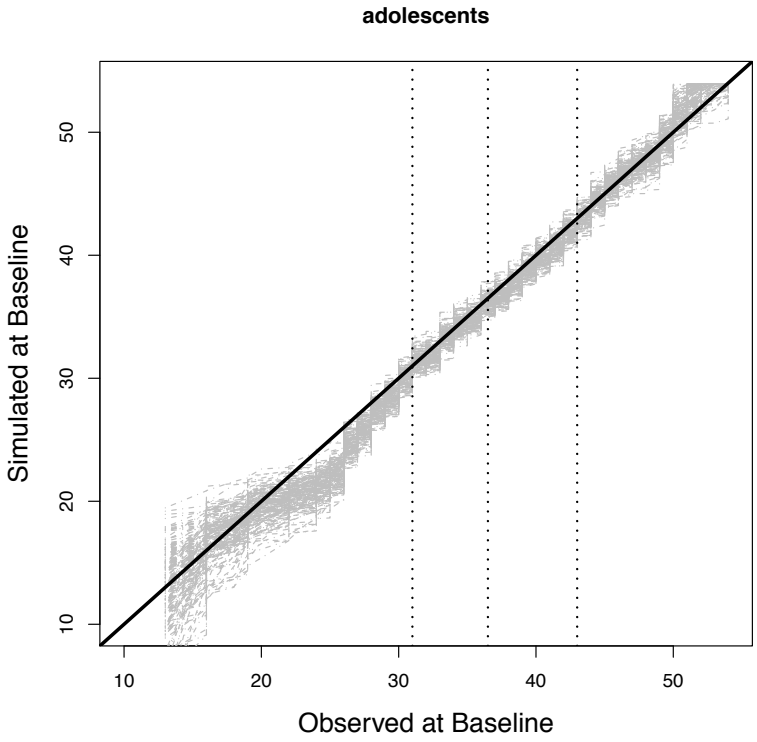
Exposure-response



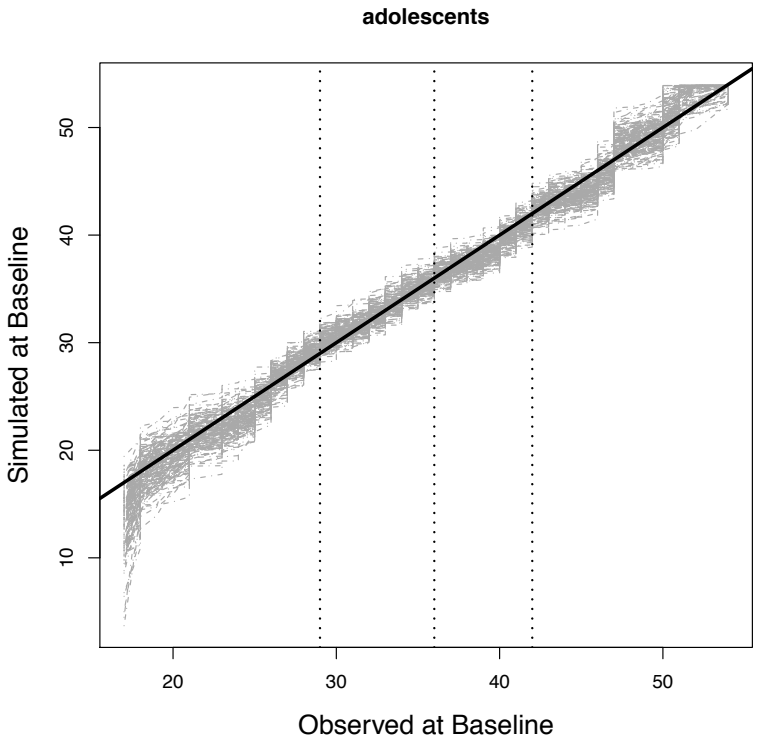
Distributions of simulated ADHD RS-IV score at endpoint within each individual are compared to the actual observed distribution of baseline values for adolescents from the model building datasets. Simulations were performed using the final placebo model and exposure-response models with correction for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

Model Checking - Baseline

Placebo



Exposure-response



Distributions of simulated ADHD RS-IV score at baseline 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.

Summary

- This analysis is the first to describe the placebo response time course of ADHD RS-IV total scores, exposure-response of GXR, and dropout pattern in this group of ADHD patients.
- Structured, organized, approach to modeling/simulation process facilitates implementation and generation of useful results.
- Days, weeks, and sometimes months of work can often be summarized in one table or figure.