A Modeling and Simulation Primer for the Design of Pediatric Pharmacokinetic Studies

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Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies

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"The study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for DRUG NAME in each pediatric sub-group with at least 80% power."

J Clin Pharmacol. 2012 Oct;52(10):1601-6

FDA Pediatric PK Study Design Recommendation

- Sample size selection for pediatric PK and safety studies has been vastly different without clear justification
- Pediatric exclusivity determination or the approval decision was affected in some cases
- Need for a uniform definition of study quality for PK studies

Describes methodological details and expectations to fulfill this requirement based on either a non-compartmental analysis (NCA) or a population PK (pop PK) modeling approach

The NCA methodology for fulfilling the quality standard requirement is relatively straightforward

Fulfilling the Requirement Using NCA

- Step 1: Derive a reasonable estimate of variability (for each age group)

$$SD = \sqrt{\log(CV\%^2 + 1)}$$

- Step 2: Calculate sample size for each age group to achieve the target

$$(\bar{CL}_{geo} \cdot e^{-t_{0.975,N-1}\frac{S}{\sqrt{N}}}, \bar{CL}_{geo} \cdot e^{t_{0.975,N-1}\frac{S}{\sqrt{N}}})$$

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Fulfilling the Requirement Using NCA

Table I Sample Size per Age Group for Various Levels of Variability to Achieve at Least 80% Power

SD	CV(%)[a]	N	Power
0.2	20	5	0.88
0.25	25	6	0.86
0.3	31	7	0.82
0.35	36	9	0.87
0.4	42	10	0.81
0.45	47	12	0.83
0.5	53	14	0.83
0.55	59	16	0.82
0.6	66	18	0.80
0.65	73	21	0.83
0.7	80	24	0.84

The pop PK methodology for fulfilling the quality standard requirement is not as straightforward as the NCA method

Fulfilling the Requirement Using PopPK Approach

- Develop popPK model from adult data
- Evaluate model
- Allometric scaling for pediatric population
- Propose pediatric design (n, number of PK samples, sample times, age, weight, model)
- Simulate replicate trials under proposed design
- Fit popPK model to replicates
- Obtain SE's for CL and V estimates and calculate CIs
- Evaluate study design for meeting acceptance criteria

Fulfilling the Requirement Using PopPK Approach

- For each simulated trial replicate, estimate log-transformed CL and V:

$$CL = \theta_1 \cdot \left(\frac{WT_i}{WT_{ref}}\right)^{\theta_2} \Longrightarrow LCL = exp(\theta_1) \cdot \left(\frac{WT_i}{WT_{ref}}\right)^{\theta_2}$$

- Calculate pooled SE:

$$SE_{\hat{LCL}} = \sqrt{\sigma_1^2 + \left[\log\left(\frac{WT}{70}\right)\right]^2 \sigma_2^2 + 2 \cdot \sigma_{12} \cdot \log\left(\frac{WT}{70}\right)}$$

- Derive 95% CIs for all replicates
- Power is determined as fraction of replicates meeting the 60% to 140% criteria

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Impact of Implementing a Quality Standard

- Provides a sound rationale to discuss the basis of sample size selection.
- Ensures objective discussion between the sponsors and regulatory agencies.
- Ensures informative design of pediatric clinical trial to derive rational dosing recommendations.
- Stimulates application in other areas where clinical pharmacology data standards do not exist, for example, pharmacokinetic studies evaluating hepatic impairment, renal impairment effects, or drug-drug interaction studies.

Questions:

We have a reasonable popPK model to describe drug disposition in adults. How do we implement this model to design a pediatric PK study and meet the suggested quality standard?

How do we conduct a pediatric PK study design evaluation within the context of the intended final analysis?

Fulfilling the Requirement Using PopPK

- Should simulated pediatric trials be pooled with adult data for model fitting?
  - Likely to be intended approach for final pediatric PK analysis
  - Adult data will highly influence all parameter estimates during design evaluation
- Should the model be fit to simulated pediatric data only?
  - Must design trial to estimate nuisance parameters (absorption, peripheral)
  - Need successful $COVARIANCE step for calculation of CIs
- Should nuisance parameters be fixed to adult values?
- Should the analysis model be simplified?

Fulfilling the Requirement Using Pop PK:
An Example Approach

- Simulate plasma concentrations for pediatric subjects under the proposed study design
- Obtain PK parameters for each replicate using the MCMC Bayes algorithm in NONMEM with selective priors
  - Informative priors from the adult PK analysis for nuisance parameters
  - Uninformative priors or CL and V, allowing the estimation to depend on the study design
- For each replicate trial, obtain the median and 95% CI for CL and V from the posterior distributions
- Power calculated as the proportion of replicates with a 95% CI that does not fall outside the reference range

Fulfilling the Requirement Using Pop PK:
An Example Approach

- Adult population PK
  - Two compartment structural model with allometric scaling
  - Oral absorption described by sequential zero/first order model
- Proposed pediatric clinical trial with sparse PK sampling
  - Single dose, four PK samples per subject
  - Twelve subjects per group
    - 2 to < 6 years
    - 18 to < 24 months
    - 12 to < 18 months
    - 6 to < 12 months
    - Newborn to < 6 months
- Dose adjust based on body size/maturation (100% renal elimination)

Population PK Simulation Model

TVCL : 10 : Clearance (L/h)
TVV : 20 : Central volume of distribution (L)
TVV2 : 60 : Peripheral volume of distribution (L)
TVQ : 3.0 : Intercompartmental clearance (L/h)

TVKA : 0.4 : First-order absorption rate (1/hr)
TVD1 : 3.0 : Zero-order absorption time(hr)
TVHILL : 3.40 : Hill coefficient for maturation
TM50 : 47.7 : PMA to reach half full maturation (weeks)

$$CL = TVCL \cdot \frac{PMA^{Hill}}{PMA^{Hill} + TM_{50}^{Hill}} \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot e^{\eta_{CL}}$$

Rhodin et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009. 24: 1(67-76)

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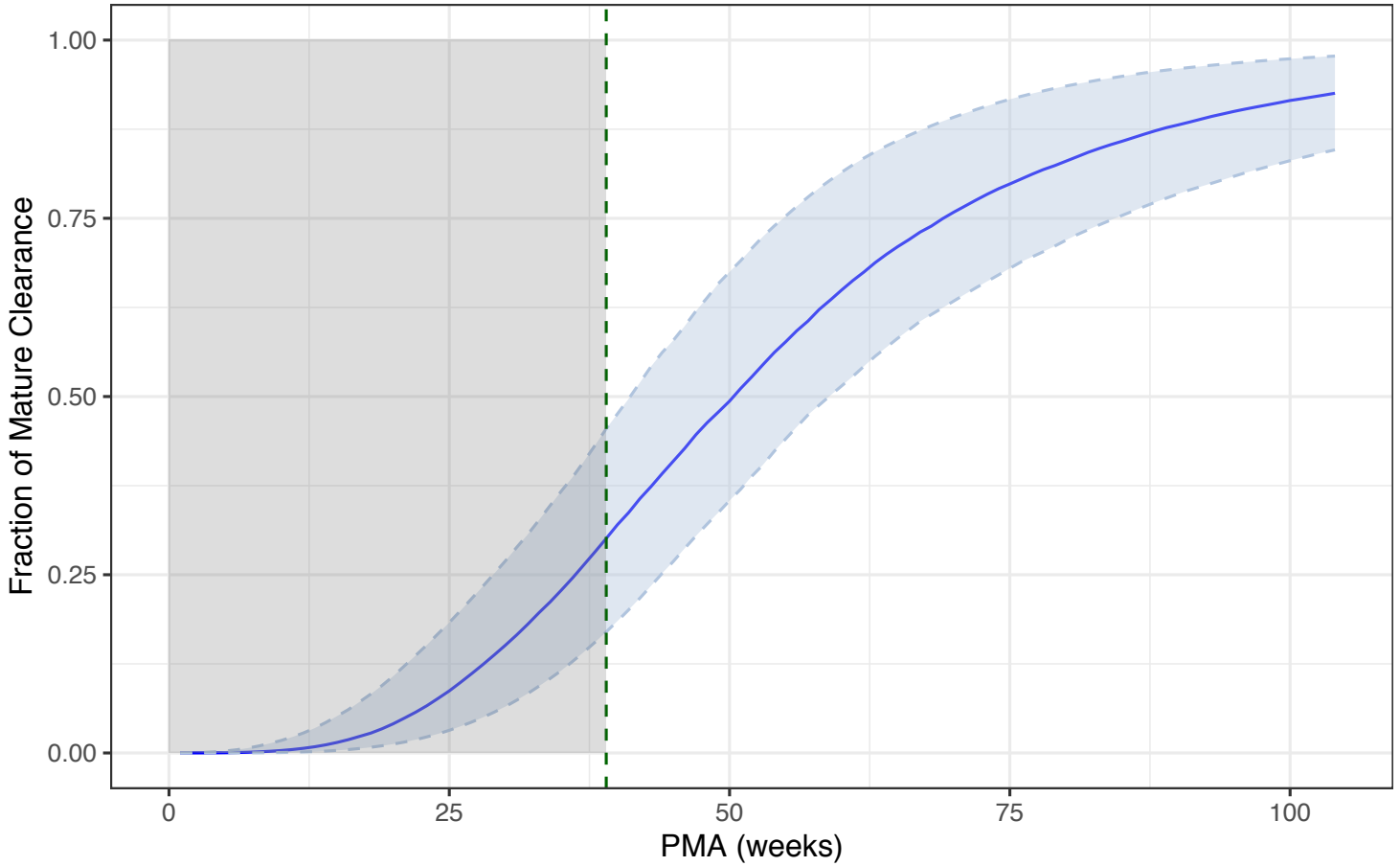
Testing Assumptions
Uncertainty in Clearance Maturation



Source code: Pediatric_SimEst_Example.R
Source graphic: ./deliv/figure/maturation.pdf

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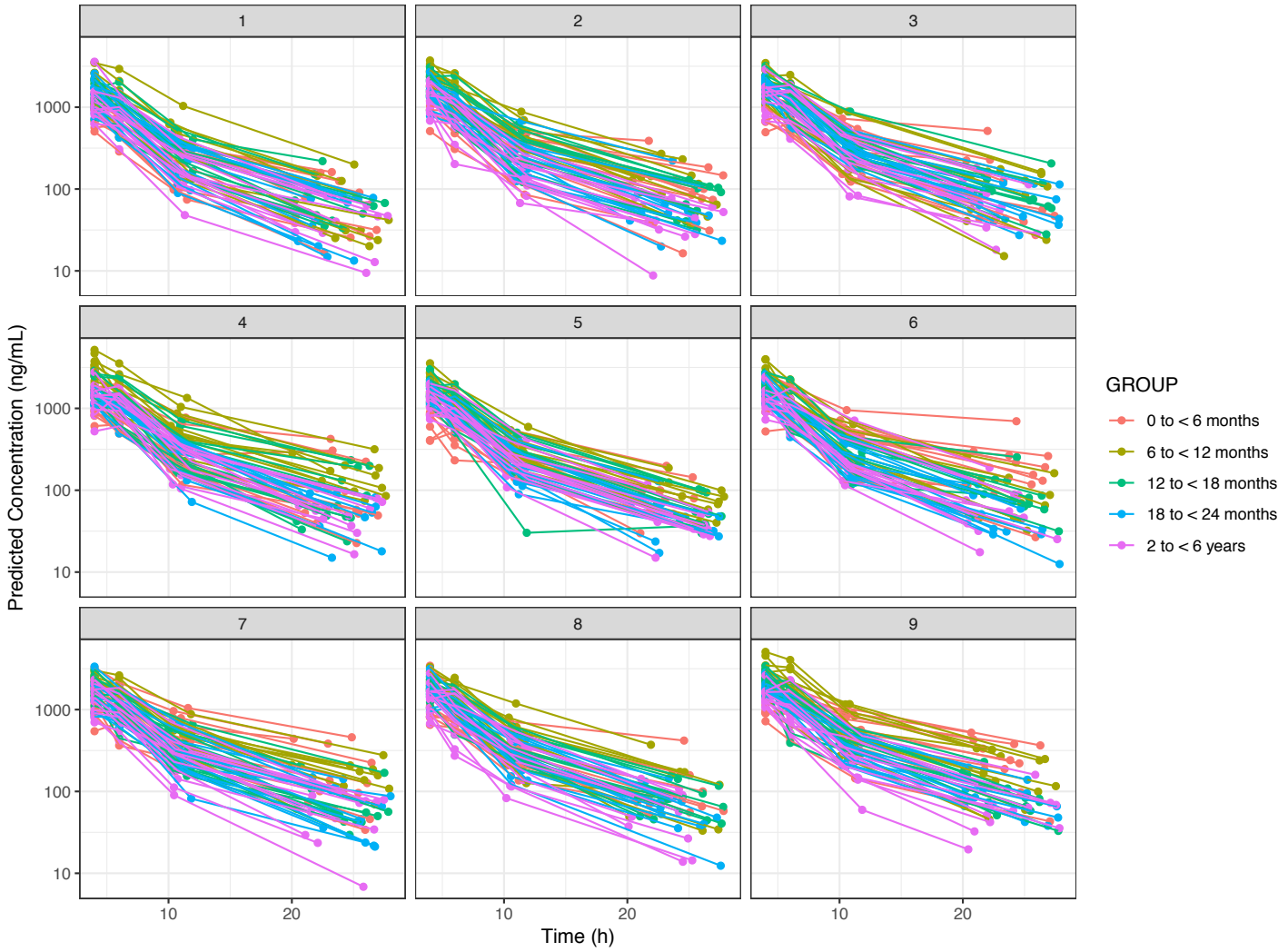
Simulated Pediatric Concentration-Time Profiles



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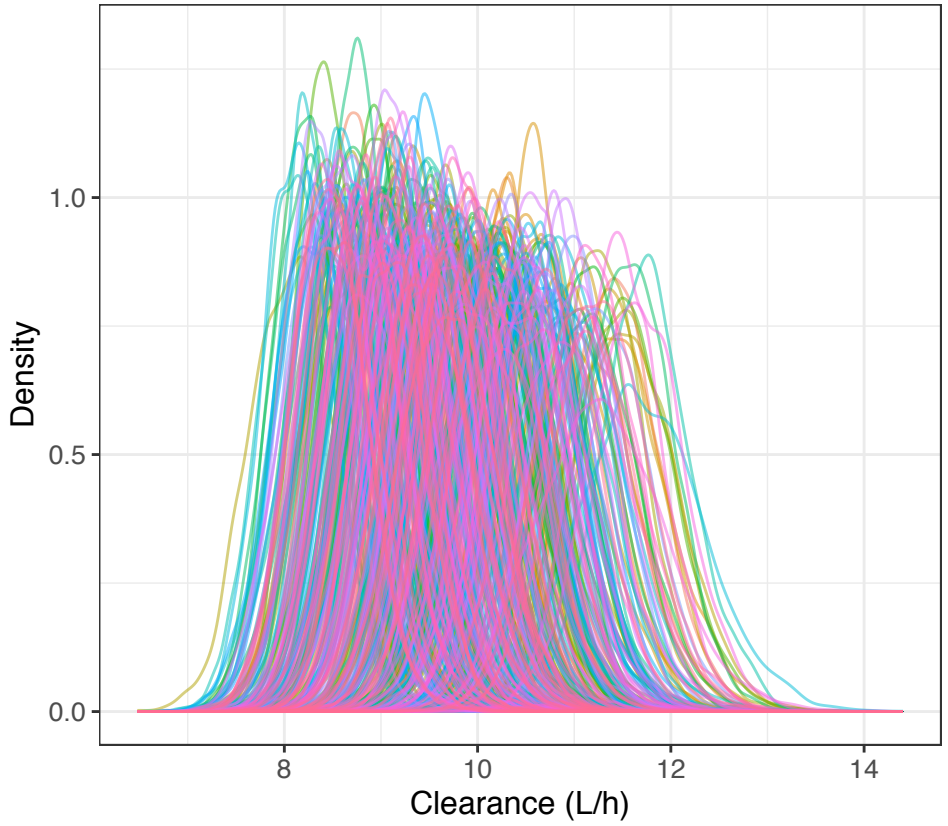
Results: Posterior Distributions



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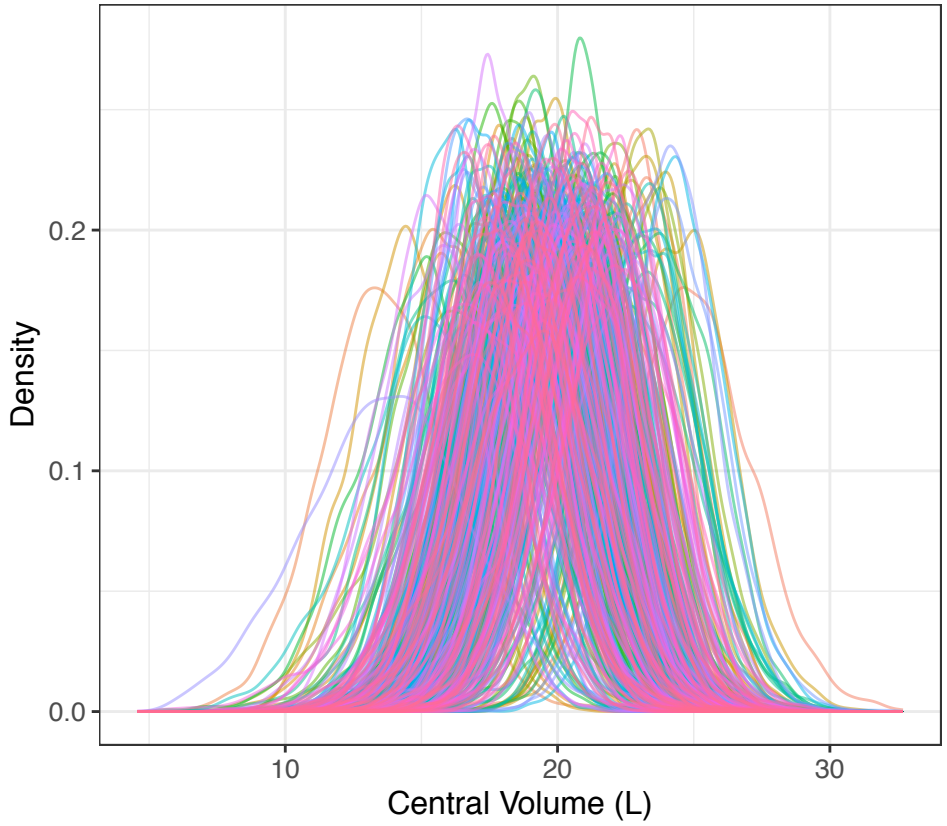

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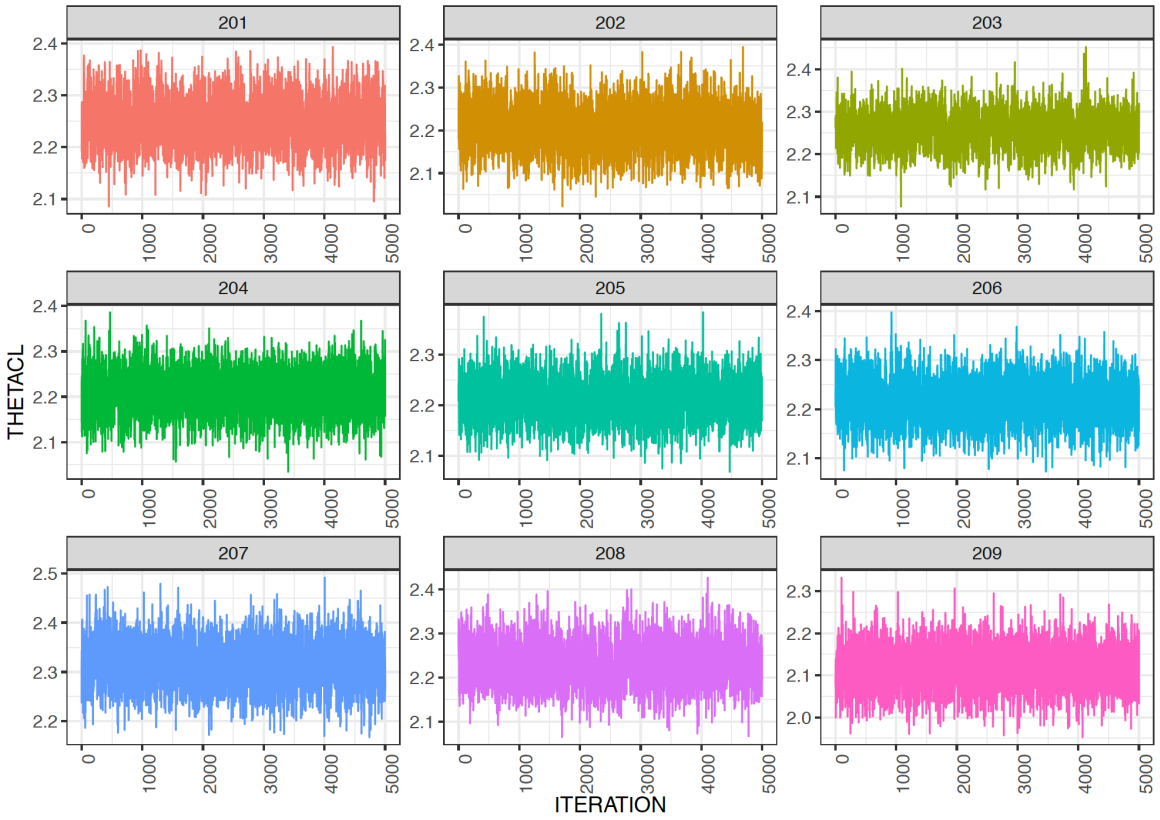
Source graphic: ./deliv/figure/V_dist_SSE.pdf

Results: Parameter Trace Plots



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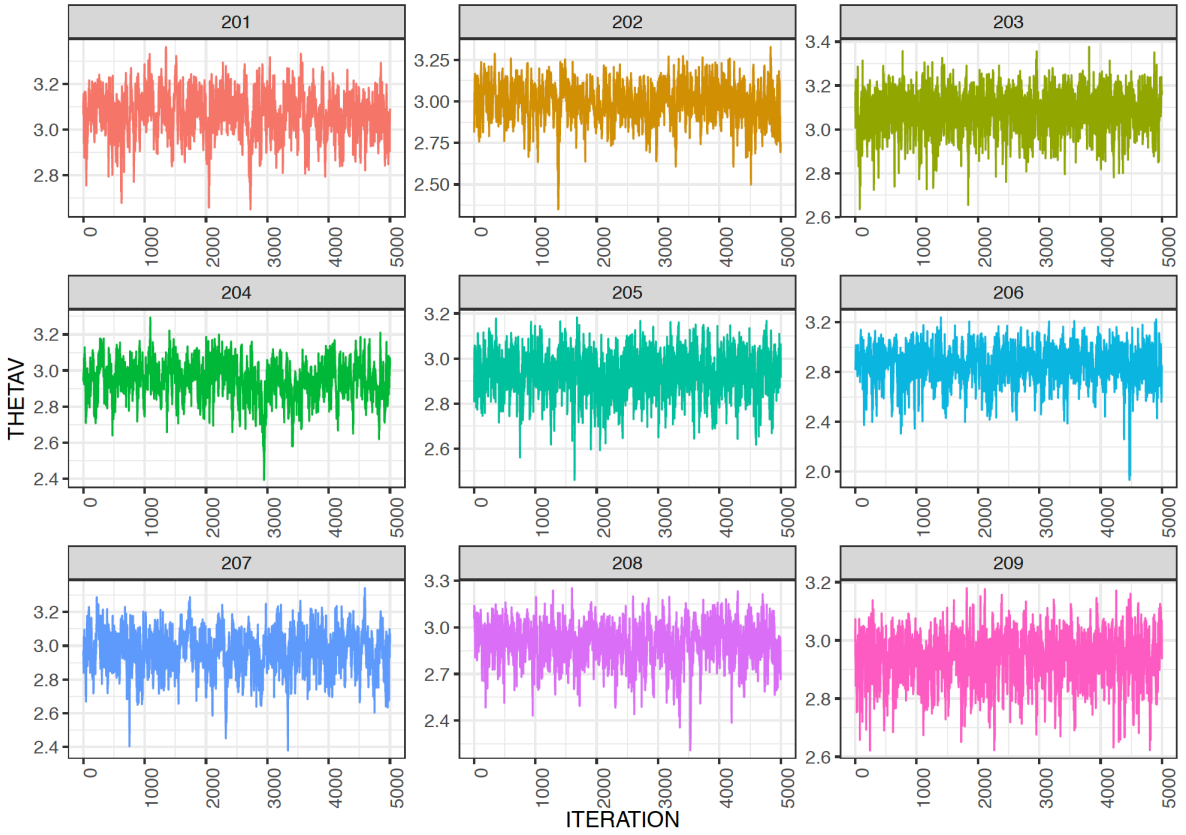

Source code: Pediatric_SimEst_Example.R
Source graphic: ./deliv/figure/V_trace.pdf

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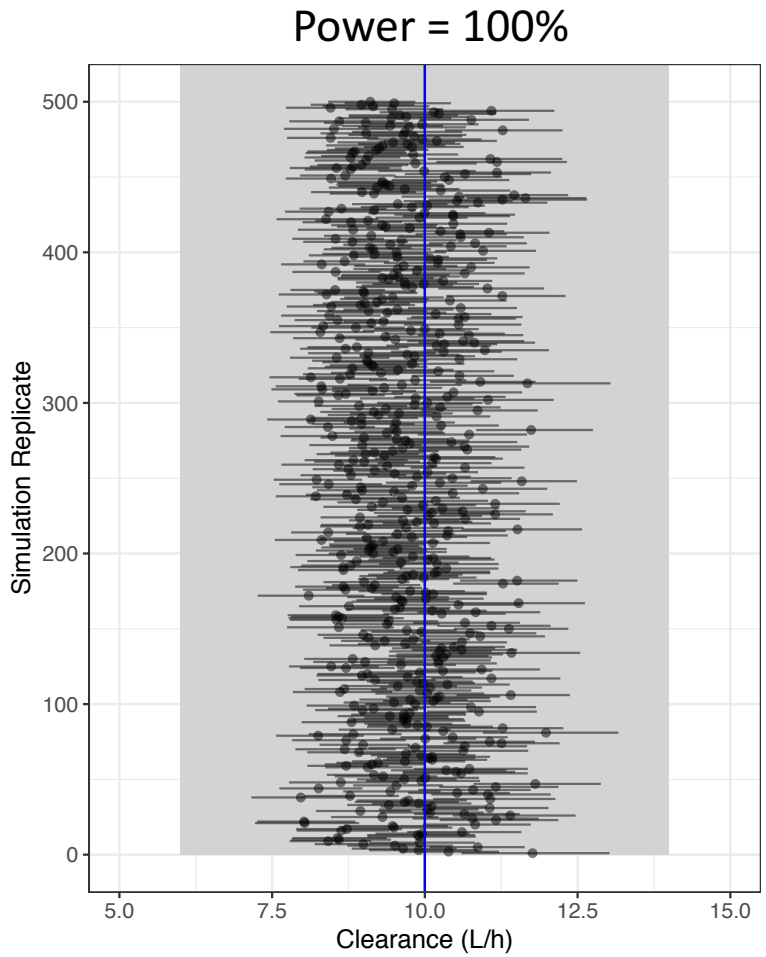
Results: Power Calculation



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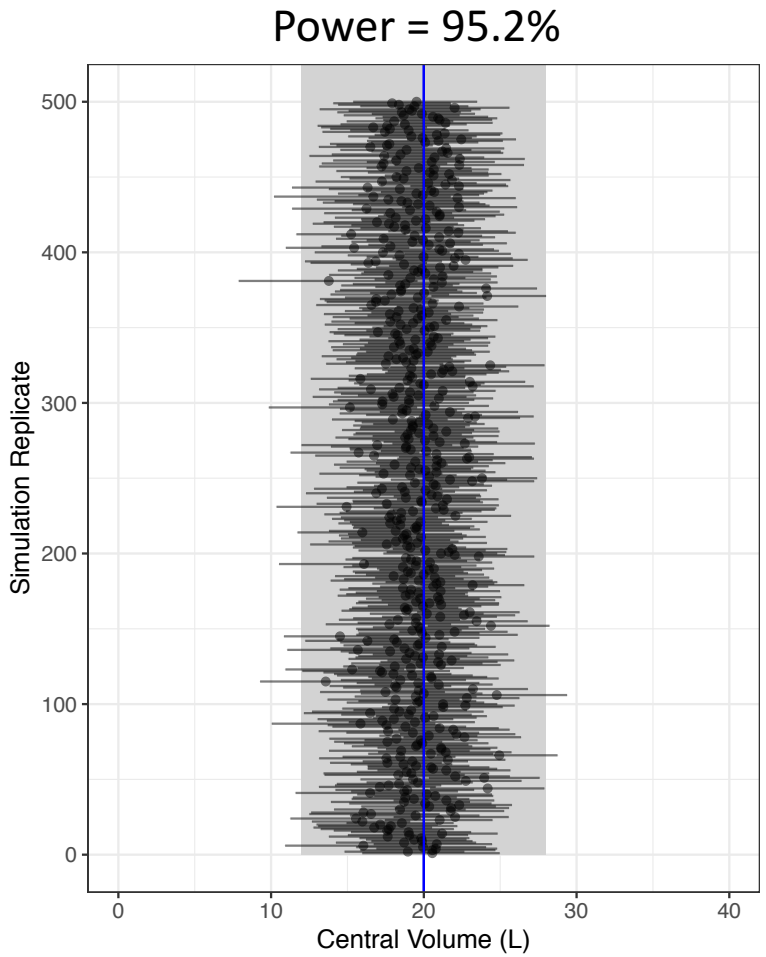

Source code: Pediatric_SimEst_Example.R
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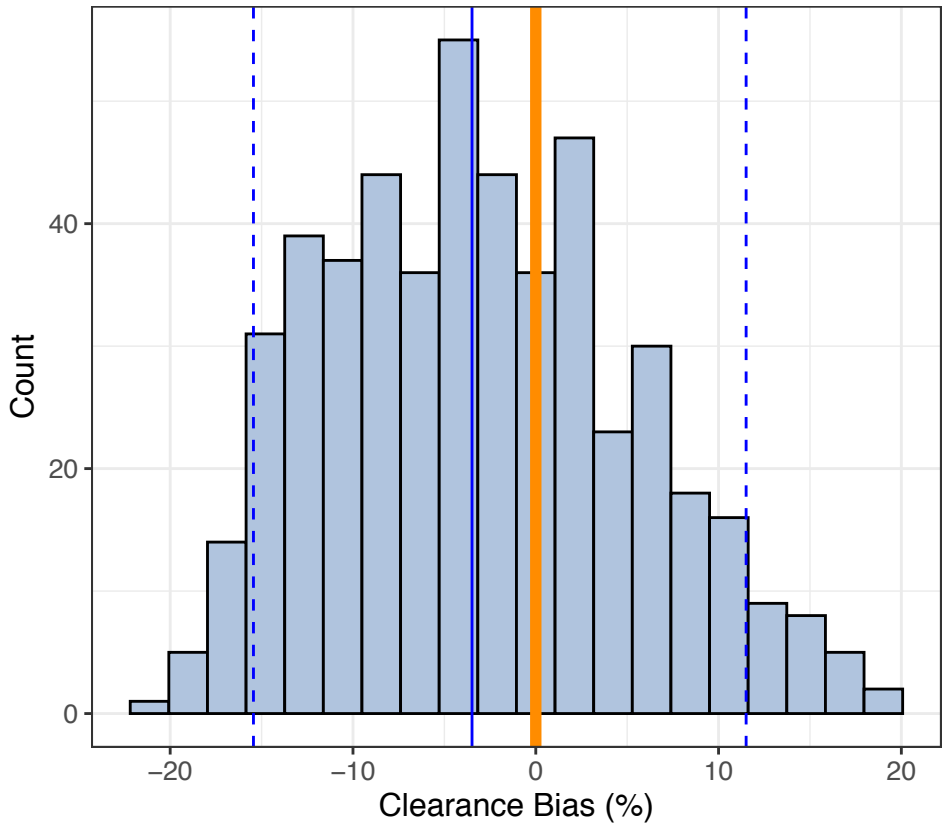
Results: Bias in Population Parameter Estimates



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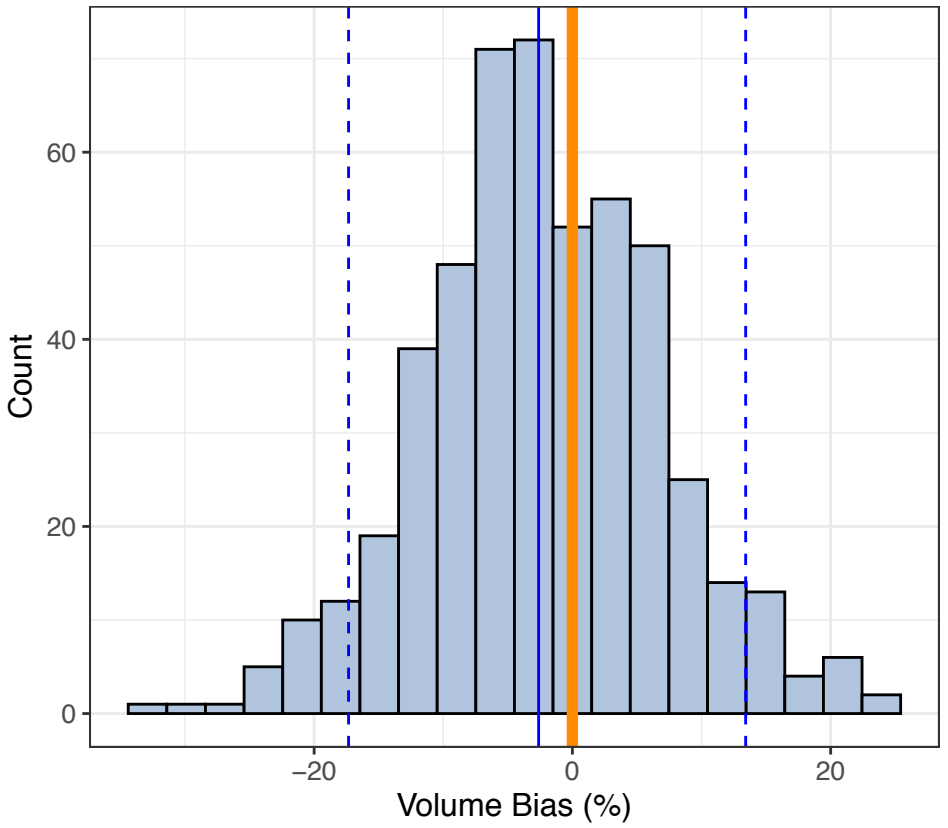

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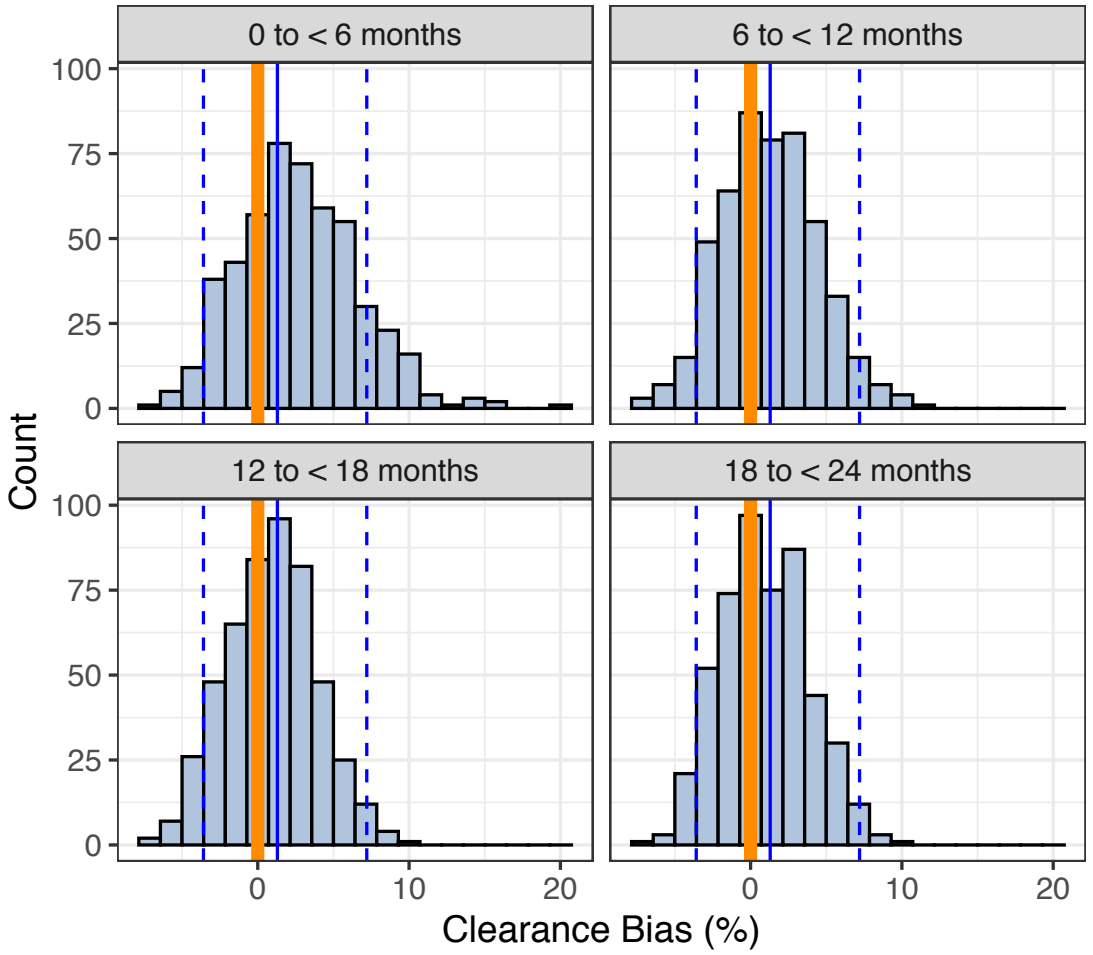
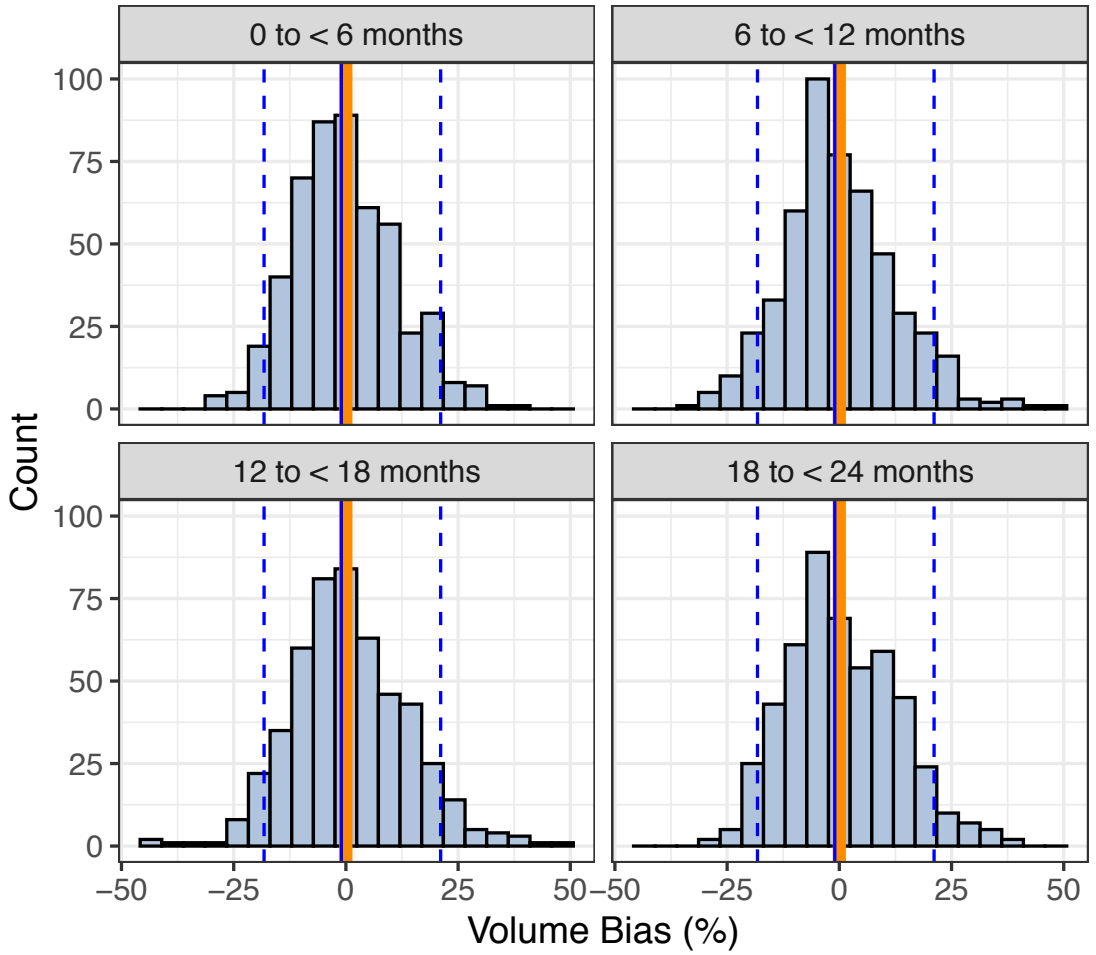
Results: Bias in Individual Parameter Estimates



Source code: Pediatric_SimEst_Example.R
Source graphic: ./deliv/figure/CL_group_bias.pdf



Source code: Pediatric_SimEst_Example.R
Source graphic: ./deliv/figure/V_group_bias.pdf

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Fulfilling the Requirement Using Pop PK:
An Example Approach

- The quality standard criteria was met using a pop PK approach (NCA not suitable for this situation)
- The trial design was evaluated within the context of the intended analysis (pooled with adult data)
- Using Bayesian methodology with select informative priors ensures that estimates of key parameters of interest are driven by the pediatric study data and not adult PK data
- FDA/EMA feedback has confirmed the acceptance of the Bayesian method for evaluating the pediatric PK study design

Questions for Consideration

- Recommendation for NCA for age subgroups, while pop PK analysis acceptable (or preferred)?
- Interested in estimating the continuous parameter relationship across the age ranges, not in individual subgroups - why not use a model-based method for assessment of design performance?
- Could calculation of SE by propagating from covariate effect estimates lead to inflated imprecision in key parameters, leading to false interpretation of information content in pediatric trial design?

Questions for Consideration

- Should practical considerations be made for populations/situations where it would be difficult satisfy the quality standard?
  - Population with rare disease
  - Quality standard applies for CL only, not Vc when designing a pediatric trial for an extended release product
  - Medical intervention does not allow for sample collection at an informative time
- Quality standard addresses precision of estimates – should it also address bias?

Recommendations for Success

- Test assumptions (uncertainty distributions, sensitivity analyses)
- The FDA recognizes that multiple methods may be applied to address the quality standard - a different approach may be applicable for your drug/circumstances
- Have an open dialog with the FDA/EMA regarding your proposed methodology, study design, and intended analysis

Bayesian Analysis for Pediatric Drug Development

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