Challenges in Developing Biologics for Pediatric Diseases

Approaches to Dose Selection, Study Design, and Analysis

Conducting studies in the pediatric population is challenging

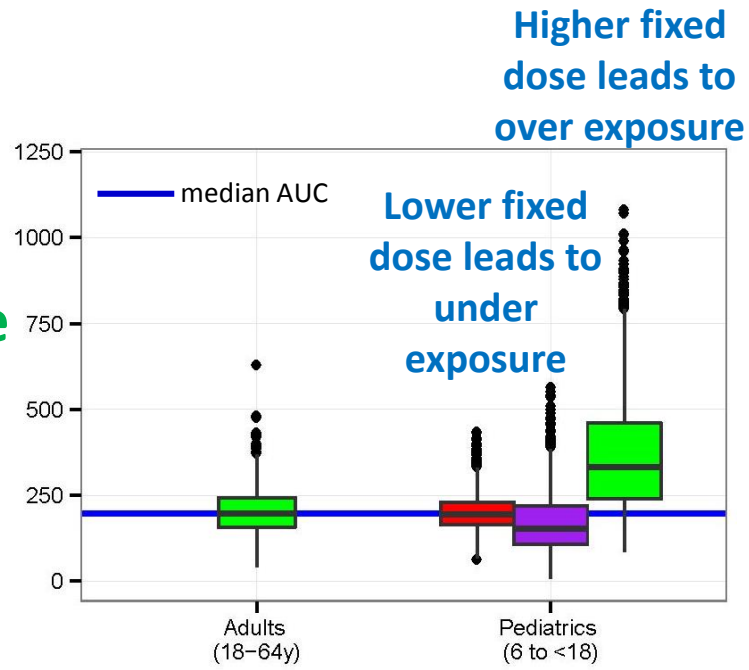
- Study goals can vary widely
  - Is it a first in pediatrics study or a study to confirm safety/efficacy?
  - Do you want to match exposures in adults?
  - Do you want to assess pharmacodynamics or a clinical measure?
- Modeling and simulation can help to address these questions
  - Selection of a fixed dose to match exposure in adults
  - Design/analysis of a study to detect PK differences in pediatric subjects
  - Model based meta-analysis to evaluate efficacy of a single arm pediatric study
  - Addressing regulatory requirements based on limited pediatric data

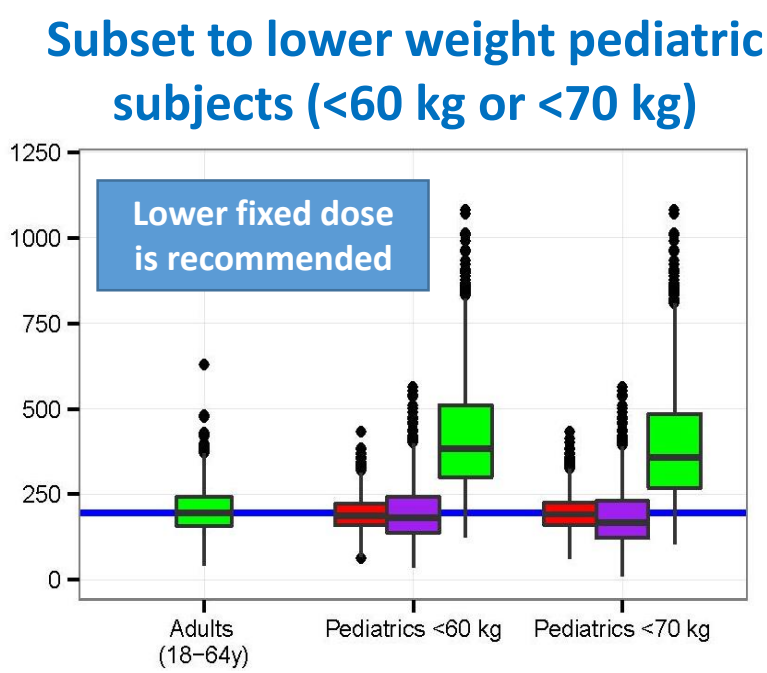
Exposure matching to guide dose selection for first in pediatric study

Higher fixed dose

Lower fixed dose

mg/kg dose





A tiered fixed dosing approach provided an adequate match to adult exposure

- Pediatric subjects with body weight ≥ 60 kg receive higher fixed dose (adult dose)
- Pediatric subjects with body weight < 60 kg receive lower fixed dose

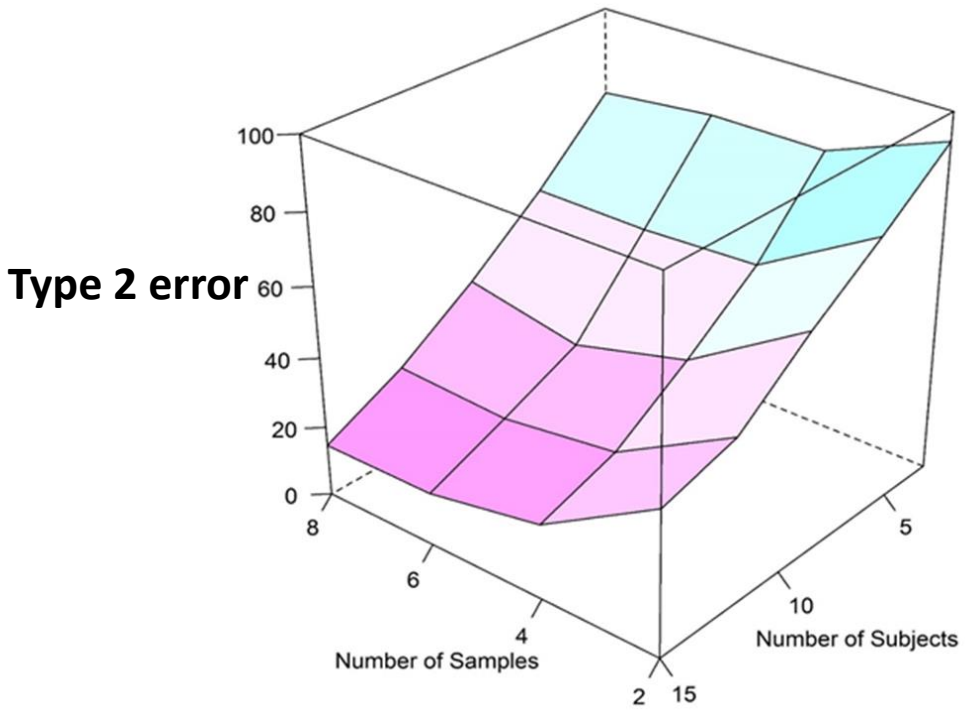
Design/analysis of a study to detect PK differences in pediatric subjects

- Studies should minimize the number of subjects and samples, while still obtaining precise estimates of key model parameters
- While optimal sampling tools provide the PK sampling times and number of subjects to robustly estimate PK parameters, the recommendations are not always feasible for pediatric studies.
- The use of informative priors (Bayesian approach) can further reduce the amount of data collection required in pediatric subjects
- Simulation based methods using Bayesian priors can determine the minimal study design needed to estimate PK (eg when pediatric clearance is the same, faster (2x/4x) or slower (0.6x/0.8x) than adult clearance) and can be used to analyze the resulting pediatric study dataset

Details of the methodology are provided in Effect of Clinical Study Design on Clearance Estimation in Pediatrics using Adult Bayesian Priors for compounds with linear PK (presented at ACCP 2014 and submitted to CPK) or non-linear PK (presented at ACOP 2015)

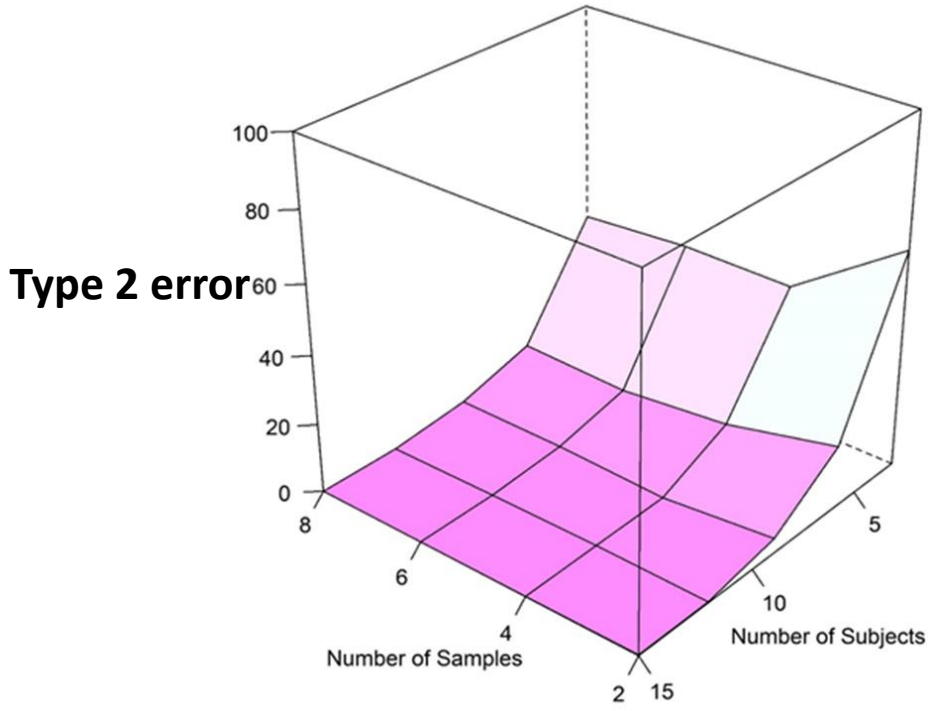
Influence of study design on estimation of pediatric clearance

1.2x Adult clearance



Detecting 1.2x clearance in pediatrics requires 15 subjects with 8 samples per period

1.4x Adult clearance



Detecting 1.4x clearance in pediatrics requires 6 subjects with 2 samples per period

Assessing comparability of efficacy based on limited data in pediatric subjects

- Pediatric studies may be conducted in rare diseases or hard to recruit populations
- Literature based meta-analysis models incorporate prognostic factors, covariates, and variability of efficacy endpoints within the disease and patient population from a database of published studies
- Based on summary factors (prognostic and covariate) from the pediatric study population, the model can
  - project efficacy of standard of care (SOC)
  - assess efficacy of novel treatments compared to SOC using clinical trial simulation
- Meta-analysis can help demonstrate treatment benefit for a single arm study or study with fewer subjects

Projected Efficacy from Meta-analysis

Projected and Observed Overall Response Rate (ORR) and Duration of Response (DOR) for Pediatric Study Population

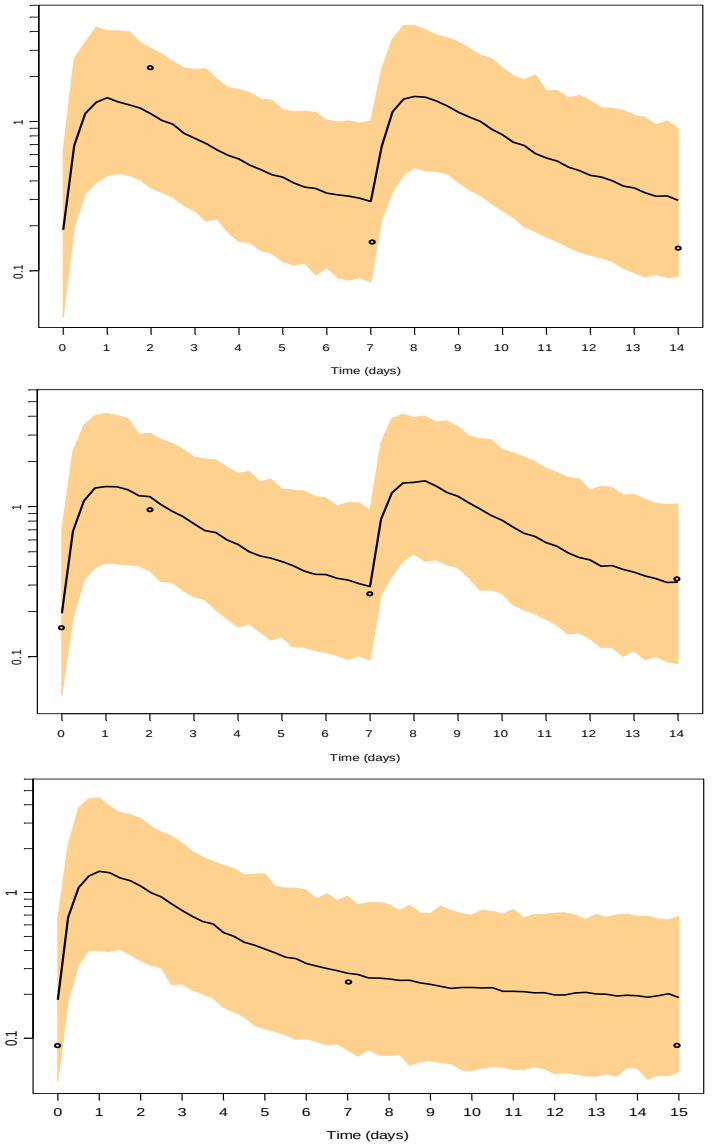
Treatment	ORR (95% CI)	DOR (95% CI)
Projected Results for Standard of Care	18.4% (6.2 – 28.4)	2.8 months (1.2 – 3.6)
Observed Results for Novel Treatment	42% (29 – 48)	5.9 months (4.0 – 7.3)

Virtual Clinical Trial Simulation Results Comparing Standard of Care to Novel Treatment

ORR (odds ratio)	DOR (hazard ratio)
3.50 (1.63 – 8.40)	0.60 (0.47 – 0.76)

PK Simulations to Satisfy Pediatric Requirement

- Requirement to evaluate PK in 15 pediatric subjects <6 years old
- After prolonged multi-year effort, only able to enroll 3 subjects <6
- Model based simulations were performed to predict exposure in the subjects <6; model was developed using PK data from adults and older pediatric subjects (6 to 18)
- Available PK data, when used in combination with simulation results, provided sufficient evidence to support that PK in subjects < 6 years old is consistent with older children (6 to 18 years of age) and adults.
- Simulations allowed completion of the regulatory requirement with fewer subjects than originally required



Modeling and simulation can play a vital role in design and analysis of pediatric studies

- Prediction of doses to match adult exposures
- Development of study designs and analysis of minimal datasets to detect differences in PK between adult and pediatric subjects
- Assessment of efficacy in pediatric studies
- Addressing pediatric requirements