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Optimizing Pediatric Drug Development in Psychiatry: Quantitative Methods to Support Extrapolation of Efficacy

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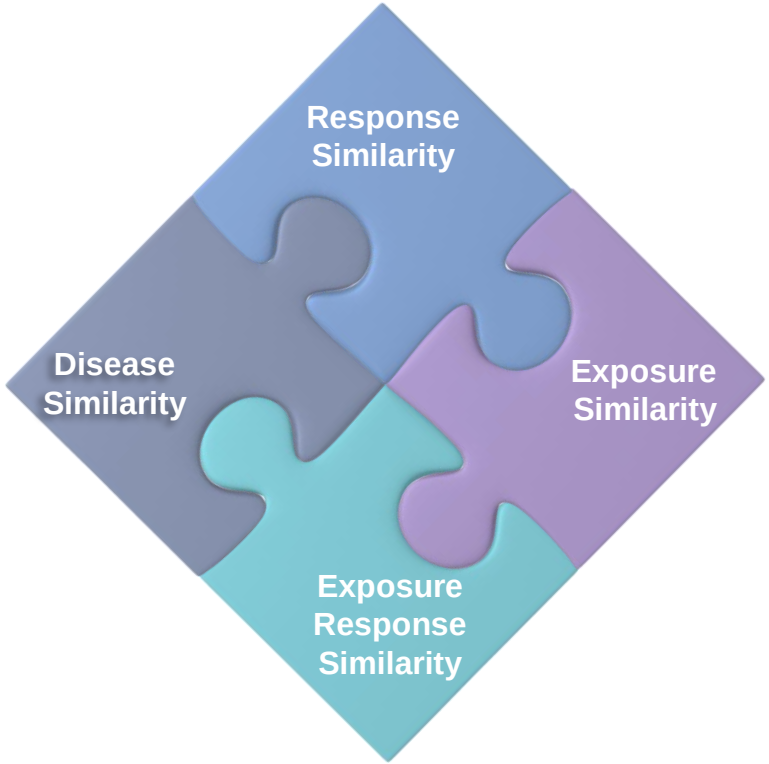
Is there Evidence to Support Full Extrapolation of Efficacy?



Pediatric Extrapolation Concept

Different disease or response to treatment ⟷ Similar disease and response to treatment

Large gaps in knowledge ⟷ High confidence

Pediatric Extrapolation Plan

Adequate and well-controlled trials ⟷ Exposure-matching/concurrent enrollment

ICH Harmonized Guidelines E11A: Pediatric Extrapolation (April 2022)

Qualitative Evidence to Build Foundation for Extrapolation

Clinical Outcome Assessments

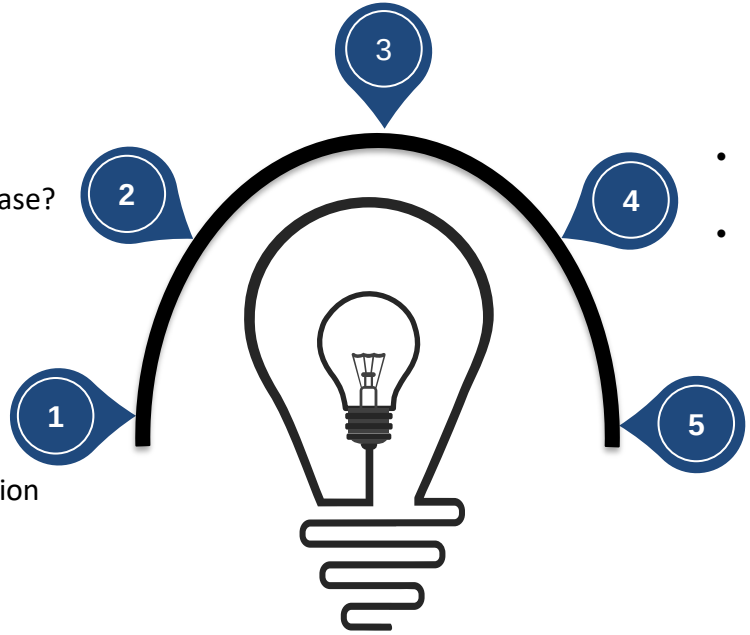
- Measurements used to assess clinical course
- Validation across age groups

Diagnostic Criteria

- What are the manifestations or diagnostic criteria that define disease?
- Disease subtypes

Study Endpoints

- Accepted efficacy short-term or long-term study endpoints
- Study design and duration



Disease Etiology and Progression

- Differences in clinical presentation
- Age-dependent phenotypic presentation
- Biomarkers common in the pathophysiology of disease

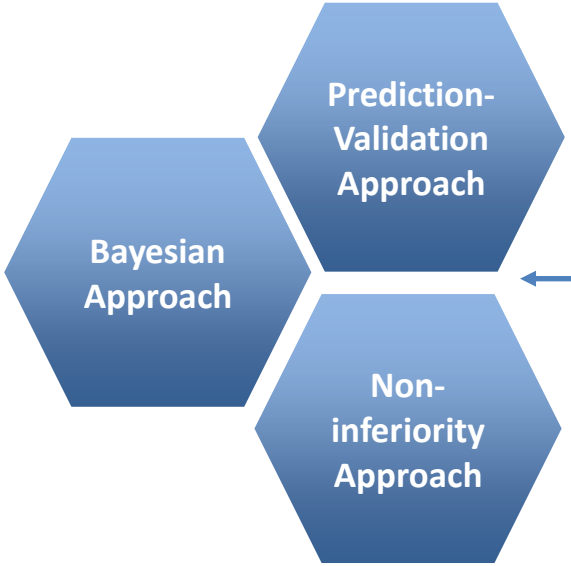
Treatment Considerations

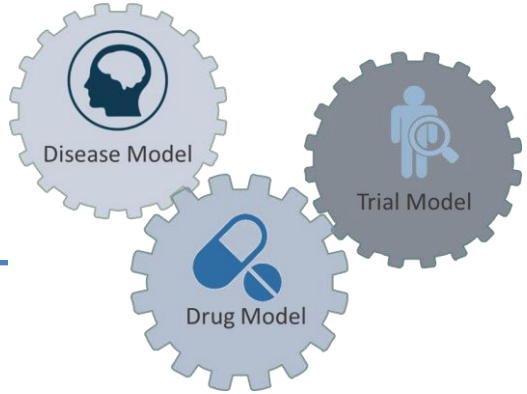
- Pharmacological and non-pharmacological interventions
- Timing of treatment relative to onset, treatment frequent, length of treatment, and dosing
- ADME and MoA

Quantitative Methods to Justify Extrapolation

1. Extrapolation is the concept of extending information and conclusions available from studies in one or more subgroups of the patient population (source) or in related conditions, to make inferences for another subgroup (target) or condition
2. Guidelines do not define similarity from a statistical perspective; analytical approaches must be tailored to the amount and types of data and the clinical setting
3. Examples of quantitative approaches are all fundamentally based on summarizing the prior information while integrating expert judgement and new data (current drug development approach for many pediatric indications is based on Bayesian thinking)

Quantitative Model-Based Methods to Justify Extrapolation





e.g., Response = Baseline – placebo effect(t) – drug effect(t)

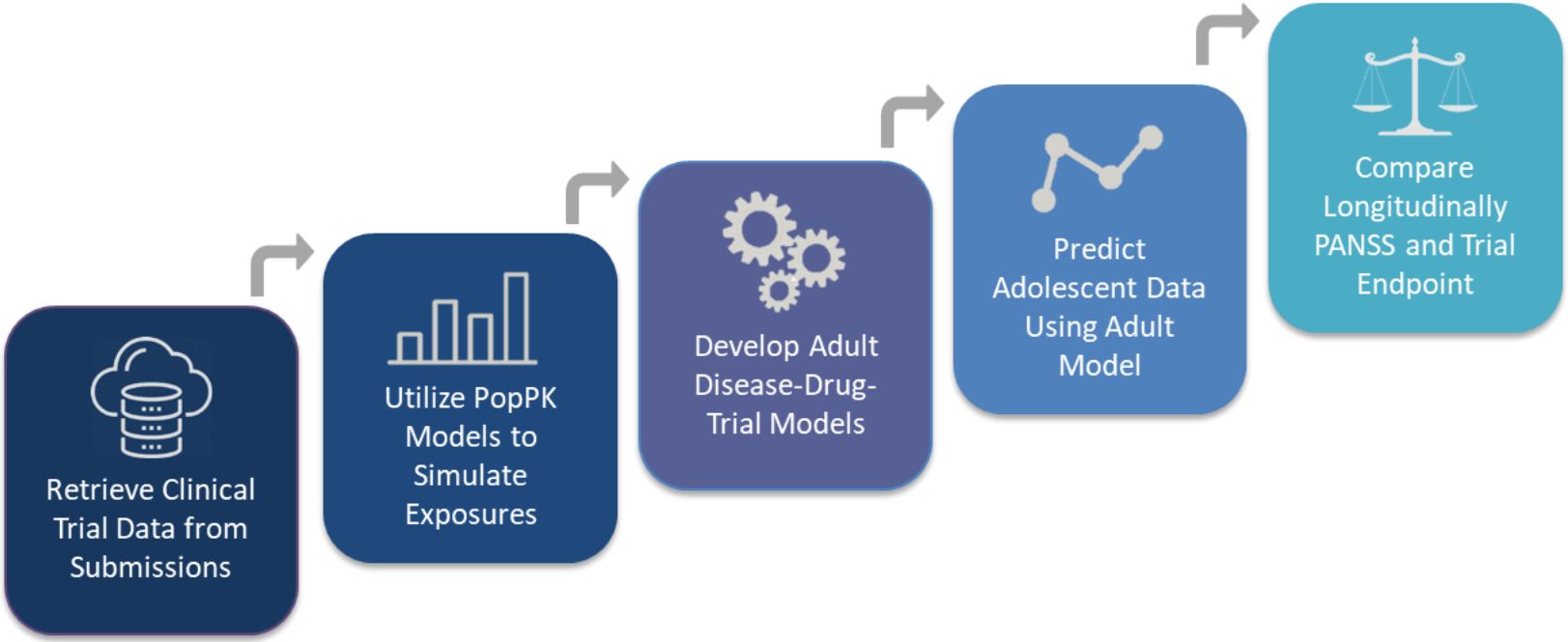
Disease Model:
-Describes natural course based on clinical outcome or biomarker
-Includes patient characteristics (e.g., baseline severity, demographics) that influence proregression

Drug Model:
-incorporates E-R relationship
-effect can be on various disease model parameters
-curative, symptomatic, or disease modifying, effects

Trial Model:
-important for trial simulation
-can incorporate patient compliance and dropouts
-useful to evaluate differences across study designs

Prediction-Validation Based Approach

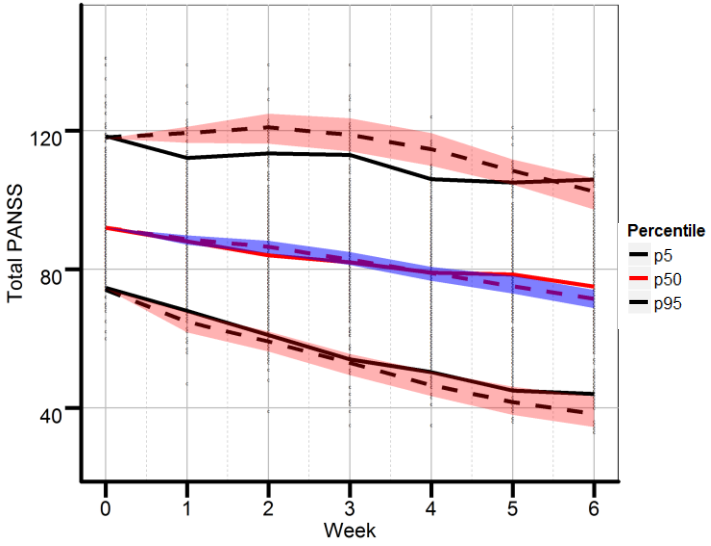
Case Example for Extrapolation in Schizophrenia

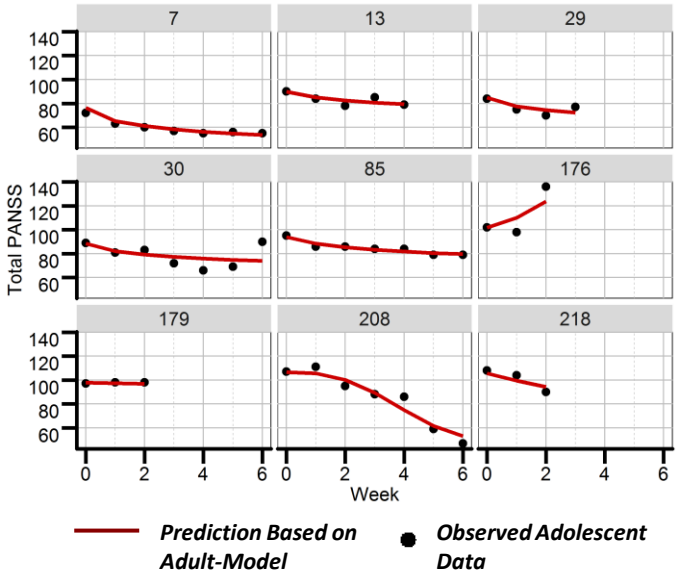


Prediction-Validation Based Approach

Case Example for Extrapolation in Schizophrenia (Disease Similarity)

$$PANSS(t) = BSL \times \left[1 - Pmax \times \left(1 - exp^{\left(-\frac{t}{TD}\right)^{POW}}\right)\right]$$



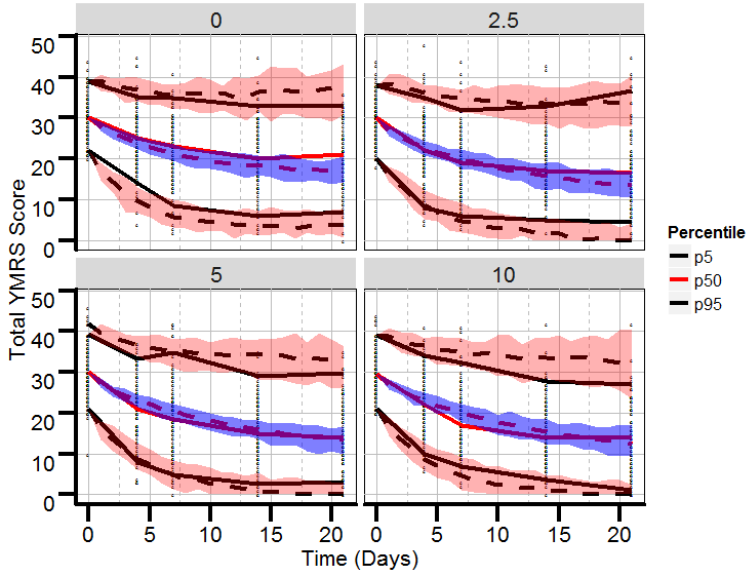


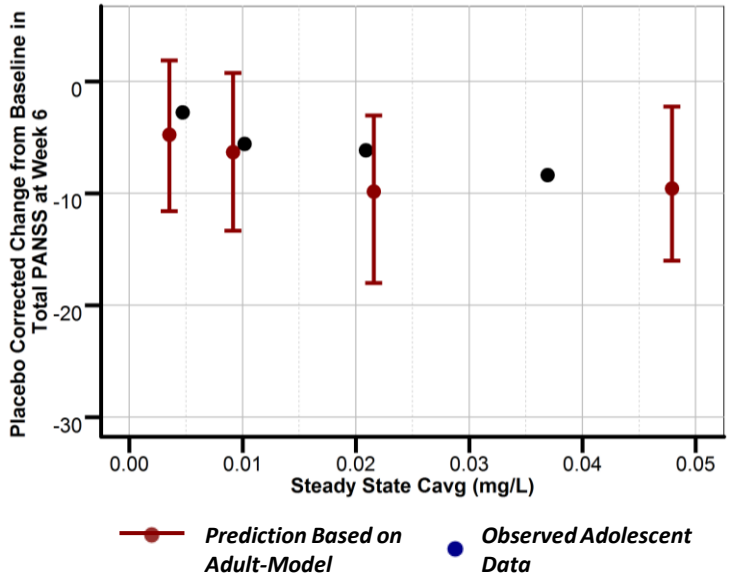
Kalaria SN, et al. Extrapolation of efficacy and dose-selection in pediatrics: a case example of atypical antipsychotics in adolescents with schizophrenia and bipolar I disorder. *J Clin Pharmacol.* 2021;61:S117-24.

Prediction-Validation Based Approach

Case Example for Extrapolation in Schizophrenia (E-R Similarity)

$$PANSS(t) = BSL \times \left[1 - Pmax \times \left(1 - exp^{\left(-\frac{t}{TD}\right)^{POW}}\right)\right] \times \left[1 - \left(\frac{Emax \times Cavg_{ss}}{EC_{50} + Cavg_{ss}}\right) \times \left(1 - exp^{(-k_T \times t)}\right)\right]$$





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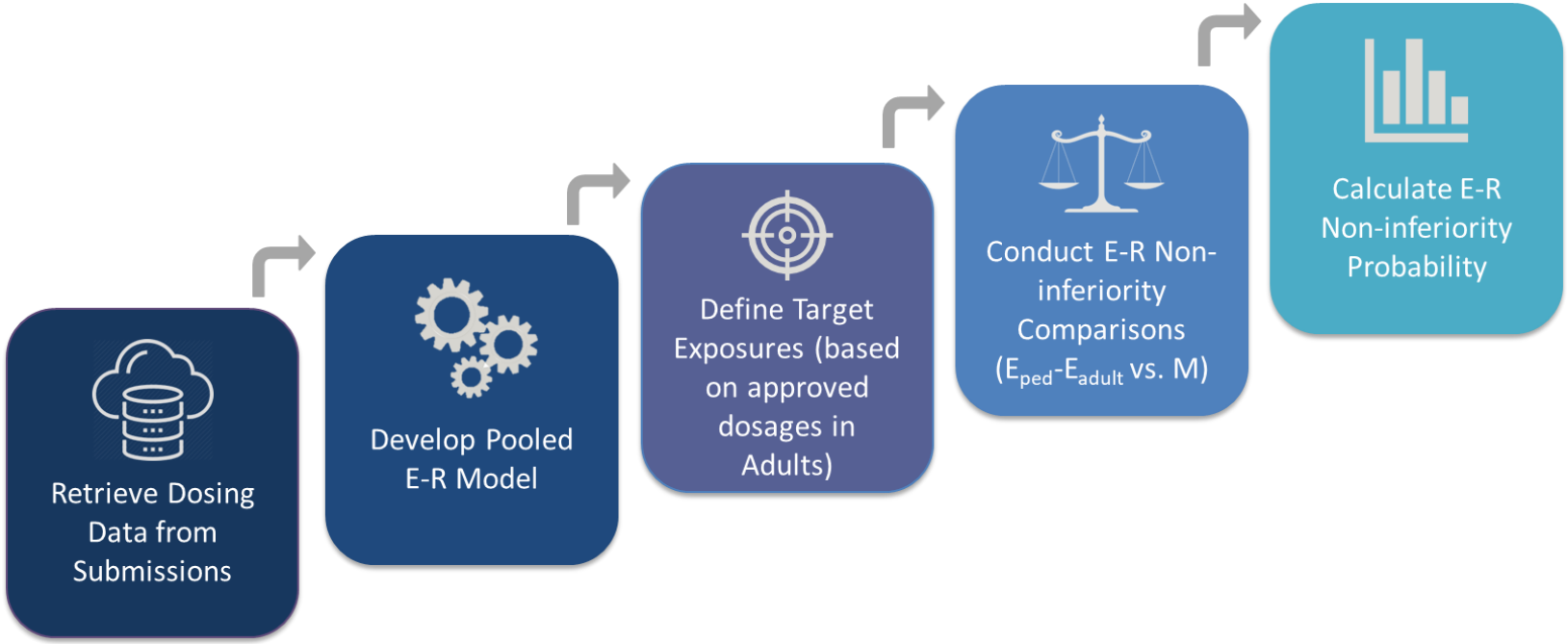
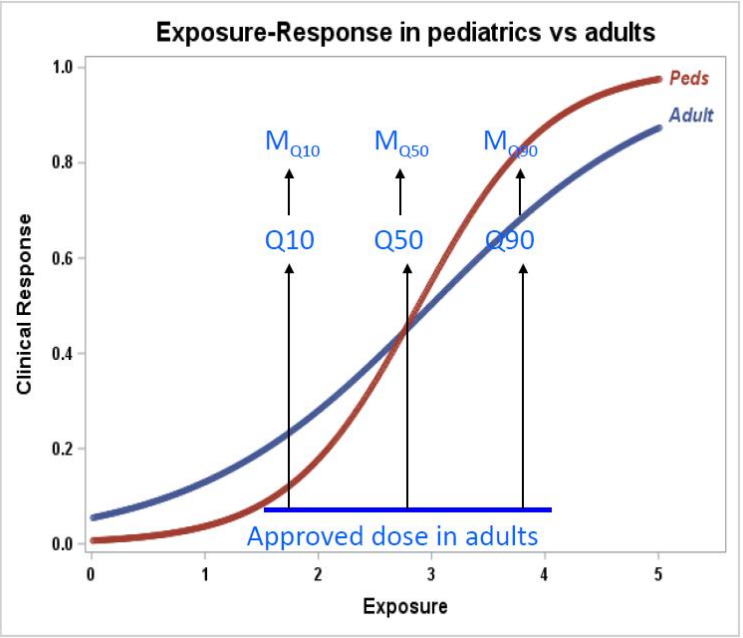
Non-Inferiority Model Based Approach

Case Examples for Extrapolation



Non-Inferiority Model Based Approach

Case Examples for Extrapolation



Quantitative Metric to Evaluate Exposure-Response Difference

- Point Estimates:
  - Use pediatric and adult exposure-response model predictions to identify a single value which serves as the "best estimate" of the efficacy difference in pediatric and adult patients against the non-inferiority margins at three exposure levels

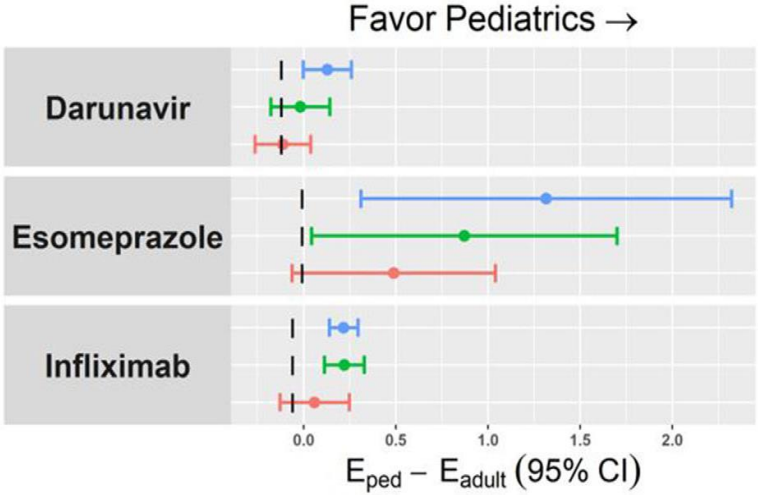
- Point Estimates with Uncertainty
  - Can estimate uncertainty using bootstrap method (resampling from the raw data) or Bayesian method (obtain posterior samples of the regression parameters for both the adults and pediatric populations and calculate the difference)
  - Calculate the percentage of these cases where the noninferiority criterion is met and compare to a decision threshold

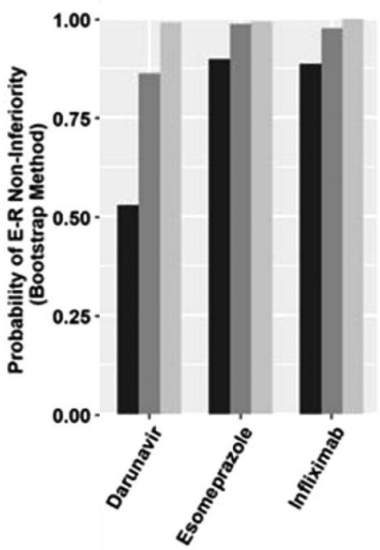
Zhang Q, et al. Applying the noninferiority paradigm to assess exposure-response similarity and dose between pediatric and adult patients. *J Clin Pharmacol.* 2021;61:S165-74.

Non-Inferiority Model Based Approach

Case Examples for Extrapolation

$$log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 \times exposure + \beta_2 \times population + \beta_3 \times (exposure\ x\ population) + \varepsilon$$





- Although none of the drugs meet the classical non-inferiority criteria for all three exposure levels (lower bound of the 95% CI cross the NI margin), the point estimates suggest non-inferiority between adults and pediatrics
- Wide confidence intervals suggest a larger sample size is required to make this a feasible approach
- Method limited by selection of noninferiority margin and decision threshold

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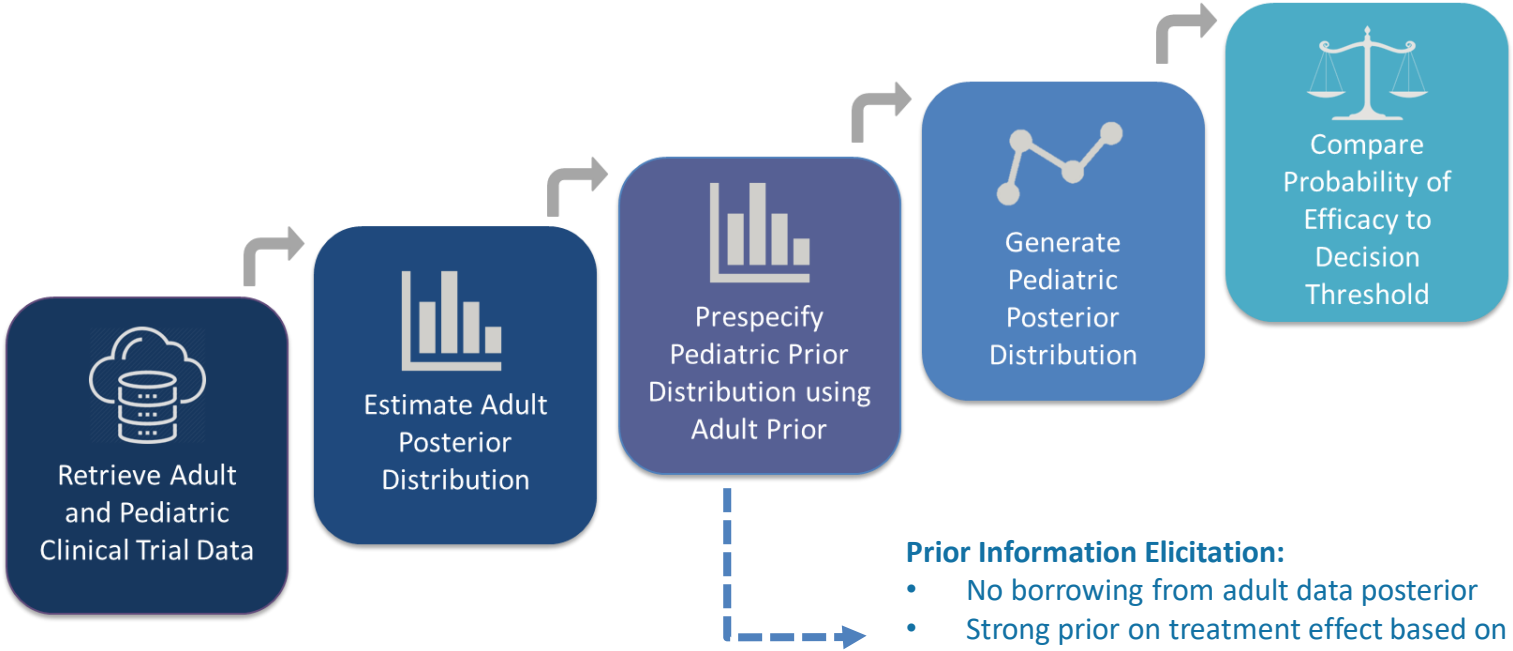
Bayesian Analysis of Pediatric Data

Case Example for Benlysta

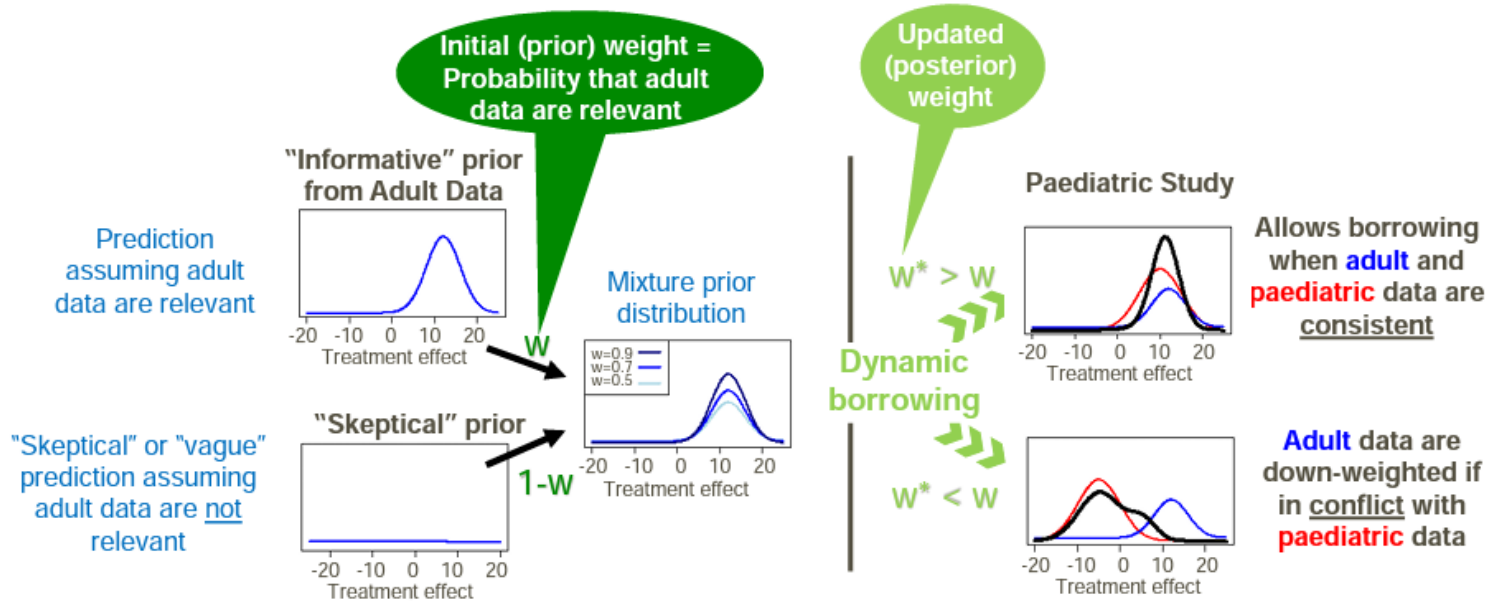


Prior Information Elicitation:

- No borrowing from adult data posterior
- Strong prior on treatment effect based on adult data
- Mixture of priors (Skeptical + Adult posterior)
- Highly skeptical prior
- Power prior

Bayesian Analysis of Pediatric Data

Case Example for Benlysta



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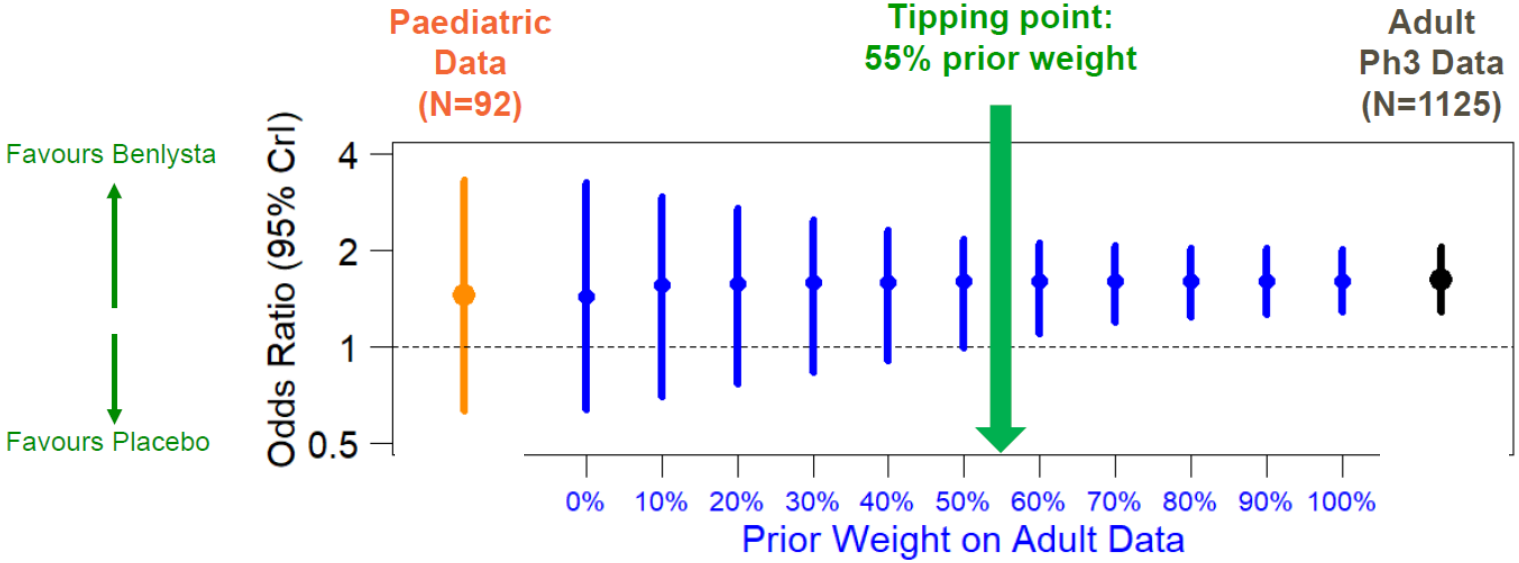
Bayesian Analysis of Pediatric Data

Case Example for Benlysta



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Bayesian Analysis of Pediatric Data

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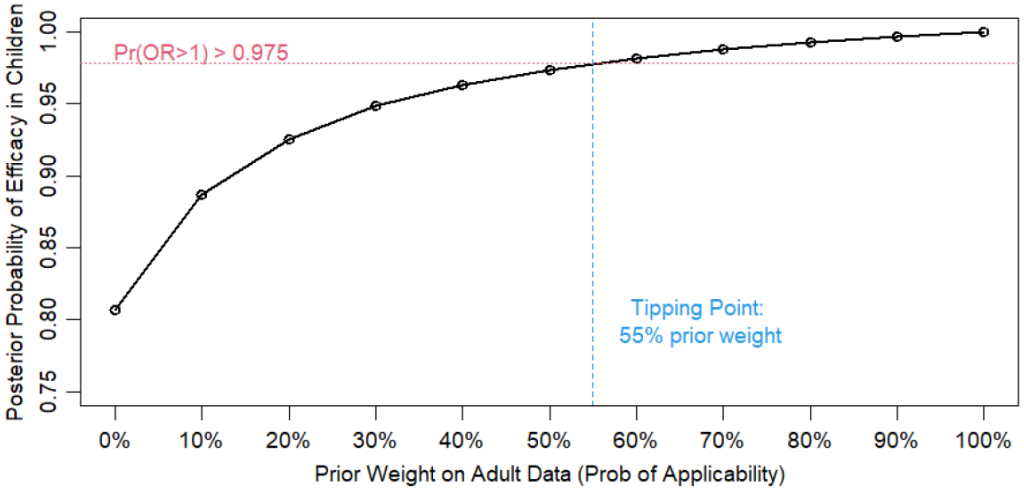

- Pediatric enrollment can be challenging in many settings, including for rare disease (low sample size typically limits ability to convincingly show evidence of a treatment effect)
- Bayesian dynamic borrowing can be a useful approach to formally incorporate adult data into pediatric clinical trials
- The results of this retrospective Bayesian analysis supported the approval in pediatrics
- Bayesian dynamic borrowing can be a more efficient way to generate evidence in challenging pediatric settings

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Acknowledgements

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