

A Bayesian is one who asks you what you think before a clinical trial in order to tell you what you think afterwards. (Senn, 1997b)

A BAYESIAN APPROACH TO INCORPORATING ADULT CLINICAL DATA INTO PEDIATRIC CLINICAL TRIALS

Jingjing Ye and James Travis, Office of Biostatistics (DB V and II)

Acknowledgement

Frank Harrell

Lisa LaVange

Mark Rothmann

Tom Permutt

Scott Komo

Laura Lee Johnson

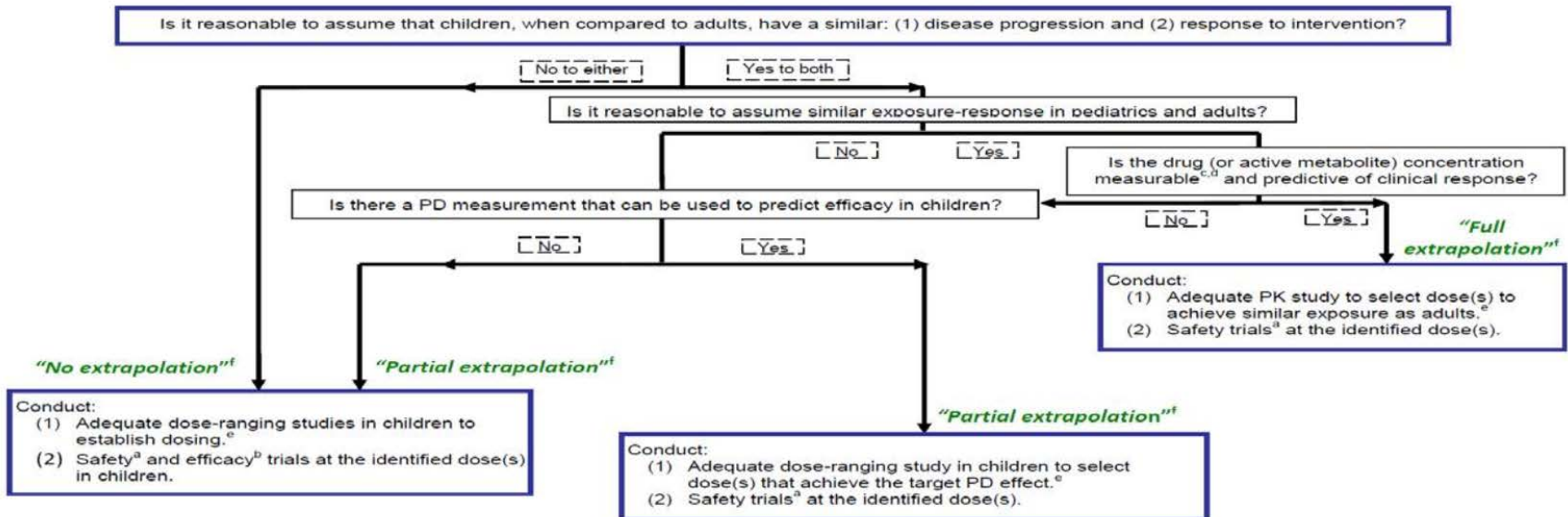
COA (Clinical Outcomes Assessment)

Staff

Overview

- In this talk we will explore a specific Bayesian approach that incorporates data from adult data in the analysis of pediatric clinical trials.
- This example is generally based on (Goodman and Sladky 2005) but used a different prior distribution.
- This approach is a variation on the equal but discounted approach described in (Spiegelhalter, Abrams et al. 2004) and discussed in (Greenhouse and Seltman 2005).

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

- a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
- b. For partial extrapolation, one efficacy trial may be sufficient.
- c. For drugs that are systemically active, the relevant measure is systemic concentration.
- d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
- e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
- f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." *Pediatrics*. 2011 Nov;128(5):e1242-9.

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products – Guidance for Industry

<https://www.fda.gov/downloads/drugs/guidances/ucm425885.pdf>

Planning a Bayesian Approach

- Elicit expert opinion on pharmacological action, dosing, disease process, tolerability, etc
- Quantify applicability – defines how to combine adult study posterior and skeptical peds stand-alone prior to form the pediatric study prior
- Conduct a Bayesian analysis on each of the individual adult studies using non-informative priors
- Bayesian meta-analysis to combine the posteriors from the adult studies
- Plan the pediatric study based on a Bayesian analysis

Bayesian Analysis

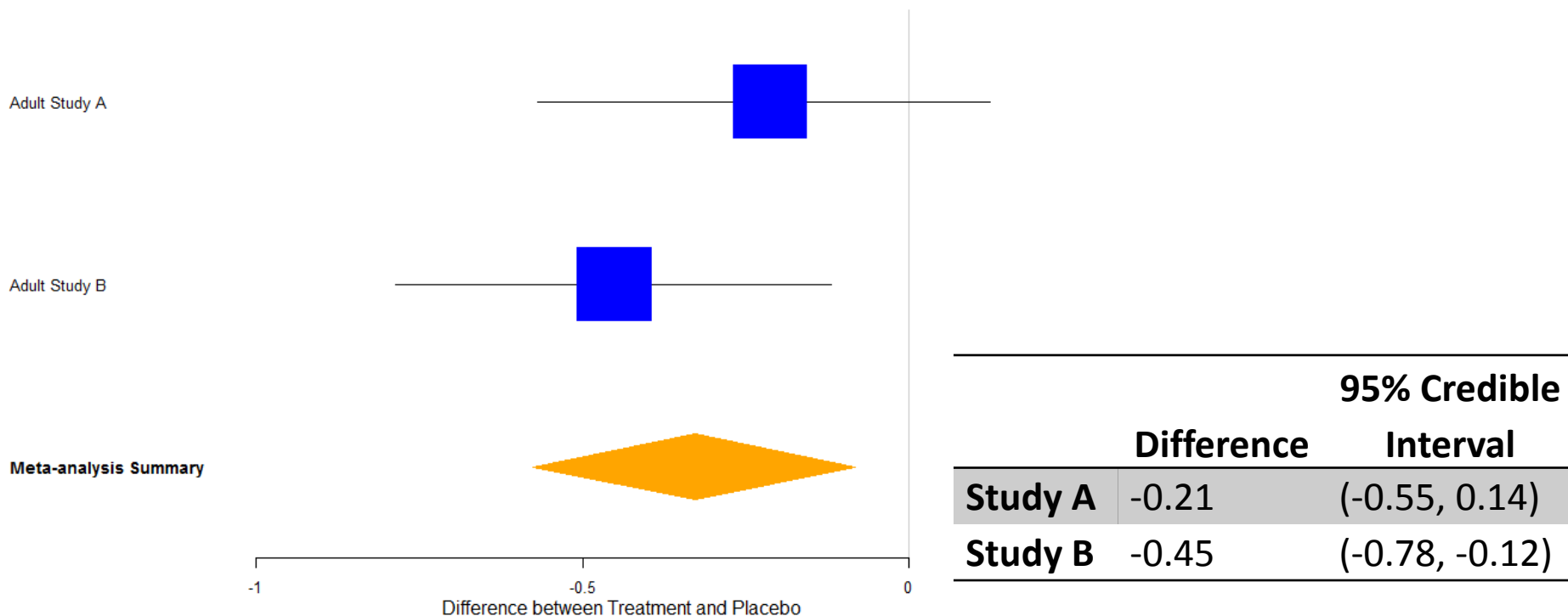
- After peds study completes, compute posterior probability of efficacy; or continuously as pediatric data accrue, if continuous monitoring is desired*
 - Could conduct sensitivity analyses to examine the impact of choice of priors
- ... But interpretation of sensitivity analyses is influenced by seeing the data

* Bayesian methods require no penalty for multiple looks

Background

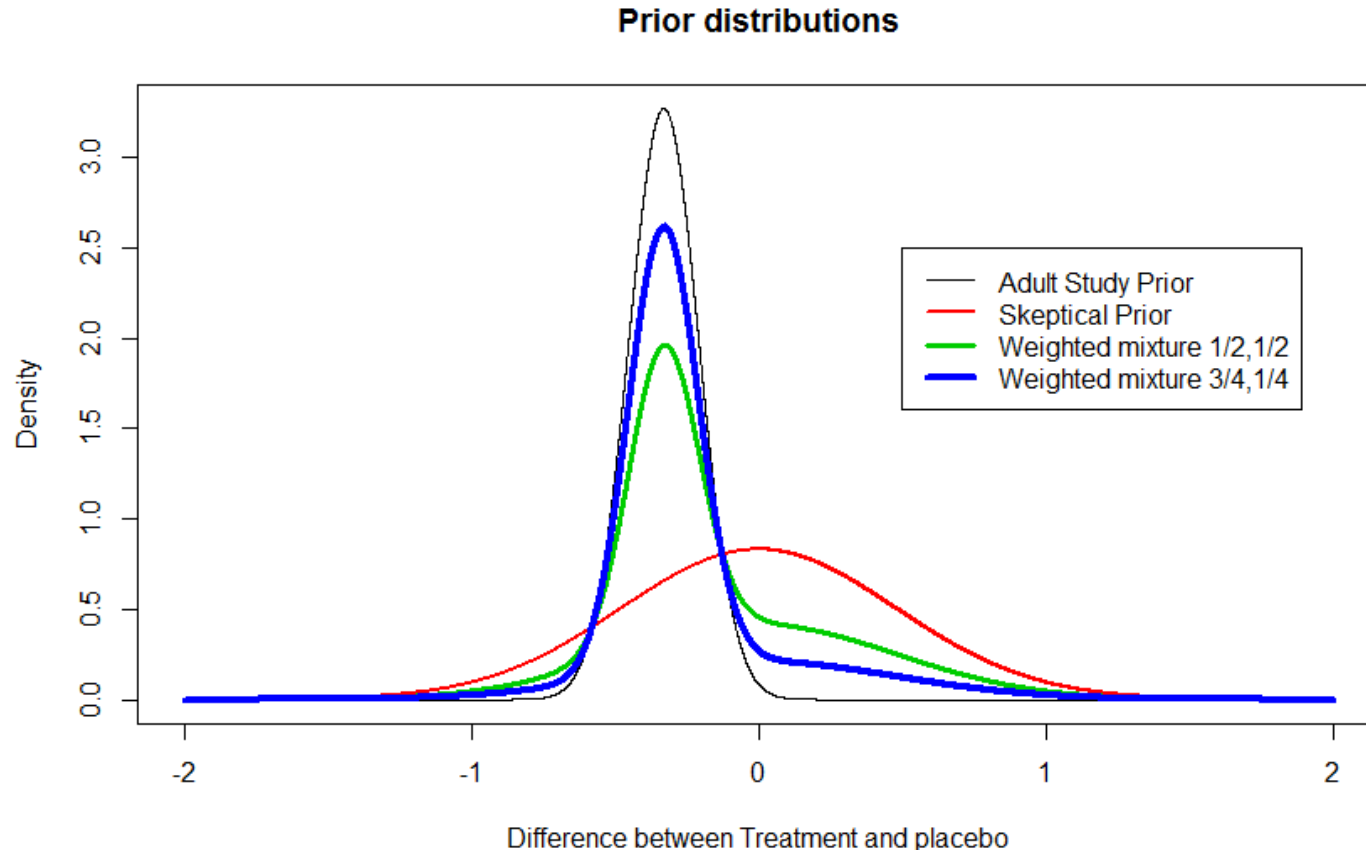
- We will now present an example of this method.
- A single product which had
 - Approval in adult indication based on two adult studies which found statistical significance for their primary endpoints;
 - A single pediatric study which did not meet statistical significance for the primary endpoint.
- The treatment effect found in pediatric study was slightly larger than the adult studies but because of slow enrollment the study was underpowered and the final result was not statistically significant.

Results of Bayesian Analysis using Adult Studies



	Difference	95% Credible Interval	Posterior Prob. of Efficacy
Study A and B	-0.33	(-0.58, -0.08)	> 99%

Graph of Pediatric Priors



Probability of applicability:

- $\text{Prior} = (1-a) * f(D) + a * g(D)$
- $f(D)$: skeptical prior $N(0, 0.48)$, $g(D)$: adult study posterior
- $a = P(\text{applicability of adult results})$

Expert Elicitation

- General background on adult studies and 3 survey questions
 - Clinical experience treating adult patients
 - Clinical experience treating pediatric patients
 - Similarities between adult and pediatric based on experience
- Survey edited by Clinical Outcomes Assessment staff
- Survey sent to FDA medical officers

Assessment of Similarity

3) On a scale of 0 to 10, how much confidence do you have in applying adult INDICATION clinical trial data to make decisions on INDICATION treatment effect for adolescent patients, where 10 means you would fully trust the adult INDICATION patient data and 0 means you would completely ignore the adult data and demand that all the evidence come from specific studies conducted within the pediatric patient population?

0

1

2

3

4

5

6

7

8

9

10

Ignore the adult data as irrelevant to adolescent patient population

Fully trust the adult data as applicable to adolescent patient population

Prior Experience

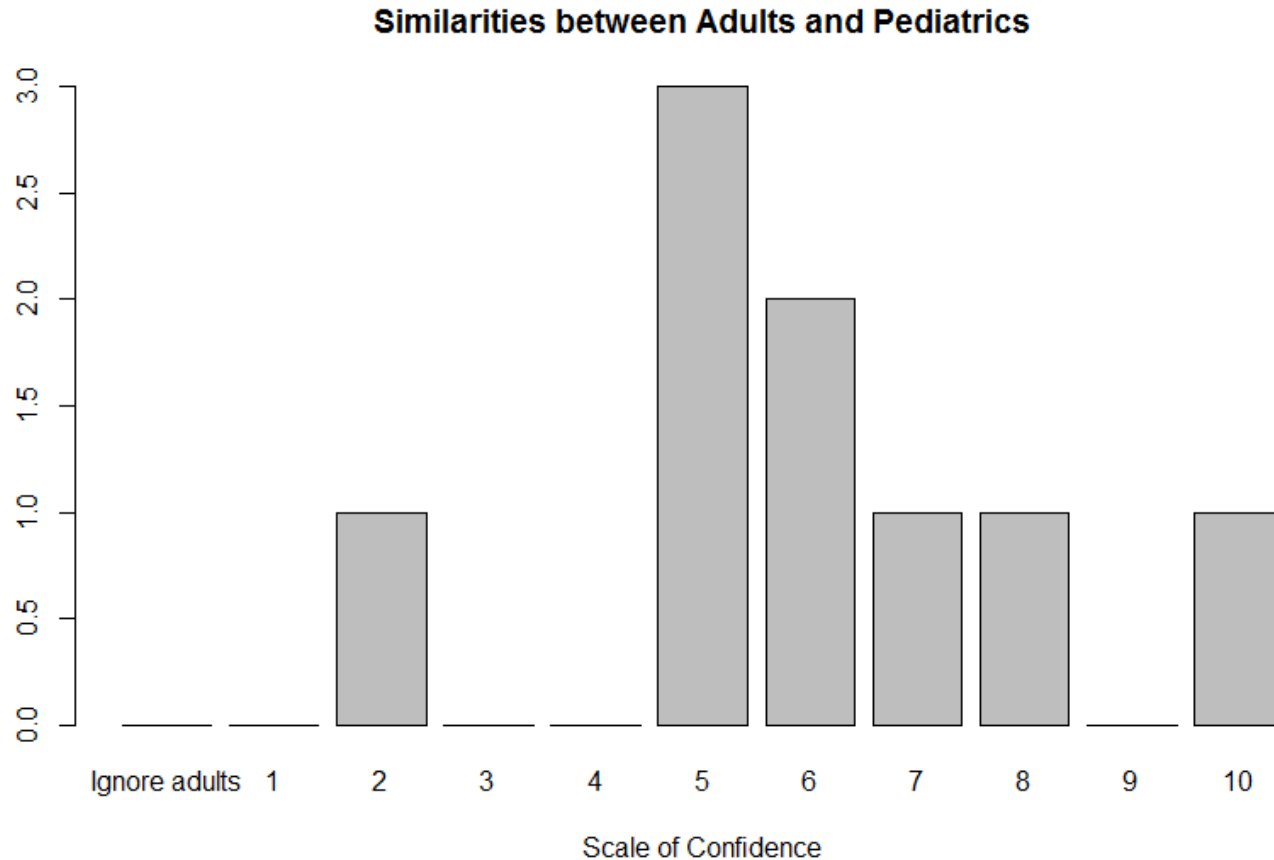
2) Please rate the extent of your previous clinical experience **treating adolescent patients (12 to <18 years of age)** with INDICATION, using a scale of 0-4, with 0 meaning “you have no experience treating **adolescent patients (12 to <18 years of age)** with INDICATION” and 4 meaning “you have extensive experience treating **adolescent patients (12 to <18 years of age)** with INDICATION”:

0	1	2	3	4
No experience treating adolescent patients (12 to <18 years of age) with INDICATION	<1 year of experience treating adolescent patients (12 to <18 years of age) with INDICATION	1-2 years of experience treating adolescent patients (12 to <18 years of age) with INDICATION	3-5 years of experience treating adolescent patients (12 to <18 years of age) with INDICATION	Extensive experience treating adolescent patients (12 to <18 years of age) with INDICATION

Expert Elicitation Results

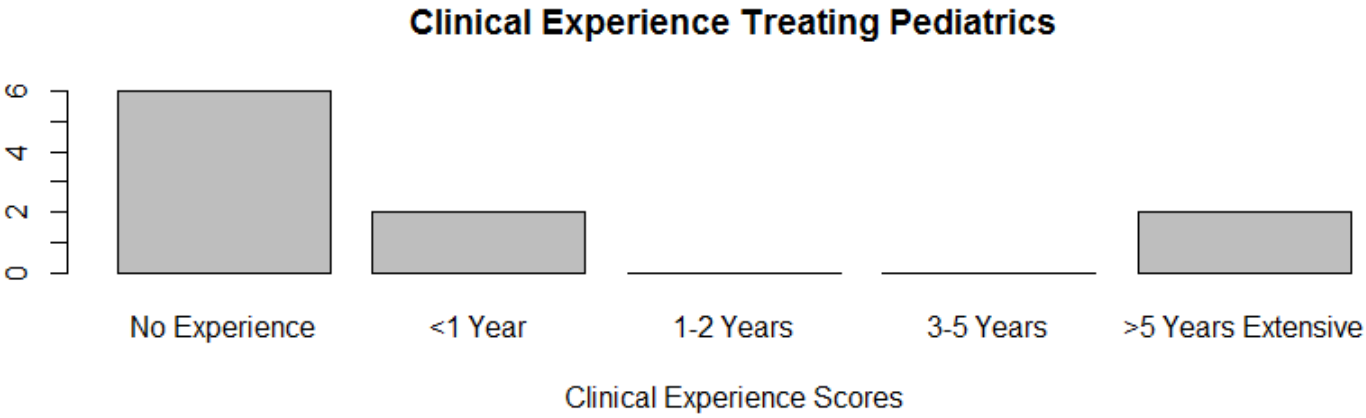
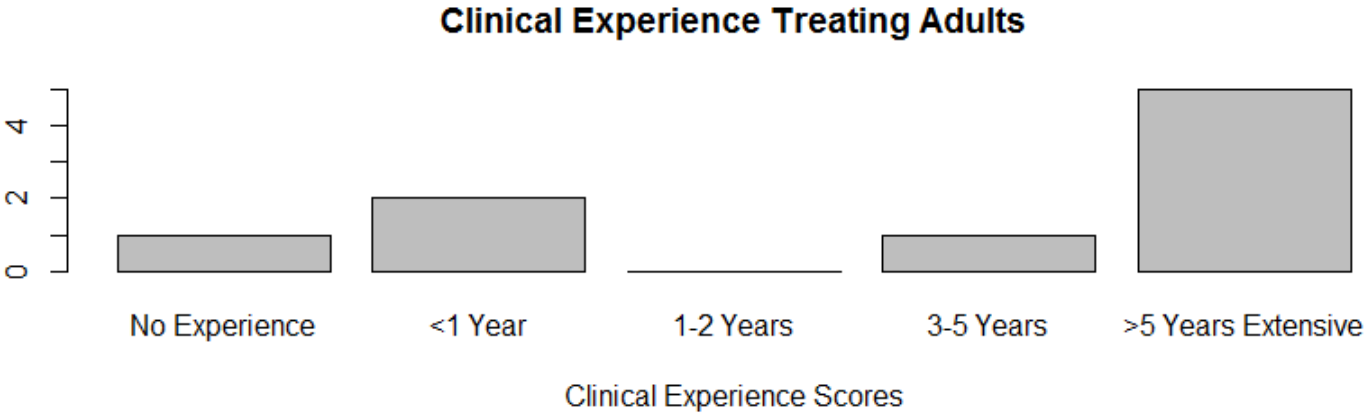


- 10 responses



- Average similarity = 6
- Median similarity = 6 --> $a=P(\text{applicability of adult results})$

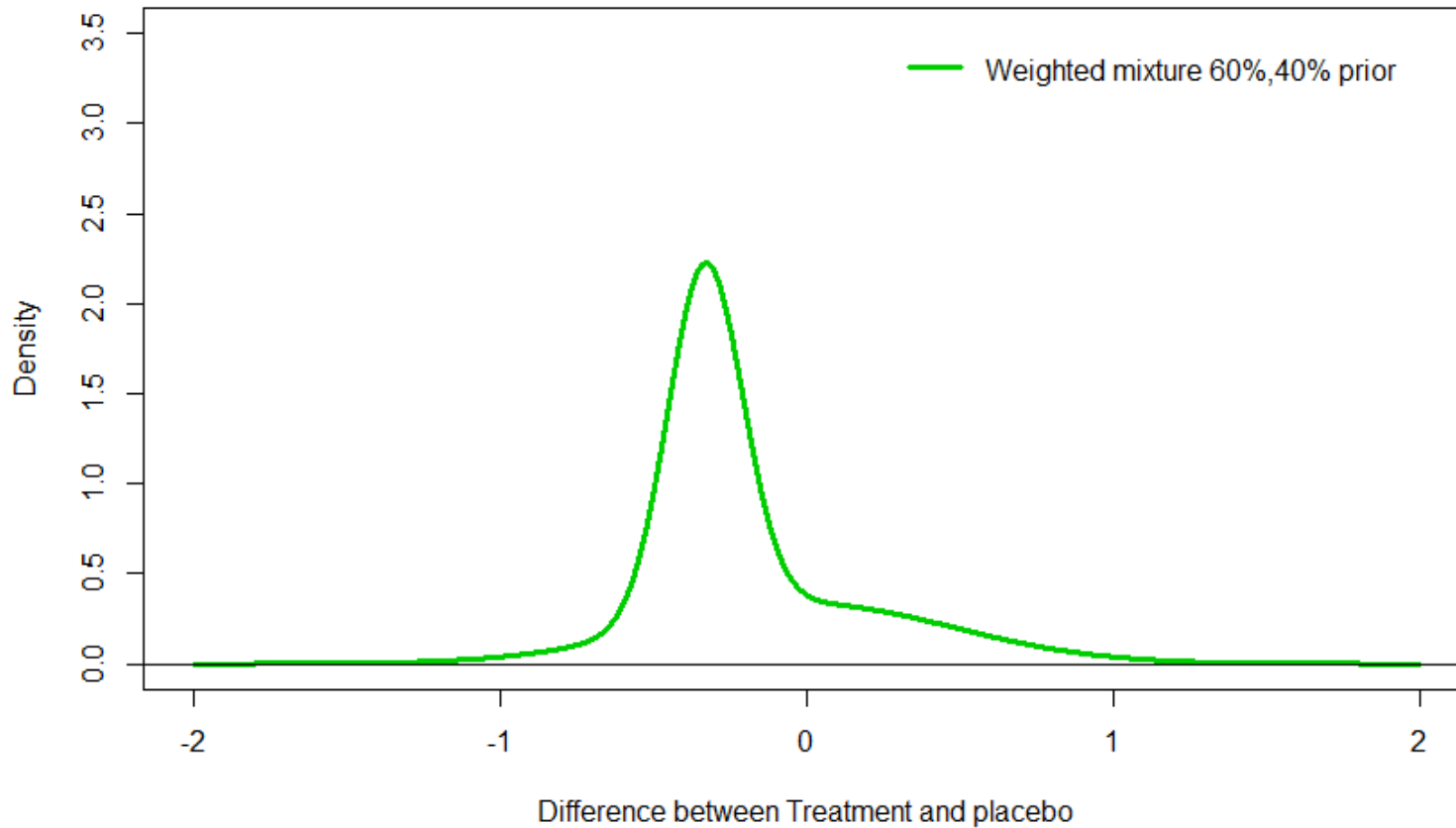
Expert Elicitation Results



Pediatric Posterior Distributions



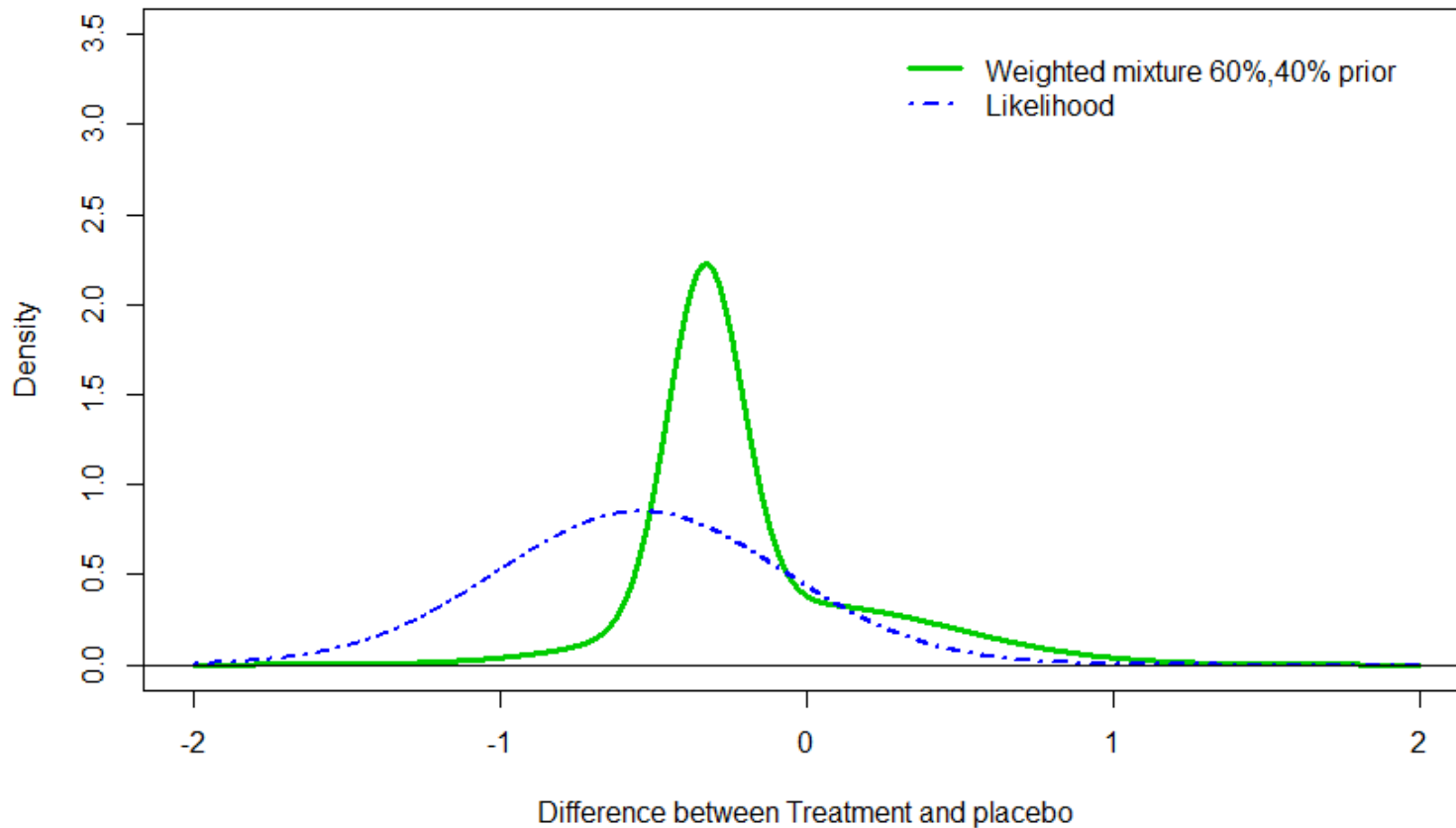
Prior vs Posterior distributions



Pediatric Posterior Distributions



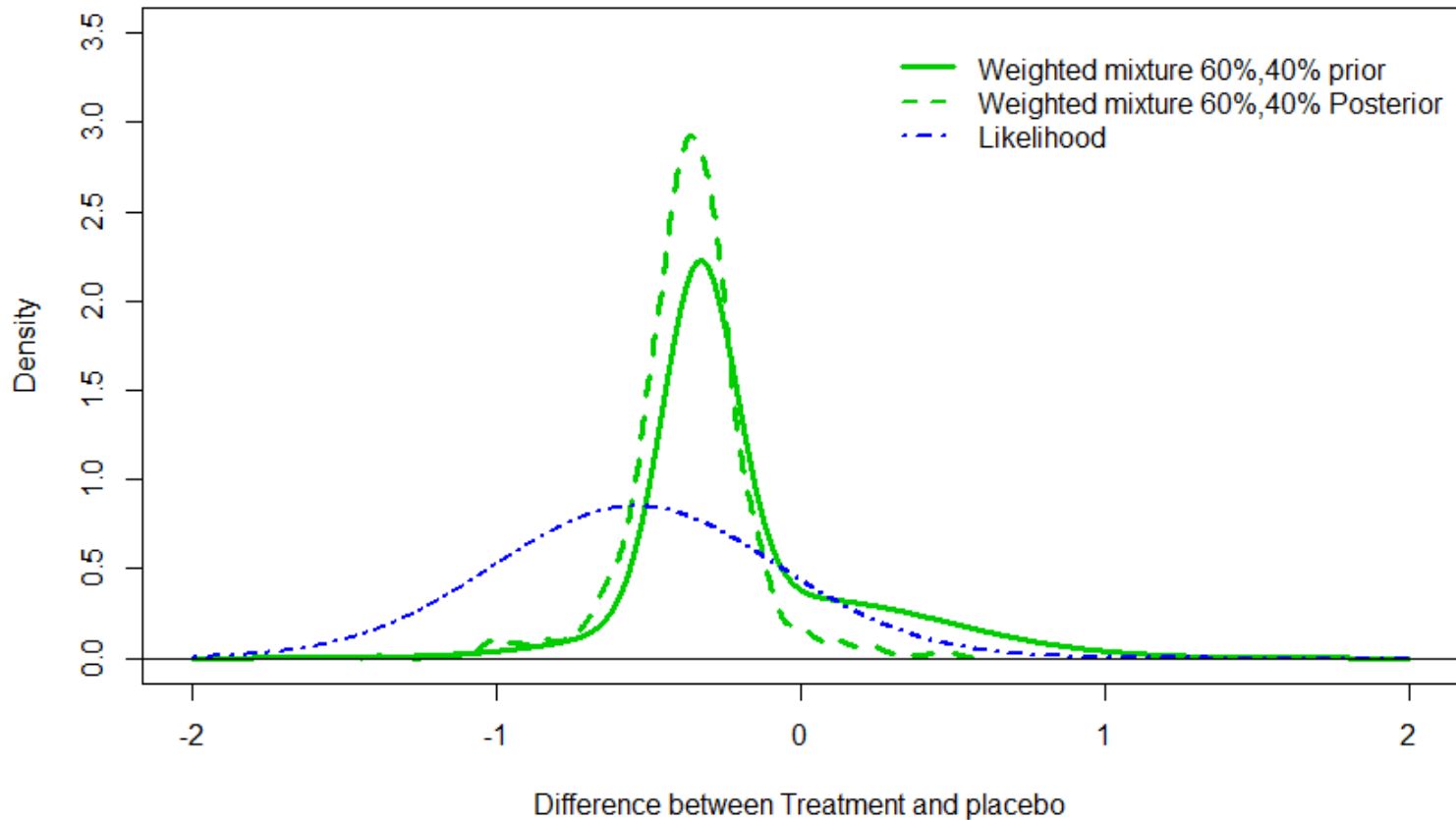
Prior vs Posterior distributions



Pediatric Posterior Distributions



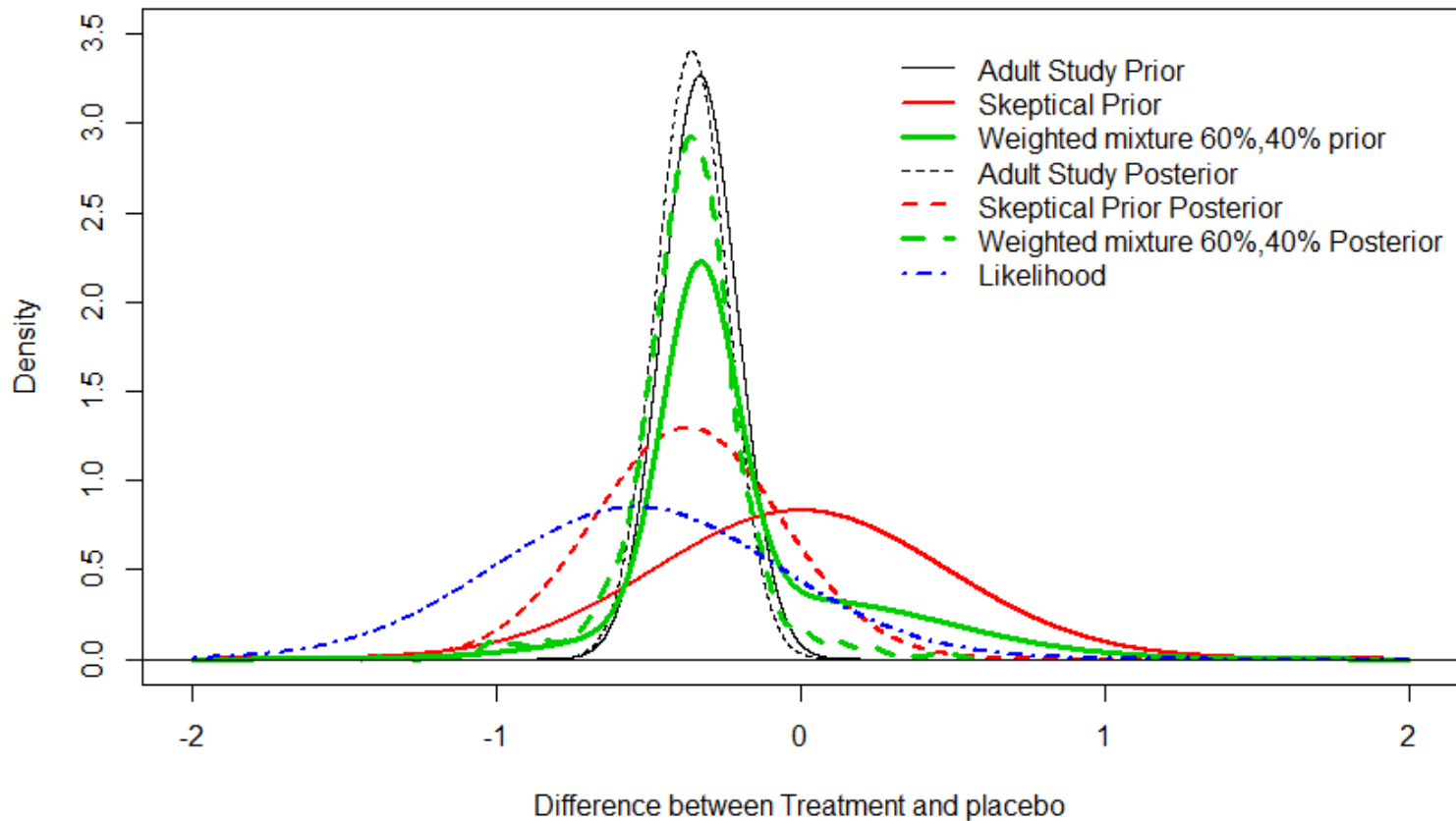
Prior vs Posterior distributions



Pediatric Posterior Distributions



Prior vs Posterior distributions

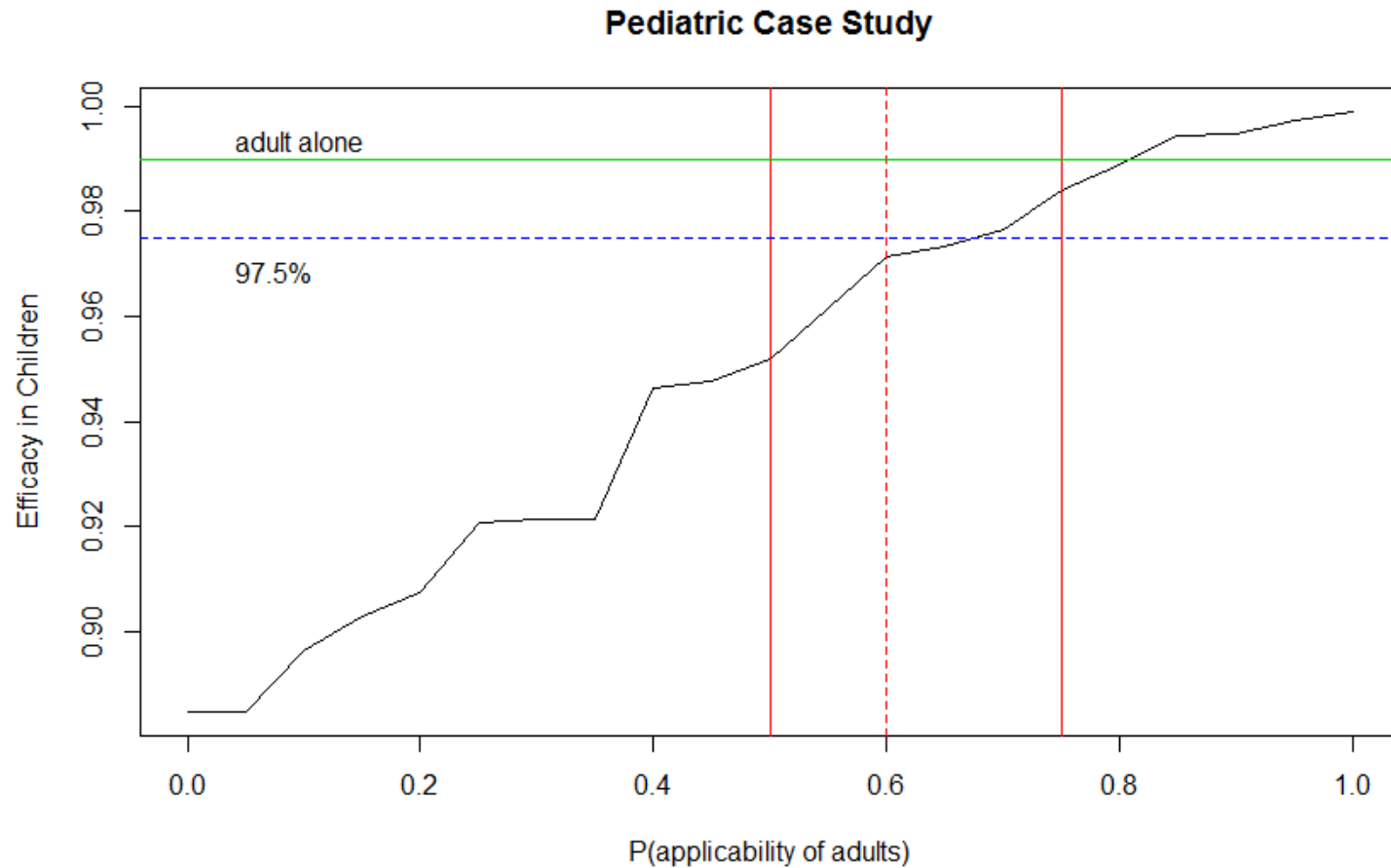




Results of Pediatric Study

Pediatric study	Difference	95% Credible Interval	Posterior Probability of Efficacy in Pediatrics
60% Adult Prior, 40% Skeptical Prior	-0.37	(-0.82,0.007)	97.3%
Adult prior (100%)	-0.36	(-0.58, -0.13)	>99.5%
Skeptical prior (0%)	-0.37	(-0.99, 0.23)	88.5%

Impact of Applicability



Conclusion

- Case study to illustrate how to formally incorporate adult data into pediatric clinical trial
- Bayesian approach provides direct measure of evidence on the clinical scale; result more intuitive and interpretable

Discussion

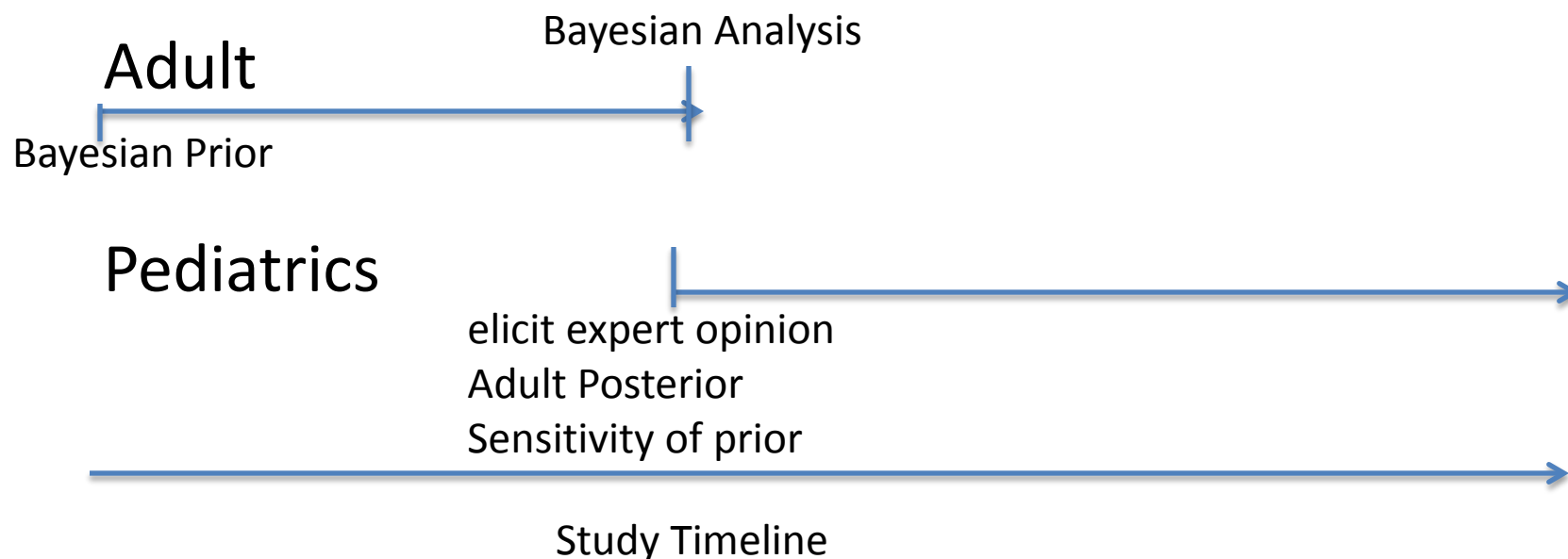
Sources of Evidence for Applicability



- The following sources of evidence are available for determining the likelihood of applicability:
 1. Clinical data from studies of products in the same therapeutic class.
 2. Clinical data from studies in the same disease, but for a different therapeutic class.
 3. Expert elicitation.

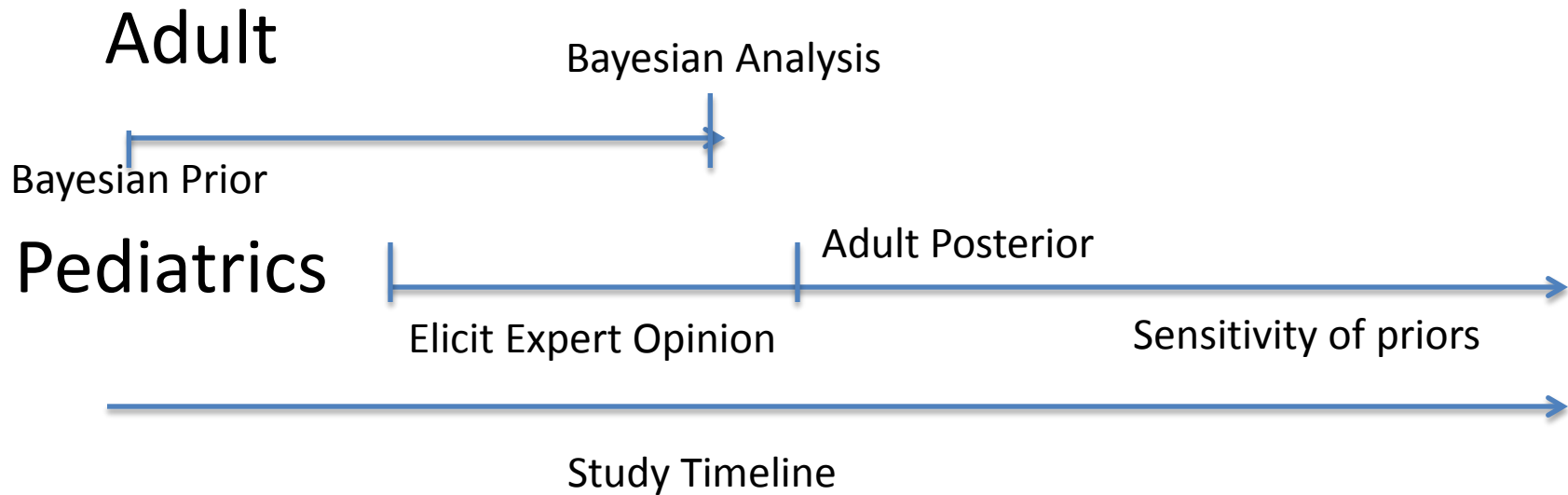
Ideal vs Practical Timeline

- Ideal



Plan Pediatric Study when adult study finished; use both expert opinion and adult posterior to design pediatric study

Practical Timeline



Practically, pediatrics ongoing before adult study finished; settle on applicability before pediatric results

References

- Spiegelhalter, D. J., Abrams, K. R., & Myles, J. P. (2004). *Bayesian approaches to clinical trials and health-care evaluation* (Vol. 13). John Wiley & Sons.
- Goodman, S. N., & Sladky, J. T. (2005). A Bayesian approach to randomized controlled trials in children utilizing information from adults: the case of Guillain-Barre. *Clinical Trials*, 2(4), 305-310.
- Greenhouse, J. B., & Seltman, H. (2005). Using prior distributions to synthesize historical evidence: comments on the Goodman–Sladky case study of IVIg in Guillain–Barre syndrome. *Clinical Trials*, 2(4), 311-318.