Considering Alternative Approaches and Trial Designs in pJIA Drug Development

pJIA Workshop

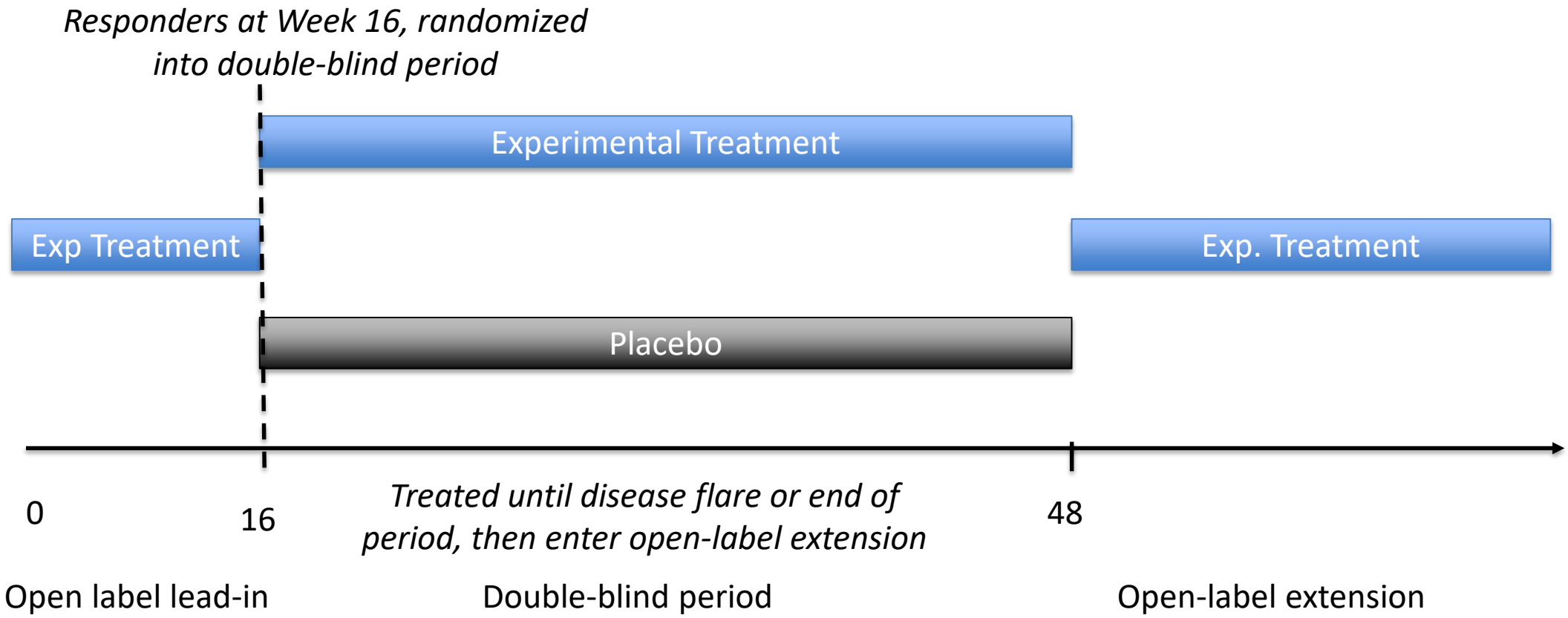
October 2, 2019

General Issues in Designing Pediatric Trials

- Difficulty recruiting and enrolling pediatric patients
  - Smaller disease population
  - Logistical issues
  - Study palatability issues
- Additional ethical requirements
  - Differences in acceptable trial designs
- Differences between pediatric and adult endpoints
- Differences between pediatric and adult disease course

Current Approach in pJIA

- Randomized-withdrawal trial designs



Randomized-Withdrawal Designs

- Benefits
  - Mitigates concerns of long-term exposure to ineffective treatment (i.e., placebo) due to immediate rescue after flare
- Disadvantages:
  - Carryover effects
  - Difficulties assessing whether underlying disease process is still active
  - Long lag times to adverse events
  - Answers a fundamentally different question than parallel-group designs

Potential Alternative Approaches in Pediatrics

- Borrowing of data
  - Adult and/or historical data
  - Using Bayesian analyses
  - Can be used in combination with PK/PD information to support decision making
- Active-controlled trials
  - Randomization and non-inferiority comparison to an active comparator
- Others (e.g., matching approaches using external controls)

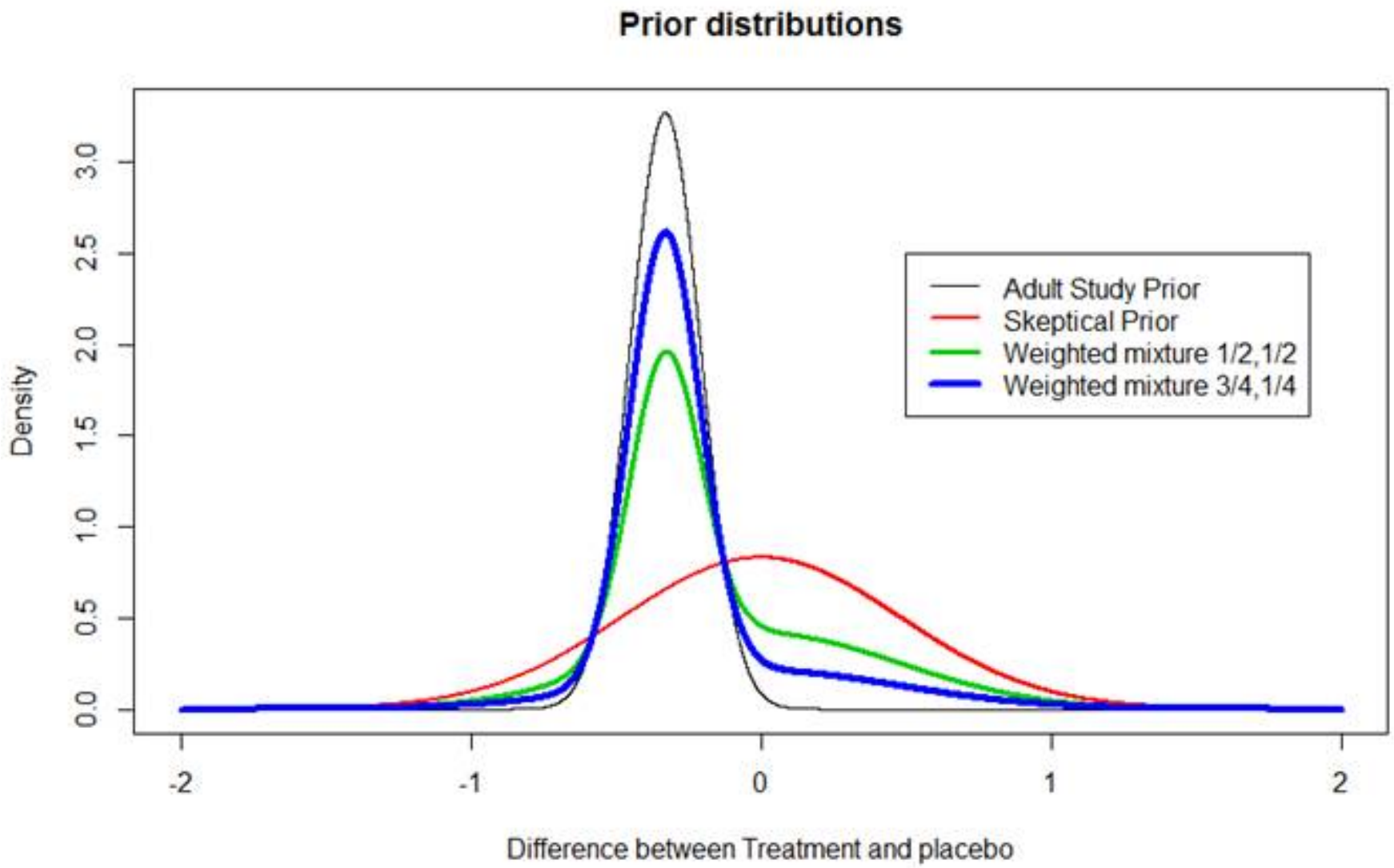
Bayesian Borrowing– Conceptual Overview

1. Evaluate the prospective source studies to establish compatibility (check endpoints, inclusion/exclusion, course of disease)
2. Summarize the information on the treatment effect from the historical (e.g., adult) studies.
3. Use that information to construct a prior for the treatment effect distribution. This will typically involve “discounting” (multiple possible methods).

Considerations for Borrowing

- Is borrowing appropriate?
  - How similar is the disease to that in the source (adult) data?
  - Is the natural history similar?
  - Can we use the same endpoints?
  - Are the trial designs amenable to borrowing?
- Second, determine the level of discounting in the prior which controls how much we rely on the borrowing
  - Often based largely on clinical judgement
  - Can we pre-specify?

“Discounting” Example - Mixture Prior



Tipping Point Analyses

- Apply a Bayesian mixture prior which borrows information for the primary endpoint from adults at a range of different weights (different levels of discounting) and assess the impact on the posterior probability

Treatment effect prior:

$$y_p \sim N(\delta_p, s_P^2)$$

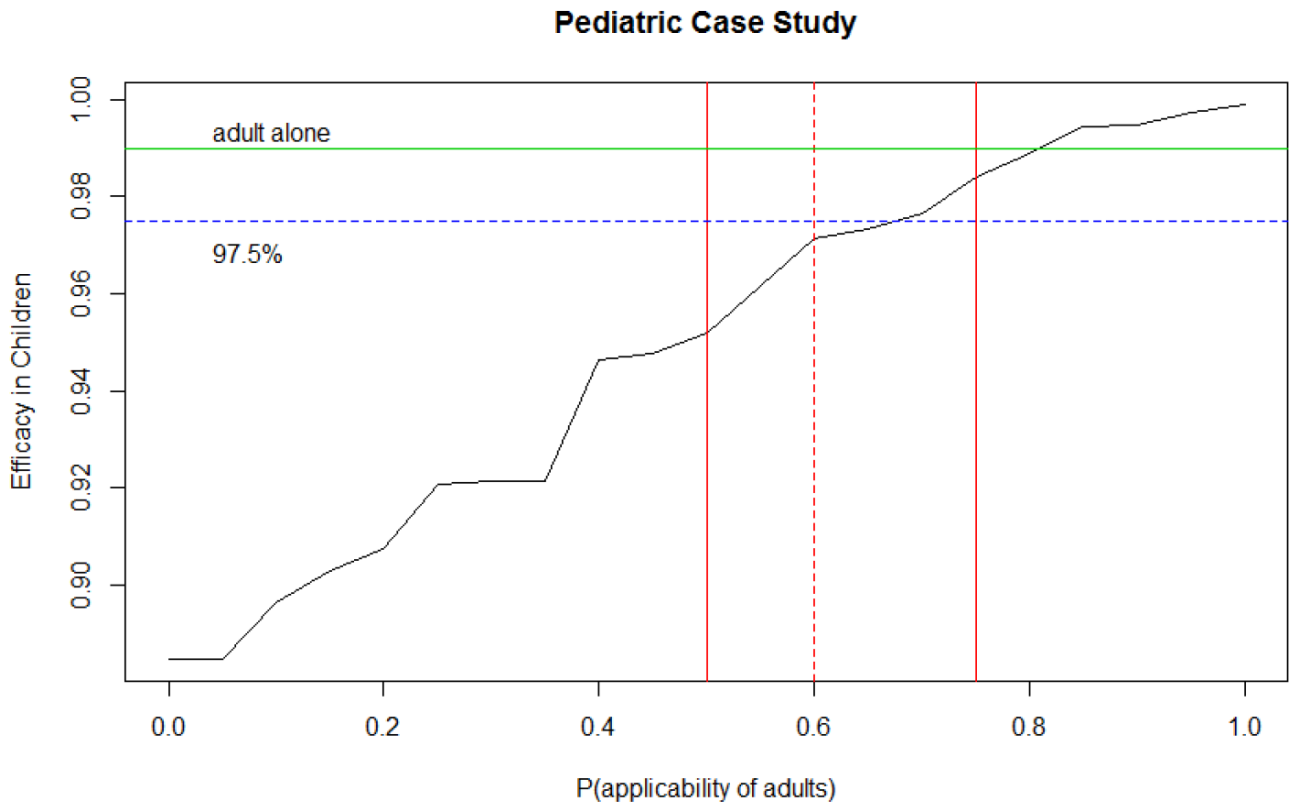
$$\delta_P \sim (1-a) \times N(0, m * s_P^2) + a \times N(Y_A, s_A^2),$$

Where: Y_A is the adult treatment effect estimate

s_A^2 is the adult variance

a is the prior weight (how much rely on borrowed info)

Bayesian Tipping Point Results



Interpretation:
A prior weight of a or larger results in a 97.5% posterior probability of efficacy (positive estimate of treatment effect) which is analogous to a rejection of the null hypothesis with a one-sided type I error of 0.025

Conclusions Using Bayesian Borrowing

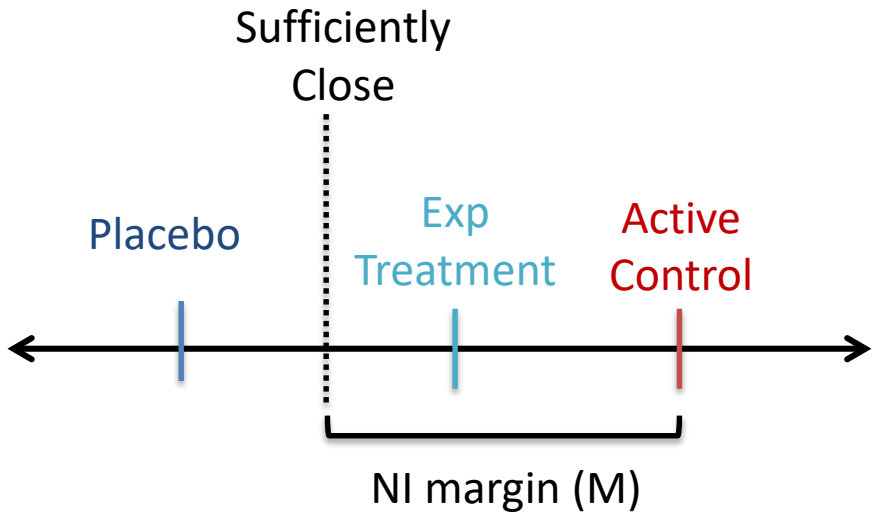
- Such an analysis may be considered supportive, with reliance on PK data to draw overall conclusions
- It is important to still assess the key baseline disease characteristics and PK similarity between the pediatric and adult study populations
- Further support may be provided by secondary efficacy endpoints and safety

Considerations of Bayesian Borrowing in pJIA

- Is borrowing appropriate?
  - How similar is the disease to that in the source (adult) data? ✓
  - Is the natural history similar? ✓
  - Can we use the same endpoints? Same trial design? ?
  - Are the trial designs amenable to borrowing? ?
- Second, determine the level of discounting in the prior which controls how much the borrowed information is relied on.
  - Largely based on clinical judgement ?
  - Ideally pre-specified

Active-Controlled Trials

- Randomize subjects to receive either active control or experimental treatment
- Comparison based on **non-inferiority**



- Goal: demonstrate that the test drug has an effect by showing **sufficiently close** to the effect of active control
- NI margin is based on estimates of treatment effects from historical placebo-controlled studies of the active control

Benefits of Active-Controlled Trials

- Eliminates issue of exposure to ineffective treatment (e.g., placebo control arm)
- Allows for long-term, reliable, controlled data (including safety data)
- Cleaner comparisons unconfounded by treatment switching
- May provide a more informative comparison

Existing Hurdles in pJIA

- Defining an NI margin
  - Traditionally informed by conservative estimate of the effect of the active control from parallel-group, *placebo-controlled trials*
  - Very few placebo-controlled trials exist for pediatrics, requiring
    1. reliance on adult data and 2. clinical judgement
- Powering this study
  - Depending on margin, may require substantially larger numbers of patients
  - May be mitigated by combining with borrowing approaches

Summary and Conclusions

- Issues exist with the current approaches to pJIA efficacy trials
- Alternative options may include borrowing from other data sources (e.g., adults) and active-controlled trials, or some combination
- Other approaches exist and could be investigated (e.g., matching, historical/external controls)
- Implementation of alternative approaches will require additional consideration and development
- Additional discussion of the subjective judgements may be needed with input from clinical colleagues (e.g., disease similarity, established efficacy in adults, knowledge of drug class, etc.)

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