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Navigating Challenges in RCT Conduct:

A Novel Bayesian Adaptive Semiparametric Approach Handling Primary and Secondary Endpoints in Pediatric Trial Design

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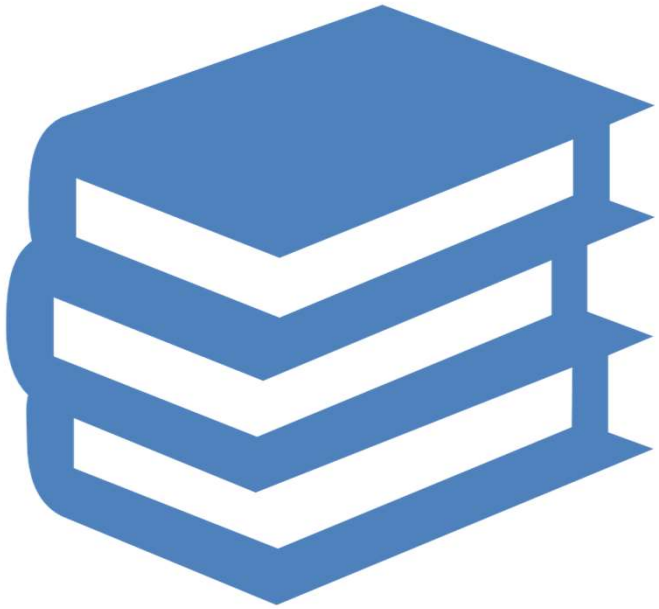
No Disclosures to declare



Background: Challenges in Pediatric RCT

- Conducting RCTs in pediatric settings presents several challenges.
  - Limited sample sizes (Huff, 2017),
  - Ethical considerations (Wightman, 2023),
  - Discordances in expert opinion about treatment effect (Linney, 2019),
  - Need to address multiple endpoints, i.e. safety secondary outcomes (Gkiourtzis, 2023).

Pediatric Nephrology (2021) 36:3681–3692
https://doi.org/10.1007/s00467-021-05117-5

ORIGINAL ARTICLE

Oral steroids for reducing kidney scarring in young children with febrile urinary tract infections: the contribution of Bayesian analysis to a randomized trial not reaching its intended sample size

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Received: 16 January 2021 / Revised: 21 April 2021 / Accepted: 4 May 2021 / Published online: 25 May 2021

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Motivating Example, Rescue Trial

- **RESCUE (REnal SCarring Urinary infEction)** trial is a randomized controlled double-blind trial
- The **study aims** to evaluate the effect of adjunctive oral steroids to prevent renal scarring in young children and infants with febrile urinary tract infections.
- **Extensive scarring** may progress to further renal injury with subsequent hypertension, decreased renal function, proteinuria, and sometimes end-stage renal disease (Peters, 2010).

- **Primary outcome** is the difference in scarring proportion between amoxicillin standard antibiotic therapy versus standard therapy + corticosteroids therapy.
- **Secondary outcome** acceptability of adjuvant steroid treatment in terms of the rate of discontinuation of treatment and the reported side effects.

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Issues in the Study Design in Pediatric RCT: The lesson learned

Issues	Proposals
• Patient retention • Highly informative Priors arising from the literature	• Advanced RCT and Bayesian approaches (Laptok, 2017) • Power Prior Approaches and discounting factors (Ibrahim, 2015)
• Issues in Incorporating Expert opinion • Secondary safety endpoints • Prior data conflict • Comunication issues	• Semiparametric B-Spline priors (Azzolina, 2022) • Two endpoints Bayesian sequential design (Gayewsky, 2023)

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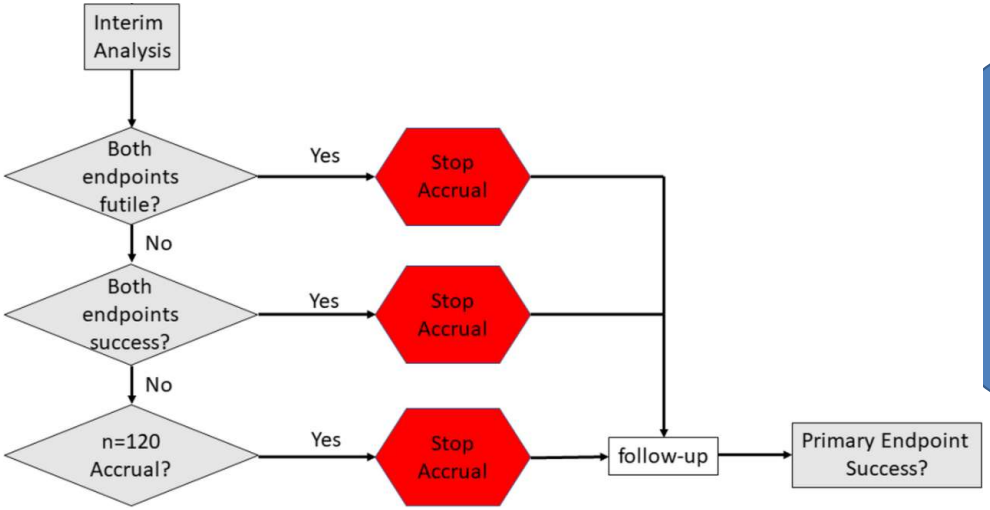
Two endpoint Bayesian sequential design



METHODOLOGY Open Access

A novel Bayesian adaptive design incorporating both primary and secondary endpoints for randomized IIB chemoprevention study of women at increased risk for breast cancer

Byron J. Gajewski[1,2*], Bruce F. Kimler[2,3], Devin C. Koestler[1,2], Dinesh Pal Mudaranthakam[1,2], Kate Young[1,2] and Carol J. Fabian[2,4]

Only Parametric Priors?

Semiparametric Priors

1. Assuming to have p elicited quantiles $y_{\alpha_1}, \dots, y_{\alpha_p}$ modeled by a linear combination of B-spline, the prior distribution may be determined optimizing this objective function:

$$f(\theta, m, S, \phi, y) = \min_{F_{-m},\dots,F_S} \left\{ \sum_{i=1}^{p} \left(\alpha_i - F\left(y_{\alpha_i}\right)\right)^2 + \phi \int_{y_0}^{y_1} f(y)^2 dy \right\}$$

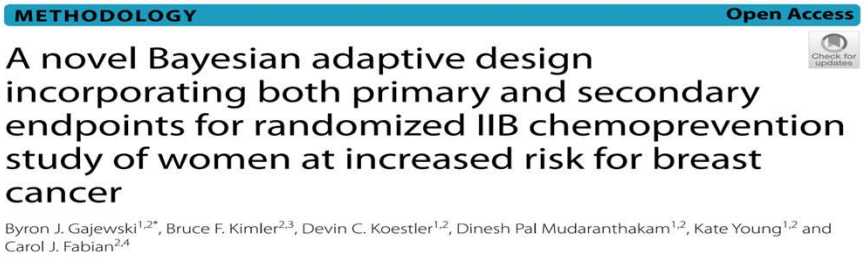
$$F_i \leq F_{i+1} \text{ for } i = -m, \dots, S-1$$

$$\text{and } F_{-m} = 0, F_S = 1$$

2. F is a spline having m degree with a sequence of S inner knot $\lambda = (\lambda_{-m}, \dots, \lambda_{S+m+1})^T$.

3. $\phi > 0$ is a balancing factor penalizing the distance between the functions $F\left(y_{\alpha_i}\right)$ adapted to the expert quantiles and the Uniform uninformative distribution in the domain $[y_0, y_1]$.

Design proposal



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+

Semiparametric Priors

Simulate the design propriety even if prior data conflict arise

Rescue Trial motivating example

Rescue Questions posed to the experts

"Based on your experience, what is the probability that a patient aged 0 to 2, with a value of procalcitonin >1 µg/L, treated with the recommended antibiotic regimen, has evidenced the presence of a renal scar event 6 months after the acute episode?"

"Based on your experience, what is the probability that a patient aged 0 to 2, with a value of procalcitonin >1 µg/L, treated with the recommended antibiotic regimen+dexametasone, has evidenced the presence of a renal scar event 6 months after the acute episode?"

Expert Opinions in Rescue Trial

Expert	Opinion Control	Opinion Treatment
1	0.3	0.5
2	0.25	0.25
3	0.15	0.3
4	0.4	0.5
5	0.3	
6	0.2	
7	0.2	0.3
8	0.3	0.25
μ	**0.26**	**0.35**
σ	0.08	0.12
α_0	8	5
β_0	22	10

Parametric Beta Priors

$\text{Beta}(\alpha, \beta)$

$$\alpha = \alpha_0 d_0 + 1$$
$$\beta = \beta_0 d_0 + 1$$

$$\alpha_0 = \left[\left(\frac{1-\mu}{\sigma^2} - \frac{1}{\mu}\right)\mu^2\right] - 1$$

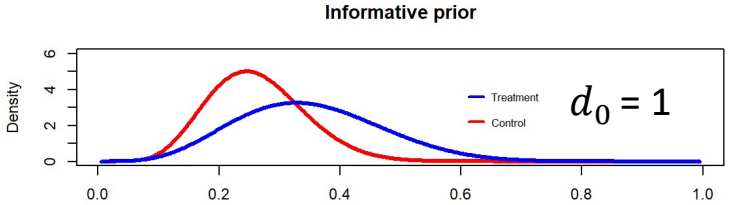
$$\beta_0 = \left[\alpha\left(\frac{1}{\mu} - 1\right)\right] - 1$$

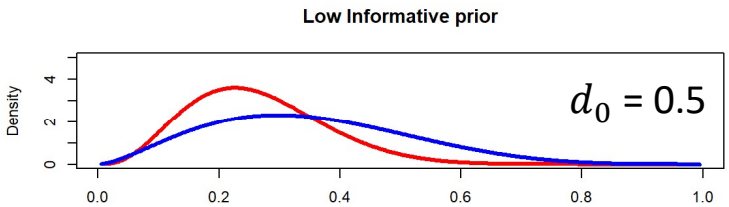
- $d_0 = 1$ Informative
- $d_0 = 0.5$ Low Informative
- $d_0 = 0$ Uninformative

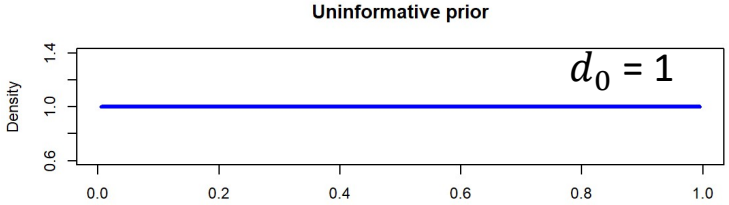
Possible Prior-Data conflict

Elicited Priors

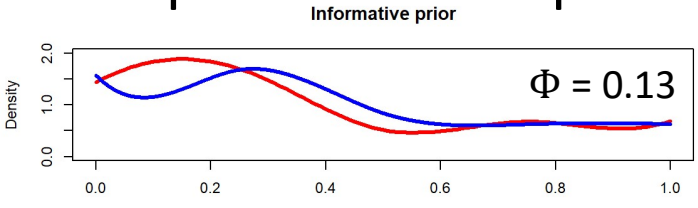
Parametric Beta

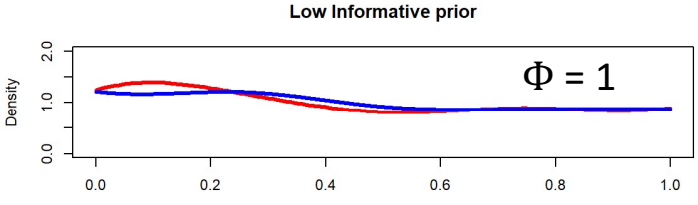


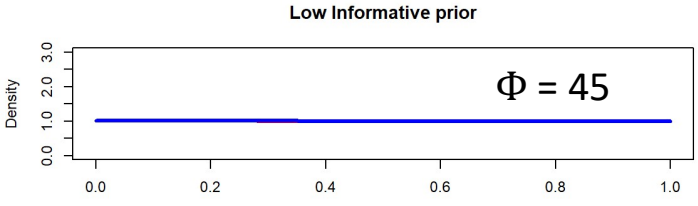




Semiparametric B Spline



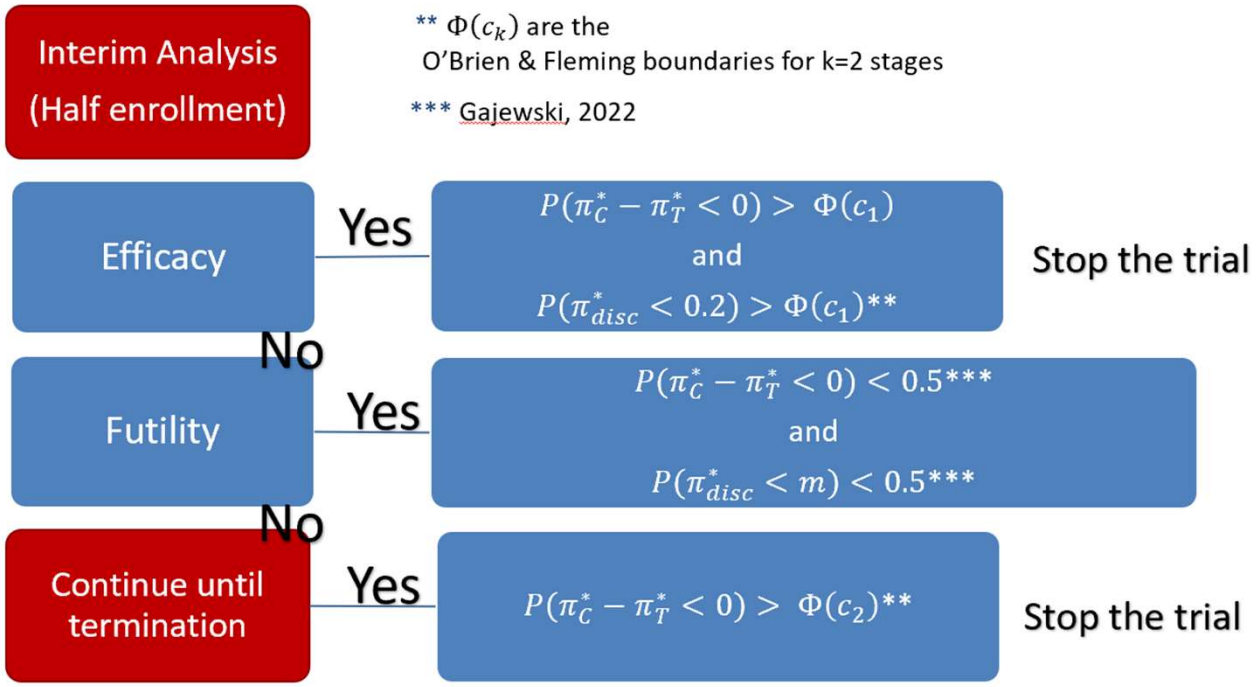




Trial design flowchart

** $pp_k = \Phi(c_k)$
c_k are the O'Brien & Fleming boundaries
Two-sided type I error of 5%.

*** Gajewski, 2022



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Simulation Plan

Data generation mechanism
Mimicking Rescue trial

$n = 40, \dots, 300\ per\ arm$

$\Pi_{control} = 0.4$

$\Pi_{control} - \Pi_{\text{treat}} = 0;\ 0.18; 0.2$

$\Pi_{disc} = 0.18, \dots 0.22$

10,000 simulated data

Analysis

Two endpoints Bayesian Sequential design with

- Semiparametric B-Spline
- Parametric Beta priors

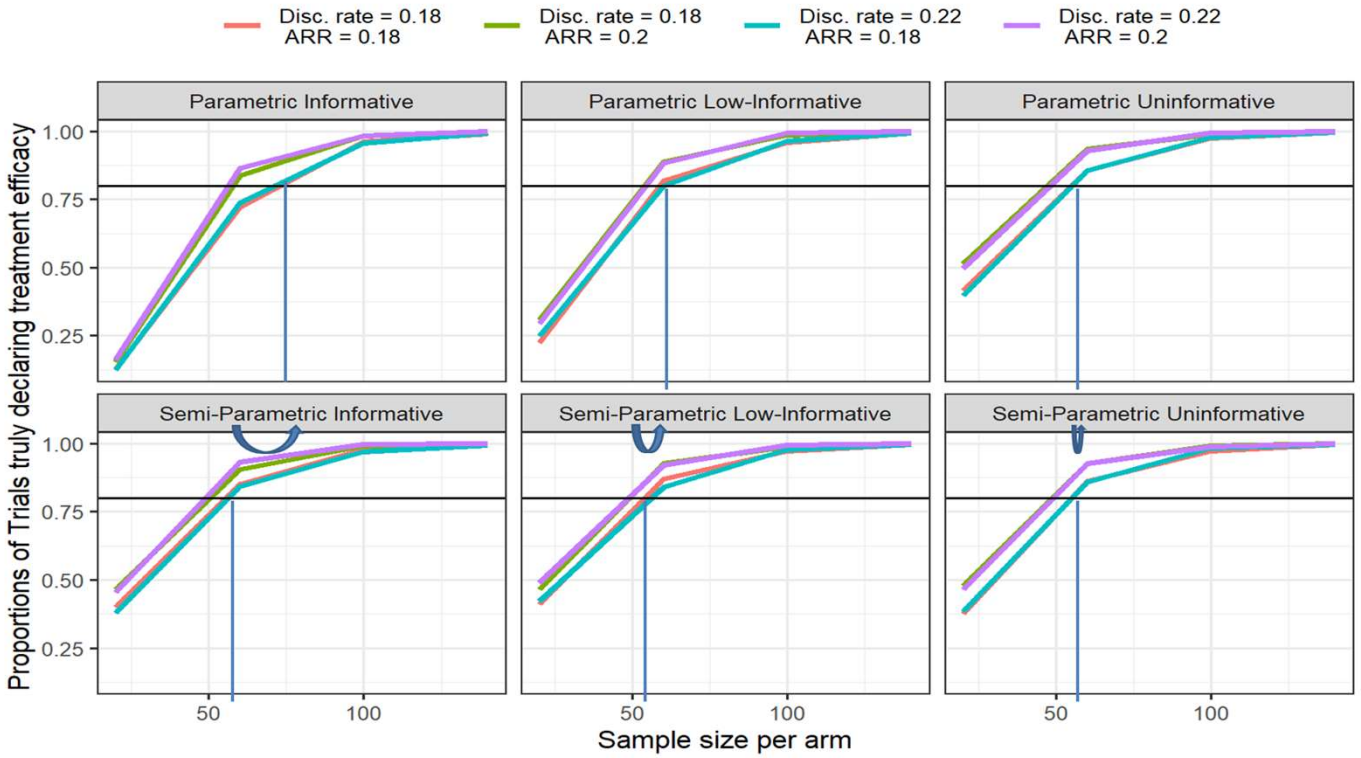
MCMC resampling:

1. $\pi^*_{control}$ from $\pi_{control}|X_{control}$,
2. $\pi^*_{treatment}$ from $\pi_{treatment}|X_{treatment}$,
3. π^*_{disc} from $\pi_{disct}|X_{disc}$,
4. $ARR = \pi^*_{control} - \pi^*_{treatment}$

Design Proprieties indicators

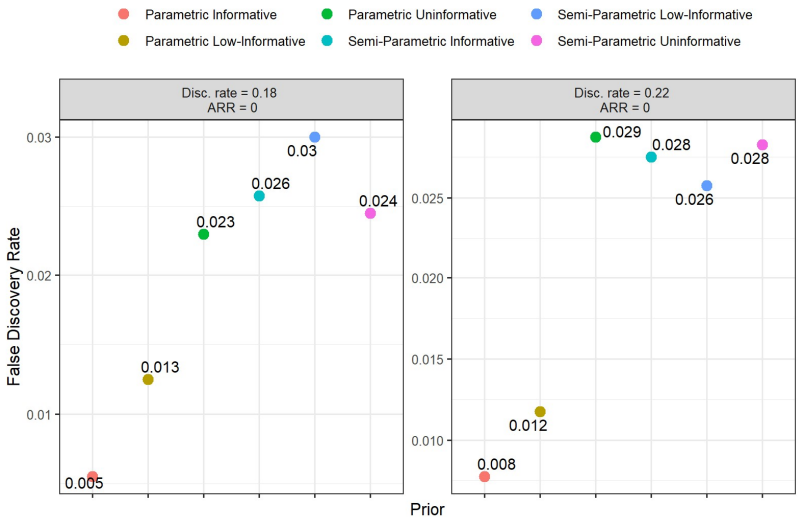
1. Percentage of trials truly declaring treatment efficacy
2. Percentage of trials declaring the treatment efficacy if the treatment does not work
3. Percentage of futility trials if the treatment is not effective

Results: Empirical Power

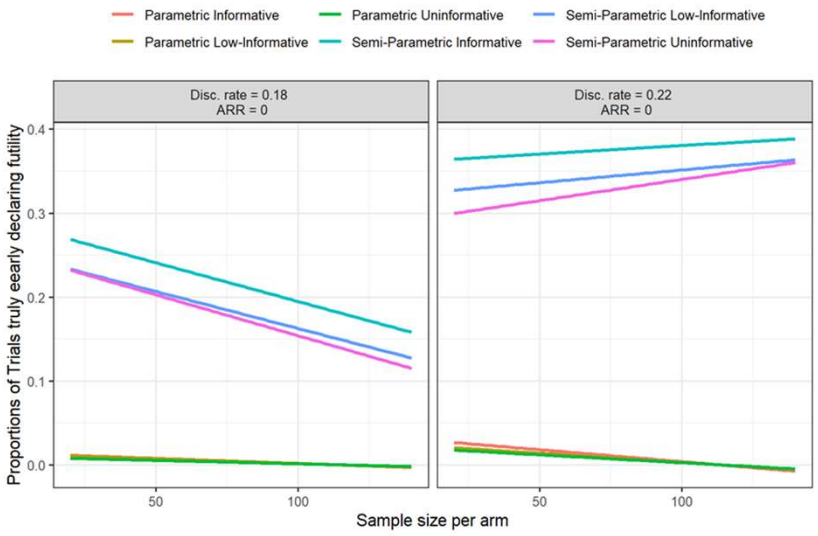


Proportions of simulated trials declaring the treatment effect, ad interim or at the end of the study, according to the sample size, simulation scenarios, and Prior Distributions

Results: False discovery rate and Correct Futility Rate



Average False Discovery Rate (FDR) over the sample size per simulation scenarios, and Prior Distributions



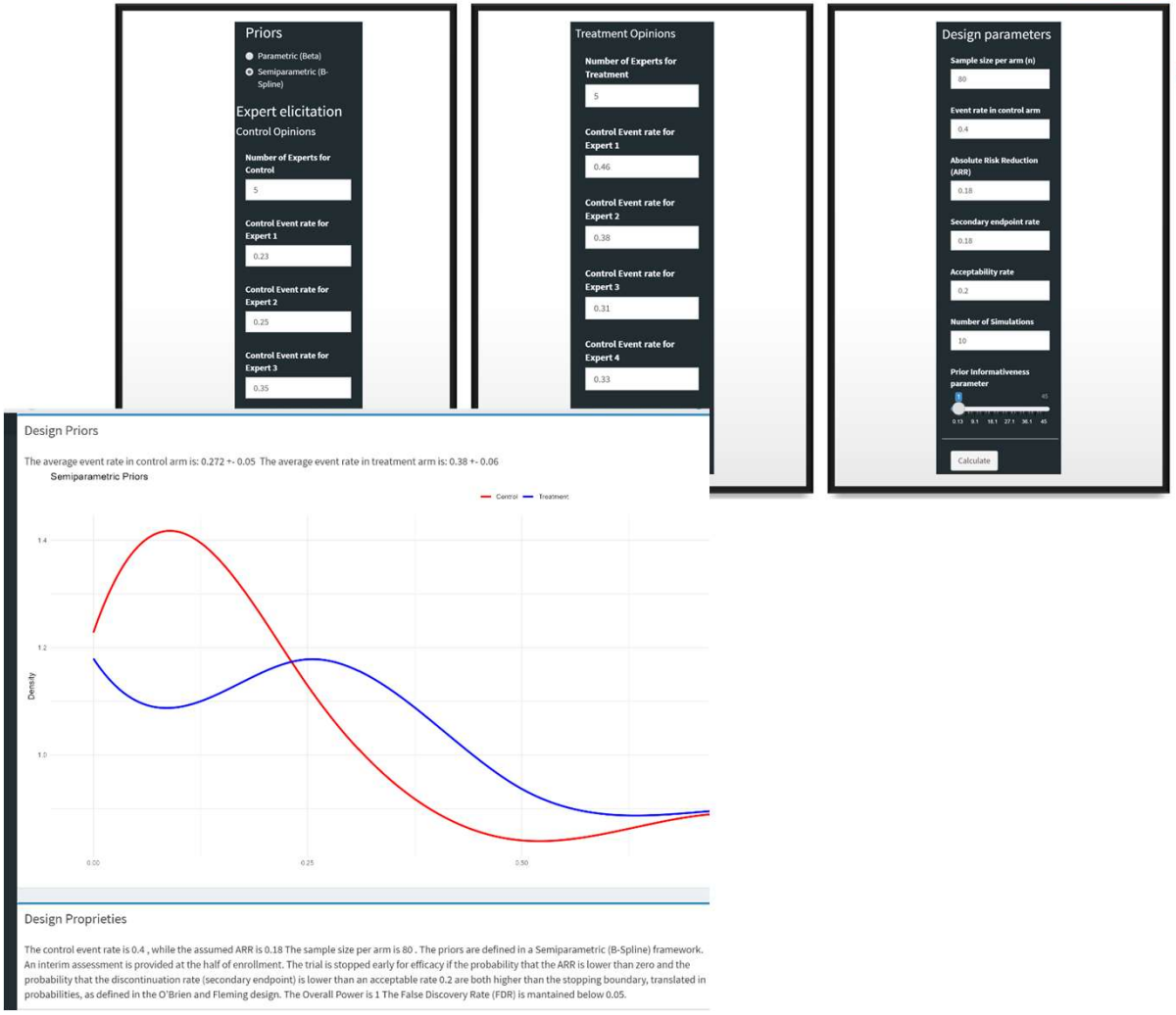
Proportions of simulated trials truly early declaring the futility ad interim, according to the sample size, simulation scenarios, and Prior Distributions

Implications

- **Enhanced Safety Monitoring**: Bayesian Sequential design aids in comprehensive evaluation of secondary safety endpoints, prioritizing pediatric patient welfare.
- **Improved Sensitivity**: Semiparametric priors outperform parametric priors, enabling precise identification of treatment effects in pediatric populations.
- **Strict Control of False Discoveries**: Maintains a nominal false discovery rate below 5%, ensuring reliable and trustworthy pediatric trial results.
- **Efficient Resource Allocation**: Allows early stopping for futility, optimizing resource utilization and expediting the development of effective pediatric treatments.

What's next?

Enhancing Advanced Design Communication and Applicability via Web Applications



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