TITLE: Navigating Challenges in Pediatric Trial Conduct: Integrating Bayesian Sequential Design with Semiparametric Elicitation for Handling Primary and Secondary Endpoints

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ABSTRACT:

This study introduces a Bayesian Adaptive Semiparametric Approach aimed at overcoming specific challenges in pediatric randomized controlled trials (RCTs), particularly in managing primary and secondary endpoints. Pediatric RCTs often face difficulties such as sparse or conflicting prior data, especially in rare diseases or conditions, making traditional methods less effective. Our approach combines Bayesian adaptive design with B-Spline Semiparametric priors, providing a flexible and dynamic framework for updating prior information with ongoing data, thus improving the accuracy and efficiency of treatment effect estimation.

The methodology's flexibility is particularly beneficial for pediatric populations, where responses to treatment can be highly variable. By utilizing semiparametric priors, the approach accommodates this variability better than traditional parametric methods, which often rely on rigid assumptions. This adaptability is important in pediatric trials, where developmental differences and smaller sample sizes necessitate more responsive and robust statistical methods.

The design's operational characteristics were evaluated through a simulation study inspired by the real-world case of the REnal SCarring Urinary infection Trial (RESCUE), a pediatric RCT. The simulation demonstrated that the semiparametric approach has a higher tendency to correctly declare the treatment effect at the study's conclusion, even when faced with recruitment challenges, uncertainty, and prior-data conflicts. Furthermore, the semiparametric design showed an improved ability to stop trials early for futility. This is a significant advantage in pediatric trials, where minimizing patient exposure to ineffective treatments is ethically important.

The study also explored the use of Bayesian stopping rules based on the Highest Posterior Density Interval (HDI) coverage for treatment effects. This method allows for continuous updating of the probability distribution of the treatment effect, providing a clear basis for decision-making even in the presence of limited data. The HDI-based stopping rules maintained a lower false discovery rate (FDR) compared to traditional parametric approaches, particularly with uninformative priors.

A Bayesian adaptive design enhanced with semiparametric priors offers a robust and flexible framework for pediatric RCTs. This approach not only improves the accuracy and efficiency of treatment effect estimation but also provides a more ethical and responsive trial design, better suited to the challenges of pediatric research. The ability to dynamically update priors and adapt to ongoing data makes this methodology particularly useful in contexts where prior data is sparse or conflicting, ensuring more reliable and conclusive trial outcomes.