INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH IN MULTIDISCIPLINARY EDUCATION
ISSN(print): 2833-4515, ISSN(online): 2833-4531
Volume 03 Issue 08 August 2024
DOI: 10.58806/ijirme.2024.v3i8n03, Impact factor- 5.138
Page No. 1306 - 1310

Enhancing Study Power in Pediatric Research through Bayesian Extrapolation

Beibei Wang[1], Li Yun, Xu Yang[2], Huang Ho[3]

ABSTRACT: Pediatric populations, comprising individuals aged 18 or younger, and rare disease populations pose significant challenges in clinical trial design due to limited participant numbers, patient sensitivity, and insufficient natural history data. Addressing these challenges often involves data extrapolation, leveraging existing data from adults to inform pediatric trials. Bayesian hierarchical modeling is increasingly recognized as a valuable tool for combining information across disparate sources, such as adult and pediatric datasets. This manuscript introduces an extension of an existing statistical model to enhance the efficiency of borrowing strength from multiple historical trials under consistent assumptions. A quantitative method is developed to improve the borrowing of historical information. The methods are illustrated with a simulation study motivated by real case study in pediatric clinical trial, and practical considerations are provided regarding the selection of prior distributions. This work aims to provide comprehensive insights and practical guidance for leveraging historical data effectively in clinical trial design.

KEYWORDS: Bayesian methods; Pediatric clinical trial; Commensurate prior; extrapolation; hierarchical model; power prior.

1 INTRODUCTION

In the analysis of pediatric clinical trials, frequentist statistical methods play a foundational role, offering robust tools for evaluating treatment efficacy and safety through traditional hypothesis testing frameworks. These methods are grounded in frequentist inference principles, which utilize sample data to draw conclusions about population parameters, typically employing techniques such as hypothesis testing and confidence interval estimation.

In pediatric trials, frequentist approaches are essential for assessing primary and secondary endpoints, evaluating treatment effects, and rigorously controlling type I error rates. Noteworthy methodologies, as discussed by Higgins et al. (2019) and Ellenberg et al. (2002) , demonstrate the application of frequentist statistics in pediatric research. These studies underscore the importance of stringent study designs, randomized protocols, and adherence to statistical assumptions to ensure robust conclusions regarding treatment efficacy and safety (Higgins et al., 2019; Ellenberg et al., 2002).

Recent contributions by Javidialsaadi et al. (2023) and Hall et al. (2013) have provided methodologies for testing hypotheses using censored and uncensored data, offering further applicability in pediatric trials. By leveraging frequentist statistical methods, researchers uphold rigorous standards of evidence-based medicine in pediatric trials, facilitating reliable assessment and comparison of treatments aimed at improving pediatric patient outcomes. However, challenges such as low patient enrollment rates can hinder study efficacy. Bayesian methodologies offer a solution by incorporating data from historical trials, provided similarities in clinical rationale, pharmacokinetics, and pharmacodynamics between populations are established.There are many Bayesian frameworks to incorporate results from historical trials to different populations. Dixon and Simon (1991) derived posterior distributions for subsetspecific treatment effect for assessing the importance of variation in treatment effect among patient subsets. Mirbakhsh et al (2023) developed an innovative method to overcome the shortcomings in available historical data, their method included producing artificial historical data in a simulation environment. The produced historical data combined with trial-and-error iterations was used to train artificial agents to achieve specific desired goals in transportation industry.Beikihassan et al. (2023) proposed a method to enhance the reliability and robustness of research findings, particularly in medical science and clinical trials. Spiegelhalter (2004) provided a systemic review for Bayesian methods in health care evaluation. Bayesian design has been considered for sample size determination for experimental designs in pediatric trials (Kaur etal (2018)), by evaluating the possibility of taking into account previous information on treatment effect and some uncertainty on unknown parameters. By leveraging Bayesian frameworks, trial designs can enhance efficiency, reduce costs, and expedite access to experimental treatments for pediatric patients. Various Bayesian approaches have been developed to integrate historical trial results into different population settings. This manuscript explores extensions to existing methods, adapting hierarchical Bayesian models to handle multiple efficacy measures from historical trials and accommodating binary endpoints where normal distributions may not apply. This research aims to provide robust statistical tools for optimizing pediatric clinical trial designs and maximizing the utility of historical data in medical research.

2 General Methods for Extrapolation

Let consider $Y_i, i = 1,2$ is the number of outcome in treatment and control groups of pediatric study respectively, and $\tilde{Y}_i, i = 1,2$ is the number of outcome in treatment and control groups of adult study. we assume that $Y_i \sim Binomial(n_i, p_i)$ and $\tilde{Y}_i \sim Binomial(\tilde{n}_i, p_{0i})$. our hypothesis testing is

$$H_0: \quad p_1 = p_2 \quad \text{v.s.} \quad H_A: \quad p_1 \neq p_2$$
$$H_0: \quad RR = 1 \quad \text{v.s.} \quad H_A: \quad RR \neq 1$$

Where $RR = p_1/p_2$. to extrapolate adult information for pediatric we consider three different ways.

2.1 Combined approach using commensurate prior model

A combined data approach combines all the data (adult and pediatric) in a single hierarchical model. We first fit a commensurate prior model (Hobbs et al (2011), and Hobbs et al(2012))). In particular, we choose a $Beta(a,b)$ distribution as our initial prior on p_{0i} and take $p_i|p_{0i} \sim Beta(kp_{0i}, k(1-p_{0i}))$ as our commensurate prior, with $k \sim Gamma(\alpha, 1)$and α assigned a fixed value. simply,

$$\begin{aligned} Y_i &\sim \text{Binomial}(n_i, p_i) \\ \tilde{Y}i &\sim \text{Binomial}(\tilde{n}_i, p_{0i}) \\ pi|p0i &\sim \text{Beta}(kp_{0i}, k(1-p_{0i})) \\ p_0i &\sim \text{Beta}(a,b) \\ k &\sim \text{Gamma}(\alpha,1) \end{aligned}$$

The commensurate prior approach then specifies a hierarchical model with posterior

$$\pi(p_i, p_{0i}, |Y_i, \tilde{Y}_i) \propto L(p_i|Y_i)L(p_{0i}|\tilde{Y}_i)\pi(p_i|p_{0i})\pi(p_{0i})\pi(k)$$

Thus the joint posterior in this case arises as

$$\pi(p_i, p_{0i}, k|Y_i, \tilde{Y}_i) \propto$$
$$pYi\, i(1-pi)ni - YipY0\tilde{}ii(1-p0i)n\tilde{}i - Y\tilde{}ipkpi\ 0i - 1(1-pi)k(1-p0i) - 1pa0i - 1(1-p0i)b - 1k\alpha - 1e - k$$

While this does not lead to a closed form for the marginal posterior $\pi(p_i|Y_i, \tilde{Y}_i)$, sampling from the distribution is routine via MCMC method.

2.2 Power prior method

We apply developing the power prior method (Ibrahim. J and Chen.M (2000)) for our data. Here we may begin by assuming that $p_i = p_{0i} = p$. We then obtain the posterior $\pi(p|Y_i, \tilde{Y}_i)$ as proportional to $L(p|Y_i)L(p|\tilde{Y}_i)\pi(p)$. The power prior approach downweights the adult likelihood by raising it to a power α_0 that is between 0 and 1. The power prior then arises as

$$\pi(p, \alpha_0|\tilde{Y}_i) \propto f(\tilde{Y}_i|p)^{\alpha_0}\pi(p)\pi(\alpha_0)$$

Then the posterior distribution is

$$\pi(p_i, p_{0i}, |Y_i, \tilde{Y}_i) \propto L(p_i|Y_i)L(p_{0i}|\tilde{Y}_i)^{\alpha_0}\pi(p)$$

Note that α_0 controls how much information will be borrowed from the adult data to supplement the fully-utilized child data; e.g., $\alpha_0 = 1$ means full borrowing from source, while $\alpha_0 = 0$

implies no borrowing. We have

$$\begin{aligned} Y_i &\sim \text{Binomial}(n_i, p) \\ \tilde{Y}i &\sim \text{Binomial}(\tilde{n}_i, p) \\ p &\sim \text{Beta}(k\mu, k(1-\mu)) \end{aligned}$$

Then,

$$\pi(p|Yi, \tilde{Y}i) \propto pYi(1-p)ni - YipY\tilde{}i\alpha 0(1-p)(n\tilde{}i - Y\tilde{}i)\alpha 0pk\mu - 1(1-p)k(1-\mu) - 1$$
$$\propto {}_pY_i + Y\tilde{}_i\alpha_0 + k\mu - 1(1-p)_{n_i} - Y_i + (\tilde{n}_i - \tilde{Y}_i)\alpha_0 + k(1-\mu) - 1$$

which is Beta(a,b) where $a = Y_i + Y\tilde{}_i\alpha_0 + k\mu - 1$ and $b = n_i - Y_i + (\tilde{n}_i - Y\tilde{}_i)\alpha_0 + k(1-\mu) - 1$.

2.3 Two-step approach

The two-step approach (Bernardo (1996)) calculates the posterior of the adult supplemental data before combining it with the likelihood of the primary data.

let consider $D_0 = \{Y_1,...,Y_k\}$ is set of historical trials and $D = \{Y_{k+1}\}$ is our current pediatric study.

$$\mathbf{Y_i|\theta \sim F(\theta)}$$
$$\mathbf{\theta \sim G(\alpha,\beta)}$$
$$\mathbf{(\alpha,\beta) \sim H}$$

where $\theta = (\theta_1,...,\theta_i)$. The likelihood of the historical trial data

$$L(\theta,\alpha,\beta|D_0) \propto \prod_{i=1}^{k} f(Y_i|\theta,\alpha,\beta)$$

Hens, the joint posterior $P(\theta,\alpha,\beta|D_0) \propto L(\theta,\alpha,\beta|D_0)\pi(\theta|\alpha,\beta)\pi(\alpha,\beta)$. Integrating out θ,α,β a prior for θ_{K+1}

$$\pi(\theta_{K+1}) = \int L(\theta,\alpha,\beta|D_0)\pi(\theta|\alpha,\beta)\pi(\alpha,\beta)d\theta d(\alpha,\beta)$$

In this approach we assume $\tilde{Y}_i$ the adult information has $Binomial(\tilde{n}_i,p_{0i})$ and use conjugate $Beta(k\mu,k(1-\mu))$ prior on p_{0i}. Note that a more flexible distribution such as a t-distribution or Dirichlet process mixture (Javidi et al (2014)), can also be considered. We complete the model specification by assigning hyperpriors $k \sim Uniform(a,b)$ and $\mu \sim Beta(\alpha,\beta)$, where the upper bound for k was chosen to be comparable to the sample size of our adult datasets. The posterior distribution for a given k and μ is $Beta(k\mu + \tilde{Y}_i, k(1-\mu) + \tilde{n}_i - \tilde{Y}_i)$.

In the first step given only the adult data, denote the posterior means of k and μ by $\hat{k}$ and $\hat{\mu}$ and use these in the prior for pediatric dataset. We assume $p_i \sim Beta(r\hat{k}\hat{\mu}, r\hat{k}(1-\hat{\mu}))$ where $r \in (0,1)$ to scale down the adult data effective sample size if there is a big difference between sample size of adult and pediatric data.

3 SIMULATION STUDY

In this section a simulation study has been conducted to evaluate power of the proposed binomial hierarchical models, and the regular frequentist model without borrowing historical

Table 1: Simulated Studies

	Pediatric	Adult1	Adult2
Sample Size	500	500	700
event rate	13%	6%	8%

data. We generate one pediatric data and 2 adult datasets to conduct the simulation.

Table 1 gives the summary statistics of each studies.

We fit three methods explained previously to this datasets and calculate power and type 1 error in different scenario.

- Scenario1:Borrowing 10% from Adult1 and 40% from Adult 2
- Scenario2: Borrowing 20% from Adult1 and 40% from Adult 2
- Scenario3: Borrowing 10% from Adult1 and 50% from Adult2
- Scenario4: Borrowing 20% from Adult 1 and 50% from Adult 2

Table 2 and 3 present the simulation results for the power and the actual Type I errors, respectively, using power prior, commensurate prior and two step approach. Table 2 indicates

Table 2: Power Calculation under Bayesian Hierarchical Models.

	Scenario1	Scenario2	Scenario3	Scenario4	Pearson's chi square power
Power Prior	92	94	92	95	
Commensurate Prior	83	85	86	88	80
Two Step Approach	85	87	88	90	

Table 3: Type 1 Error Calculation under Bayesian Hierarchical Models.

	Scenario1	Scenario2	Scenario3	Scenario4	Frequentist Type 1 Error
Power Prior	0.07	0.08	0.1	0.12	
Commensurate Prior	0.048	0.049	0.053	0.058	0.05
Two Step Approach	0.05	0.055	0.051	0.06	

that the powers observed in Bayesian methods generally exceed those observed in frequentist method. Additionally, as the extent of borrowing increases across all three methods, there is a corresponding increase in power. Table 3 illustrates that while the frequentist method maintains Type I error control, all Bayesian methods show some degree of inflation. However, the Commensurate prior and two-step models effectively control Type I error across various scenarios compared to the power prior model, which exhibits greater sensitivity to increased borrowing. This inflation is a characteristic of Bayesian methods when incorporating information from successful historical trials and should be carefully weighed against the gains in statistical power. The FDA's "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials" discusses the possibility of adjusting Type I error thresholds when leveraging favorable prior information, emphasizing the need for a case-by-case evaluation considering multiple factors.

4 DISCUSSION

Bayesian designs in pediatric trials can increase efficiency and reduce required sample sizes by leveraging data from historical trials, under conditions where evidence suggests similar treatment responses between current and past studies. In this manuscript, we extend Schoenfeld's Bayesian hierarchical model to accommodate binary endpoints, both with and without normal approximation. Building upon Schoenfeld's framework, which links a single historical trial to the current trial via a variance parameter in the prior distribution for treatment efficacy, our extension incorporates strength from multiple historical trials. We develop closed-form quantitative formulas to facilitate straightforward implementation. Simulation studies demonstrate that the operating characteristics, including power and Type I error rates, align closely with theoretical expectations. As emphasized in FDA guidance on complex trial designs, thorough evaluation of these characteristics is essential, with considerations for Bayesian inference and sensitivity analyses of prior distributions to ensure robustness in trial design. Early engagement with regulatory agencies to secure agreement on the Bayesian approach prior to trial initiation is crucial. thesehe hierarchical models and analytic methods proposed can be adapted for trials with different randomization ratios with minor adjustments to the analytic framework.

REFERENCES

1) Dixon DO, SimonSimon R. Bayesian subset analysis. Biometrics. 1991;47:871–81.
2) Higgins JPT, Thomas J, Chandler J, et al. (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.
3) Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. Ann Intern Med. 2000;133(6):455-463.
4) A. Mirbakhsh, J. Lee, and D. Besenski, (2023), Spring–Mass–Damper-Based Platooning Logic for Automated Vehicles, Transportation Research Record: Journal of the Transportation Research Board, vol. 2677, no. 5. SAGE Publications, pp. 1264–1274, Feb. 04 , 2023. doi: 10.1177/03611981221143121.
5) Mirbakhsh, A., Lee, J. and Besenski, D. (2023), Development of a Signal-Free Intersection Control System for CAVs and Corridor Level Impact Assessment, Journal of FutureTransportation, 3, 552-567. https://doi.org/10.3390/futuretransp3020032
6) Food US, Administration Drug. Interacting with the fda on complex innovative trial designs for drugs and biological products. US Department of Health and Human Services, Federal Registrar. https ://www.fda.gov/media /13089 7/downl oad. 2019.
7) Javidialsaadi, A., Mondal, S., Subramanian, S. (2023). Model checks for two-sample location-scale. Journal of Nonparametric Statistics, 1–31. https://doi.org/10.1080/10485252.2023.2243350
8) Hall, P., Lombard, F., and Potgieter, C.J. (2013), 'A New Approach to Function Based Hypothesis Testing in Location-Scale Families', Technometrics, 55, 215–223.
9) Kaur A, Skoner D, Ibrahim J, Li Q, Lockey RF, Blaiss M, Bufe A, Andersen JS, Canonica GW, Nolte H. Effect of grass sublingual tablet immunotherapy is similar in children and adults: a bayesian approach to design pediatric sublingual immunotherapy trials. J Allergy Clin Immunol. 2018;141(5):1744–9
10) Jose M Bernardo. The concept of exchangeability and its applications. Far East Journal of Mathematical Sciences, 4:111122, 1996.

11) Beikihassan, Ehsan, et al. ”Resource-constrained knowledge diffusion processes inspired by human peer learning.” ECAI 2023. IOS Press, 2023. 214-222.
12) Joseph G Ibrahim and Ming-Hui Chen. Power prior distributions for regression models. Statistical Science, 15:4660, 2000.
13) Joseph G Ibrahim and Ming-Hui Chen. Power prior distributions for regression models. Statistical Science, 15:4660, 2000
14) Brian P Hobbs, Daniel J Sargent, and Bradley P Carlin. Commensurate priors for incorporating historical information in clinical trials using general and generalized linear models. Bayesian Analysis, 7(3):639674, 2012.
15) Javidi A, Rahpeima S, Jafari Khaledi M. Introducing of Dirichlet process prior in the Nonparametric Bayesian models frame work. Andishe 2014; 18 (2) :61-72 URL: http://andisheyeamari.irstat.ir/article-1-249-en.html