Literature Review of Statistical Methods Comparisons Through Simulations When **Using External Control Arm for Regulatory or HTA Submissions**

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INTRODUCTION

- The use of external control arms (ECAs) to augment or use in place of a concurrent internal control in randomized trials can be particularly useful in studies for which patient recruitment may be difficult (eg, rare diseases) or an ethical treatment comparator is not available^{1,2}
- In February 2023, the US Food and Drug Safety Administration released draft guidance on externally controlled trials for drug and biological products³
- The draft guidance highlights the importance of developing an appropriate statistical plan in advance, accounting for bias, and assessing comparability between study arms
- However, there was no consensus regarding the selection of the appropriate statistical methods when constructing an ECA

RESULTS

Targeted literature search

• Of the 122 articles identified in our literature search, 15 statistical articles suitable for summary were selected (Table 1)

Table 1 Summary of Targeted Literature Search

| Citation | Method | Outcomes | Example/case | Conclusion |
|---|---|---|--|--|
| Baron et al. J <i>Biopharm Stat</i> . 2022⁵ | Novel method that integrates PS and Bayesian divide-and-conquer techniques (3 priors used: double hierarchical prior, robust mixture prior, or power prior) to combine stratum-specific parameters and estimate the parameter of interest | Versatile | Simulation | When there was an indata, only the proposision of the pro |
| | | | | When covariates of t nonstratified approact |
| Lin and Lin. J <i>Biopharm Stat.</i> 2022 ⁶ | Review of PS-based methods under the Bayesian framework, including recommendations for reporting in clinical studies | Versatile | Cardiovascular and oncology examples | Different scenarios ir using RWD as prior in as a standalone sour |
| | | | | Incorporating PS for promising approach |
| | | | | Challenges and limitation confounding bias, tra |
| Lin et al. <i>Pharm</i> Stat. 2022 ⁷ | 2 Methods to ensure exchangeability based on either PS matching or Bayesian approach with discounting by coefficient of overlap | Not outcome driven | Simulations | The proposed methor reflect the variability exchangeability with |
| Sawamoto et al. <i>Pharm Stat.</i> 2022 ⁸ | Bayesian adaptive randomization design that incorporates PS- matched historical controls to adjust for covariate imbalance | Time-to-event outcomes (eg, PFS) | Simulation | The proposed design rate than convention |
| | | | | Practical guidance or provided |
| Wang et al. J <i>Biopharm Stat</i> . 2022⁴ | PS adjustment methods (eg, stratification, weighting, matching) integrated with Bayesian priors (eg, power prior, commensurate prior) for augmented controls | Binary | Simulation and oncology example | PS adjustment integrated tool for augmenting or relevant |
| Wang et al. <i>arXiv</i> (preprint). 2022 ⁹ | Method that integrates PS adjustment and Bayesian dynamic borrowing using power prior | Continuous or binary | Simulation and oncology example | The proposed methors with historical control imbalance and heter |
| Liu et al. <i>Stat</i> <i>Med</i> . 2021 ¹⁰ | Novel method that integrates stratification on the PS and Bayesian meta-analytic-predictive prior | Versatile | Simulation and oncology example | The proposed method current trial data com |
| Roychoudhury et al. <i>Stat Med</i> . 2020 ¹¹ | Bayesian meta-analytic approach to leverage historical control data based on a robust hierarchical model for piecewise exponential time-to-event data, which allows for flexible modeling of the hazard function over time and accounts for heterogeneity and uncertainty across historical sources | Time-to-event endpoint (eg, survival) | Oncology examples | The proposed methors sources of historical |
| | | | | Practical guidance for was provided |
| Lin et al. <i>Pharm</i> Stat. 2019 ¹² | 2 Matching schemes based on PS estimated through generalized boosted methods to incorporate external data into Bayesian analysis of clinical trials with disproportionate allocation | Binary | Antibacterial drug development example | The proposed methor augmented control g |
| Lim et al. <i>Ther</i> <i>Innov Regul Sci.</i> 2018 ¹³ | Review of frequentist and Bayesian approaches as used in drug studies that included historical control data | N/A | N/A | High-level summary regulatory audience |
| Lin et al. <i>Pharm</i> Stat. 2018 ¹⁴ | 2 PS-matching methods (pair matching and nearest-neighbor matching adjusted by caliper) to augment current control data from an RCT with those from a historic control | Binary | Antibacterial drug development example | Both PS-matching sc treatment response a historic data |
| Zhao et al. Health Serv Outcomes Res Methodol. 2016 ¹⁵ | PS-matching and Bayesian commensurate prior integrated method | Binary | Simulation and antiretroviral example | This method has utili to augment data from |
| Viele et al. <i>Pharm Stat.</i> 2014 ¹⁶ | Comparison and review of methods for borrowing historical control data | Binary | Simulation | The borrowing behaves and MSE) based on contract on c |
| Hobbs et al. <i>Bayesian Anal.</i> 2012 ¹⁷ | Extension of commensurate power priors ¹⁸ for general linear and general linear mixed models for Gaussian and non-Gaussian responses | Versatile | Simulation and oncology examples | These methods can i multiple historic sour |
| Hobbs et al. <i>Biometrics</i> . 2011 ¹⁸ | Multiple classes of hierarchical Bayesian models that incorporate a measure of how commensurate historical Gaussian data are with current Gaussian data (eg, commensurate power priors) | Continuous | Simulation and oncology examples | Adaptive borrowing in current and historica controlling for type I |

OBJECTIVE

approaches

METHODS

- score Bayesian"
- considered; congress abstracts were excluded
- relevance

To perform a targeted literature search of statistical methods used in the analysis of ECA-supported trials and identify the most robust

 For identification of statistical methods used in ECA-supported trials, a targeted literature search was conducted on Google and PubMed using the search string "external control statistical method propensity

- Articles published in English between 2011 and July 2022 were

- A total of 122 articles were retrieved and manually curated for

- mbalance in the covariates of the external and current trial sed method using a hierarchical prior approach resulted in a red with the nonstratified versions
- the external and current trial data were balanced, the nes performed better
- ncorporating external data with or without RCTs are discussed: nformation, as augmented controls, as sensitivity analysis, and rce of evidence
- ^r evidence synthesis under a Bayesian framework is a to leverage RWD for clinical studies
- tations of this approach include data quality, selection bias, ansportability bias, and computational complexity ods can produce more realistic and informative priors that
- y and uncertainty in the historical data, while maintaining n the current data In can achieve comparable or better power and type I error
- nal designs while reducing sample size and bias on how to implement the proposed design in real trials was

rated with Bayesian commensurate priors can be a useful control designs when historical control data are available and

od is a useful tool for augmenting small or imbalanced RCTs ol data using Bayesian methods while accounting for covariate

od better accounted for heterogeneity between external and mpared with the PS-power prior method

nod is a novel and flexible framework that can handle various data with different levels of relevance and compatibility or implementing the method and evaluating its performance

od can be useful for designing and analyzing trials with groups, especially when internal data are limited or imbalanced

of statistical approaches targeted toward an industry and

chemes to augment control data can reduce bias in estimating e and increase efficiency compared with random sampling of

ility for adaptive borrowing of data from observational studies m an RCT

avior of different methods is compared (by power, type I error, changes in user-controlled parameters

improve the bias-variance tradeoff when using data from

in Gaussian settings based on commensurability between al data can obtain more power than no borrowing while error

- Overall, articles discussed or proposed ECA construction methods that focused on propensity score (PS), Bayesian methods with different priors, or integrated approaches -However, most articles did not examine which approach was the most robust
- We identified 1 comprehensive study by Wang et al⁴ that compared the properties of PS ± Bayesian methods in different combinations; the findings of this study are summarized below

Case study of Wang et al.⁴

• PS ± Bayesian integrated approaches in addition to 2 naive methods (no borrowing; full borrowing) were evaluated in varying combinations (**Table 2**)

Table 2. Summary of Methods Evaluated⁴

| Naive methods | | | | | | | | | |
|--|------------|-----|------|--|--|--|--|--|--|
| No borrowing | | | | | | | | | |
| Full borrowing (pooling) | | | | | | | | | |
| PS methods or two-stage integrated methods | | | | | | | | | |
| | PS methods | | | | | | | | |
| | PSM | PSS | IPTW | | | | | | |
| PS matching methods | | | | | | | | | |
| DS stratification matheds | | | | | | | | | |
| P5 stratification methods | | | | | | | | | |
| | | | | | | | | | |
| IPTW methods | | | | | | | | | |
| | | | | | | | | | |

Each row represents a different set of methods evaluated. CP, commensurate prior; IPTW, inverse probability of treatment weighting; PP, power prior; PS, propensity score; PSM, propensity score matching; PSS, propensity score stratification.

The performance of these different approaches was compared using simulated data of a phase 2 randomized (2:1) controlled trial of treatment group E (n=80) vs control group CD (n=40) and a historical control group CH (n=300; all from 1 study)





CDD, covariate distribution difference; IPTW, inverse probability of treatment weighting; MSE, mean squared error; PS, propensity score.



- The impact on treatment effect estimation was assessed across multiple simulation scenarios Different treatment effect sizes
- Drift in outcome from time trend, covariate distribution difference (CDD), or both Unmeasured vs measured confounding
- Common criteria to compare the different methods, including bias, type I error, and power, were assessed for each scenario (**Figure 1**)
- For the nonfrequentist approaches in simulations when there was no drift in treatment outcome (**Figure 1**, scenarios 1 and 2)
- Estimates were almost unbiased when PS modeling alone or combined with commensurate prior was used
- Simulated type I errors were close to 0.025, mean squared error ratios were all <1, and coverage was ≥95
- Mean CI widths were lower and greater power was obtained for the PS-only methods vs the 2-stage approaches
- The most power was achieved using inverse probability of treatment weighting (IPTW) only or PS stratification only
- For the nonfrequentist approaches in simulations when there was drift in treatment outcome (Figure 1, scenarios 3-8)
- Biases tended to be greater when PS-only vs 2-stage methods were used; however, the biases approached 0 in scenarios 4 and 7 when drift was attributed to CDD alone • Drift from time trend, whether alone or in combination with CDD (scenarios 3, 5, 6, and 8),
- resulted in larger biases
- Type I error was generally lower with the 2-stage vs PS-only methods • Type I error was especially pronounced when drift from time trend alone was negative
- (scenario 6) and PS-stratification only or IPTW-only methods were used - Mean CI widths were lower for the PS-matching and PS-stratification only methods vs the 2-stage
- approaches • Greater variation in mean CI width was observed across scenarios for the IPTW-only and IPTW + trimming approaches
- Coverage was lowest when there was drift from time trend alone (scenarios 3 and 6) and PSstratification only or IPTW-only methods were used

CONCLUSIONS

There is a lack of consensus regarding which statistical method is best for constructing ECAs, particularly when outcomes differ between the current and historical trial(s)

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- This literature review provided valuable information on different statistical methods used to construct ECAs, such as PS, Bayesian with different priors, or integrated approaches
- The analysis of Wang et al⁴ demonstrated that PS-Bayesian integrated methods tended to result in lower bias and type I error than PS-only methods when outcome distributions between the current control and historical control were similar
- As highlighted by Wang et al,⁴ these approaches, whether PS only or 2 stage, are not recommended for scenarios in which treatment efficacy substantially differs between the current study and the ECA
- Higher response rates in the historical vs current control may lead to inaccurate conclusions that the treatment does not have an effect
- The findings of Wang et al⁴ suggest that trialspecific simulations can help find a "sweet" spot" that balances all criteria to help devise a statistical approach for ECA-supported trials

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DISCLOSURES

BY, KL, SX, and SL are all employees of BeiGene and own stock in BeiGene

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