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Introduction to Special Issue on Leveraging External Data to Improve Trial Efficiency

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External data have been always used for new trial designs, analyses or interpretation. For example, to determine sample size at the design stage, all available and relevant external data are summarized to generate the best educated treatment effect assumptions for superiority trials, goal posts for equivalence trials, and noninferiority margins for noninferiority trials. After the trial analysis, the summary of external data can at a minimum to contextualize the new trial results.

Formally incorporating external data (we use "external data" and "historical data" interchangeably) into a new trial analysis can be dated back at least to 1976. Pocock [1] proposed guidance on how to select external data to minimize bias and a Bayesian approach to combining data. However, its development has not been active until recently. To see this, we searched in Google Scholar with the criterion of including "trial" and "historical" and "control or data" in the paper title from 2006 to 2020. The result is in Table 1. It is clear that the number of papers on this topic has increased exponentially in the last decade.

The following three drivers account for this exponential increase.

1. Maturity of statistical methodology. The staple statistical method for clinical trials has been frequentist. The conventional approach is to report point estimates, p-values and 95% confidence intervals. However, increased acceptance of adaptive designs has also revived the adoption of Bayesian approach in clinical trials with increased publications on statistical methodology and applications. Statistically, Bayesian approach as suggested initially by Pocock [1] and a natural way for synthesizing information from different sources, has become the primary statistical tools for incorporating external data in new trial design and analysis.
2. Relevant data availability. In drug development, data are money. A sponsor usually only publishes summary level data as trial results. A lot of data are kept privacy by the sponsor because it spends so much money collecting them. This

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Table 1 Number of papers meeting the search criterion every 5 years between 2006 and 2020

Year	Number of papers meeting search criterion
2016–2020	27
2011–2015	9
2006–2010	2

significantly impedes the valid recycle of the data (e.g., control or placebo data) by others, a clear waste of resources. In 2019, European Medicines Agency published its policy on publication of clinical data for medicinal products for human use, encouraging sharing clinical data. FDA and other regulatory agencies have made similar requirements. Such initiatives have spurred data sharing in the industry without compromising intellectual property. One example is TransCelerate's Historical Trial Data Sharing initiative, which enables the sharing of data to maximize the value of clinical data collected historically in the placebo and standard of care control arms of clinical trials. Such data are often exactly the external data that can be leveraged in a new trial design and analysis.

3. Regulatory support. For example, In FDA's adaptive design guidance [2] and complex innovative trial designs guidance [3] it is explicitly suggested that Bayesian approach is the way for borrowing information from external sources. This means regulatory agencies are open to trial design and analysis leveraging external data. We had an experience of discussing a trial borrowing historical placebo data with FDA in a teleconference. FDA was supportive of such design and willing to review the trial statistical analysis plan.

Stimulated by this opportunity, we have the great pleasure to co-edit this special issue dedicated to "leveraging external data to improve trial efficiency". The call for contribution to the special issue was received with extraordinary enthusiasm, leading to 13 submissions, of which 11 are accepted for publications. Two manuscripts [4, 5] have been published in *Statistics in Biosciences* as regular papers. This special issue contains the remaining nine manuscripts. They cover new statistical methods for exploring impact of data-prior conflict or bias on trial design and analysis, leveraging various types of historical control data, and other topics.

When leveraging external data, a major concern is the potential bias to the point estimate, false decision rates and accordingly trial results interpretation. Yuan et al. developed three conditional borrowing approaches based on the borrowing-by-part prior, hierarchical prior, and robust mixture prior. They demonstrated through simulation the superiority of conditional borrowing to unconditional borrowing or no-borrowing in terms of power and type I error rate. Zhang et al. also explored the impact of prior-data conflict on false rates and proposed a simple approach to determining the borrowing amount at the design stage based on these operating characteristics. In rare diseases, natural historic trend is often borrowed to increase the efficiency of a single-arm or randomized two-arm trial. However, ignored placebo effect may increase the false-positive rates. Monseur

et al. investigated such impact and proposed a Bayesian change-point method to protect from placebo effect and provided better control of false decision rates. More extensively, Shan et al. considered bias sources of regulatory concerns, external data lack of concurrency, unmeasured covariates, covariate measurement error, and outcome measurement error, and their impact on four statistical methods for leveraging external data into a 2-arm trial, matching and bias adjustment, power prior, meta-analytic predictive prior, and test-and-pool. Some recommendations were given for these methods.

When patient-level data are available, propensity score-based methods can be used to adjust any potential differences in patient baseline characteristics. Majumdar et al. detailed process and regulatory interaction experiences of incorporating an external control arm created from patient registry data suing propensity score approach. This external control arm allowed for evaluating the treatment difference in a single arm trial. Methods other than propensity score matching are available for creating external control arms. Wang et al. reviewed such methods including G-methods and targeted learning and recommended by simulation that propensity score matching should be used when the historical data sample size is large while targeted maximum likelihood estimation coupled with super learner is a robust approach for estimating both average treatment effect and average treatment effects among treated.

In some survival clinical trials, joint modeling survival data and a relevant longitudinal continuous endpoint is recommended. Sheikh et al. proposed a new partial borrowing-by-parts power prior approach to leveraging both longitudinal data and survival data to analyze a new trial. This approach allowed to borrow two types of data separately, to borrow a subset of data, and to borrow information through the parameters shared by both data sets.

Drug development should always include a pediatric study plan. Since children are a vulnerable population, it is imperative to stop a pediatric trial early if interim data points to lack of efficacy. Ye and Reaman explored how to leverage external data in improving performance of early futility assessment. The traditional Simon's 2-stage design and Bayesian monitoring approach were compared.

Predictive biomarkers are important to identify the right patient population for a treatment and improve the probability of success of the trial. The threshold of a predictive marker drives tradeoff between the target population (market) size and the treatment effect size. Hui and Guo proposed a likelihood-based approach to determining an optimal threshold that could provide a good balance.

Leveraging external data provides both opportunities and challenges to the industry and regulatory agencies. Statistical methodology research will continue to advance. However, more trials leveraging external data are required to provide operational experiences for the industry and review experiences for regulatory agencies. We hope the methodologies and applications in this special issue will shed some light on this evolving area and stimulate more research and applications in the future.

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