Wednesday 24 July 2024

09:00-10:30 Invited Session 6 (Main Room)

Bayesian methods in clinical development (Chair: Marcia Rueckbeil)

Bayesian approaches in clinical development: methods and case studies

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There is growing interest in use of Bayesian clinical trials designs with informative prior distributions in settings where it may be advantageous to combine multiple sources of evidence, such as extrapolation of adult data to pediatric populations, or to borrow control data from previous clinical trials to augment a new randomised clinical trial (RCT) in the same population and indication.

When incorporating external data into the analysis of an RCT, a key concern is the potential for bias due to "drift" between the external data and the true response in the new trial. This drift could bias the assessment of control response or treatment effect, leading to misguided decisions (e.g. the approval of ineffective therapies or false non-approval). In addition to careful selection of the external dataset, the use of dynamic Bayesian borrowing methods (e.g. [1]) has also become common practice to help mitigate the risk of bias by dynamically down-weighting the external prior information when the outcome data are inconsistent with the observed outcomes in the new study.

Recently, there have been methodological contributions that seek to combine methods that adjust for imbalances in measured baseline covariates between the external and new trial subjects (e.g. propensity score matching/weighting or regression adjustment) and dynamic borrowing to account for unmeasured confounding not captured by measured baseline characteristics (e.g. [2]).

In descriptions of Bayesian designs it is common to find an evaluation of the associated classical (i.e. frequentist or conditional) type I error. However, it is known that this type I error cannot be strictly controlled and depending on several factors, it can be above, below or equal to its nominal level. Additional alternative operating characteristics have recently been proposed [3] to complement classical type 1 error and power to take an informed decision about the risk of false positive and false negative conclusions when using Bayesian clinical trial designs.

In this talk we illustrate some of these recent methodological developments by describing the use of inverse probability weighted robust mixture priors and their application to an ongoing clinical trial that utilizes a hybrid control arm comprised of internal and dynamically borrowed external controls. We will then describe an expanded set of metrics, including the average type I error [3], that can be used to evaluate the operating characteristics of the proposed design, and allow optimizing the trade-off between potential bias versus efficiency gain of Bayesian designs using external data.

References

[1] Schmidli et al. Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics. 2014;70(4):1023-1032. doi:10.1111/biom.12242

[2] Callegaro et al. Dynamic borrowing of historical controls adjusting for covariates in vaccine efficacy clinical trials. Pharmaceutical Statistics. 2024; doi:10.1002/pst.2384

[3] Best et al. Beyond the classical type I error: Bayesian metrics for Bayesian designs using informative priors. Statistics in Biopharmaceutical Research. 2024; doi.org/10.1080/19466315.2024.2342817