Application of a novel Bayesian Dynamic Borrowing approach using anonymized Finnish Real-World Data as an **E**xternal **C**ontrol **A**rm to augment an internal control arm of a randomized clinical trial

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Objectives:

Apply a Bayesian dynamic borrowing approach, calibrating both baseline and outcome differences to quantitatively determine the extent of external real-world data (RWD) that can be utilized as an external control.

Methods

Randomized trial design

The randomized clinical trial (RCT) was a phase II clinical trial with two investigational treatment arms and one arm (n=250) as the internal control arm (ICA). At the end of the trial, the primary endpoint of time to event of a composite bleeding endpoint was evaluated in each treatment arm; additionally, different events making up the primary composite endpoint were individually assessed.

Finnish Real-World Data (F-RWD)

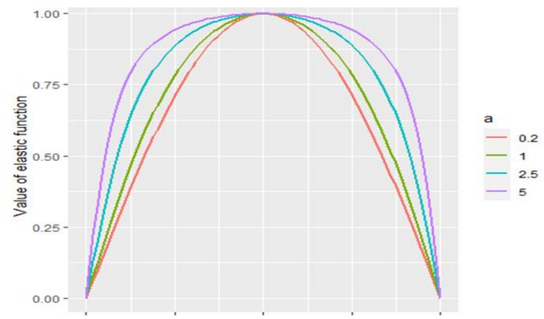
Finnish Healthcare records fulfilling the RCTs eligibility criteria between January 1, 2013 through September 30, 2019 were used to build an ECA. Anonymized baseline data was collected for one year before the inclusion (baseline for hypertension extended to cover five years before the inclusion and two years for weight/BMI) and followed-up maximally up to December 31, 2020.

Statistical Analysis

Various candidate propensity score (PS) models for the probability of being in the ICA were evaluated using all available known confounders. The proposed Bayesian Dynamic Borrowing approach is then implemented in the following steps:

- Propensity score integrated power prior: $L(\theta|D)\{\sum_{s=1}^{S} L(\theta|D_{s0})^{\alpha_{s0}}\}\pi_0(\theta)$, where D_{s0} is the data of external subjects in stratum s and α_{s0} is the power parameter for stratum s
- To calculate the power parameter: First weigh the proportion of a given target number of external subjects (A) to borrow from each strata: $v_s = r_s / \sum_{i=1}^{S} r_s$, Where r_s is the overlapping probability of PS distributions of current and external subjects in stratum s; The power prior for each stratum is then defined as: $\alpha_s = min(1, \frac{A}{n_{0s}} v_s)$
- Elastic prior method: $PPV = \Pr(\bar{\pi} > \bar{y}_0|y)$ where $\bar{y}_0$ is the mean binary outcome of the external data and $\bar{\pi}$ is the predictive distribution of the sample mean of external data given the current data y. It indicates how likely $\bar{y}_0$ resulted from the same random mechanism of the current data. $g(PPV) = \frac{\arctan(a \times \sin(\mathrm{PPV} * \pi))}{\arctan(a)}$ where PPV is the posterior predictive probability, $arctan$ is the arctangent function, sin is the sine function, π is the mathematical constant *"pi"*, and $a > 0$ is a scaler parameter.
- Comprehensive double adjustment: Combine the PS-integrated power prior approach with the elastic function by:
- Calibration step: Calibrate the predictive probability of observing a mean of external data ($\tilde{y}_0$) being greater than the observed mean ($\bar{y}_0$) given the current data (*y*) in each stratum as the Posterior Predictive P-Value: $PPV_s = \Pr(\tilde{y}_0 > \bar{y}_0|y)$
- Use the elastic function $g(PPV_s) = \frac{\arctan(a \times \sin(PPV_s * \pi))}{\arctan(a)}$ to determine a further discounting factor for each stratum
- Then continue: Conduct Bayesian analysis of the PS-integrated power prior to obtain stratum-specific posterior estimation of θ_s, then sum the overall posterior estimation of θ as a weighted mean of θ_s's, which is $\sum_{s=1}^{S} \theta_s / S$ if there is same number of current subjects in each stratum

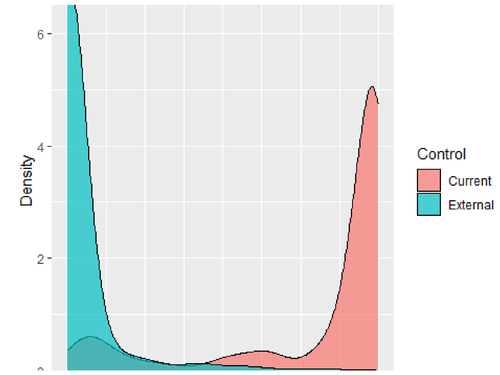
Figure 1: Elastic Functions given size of scaler parameter, a



Results:

- The RCT had n=505 participants randomized to the experimental arms and n=250 to the ICA.
- A pool of eligible Finnish RWD (n=3373) was established, of which n=1002 had overlapping PS with ICA participants and were selected as ECA; among the ECA, 6.8% had a bleeding event compared to 2.4% in the ICA.
- The double-adjusting BDB resulted in an equivalent borrowing of n=64 participants from the ECA, with a posterior mean 2.6% (95% credible interval: 0.9%, 4.5%) reduction in bleeding events (experiment vs augmented control), strengthening the evidence observed in the RCT.

Figure 2: Overlap of probability density PS for Internal control and External control arms



Conclusion:

- The comprehensive Bayesian dynamic borrowing approach extends PS-integrated methods by discounting external data based on baseline and outcome differences. Finnish RWD was used to apply the comprehensive Bayesian dynamic borrowing approach to augment the ICA of an RCT, using RWD to increase the number of controls used for comparison.
- Future work is to apply this methodology to a survival analysis setting by incorporating a time to event element. Additionally, this method can be applied in a regulatory setting utilizing interim analyses and sample size re-estimation to account for differences between pre-planned amount of external data to borrow versus actual amount to borrow.

References

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