Bayesian Dynamic Borrowing to Enhance Evidence for New Therapies

A practical approach to leverage the totality of evidence to reduce uncertainty in efficacy outcomes

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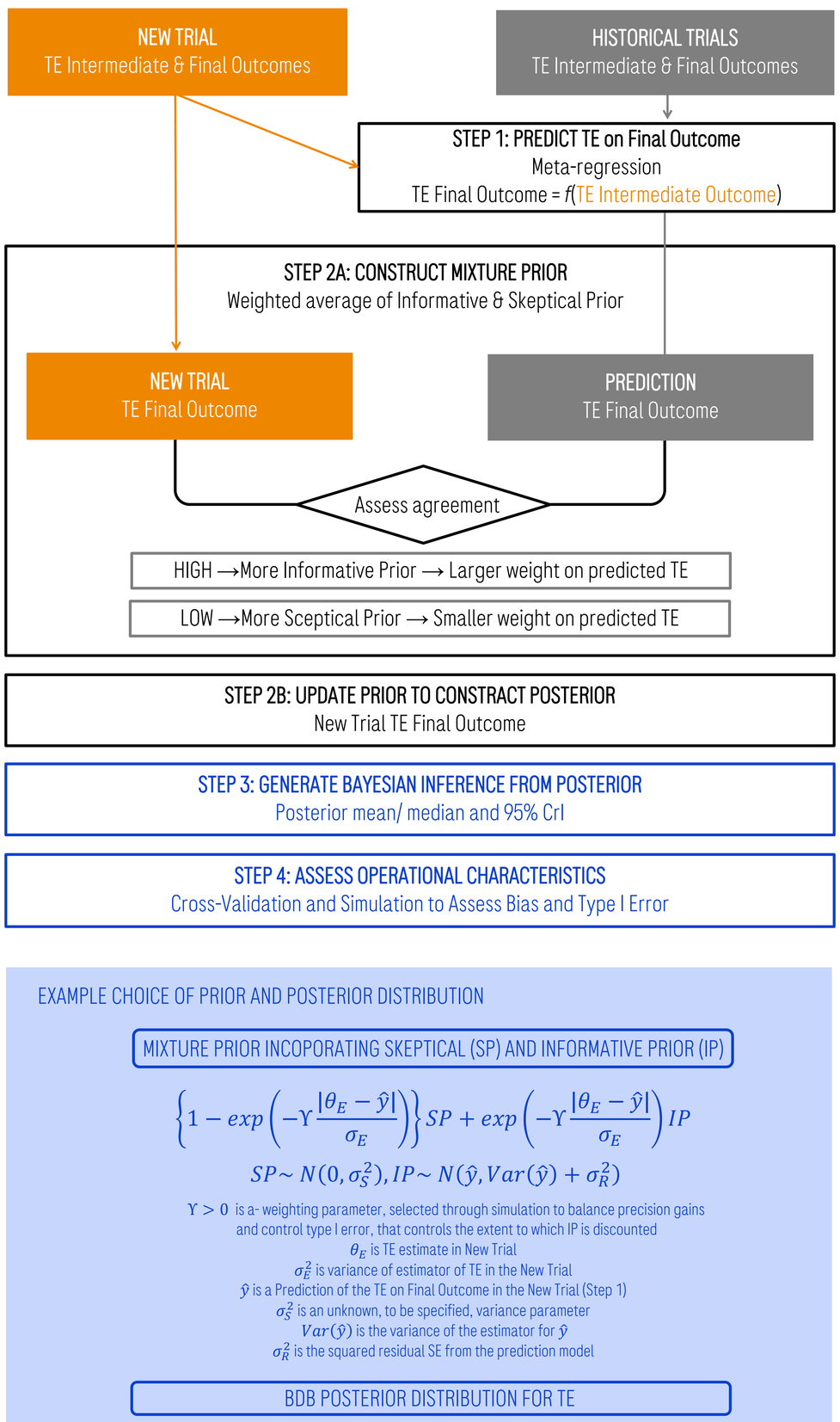
BACKGROUND AND OBJECTIVE

- In rare or slowly progressing diseases, or where ethical considerations limit the use of placebo controls, large randomized controlled trials are often infeasible.[1-3] Consequently, limited data can increase uncertainty around the estimated treatment effects (TEs), delaying regulatory approval and patient access to effective therapies.[4] To optimize trial efficiency, researchers frequently rely on composite or surrogate endpoints, adaptive designs, or external control arms.[5-7]
- Bayesian methods have gained traction for improving the estimation and interpretation of TEs by integrating prior information and adapting dynamically to new data.[8-16] Among these, Bayesian Dynamic Borrowing (BDB) provides a principled framework for incorporating historical data while adjusting the extent of borrowing based on the similarity between historical and new trial data.[17-18]
- BDB has been applied across diverse contexts, including pediatric extrapolation, rare disease trials, subgroup analyses, and health technology assessments, to strengthen evidence and reduce uncertainty in treatment effect estimates.[19-21]
- In this study we demonstrate the application of BDB as a method to enhance precision in estimating TEs for underpowered efficacy components of a composite endpoint.

METHODS

FIGURE 1. HIGH-LEVEL DEPICTION OF BDB METHODOLOGY



EXAMPLE CHOICE OF PRIOR AND POSTERIOR DISTRIBUTION

MIXTURE PRIOR INCOPORATING SKEPTICAL (SP) AND INFORMATIVE PRIOR (IP)

$$\left\{1 - exp\left(-\Upsilon\frac{|\theta_E - \hat{y}|}{\sigma_E}\right)\right\}SP + exp\left(-\Upsilon\frac{|\theta_E - \hat{y}|}{\sigma_E}\right)IP$$

$$SP \sim N(0, \sigma_S^2), IP \sim N(\hat{y}, Var(\hat{y}) + \sigma_R^2)$$

$\Upsilon > 0$ is a- weighting parameter, selected through simulation to balance precision gains and control type I error, that controls the extent to which IP is discounted
θ_E is TE estimate in New Trial
σ_E^2 is variance of estimator of TE in the New Trial
$\hat{y}$ is a Prediction of the TE on Final Outcome in the New Trial (Step 1)
σ_S^2 is an unknown, to be specified, variance parameter
$Var(\hat{y})$ is the variance of the estimator for $\hat{y}$
σ_R^2 is the squared residual SE from the prediction model

BDB POSTERIOR DISTRIBUTION FOR TE

$$\beta_E \mid \hat{\theta}_E = \theta_E \sim N\left(\frac{\sigma_P^2}{\sigma_P^2 + \sigma_E^2}\theta_E + \frac{\sigma_E^2}{\sigma_P^2 + \sigma_E^2}\mu_P, \frac{\sigma_P^2\,\sigma_E^2}{\sigma_P^2 + \sigma_E^2}\right)$$

β_E is the true TE
$\hat{\theta}_E$ is the estimator of TE in the New Trial
μ_P is the mean of the Mixture Prior distribution above
σ_P^2 is the variance of the Mixture Prior above

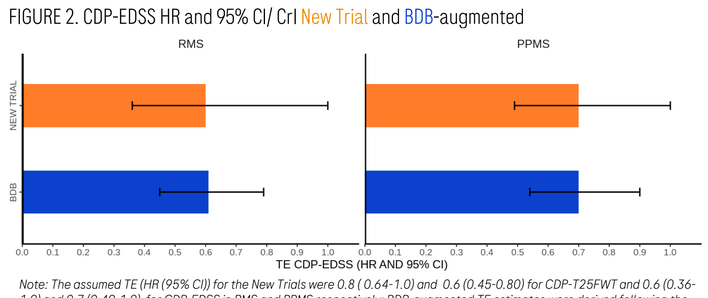
CASE STUDY: Multiple Sclerosis

- The broad use of highly effective therapies reduced event rates in conventional multiple sclerosis (MS) disability measures (i.e. CDP-EDSS),[21] prompting clinical programs to adopt composite confirmed disability progression (cCDP) as the primary efficacy endpoint.[22-25]
- New trials are powered for cCDP but not its individual components. Of these, TE on CDP-EDSS component is of particular interest to decision-makers as it is the main contributor to disability accumulation and related costs.[7]
- BDB was applied to *hypothetical* MS trials to improve precision of TE estimate on CDP-EDSS (Final Outcome) by leveraging the correlation between TE CDP-EDSS and TE CDP-T25FWT(Intermediate Outcome) and historical data.[26]

RESULTS

BDB: BDB TE ESTIMATE EQUAL TO NEW TRIAL BUT WITH LOWER UNCERTAINTY

FIGURE 2. CDP-EDSS HR and 95% CI/ CrI New Trial and BDB-augmented

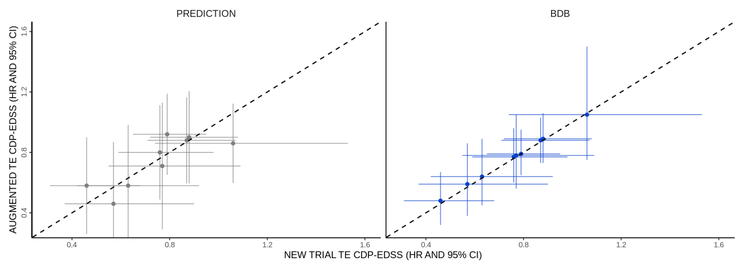


Note: The assumed TE (HR (95% CI)) for the New Trials were 0.8 (0.64-1.0) and 0.6 (0.45-0.80) for CDP-T25FWT and 0.6 (0.36-1.0) and 0.7 (0.49-1.0) for CDP-EDSS in RMS and PPMS respectively; BDB-augmented TE estimates were derived following the methodology illustrated in Fig 1. BDB = Bayesian Dynamic Borrowing; HR = Hazard Ratio; PPMS = Primary Progressive Multiple Sclerosis; RMS = Relapsing Multiple Sclerosis; CI = Confidence Interval; CrI = Credible Interval.

- While maintaining the point estimate, BDB narrowed CI in *hypothetical* New Trials: RMS from 0.60 (95% CI 0.36–1.00) to 0.61 (95% CrI 0.45–0.79); PPMS from 0.70 (95% CI 0.49–1.00) to 0.70 (95% CrI 0.54–0.90).

LEAVE ONE OUT CROSS-VALIDATION: BDB LIMITED BIAS *vs* META-REGRESSION AND REDUCED UNCERTAINTY BY AS MUCH AS 19%

FIGURE 3. CDP-EDSS HR and 95% CI/ CrI obtained from Prediction (meta-regression) and BDB

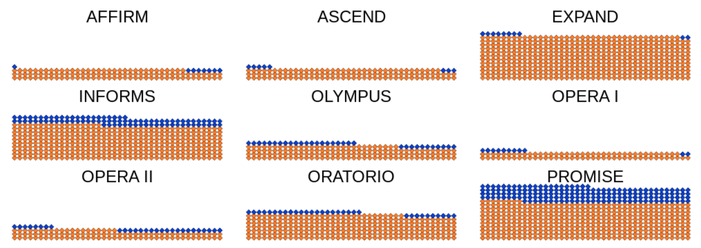


Note: Table shows results from a leave-one-trial-out cross-validation to evaluate BDB on empirical trial data. For each historical trial, a prediction model was fitted excluding that trial, and BDB was then applied to estimate the TE on CDP-EDSS and its 95% CrI; Each dot is TE from each historical trial. See QR Code for link to Poster Abstract and Supplementary Materials for outputs in tabular format. BDB = Bayesian Dynamic Borrowing; HR = Hazard Ratio; CI = Confidence Interval; CrI = Credible Interval.

- Unlike meta-regression, BDB TE estimates consistently matched NEW TRIAL.
- BDB reduced uncertainty modestly (1–7%) when observed and predicted effects deviated (i.e. AFFIRM, ASCEND, EXPAND), but substantially (10–19%) when they aligned (i.e. INFORM, PROMISE) or when trial data were less mature (i.e. OLYMPUS, OPERA II).

LEAVE ONE OUT CROSS-VALIDATION: BDB REDUCTION IN SD IS EQUIVALENT TO UP TO 42% GAIN IN NUMBER OF EVENTS

FIGURE 4. Number of CDP-EDSS events in New Trial and additional events with BDB



Note: Schoenfeld approximation[27] was used to translate the reduction in posterior SD achieved with BDB into the number of additional CDP-EDSS (one dot = 1 event); *See QR Code for link to Poster Abstract and Supplementary Materials for outputs in tabular format. BDB = Bayesian Dynamic Borrowing; SD = Standard Deviation.*

Reduction in uncertainty of TE estimates from BDB roughly translates to an increase in the number of events by over 20% in OLYMPUS, INFORMS, OPERA II, and as much as 42% in PROMISE.

SIMULATIONS: BDB YEILDED UNBIASED TE ESTIMATE WITH REDUCED VARIABILITY AND MINIMAL TYPE I ERROR INFLATION

TABLE 1. SIMULATED BDB UNDER NULL TREATMENT EFFECT: BIAS AND TYPE I ERROR

Trial Setting	Mean HR	Bias	SD	Type I Error
RMS	0.993	-0.007	0.240	6.41%
PPMS	0.955	-0.005	0.160	4.20%

Note: Table shows results of simulation experiments (n = 10,000) to evaluate the performance of BDB in controlling type I error under the null hypothesis of no treatment effect (HR = 1). For each iteration, pairs of TE estimates for CDP-T25FWT and CDP-EDSS were drawn from a bivariate normal distribution using trial-specific variances and a correlation of 0.8 between endpoints. BDB was applied to each simulated dataset, with bias defined as the mean log HR minus 0 and type I error as the proportion of simulations where the upper bound of the 95% CrI for the log HR was < 0; See QR Code for link to Poster Abstract and Supplementary Materials for outputs in tabular format; BDB = Bayesian Dynamic Borrowing; CrI = Credible Interval; HR = Hazard Ratio; PPMS = Primary Progressive Multiple Sclerosis; RMS = Relapsing Multiple Sclerosis; SD = Standard Deviation.

- BDB mean HR ≈ 1 → bias ≈ 0.
- BDB reduced variability in TE estimates (SD from 0.261→0.240 in RMS; 0.182→0.160 in PPMS).
- Type I error minimally inflated.

CONCLUSIONS

BDB supports interpretation of clinically meaningful components, improving confidence in efficacy signals without biasing effect magnitude.

Simulations and empirical analyses demonstrated that BDB reduced uncertainty while maintaining low bias and controlling Type I error.

This methodology is practical, transparent, and applicable with aggregate-level data.

Appropriate allowance for correlation and associated uncertainty induced by multiple data sources informing different components of the model can be achieved using MCMC.

As regulatory and HTA bodies increasingly embrace Bayesian methods, BDB is an attractive approach to enhance evidence synthesis and accelerate decision-making.

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Poster and SM

R code