Covariate-Adjusted Empirical Bayes Power Priors
for Robust Historical Borrowing in Clinical Trials

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Why Historical Borrowing?

Trauma resuscitation setting

Trauma Resuscitation Requiring Massive Tranfusion: Large Phase III Trials

PROPPR: NIH/DoD (2015) · N=660
1:1:1 vs 1:1:2 ·24-hr mortality · Frequentist

TAP Study: CSL Behring (2024) · N=8,000
4F-PCC+SoC vs placebo+SoC · 6-hr mortality · Bayesian

TROOP: NIH/DoD (2027) · N=1,100
Whole blood vs 1:1:1 ·6-hr mortality · Bayesian

Common characteristics: EFIC -> low event rate -> slow enrollment -> costly/large N -> exploit historical information?

Why Borrow Historical Data?

- Increase statistical power
- Reduce required sample size

Key Challenges

- Population differences: eligibility
- Secular changes: era, mortality rate
- Naïve borrowing often inflates Type I error

Leveraging Historical Controls in TROOP

	PROPPR	TROOP
Role	Historical information	Current randomized evidence
Relevant arm	Component therapy 1:1:1 (Intervention)	Component therapy 1:1:1 (Control)
Challenge	Slight historical-current incompatibility	Burden/cost of large trials

Goal

Use relevant PROPPR historical information to improve efficiency while protecting against inappropriate borrowing.

Addressing Two Sources of Conflict

Principled integration of complementary borrowing strategies

Step 1: Population Mismatch (X)

Challenge:

- Slightly different eligibility criteria
- Not all historical patients are directly comparable

Solution:

- Brizzi et al. (2023)-style **covariate transport**:
  - Project historical outcomes onto the TROOP target population
- Construct an informative Beta prior for TROOP control arm mortality

Step 2: Outcome Inconsistency (Y)

Challenge:

- Secular trend may influence current mortality
- Full borrowing can inflate type I error

Solution:

- Penalized empirical Bayes power prior
- Estimate $\hat{\delta}$ from current control and transported historical data.
- Discount transported pseudo-counts by $\hat{\delta}$

Overview of the Proposed Framework

Three-step historical borrowing pipeline

Step 1
Model-Informed Prior

Transport PROPPR to TROOP

Adapted from Brizzi et al. (2023)

→

Step 2
Standard Empirical Bayes Borrowing

Use existing borrowing framework $\hat{\delta}$

Adapted from Gravestock & Held (2019)

→

Step 3
Penalized EB

Penalized estimation of δ

New contribution

Novel contribution: Principled integration of covariate transport with penalized EB estimation of adaptive historical borrowing.

Step 1: Model-Informed Prior

Transporting PROPPR onto TROOP covariate distribution

1. Fit logistic model to PROPPR (Historical) 1:1:1 arm: $\text{logit}[P(Y{=}1)] = \beta_0 + \beta_1 \text{AGE} + \beta_2 \text{SEX} + \beta_3 \texttt{pre_blood}$
2. Filter $N_{\text{elig}} = 310$ PROPPR patients meeting TROOP criterion$\rightarrow$ design matrix $\mathbf{X}_{\text{elig}}$
3. Draw 10^6 samples from the MVN distribution of estimated coefficients; calculate $\pi_H^{*(t)}$ = mean predicted mortality for each draw = $\overline{\text{logit}}^{-1}(\mathbf{X}_{\text{elig}}\beta^{(t)})$
4. **Our implementation:** Moment-match this distn to a beta:

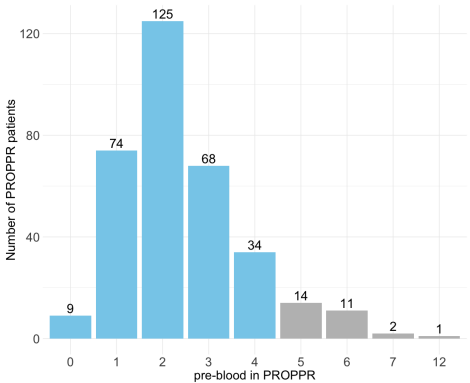
$$\pi_H^* \sim \text{Beta}(31.34,\ 278.98)$$

$$\approx 308 \text{ pseudo-patients}, \approx 30 \text{ pseudo-deaths}$$

Mean mortality: 10.10% 95% CI: (7.13%, 13.81%)

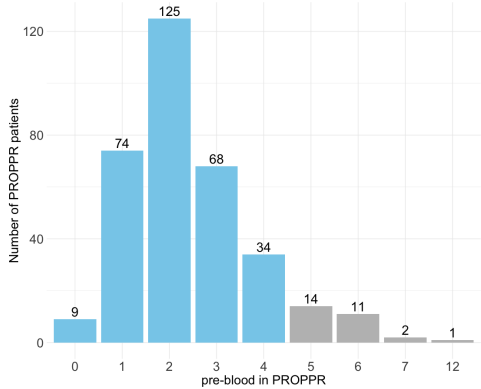
Transported distribution by MOM as a Beta prior:

$$a = \hat{\mu}\left[\frac{\hat{\mu}(1-\hat{\mu})}{\hat{\sigma}^2} - 1\right], \qquad b = (1-\hat{\mu})\left[\frac{\hat{\mu}(1-\hat{\mu})}{\hat{\sigma}^2} - 1\right]$$

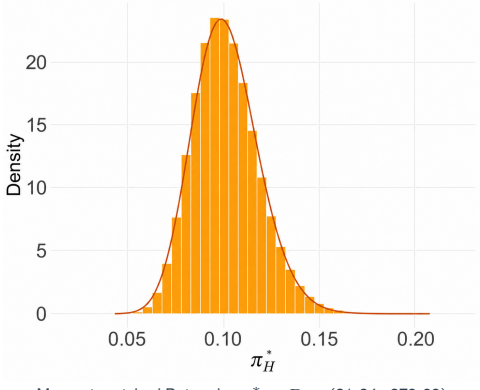


PROPPR patients meeting TROOP eligibility ($N = 310$)

Step 1: Resulting Model-Informed Prior



Transported PROPPR Patients ($N = 310$)



Moment-matched Beta prior $\pi_H^* \sim \text{Beta}(31.34,\ 278.98)$

The covariate-eligible subgroup (left) directly informs the model-informed prior (right). Its moment matched parameters/counts become historical counts entering in Step 2 described below.

Step 2: Empirical Bayes Power Prior

Ibrahim & Chen (2000); Duan & Ye (2006)

Historical information is incorporated by raising the historical likelihood to a power $\delta \in [0, 1]$, where δ determines the amount of borrowing.

$$p_{\text{pow}}(\pi_0 \mid D_H, \delta) \propto L_H(\pi_0)^{\delta}\, p_0(\pi_0), \qquad 0 \leq \delta \leq 1.$$

$\delta = 0$

No borrowing

Ignore historical information

$\delta = 0.5$

Partial borrowing

Borrow half of the historical information

$\delta = 1$

Full borrowing

Borrow all historical information

Exact Closed-Form Marginal Likelihood

Estimate the discount parameter by maximizing the marginal likelihood of observed TROOP control-arm data (Ye et al 2022) where π_0 is unknown shared baseline mortality probability:

$$L(\delta; D_C, D_H) = \int L_C(\pi_0)\, p_{\text{pow}}(\pi_0 \mid D_H, \delta)\, d\pi_0$$

Estimate δ by empirical Bayes:

$$\hat{\delta} = \arg \max_{\delta \in [0,1]} L(\delta; D_C, D_H)$$

For single arm borrowing:
For binomial mortality outcomes with prior $\pi_0 \sim \text{Beta}(a_0, b_0)$, the marginal likelihood simplifies to an exact ratio of betas:

$$L(\delta; D_C, D_H) = \frac{B(s_C + \delta s_H^* + a_0,\ (n_C - s_C) + \delta(n_H^* - s_H^*) + b_0)}{B\big(\delta s_H^* + a_0,\ \delta(n_H^* - s_H^*) + b_0\big)}$$

Key insight

Key insight: Working on the probability scale, we incorporate the covariate-transported historical (PROPPR) information into L_H^* though effective counts s_H^*, n_{H*}. Beta-binomial conjugacy then yields an exact closed-form marginal likelihood. This enables fast one-dimensional optimization of $\hat{\delta}$ using Brent's method.

Step 3: Penalized Empirical Bayes

Novel contribution: Penalty prevents excessive borrowing

Limitation of Standard Empirical Bayes

Standard EB frequently estimates $\hat{\delta} \approx 1$ even under moderate current/historical disagreement $\Rightarrow$ excessive borrowing.

Penalized Objective

$$\hat{\delta}_{pEB} = \underset{\delta \in [0,1]}{\arg\max} \left\{ \log L(\delta; D_{\text{Current}}, D_{\text{Historical}}) + \omega \cdot \log(1-\delta) \right\}, \quad \omega = \sqrt{|\hat{\pi}_H - \hat{\pi}_C|}$$

Advantages

- ✓ Not ad hoc: Bayesian MAP interpretation
- ✓ Data-adaptive borrowing
- ✓ Greater conflict $\Rightarrow$ greater discounting
- ✓ Reduces Type I error inflation while retaining power.

Final Treatment-Effect Analysis

1. **Update the TROOP control arm**
   - Combine observed TROOP control outcomes with historical pseudo-counts discounted by $\hat{\delta}$.

$$\pi_C \mid D_C, D_H, \hat{\delta} \sim \text{Beta}\Big(s_C + \hat{\delta} s_H^* + 1,\ n_C - s_C + \hat{\delta}(n_H^* - s_H^*) + 1\Big).$$

2. **Estimate treatment-arm mortality from TROOP data alone**
   - No historical information is borrowed for the treatment arm.

$$\pi_T \mid D_T \sim \text{Beta}(s_T + 1,\ n_T - s_T + 1).$$

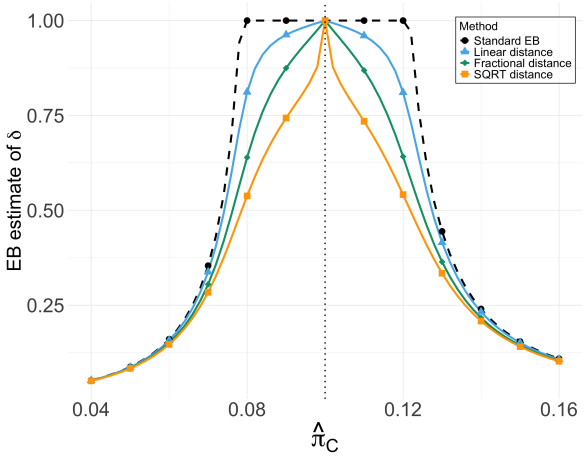
3. **Assess treatment superiority**

$$\Pr\Big(\pi_T < \pi_C \mid D_C, D_T, D_H, \hat{\delta}\Big) > 0.975.$$

Death is the adverse outcome; superiority is declared when the posterior probability that treatment mortality is lower than control exceeds 0.975.

Borrowing Strength Across Methods

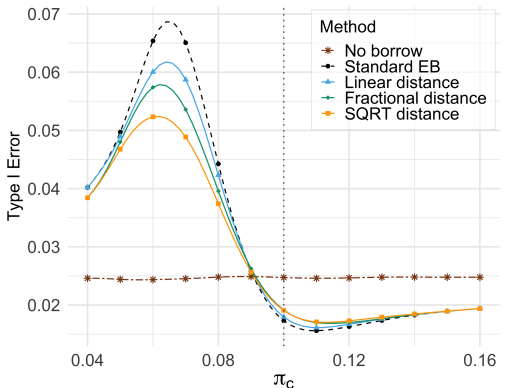
$\hat{\delta}$ as a function of current trial outcome proportion, 0.1



- Vertical dotted line $= \pi_H = 0.10$
- Standard EB retains full borrowing
- All penalization reduces full borrowing.
- SQRT reduces borrowing most sharply under disagreement

Type I Error

Null $\pi_T = \pi_C$ · ***Bayesian superiority*** $P(\pi_T < \pi_C | D) > 0.975$ · $\pi_H = 0.10$ · $n_C = n_T = 500$

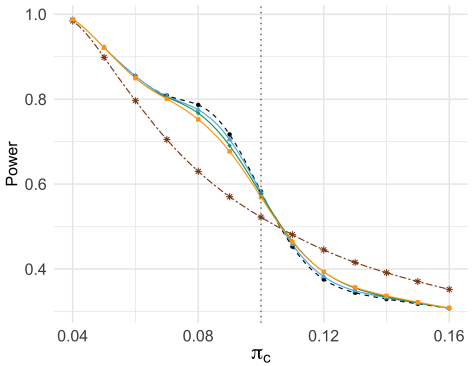


Operating characteristics computed by enumerating all possible pairs of control- and treatment-arm death counts for each true control mortality rate. For each pair, estimate borrowing parameter and apply the posterior superiority rule.

- No-borrow: maintains 0.025 throughout ✓
- T1E above nominal when $\pi_C << \pi_H$ (historical pulls π_C upward)
- Standard EB: inflates to 0.069 (nearly 3× nominal) ×
- SQRT-penalized: peaks at 0.052 — 24% reduction ✓

Power

Alternative $\pi_T = \pi_C - 0.035 \cdot \pi_H = 0.10 \cdot n_C = n_T = 500$

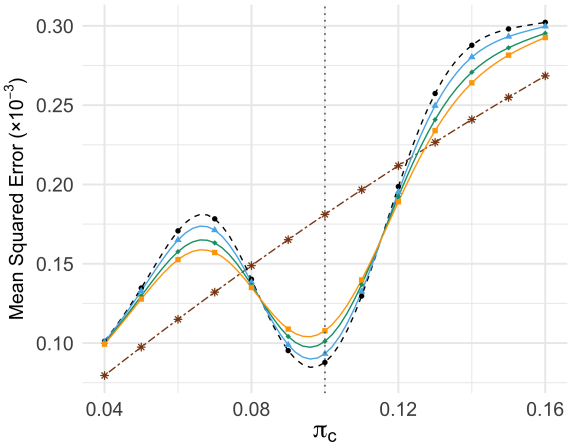


π_C=true control mortality rate; effect size 0.035; estimate outcome-specific $\hat{\delta}$; exact binomial enumeration using covariate-transported PROPPR information and beta(1,1) priors.

- All borrowing methods increase power.
- Differences between borrowing methods are small.
- SQRT penalty preserves power while improving Type I error.

Operating Characteristics: MSE

Alternative $\pi_T = \pi_C - 0.035 \cdot \pi_H = 0.10 \cdot n_C = n_T = 500$



- Typical variance bias tradeoff.
- SQRT penalty has favorable compromise among TIE, power, MSE

TROOP-Motivated Simulation Results

GLMM · *Site REs* · *ICC*= 0.025 · $\pi_H = 0.101$

Scenario	π_C	Type I Error		Mean $\hat{\delta}$	
		SQRT-pEB	Std EB	SQRT-pEB	Std EB
$\pi_C = \pi_H - 0.050$	0.053	**0.047**	0.057	0.199	0.275
$\pi_C = \pi_H - 0.045$	0.058	**0.050**	0.059	0.252	0.359
$\pi_C = \pi_H - 0.035$	0.068	**0.044**	0.054	0.362	0.526
$\pi_C = \pi_H - 0.020$	0.083	**0.041**	0.049	0.500	0.730
$\pi_C = \pi_H$	0.103	**0.021**	0.022	0.540	0.787
$\pi_C = \pi_H + 0.020$	0.123	0.020	0.020	0.446	0.639
$\pi_C = \pi_H + 0.035$	0.138	0.020	0.019	0.320	0.457

1. Mean $\hat{\delta}$ shows standard EB borrows more aggressively; 2. SQRT-pEB controls T1E better in both directions.

Summary

1. Model-Informed Prior

Covariate (**X**) transport addresses population mismatch before borrowing.

2. Exact Closed Form for $\hat{\delta}$

We show an exact closed-form marginal likelihood for δ (borrowing **Y**).

3. Penalized EB

Standard EB over-borrows. Principled data-adaptive penalty discourages excessive borrowing.

Limitations and Future Directions

- **Multiple historical trials**: Extend pipeline to incorporate additional studies
- **Binary outcomes**: Extend to continuous or other outcomes.
- **Type I Error not uniformly controlled**: EB reduces but does not eliminate inflation
- **Heuristic penalty selection**: SQRT not shown to be formally optimal

Thank You

Questions welcome

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