Sample size reestimation in two-arm trials using doubly robust estimators for marginal treatment effects

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Introduction

- **Randomised clinical trials** (RCTs) are the gold standard for evaluating treatment efficacy
- Regulatory agencies (FDA, EMA) recommend adjusting for prognostic baseline covariates[1]

[1] FDA, *Adjusting for Covariates in Randomized Clinical Trials*, 2023.

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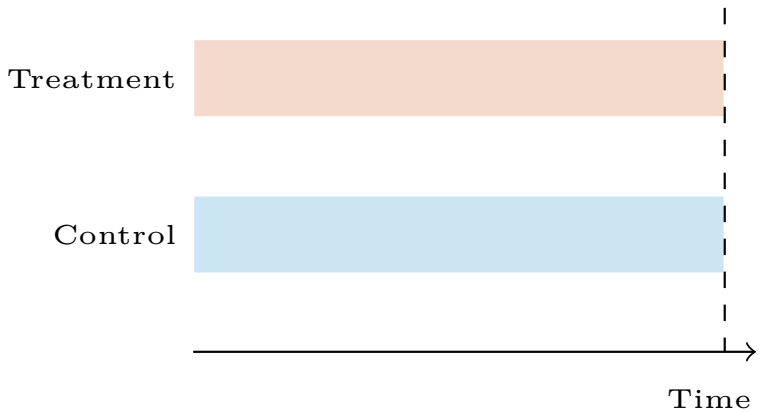

$$\Delta = \text{RMST}_1 - \text{RMST}_0,$$

$$\begin{cases} H_0 : \Delta \leq 0, \\ H_1 : \Delta > 0. \end{cases}$$

Difference in restricted mean survival time (RMST)

The marginal treatment effect is

$$\Delta = \text{RMST}_1(\tau) - \text{RMST}_0(\tau) = \int_0^\tau S_1(t)\,\mathrm{d}t - \int_0^\tau S_0(t)\,\mathrm{d}t$$

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Estimands and estimators for Δ

Covariate adjustment refers to the use of prognostic baseline covariates to improve statistical efficiency for estimating and testing treatment effects.

Marginal estimand

$$\Delta = \mathbb{E}_Z\Big[\mathbb{E}(T \mid A{=}1, Z) - \mathbb{E}(T \mid A{=}0, Z)\Big]$$

- Averages over the covariate distribution
- Estimators of Δ:
  - **Unadjusted:** Kaplan–Meier (KM)-based estimator
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Conditional estimand

$$\Delta(z) = \mathbb{E}(T \mid A{=}1, Z{=}z) - \mathbb{E}(T \mid A{=}0, Z{=}z)$$

- Treatment effect for a specific covariate profile
- Estimators of $\Delta(z)$:
  - Cox model

Doubly robust (DR) estimators

Doubly robust estimators combine a **model for the outcome** and a **model for treatment assignment**, remaining consistent if either model is correctly specified[2]

- Useful for targeting a marginal estimand while adjusting for covariates
- More complex variance than unadjusted estimators

[2] Robins, Rotnitzky & Zhao, JASA, 1995.

Zhang & Schaubel's doubly robust estimator[3]

Estimand: $\Delta = \text{RMST}_1(\tau) - \text{RMST}_0(\tau)$

Strategy:

1. Build a model for the outcome: $\lambda(t \mid A_i{=}j, Z_i) = \lambda_{0j}(t)\, e^{\beta_j^\top Z_i}$
2. Build the weights for the IPTW: $w_{ij} = \frac{\mathbb{I}(A_i{=}j)}{P(A_i{=}j \mid Z_i)}$

[3] Zhang & Schaubel, *Contrasting treatment-specific survival using double-robust estimators*. SiM, 2012.

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2. Build the weights for the IPTW: $w_{ij} = \frac{\mathbb{I}(A_i{=}j)}{P(A_i{=}j \mid Z_i)}$
3. Combine to obtain a doubly robust estimator for $\widehat{\Lambda}_j(t)$ that we need for $\widehat{\Delta}_{\text{dr}}$
4. Obtain the doubly robust estimator $\widehat{\Delta}_{\text{dr}}$

$$\widehat{\Delta}_{\text{dr}} = \int_0^\tau e^{-\widehat{\Lambda}_1(t)} \mathrm{d}t - \int_0^\tau e^{-\widehat{\Lambda}_0(t)} \mathrm{d}t$$

- In RCTs, due to randomisation, the treatment assignment is known $\Rightarrow$ DR is consistent

[3] Zhang & Schaubel, *Contrasting treatment-specific survival using double-robust estimators*. SiM, 2012.

Variance of the DR estimator

Asymptotically, under H_0,

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The asymptotic variance $\sigma^2 = \text{Var}(\widehat{\Delta}_{\text{dr}})$ depends on several components:

$$\sigma^2 = \underbrace{\cancel{\text{IPTW model}}}_{\text{vanishes in RCTs}}$$

$$+ \text{ Cox model Score and Fisher's information matrix}$$

$$+ \underbrace{\text{Censoring distribution} + \text{Covariate distribution}}_{\text{nuisance parameters}}$$

Our goal

Goal: Sample size calculation in a survival trial targeting a marginal estimand using a covariate-adjusted, doubly robust estimator for the RMST difference.

Challenge: The required sample size depends on the Δ estimator's variance:

$$n = \frac{\sigma^2 \left(z_\alpha + z_\beta\right)^2}{\Delta^2}$$

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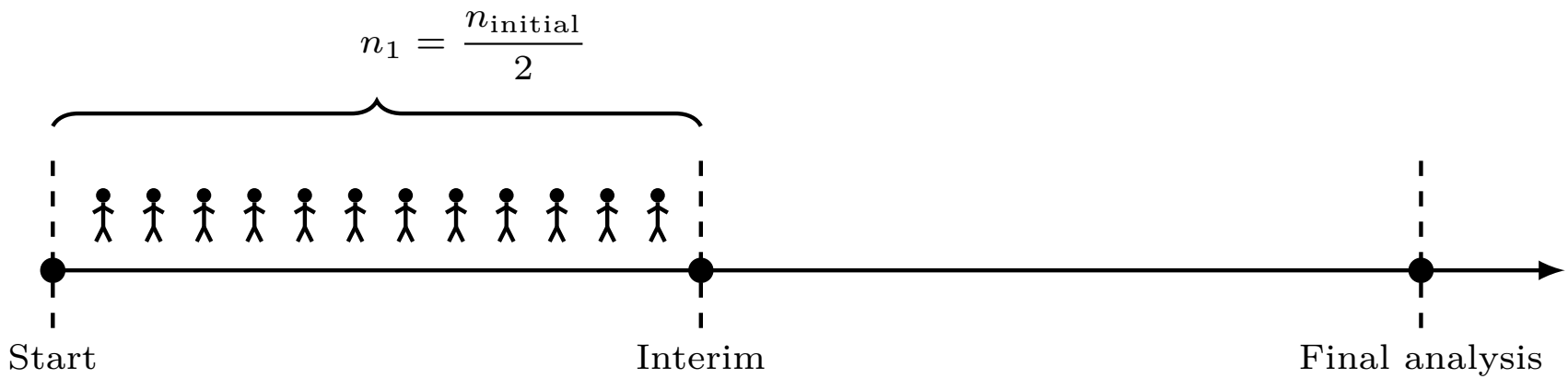
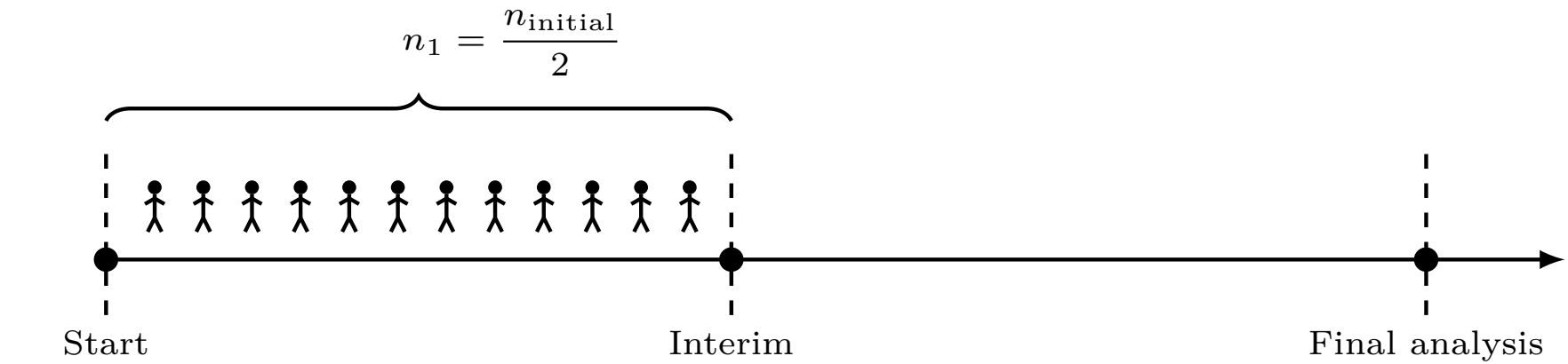
$\Longrightarrow$ Estimate σ^2 during the trial and reestimate the sample size.

Sample size reestimation

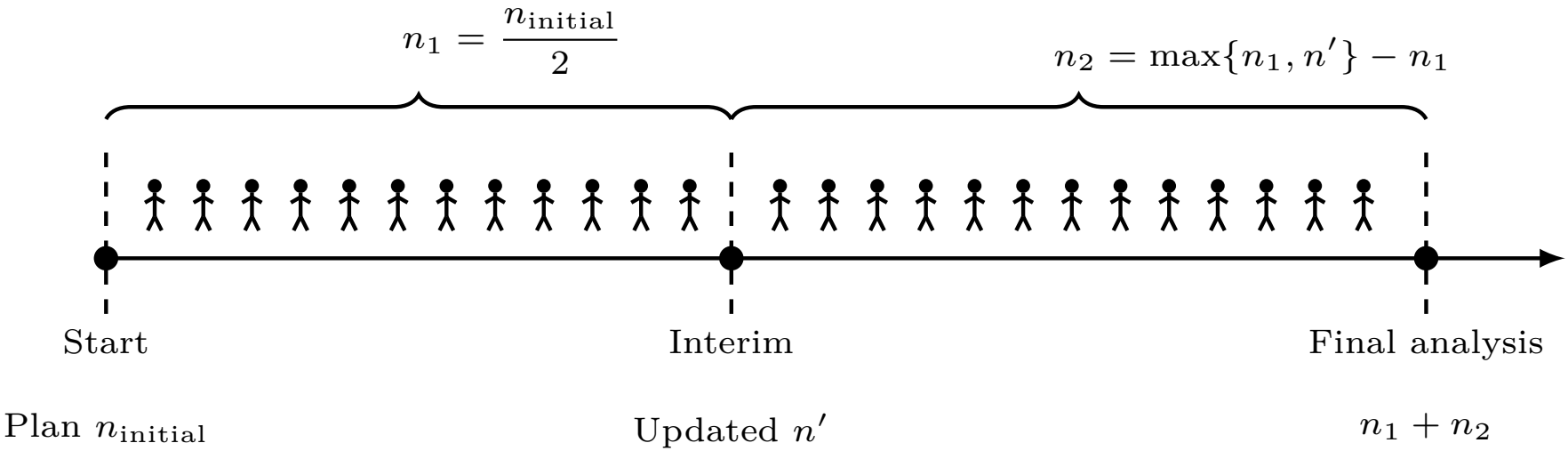


Plan n_{initial}

Sample size reestimation



Sample size reestimation



Sample size reestimation

1. **Initial sample size** n_{initial}: Computed using the variance of the KM-based estimator

2. **Interim analysis** at $n_1 = \frac{n_{\text{initial}}}{2}$: estimate $\widehat{\text{Var}}(\widehat{\Delta}_{\text{dr}})$ from accumulated data

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3. **Update** the sample size:

$$n' = \frac{\widehat{\text{Var}}(\widehat{\Delta}_{\text{dr}})\,(z_\alpha + z_\beta)^2}{\Delta^2}, \qquad n_2 = \max\{n_1,\, n'\} - n_1$$

4. **Final test** using all $n_1 + n_2$ participants:

$$\mathcal{Z} = \frac{\widehat{\Delta}_{\text{dr}}}{\sqrt{\widehat{\text{Var}}(\widehat{\Delta}_{\text{dr}})}} \overset{H_0}{\sim} N(0,1)$$

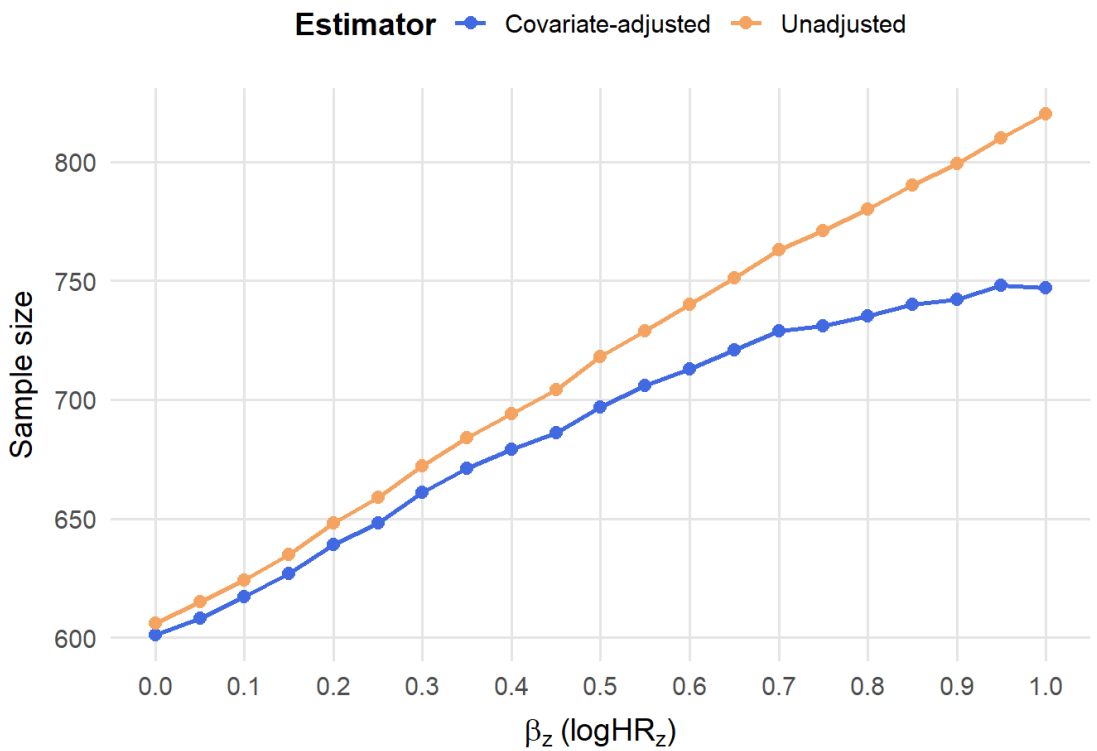
Simulation study

Goal: Evaluate how the DR variance affects the required sample size and the operating characteristics of the proposed design.

Data generating mechanism

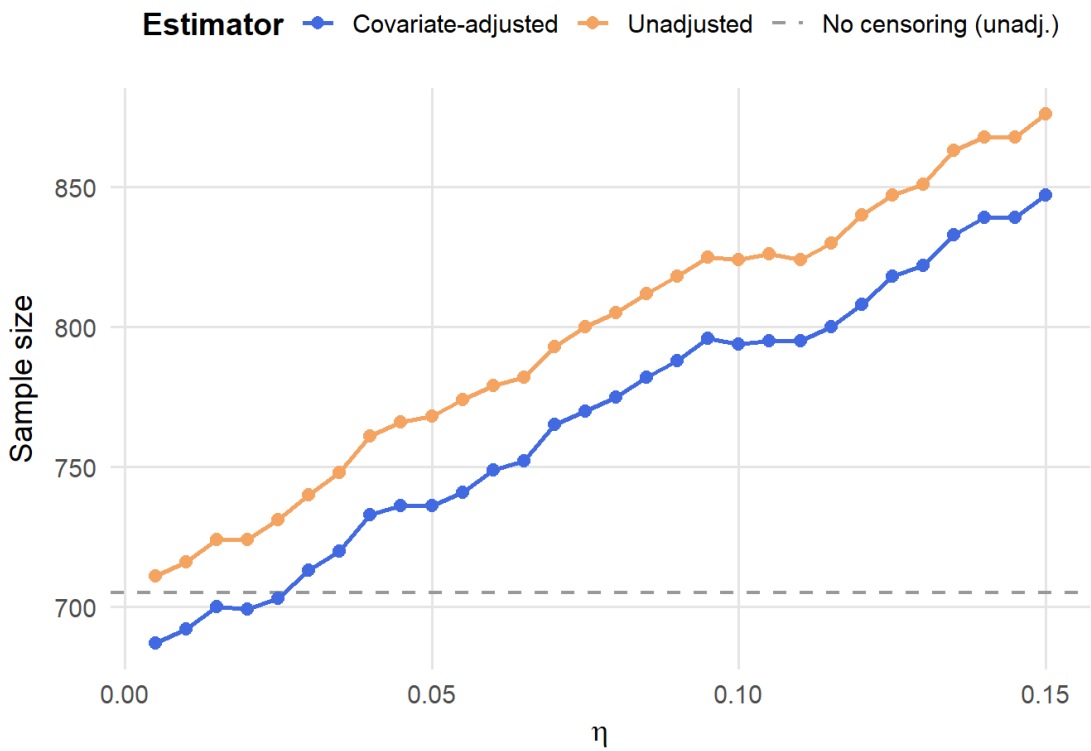
- $T \sim \exp(\lambda)$, $C \sim \exp(\eta)$
- Binary covariate Z, $p_z = 0.4$
- Cox model with log-HR β_z for Z
- $\Delta = 0.28$, $\tau = 5$
- $n_{\text{sim}} = 1000$; initial $n = 720$

Prognostic strength of the covariate



- As β_z increases, the DR estimator gains efficiency relative to the unadjusted estimator
- The stronger the prognostic covariate, the greater the reduction in required sample size

Censoring proportion



- Higher censoring increases variance ⇒ larger required sample size for both estimators
- The DR estimator **consistently requires less sample size** than the unadjusted estimator across all censoring levels

Conclusions

- Current regulatory practice allows using an unadjusted estimator for sample size calculation, although it may be conservative.
- Covariate adjustment leads to efficiency gains, and the doubly robust estimator yields robustness.

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- Current regulatory practice allows using an unadjusted estimator for sample size calculation, although it may be conservative.
- Covariate adjustment leads to efficiency gains, and the doubly robust estimator yields robustness.
- The variance of the doubly robust RMST estimator depends on nuisance parameters unknown at the design stage.
- These gains can translate to a smaller required sample size.
- We proposed an adaptive two-stage design that leads to the necessary sample size to achieve the target power at the significance level.

Next steps

- Formally describe and compare the blinded and unblinded estimation of the variance.
- Study the efficiency gains and the type I error control of this adaptive design under different scenarios.
- Discuss whether all the parts of the DR variance need to be estimated at the interim analysis.

Selected references

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Thank you for your attention!

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