

Covariate Adjustment in RCTs: Practical Implementation and Outlook

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Software Subteam

Outline

Practical implementation of covariate
adjustment methodology

The RobinCar
Family

Using Covariates
in Design
and Analysis

Dealing with
Imperfect data

Approaches for
High-Dimensional
Data

Time-to-Event
Estimands

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The RobinCar Family



*Supported by the ASA Biopharmaceutical
Section Covariate Adjustment Working Group*



The RobinCar Family



Link to arXiv preprint with all of the methods here (+ additional ones)

RobinCar

RobinCar2

Standardization using canonical generalized linear models



Standardization using SuperLearner
(includes augmentation term for bias correction and cross-fitting)



Covariate-adjusted log-rank test and marginal hazard ratio
(+ option for stratifying the test)



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High-Dimensional
Data

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Estimands

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Practical implementation of covariate
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High-Dimensional
Data

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Using Covariates in Design and Analysis

- Trials commonly use **covariates at the design stage** during randomization:
 - E.g., stratified permuted block randomization*, stratified biased coin, Pocock and Simon's minimization.
- This breaks the “independent and identically distributed” assumption that is commonly employed in the theoretical analysis of estimators.

Bannick et al. (2025) *Biometrika*; Ye et al. (2024) *JASA*:



AIPW (or G-computation) estimators are still consistent for marginal estimand.



Variance estimators that are valid under simple randomization may not be valid under other randomization schemes.

* Stratified permuted block randomization is *not* the same thing as stratified randomization. Stratified randomization has the same asymptotic properties as simple randomization.

Using Covariates in Design and Analysis

- Ignoring the randomization scheme often leads to conservative inference.
- An important exception is using a canonical generalized linear **interaction model** with the **randomization variables included as covariates**.
- The asymptotic variance of the G-computation estimator based on the working model below is **invariant to the randomization scheme**.

$$E(Y|A = a, Z, X) = g^{-1}(\nu_a + \gamma_a Z + \beta_a X)$$

↓
Treatment
assignment

Canonical link
function

↓
Discrete covariates
used in randomization

↓
Other
covariates

RobinCar provides variance estimators under several randomization schemes if you choose not to use this working model.

Using Covariates in Design and Analysis

- When doing a **log-rank test**, any variables used as the design stage need to either be accounted for via stratification (stratified log-rank test), or through covariate adjustment (covariate-adjusted log-rank test).
- The choice of approach should be driven by the *null hypothesis (and estimand) of interest*.

Unconditional Null

(corresponds to marginal HR)

$$H_0 : \lambda_1(t) = \lambda_0(t)$$

- Covariate-adjusted log-rank test
(same null as log-rank test)

Conditional Null

(for all levels of Z)

$$H_0 : \lambda_1(t|Z) = \lambda_0(t|Z)$$

- Stratified log-rank test
- Covariate-adjusted stratified log-rank test

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adjustment methodology

The RobinCar
Family

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in Design
and Analysis

Dealing with
Imperfect data

Approaches for
High-Dimensional
Data

Time-to-Event
Estimands

Outline

Practical implementation of covariate
adjustment methodology

The RobinCar
Family

Using Covariates
in Design
and Analysis

Dealing with
Imperfect data

Approaches for
High-Dimensional
Data

Time-to-Event
Estimands

Dealing with Imperfect Data:

Missing Data

- RobinCar and RobinCar2 require users to provide a **complete** dataset.
- **Missing covariate data** can be imputed and still lead to efficiency gains!*
- **Missing outcome data** is more complicated, but it needs to be dealt with regardless of whether covariate adjustment is used.

* See: Zhao and Ding (2022) in JASA; or Song, Hughes, and Ye (2024) in Biometrics.

Dealing with Imperfect Data:

Finite Samples

- Asymptotic variance is one thing – constructing a well-behaved variance estimator in finite samples is another!
- **Influence function-based variance estimators** require plug-in estimates for quantities relating to the working model $f_a(x) = E(Y|A = a, X = x)$
 - Different variance options for situations where
 - the outcome is zero-inflated, or
 - distribution of covariates differs substantially by treatment group
- **Sandwich-based variance estimators** have correction terms that may perform well in finite samples – but this is only a valid approach for ANCOVA (linear model, no interactions, linear contrast).

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Family

Using Covariates
in Design
and Analysis

Dealing with
Imperfect data

Approaches for
High-Dimensional
Data

Time-to-Event
Estimands

Outline

Practical implementation of covariate
adjustment methodology

The RobinCar
Family

Using Covariates
in Design
and Analysis

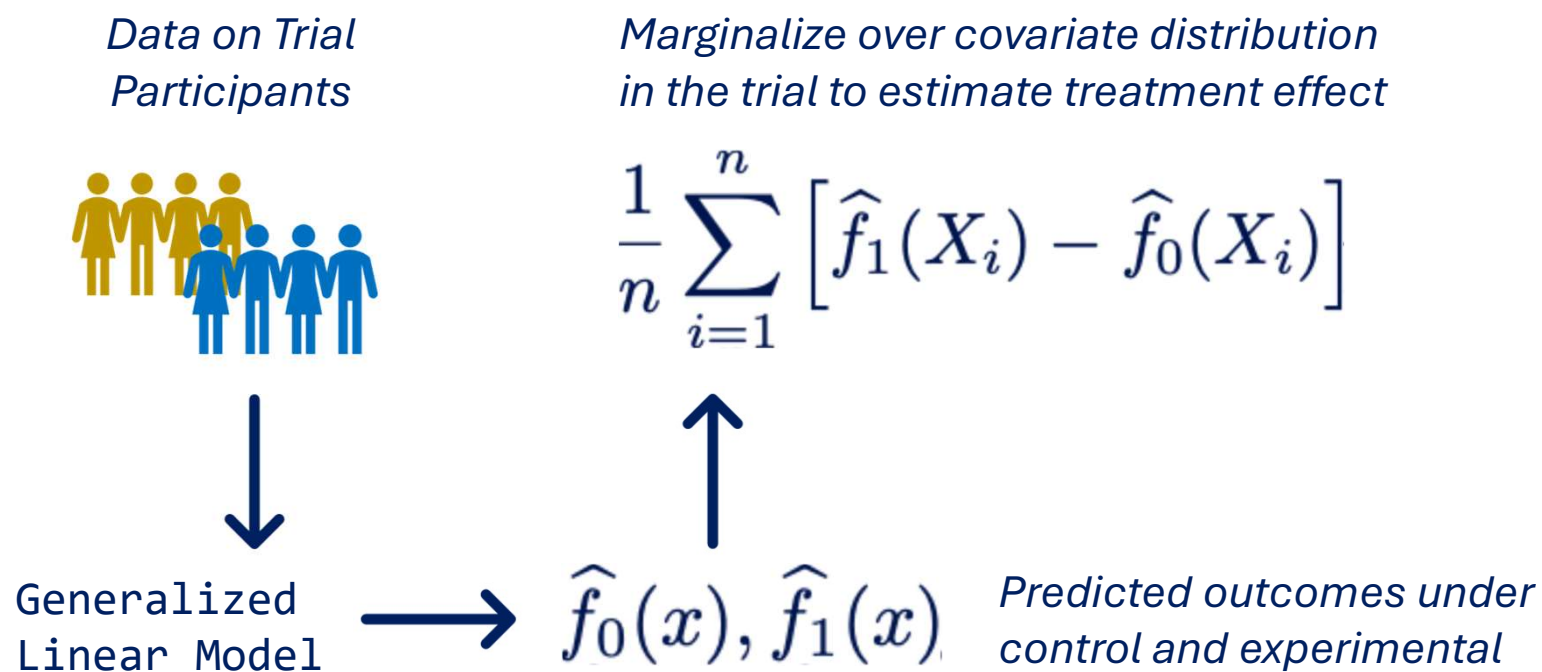
Dealing with
Imperfect data

Approaches for
High-Dimensional
Data

Time-to-Event
Estimands

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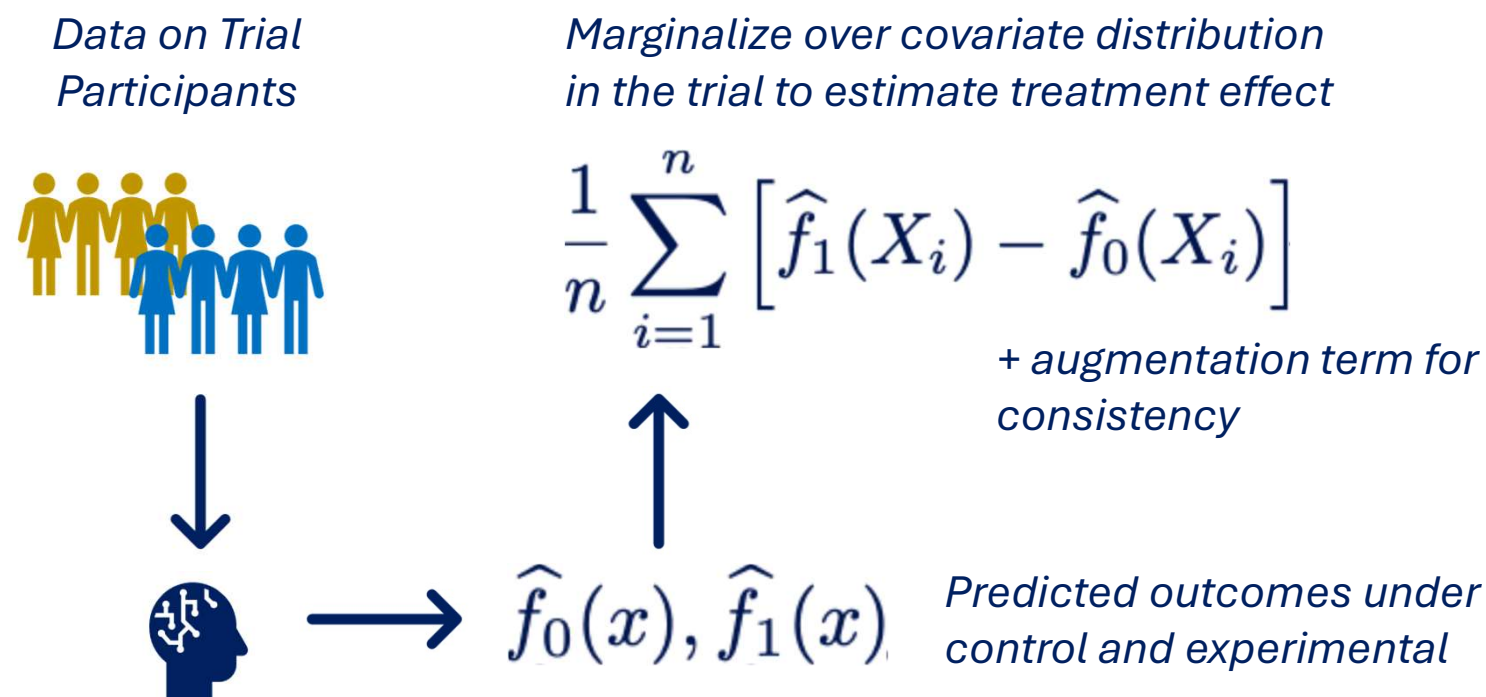
Approach 1: Use a “simple” model with lots of covariates.



Approaches for High-Dimensional Data

Approach 1: Use a “simple” model with lots of covariates.

Approach 2: Use an ML or AI model with lots of covariates.



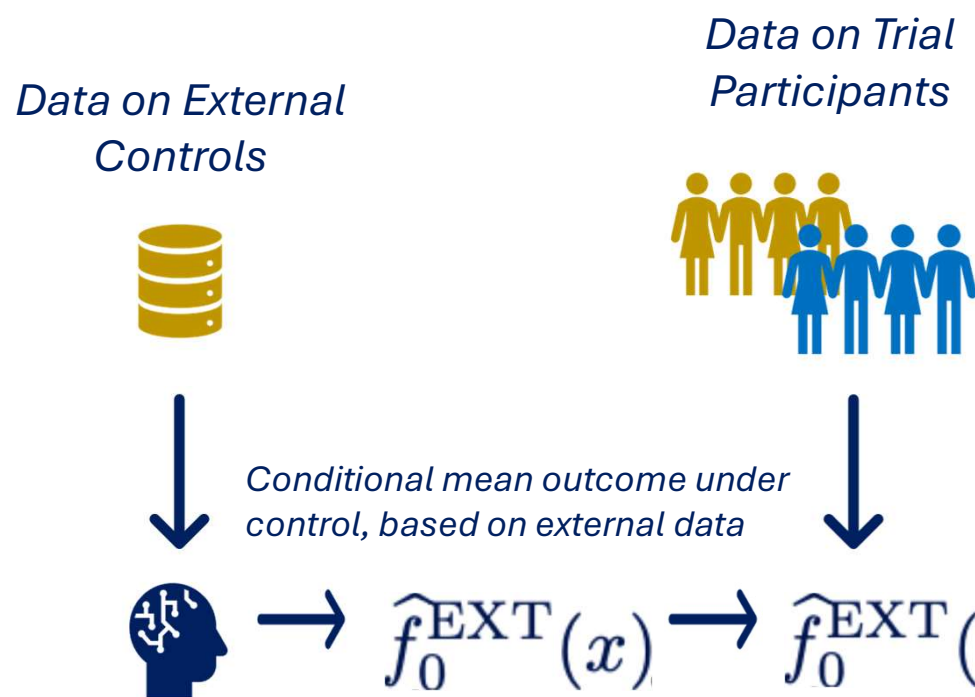
Approaches for High-Dimensional Data

Approach 1: Use a “simple” model with lots of covariates.

Approach 2: Use an ML or AI model with lots of covariates.

Schuler et al. (2021) *Int. J Biostat.*

Approach 3: Use an ANCOVA model with one pre-trained covariate (“super covariate”).



All three of these methods are supported in RobinCar (you must provide the super covariate).

Approach 2 requires cross-fitting to make sure you're not overfitting to the trial data.

Approach 3 only captures the covariate association with outcomes under control conditions (not experimental treatment).

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Family

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Dealing with
Imperfect data

Approaches for
High-Dimensional
Data

Time-to-Event
Estimands

Outline

Practical implementation of covariate
adjustment methodology

The RobinCar
Family

Using Covariates
in Design
and Analysis

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Imperfect data

Approaches for
High-Dimensional
Data

Time-to-Event
Estimands

Time-to-Event Estimands

- With time-to-event data, there could be several estimands of interest:
 - Comparing two full survival curves visually.
 - A comparison of some summary metric of the curves: E.g., difference in restricted mean survival time, difference in survival probability at a landmark time.
 - Marginal hazard ratio.
- Shao, Zhang, and Ye (2026) in *SBR*: estimate treatment propensity using logistic model, and inverse-weight the event and at-risk processes in the typical Kaplan-Meier estimator form.

$$\hat{S}_a(t) = \prod_{t_j \leq t} \left(1 - \frac{d_a(t_j)}{r_a(t_j)} \right)$$

Kaplan-Meier Estimator

$$\hat{S}_a^w(t) = \prod_{t_j \leq t} \left(1 - \frac{d_a^w(t_j)}{r_a^w(t_j)} \right)$$

Weighted Kaplan-Meier Estimator

Thank you for listening!

RobinCar Collaborators

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Daniel Sabanes Bove	<i>Novartis / RCONIS</i>
Faith Bian	<i>Eli Lilly</i>
Dong Xi	<i>Gilead</i>
Gregory Chen	<i>Merck</i>
Liming Li	<i>Roche / AstraZeneca</i>