

# Leveraging Prognostic Baseline Variables to Gain Precision in Randomized Trials

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See 2017 paper in *Contemporary Clinical Trials*:

<https://goo.gl/IAFVS8> with software in R and STATA

Key papers referenced below available: **projectdidact.org**



## **PI on PCORI funded project: “Innovative Randomized Trial Designs to Generate Stronger Evidence about Subpopulation Benefits and Harms”** Specific Aims:

- 1 Develop and evaluate new adaptive enrichment designs for time-to-event and other delayed outcomes.
- 2 Conduct extensive simulation studies.
- 3 Produce user-friendly, free, open-source software to find best design to answer a clinical investigator’s research question.

## **PI on FDA funded project to demonstrate strengths and weaknesses of new adaptive trial designs in the following clinical applications:**

stroke treatment (Dan Hanley), slowing progression of Alzheimer’s disease (Michela Gallagher), cardiac resynchronization devices (Boston Scientific), and HIV prevention (Craig Hendrix)

# Use of Covariate Adjustment in Randomized Trials: Two Surveys

Pocock et al. (2002) surveyed 50 randomized clinical trial reports.  
Findings:

- 1 36 used covariate adjustment.
- 2 12 reports emphasized adjusted over unadjusted analysis.

“The statistical emphasis on covariate adjustment is quite complex and often poorly understood, and there remains confusion as to what is an appropriate statistical strategy.”

Similar conclusions in survey by Austin et al. (2010) titled: “A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals.”

# Challenges and Project Goals

## Challenges:

- Many approaches to covariate adjustment and no clear guidance on which methods have consistently good performance.
- The choice of method is important since some have major flaws.
- Software implementing some methods is not readily available.

## We will address above challenges by:

- Providing free, open-source software implementing several recommended methods in R and SAS.
- Quick assessment tool to determine if adjustment potentially useful in trial being planned.
- Teaching short-courses, including case-studies in multiple disease areas, explaining covariate adjustment and how to use the software.

All above will be available at [projectdidact.org](http://projectdidact.org) at end of project.

# Example 1: Planning MISTIE Phase III Stroke Trial

Problem: Confirmatory trial of new surgical treatment for intracerebral hemorrhage (PI: Daniel Hanley).

- Primary Outcome  $Y$ : modified Rankin Scale  $\leq 3$  at 180 days from enrollment.
- Study arms  $A$ : surgery vs. standard of care.
- Baseline variables  $B$ : NIH Stroke Scale, clot volume, and location.

Goal: Estimate Avg. Treatment Effect

$$P(Y = 1|A = 1) - P(Y = 1|A = 0).$$

Simulated trials based on resampling participants from MISTIE Phase II data.

- 38% precision gain from adjusted estimator compared to unadjusted.
- Equivalent to 28%  $(1 - \frac{1}{1.38})$  reduction in required sample size.

## Example 2: Planning Alzheimer's Disease Trial

Problem: Confirmatory trial of new treatment for preventing progression from mild cognitive impairment to Alzheimer's Disease (PI: Michela Gallagher).

- Primary Outcome  $Y$ : Change in Clinical Dementia Rating (CDR) at 2 years vs. baseline.
- Study arms  $A$ : new drug vs. placebo.
- Baseline variables  $B$ : CDR, ApoE4 genotype, concurrent medications, brain structure measurements.

Goal: Estimate Avg. Treatment Effect  $E(Y|A = 1) - E(Y|A = 0)$ .  
Simulated trials based on resampling participants from Alzheimer's Disease Neuroimaging Initiative (ADNI).

- 13% precision gain from adjusted estimator compared to unadjusted.
- Equivalent to 12%  $(1 - \frac{1}{1.13})$  reduction in required sample size.

# Goal of Covariate Adjustment

- Population Average Treatment Effect is a contrast between mean outcome if all were assigned to treatment versus all assigned to control. (Intention To Treat)
- **Goal: Estimation of Average Treatment Effect in a Randomized Trial.**  
If baseline variables prognostic for outcome, can improve precision compared to unadjusted estimator.
- We require estimators to be consistent (i.e., converge to Average Treatment Effect) without making any parametric model assumptions.

**Covariate adjustment has potential to substantially improve precision (shorter CI's), reduce sample size, and reduce trial duration.**

Intuition: Gain precision by adjusting for chance imbalances in prognostic baseline variables between study arms.



# Definition: Population Average Treatment Effect

Primary outcome  $Y$ , study arm  $A$ , and baseline variable vector  $B$ .

Population mean outcome under treatment and control:

$$\mu_1 = E(Y|A = 1) \text{ and } \mu_0 = E(Y|A = 0).$$

**Population Average Treatment Effect:** contrast between  $\mu_1, \mu_0$ .

Examples of Population Average Treatment Effects:

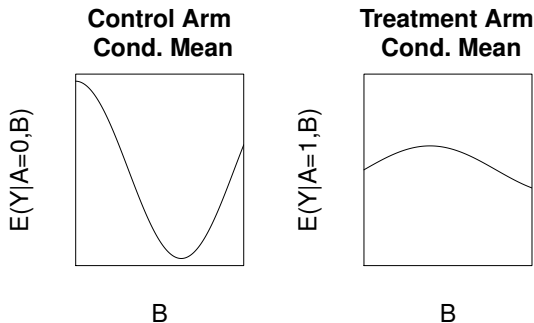
- If continuous outcome, mean difference:  $\mu_1 - \mu_0$ .
- If binary outcome, then
$$\mu_1 = P(Y = 1|A = 1), \quad \mu_0 = P(Y = 1|A = 0).$$
  - risk difference:  $\mu_1 - \mu_0$ .
  - relative risk:  $\mu_1/\mu_0$ .
  - log odds ratio (OR):  $\log \left[ \frac{\mu_1/(1 - \mu_1)}{\mu_0/(1 - \mu_0)} \right]$ .

- **Goal: Estimation of Average Treatment Effect in a Randomized Trial.** Require consistent and interpretable estimators.
- **Not Goal:** Estimation of Conditional (within stratum of  $B$ ) Treatment Effects, e.g.,  $E(Y|A = 1, B) - E(Y|A = 0, B)$ . Conditional Treatment Effects would be useful to know, but typically require model assumptions (such as linear or logistic model) and uninterpretable under model misspecification.
- **Not Goal:** Finding subpopulations who benefit.

# We Do Not Make Any Parametric Model Assumptions

- Population distribution of  $Y$  given  $A, B$  may differ arbitrarily from, e.g., linear regr. model  $E(Y|A, B) = \beta_0 + \beta_1 A + \beta_2 B$ .
- True relationships among  $B, A, Y$  may be much more complex than this.
- We require consistent estimators under arbitrary model misspecification.

Hypothetical Example of Misspecification:



## Example: ANCOVA estimator

For continuous outcome  $Y$ :

- Fit linear regression model  $E(Y|A, B) = \beta_0 + \beta_1 A + \beta_2 B$ .
- Estimator of Average Treatment Effect  
 $E(Y|A = 1) - E(Y|A = 0)$  is  $\hat{\beta}_1$ .

Some remarkable properties of ANCOVA estimator  $\hat{\beta}_1$  (Yang and Tsiatis, 2001):

- Consistent (converges to average treatment effect) **under arbitrary model misspecification**.
- Equal or better precision (asymptotically) than unadjusted estimator (difference between sample means).

# Covariate Adjustment with Binary Outcomes

For dichotomous  $Y$ :

- Fit logistic regression model for  $P(Y = 1|A, B) = \text{logit}^{-1}(\beta_0 + \beta_1 A + \beta_2 B)$ .
- Compute standardized estimators for treatment specific means  $\mu_0, \mu_1$ :
  - $\hat{\mu}_0 = \frac{1}{n} \sum_{i=1}^n \text{logit}^{-1}(\hat{\beta}_0 + \hat{\beta}_2 B_i)$
  - $\hat{\mu}_1 = \frac{1}{n} \sum_{i=1}^n \text{logit}^{-1}(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 B_i)$
- Estimator is contrast of interest between  $\mu_1, \mu_0$ , e.g., risk difference  $\hat{\mu}_1 - \hat{\mu}_0$ .

Estimator  $\hat{\mu}_1 - \hat{\mu}_0$  consistent **under arbitrary model misspecification** (Scharfstein, Rotnitzky, Robins, 1999; Moore and van der Laan, 2009).

Same holds for log OR:  $\log \left[ \frac{\hat{\mu}_1 / (1 - \hat{\mu}_1)}{\hat{\mu}_0 / (1 - \hat{\mu}_0)} \right]$ .

Note: estimated coefficient  $\hat{\beta}_1$  **not** consistent for (unconditional) log OR, even when model correct.

For dichotomous  $Y$ :

- Fit logistic regression model for  $P(Y = 1|A, B) = \text{logit}^{-1}(\beta_0 + \beta_1 A + \beta_2 B)$ .
- Compute standardized estimators for treatment specific means  $\mu_0, \mu_1$ :
  - $\hat{\mu}_0 = \frac{1}{n} \sum_{i=1}^n \text{logit}^{-1}(\hat{\beta}_0 + \hat{\beta}_2 B_i)$
  - $\hat{\mu}_1 = \frac{1}{n} \sum_{i=1}^n \text{logit}^{-1}(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 B_i)$
- Estimator of risk difference is  $\hat{\mu}_1 - \hat{\mu}_0$ .

Estimator consistent under arbitrary model misspecification, but not necessarily as or more precise as unadjusted estimator.

Colantuoni and Rosenblum (2015) add step to above estimator that guarantees consistent and as or more precise than unadjusted. It is special case of estimators from Rotnitzky et al. (2012), and related to Robins (2007). Estimator of Tan (2010) has same property.

# Handling Missing Outcome Data

- Unless outcome missing completely at random (MCAR), unadjusted estimator inconsistent.
- Easy to modify covariate adjusted estimator to also adjust for missing outcomes.
- Under missing at random assumption (MAR, i.e., missingness independent of potential outcome given baseline variables), covariate adjusted estimator that also models missingness is consistent if this model or outcome regression model correct.

In simulated trials based on MISTIE Phase II data.

- Under MCAR, gain precision.
- Under MAR, Bias and MSE reduction.

- Must prespecify method and variables. Also report unadjusted.
- Best when combined with information monitoring (can get sample size reduction even under null).
- Efficiency gains (as percent) similar for small and large trials. (May be most important in large trials.)
- Caution: not too many variables (depends on sample size).
- Caution: when estimating standard error and/or constructing CI, use bootstrap or sandwich estimator.



# Bottom Line: Pros/Cons in Using Covariate Adjustment

- **Pro:** Covariate adjustment as described above gives consistent estimator of average treatment effect (same quantity estimated by unadjusted estimator); does not require parametric model assumptions.
- **Pro:** If baseline variable(s) strongly prognostic for outcome, covariate adjustment can substantially improve precision + power (or reduce sample size) vs. unadjusted estimator.
- **Pro:** Covariate adjustment useful even in large trials; that's where biggest equivalent sample size reduction
- **Con:** Can lose efficiency (at small sample size) if all baseline variables pure noise, but losses small.  
In simulations, 2% loss at sample size 100; < 1% loss at sample size 1000 (Colantuoni and Rosenblum 2015).
- **Recommendation:** can try out diagnostic in our paper and if get substantial signal that baseline variables prognostic, consider covariate adjustment.

- Austin, Peter C., et al. A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals. *Journal of clinical epidemiology* 63.2 (2010): 142-153.
- Colantuoni, E. and Rosenblum, M. (2015) Leveraging Prognostic Baseline Variables to Gain Precision in Randomized Trials. *Statistics in Medicine*. 34(18), 2602-2617. <http://goo.gl/evGHF6>
- Diaz, I., Colantuoni, E., Rosenblum, M. Enhanced Precision in the Analysis of Randomized Trials with Ordinal Outcomes. Conditional acceptance at Biometrics. Working paper: <http://goo.gl/N61CST>
- Moore K, van der Laan MJ. Covariate adjustment in randomized trials with binary outcomes: targeted maximum likelihood estimation. *Statistics in Medicine* 2009; 28(1):39-64.

- Pocock, S. J., Assmann, S. E., Enos, L. E., and Kasten, L. E. (2002). Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Statistics in medicine*, 21(19), 2917-2930.
- Robins JM, Sued M, Lei-Gomez Q, Rotnitzky A. Double-robustness with improved efficiency in missing and causal inference models. Technical Report, Harvard School of Public Health, 2007
- Rotnitzky A, Lei Q, Sued M, Robins JM. Improved double-robust estimation in missing data and causal inference models. *Biometrika* 2012; 99(2):439-456.
- Rubin D, van der Laan MJ. Empirical efficiency maximization: improved locally efficient covariate adjustment in randomized experiments and survival analysis. *International Journal of Biostatistics* 2008; 4(1):Article 5.

- Scharfstein, D.O., Rotnitzky, A., and Robins, J.M. Adjusting for nonignorable drop-out using semiparametric nonresponse models. *Journal of the American Statistical Association* 94, 1096–1120 (with Rejoinder, 1135–1146), 1999.
- Steingrimsson, Jon Arni; Hanley, Daniel F.; and Rosenblum, Michael. Improving precision by adjusting for prognostic baseline variables in randomized trials with binary outcomes, without regression model assumptions, *Contemporary Clinical Trials*, 2017, <http://doi.org/10.1016/j.cct.2016.12.026>
- Tan Z. Bounded, efficient and doubly robust estimating equations for marginal and nested structural models. *Biometrika* 2010; 97:661-682.
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