Module 17: Adaptive Enrichment Designs

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Course Outline

Part I: Innovations in Analyzing Standard Randomized Trial Designs

- Section 1: Leveraging Prognostic Baseline Variables to Gain Precision in Estimating the Average Treatment Effect
- Section 2: Adaptive Designs Overview: FDA Draft Guidances for Drugs And Biologics; Skeptics' Points of View

Course Outline

Part II: Adaptive Enrichment Designs

Section 3. Two-Stage Adaptive Enrichment Designs: Confidence Intervals

Section 4. Optimal multiple hypothesis testing methods for the overall population and for subpopulations (1 and 2 stage)

Section 5. Multiple Stage Adaptive Enrichment Designs

Section 6. Adaptive Designs Software

Module 1: Leveraging Prognostic Baseline Variables to Gain Precision in Randomized Trials

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Covariate Adjustment in Randomized Trials: A Survey

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 properties of covariate-adjustment are quite complex and often poorly understood, and there remains confusion as to what is an appropriate statistical strategy."

Saquib, Saquib, Ioannidis (2013) surveyed 200 randomized clinical trial reports.
42% used some form of covariate adjustment.

Covariate Adjustment in Randomized Trials: EMA Guideline

2015 Guideline by the the European Medicines Agency:

> *In case of a strong or moderate association between a baseline covariate(s) and the primary outcome measure, adjustment for such covariate(s) generally improves the efficiency of the analysis and avoids conditional bias from chance covariate imbalance.*

We address the following challenge: there are multiple statistical methods for adjusting for baseline variables, and little guidance on which to use.

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:
$\mu_1 = E(Y|A=1)$ and $\mu_0 = E(Y|A=0)$.
Population Average Treatment Effect: contrast between μ_1, μ_0.

Examples of Population Average Treatment Effects:

- If continuous outcome, mean difference: $\mu_1 - \mu_0$.
- If binary outcome, then
  $\mu_1 = P(Y=1|A=1)$, $\mu_0 = P(Y=1|A=0)$.
  - risk difference: $\mu_1 - \mu_0$.
  - relative risk: μ_1/μ_0.
  - log odds ratio (OR): $\log\left[\{\mu_1/(1-\mu_1)\}/\{\mu_0/(1-\mu_0)\}\right]$.

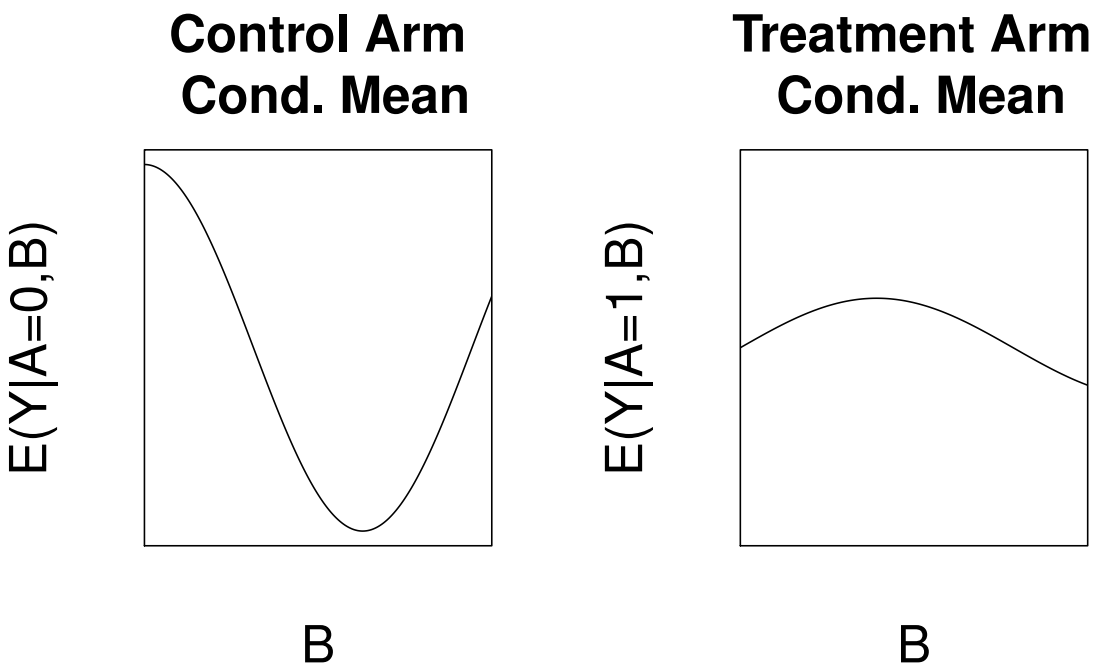
NOT the Goals of Covariate Adjustment

- Not: Estimation of Conditional (within stratum of B) Treatment Effects, e.g., $E(Y|A=1,B) - E(Y|A=0,B)$.
- Not: 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:



Assumptions

We assume:

- Treatment Randomized (A independent of B) by design.
- Participant data vectors (B_i, A_i, Y_i), for $i = 1$ to n, independent, identically distributed draws from unknown distribution P.

These assumptions (or similar) are needed for standard, unadjusted estimator to be consistent (converge to average treatment effect).

No assumptions on the relationship among B, A, Y except randomization (A, B independent).

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).

Example: 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.

Intuition: How does Covariate Adjustment Work?

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 $\hat{\beta}_1$.

$\hat{\beta}_1$ consistent under arbitrary model misspecification, and equal or better precision (asymptotically) than unadjusted estimator.

Intuition: Adjusts for chance imbalances in prognostic baseline variables between study arms.

Consider simpler covariate adjusted estimator if B single dichotomous variable:
First compute difference between sample means within each stratum of B; then combine proportional to overall prevalence of B.

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 μ_0, μ_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 constrast of interest between μ_1, μ_0, e.g., risk difference $\hat{\mu}_1 - \hat{\mu}_0$.

Estimator $\hat{\mu}_1 - \hat{\mu}_0$ consistent **under arbitrary model misspecification** (Moore and van der Laan, 2009).
Same holds for log OR: $\log\left[\{\hat{\mu}_1/(1-\hat{\mu}_1)\}/\{\hat{\mu}_0/(1-\hat{\mu}_0)\}\right]$.

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

Example: 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 ≤ 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.

Improved 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 μ_0, μ_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 basline 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.

Covariate Adjustment

- Prespecify method + 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.
- 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.

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