

Improving Efficiency of Inferences in Randomized Clinical Trials Using Auxiliary Covariates

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Outline

1. Introduction
2. Reasons for Covariate Adjustment
3. Conditional vs Unconditional Inference
4. Semiparametric Theory
5. Implementation
6. Simulations
7. Discussion

Introduction

Primary objective of a randomized clinical trial: *Compare treatments* with respect to some *outcome* of interest, for example

- *Continuous response*: compare on the basis of *treatment means*
- *Binary response*: compare on the basis of *odds ratio*
- *Time to event*: compare on the basis of *treatment-specific hazard ratio*

In addition to outcome and treatment assignment: *Baseline auxiliary covariates*

- *Demographic*, *physiologic* characteristics
- Prior *treatment* and *medical history*
- *Baseline* measure(s) of the outcome

Reasons for Covariate Adjustment

Ordinarily: Inferences on treatment comparisons based *only on data on outcome and treatment assignment*

“Covariate adjustment:” with auxiliary baseline covariates has been advocated

- to account for chance imbalances in baseline covariates
- to gain efficiency
- *Extensive literature*: Senn (1989), Hauck et al. (1998), Koch et al. (1998), Tangen and Koch (1999), Pocock et al. (2002), ...
- *Extensive concerns*: Potential *bias* due to post hoc (*subjective*) selection of covariates to use, and...
- ...temptation to engage in a “*fishing expedition*” for the *most dramatic* effect
- \Rightarrow *Trialists* and *regulatory authorities* reluctant to endorse

Covariate Adjustment

Standard approach to adjustment: *Direct regression modeling*

- Model outcome as a function of treatment assignment *and* covariates
- \Rightarrow *Inextricable link* between parameters involved in treatment comparisons and the “*adjustment*”

Our objective: A *general methodology* for using auxiliary covariates that leads to *more efficient* estimators

- Based on the *theory of semiparametrics* (e.g., Tsiatis, 2006)
- *Separates* parameters involved in treatment comparisons from the “*adjustment*” . . .
- . . . and hence leads to a *principled approach* to implementation that can obviate the usual concerns

Notation

- Data: $(Y_i, Z_i, X_i), i = 1, \dots, n$, (iid) where for patient i
- Y_i response variable (discrete, continuous, longitudinal, censored)
- Z_i denotes treatment assignment (For simplicity we will consider only two treatments, but methods generalize easily to more than two treatments)
- Z_i (1=treatment, 0=control), $P(Z_i = 1) = \pi$
- X_i denotes other baseline covariates measured prior to randomization
- $X \perp\!\!\!\perp Z$

Unconditional Inference

Example 1: *continuous response* Y

$$E(Y | Z) = \alpha + \beta Z$$

- Here the parameter of interest is $\beta = E(Y|Z = 1) - E(Y|Z = 0) =$
difference in treatment means

Example 2: *binary response* ($Y = 0, 1$)

$$\text{logit}\{E(Y | Z)\} = \text{logit}\{P(Y = 1|Z)\} = \alpha + \beta Z$$

- Here the parameter of interest is $\beta =$ *Log-odds ratio* for treatments 1 and 0

Unconditional Inference

Example 3: *Time to event (censored data)*

- Here the data are represented as $(U_i, \Delta_i, Z_i, X_i), i = 1, \dots, n$
 - U_i is time to failure or censoring $= \min(T_i, C_i)$
 - Δ_i is failure indicator $= I(T_i \leq C_i)$
 - As before Z_i is treatment indicator and X_i denotes baseline covariates
- *Proportional hazards model*

$$\lambda(t|Z) = \lambda_0(t) \exp(\beta Z),$$

where $\lambda(t|Z)$ denotes the conditional hazard rate of failing at time t given treatment Z

- The parameter of interest is $\beta = \text{Log-hazard ratio}$ for treatments 1 and 0

Conditional versus unconditional inference

Focus of inference: Comparisons based on β are *unconditional*

- Treatment effect *averaged across the population*
- E.g., $\beta = E(Y|Z = 1) - E(Y|Z = 0)$ in Example 1

Alternative: Comparison *conditional* on subset of the population with $X = x$; e.g., in Example 1

$$\beta_x = E(Y|X = x, Z = 1) - E(Y|X = x, Z = 0)$$

- *ANCOVA model* $E(Y|X, Z) = \alpha_0 + \alpha_1^T X + \phi Z$
- $\phi = \beta_x = \beta$ if ANCOVA model *correct*
- OLS estimator for ϕ is consistent for β *regardless*
- ANCOVA is used for *covariate adjustment*
(*direct regression modeling*)
- *Conditional* vs. *unconditional* not a *big deal*

Conditional versus unconditional inference

Conditional vs. unconditional is a big deal: E.g., *binary outcome*

- *Unconditional model*

$$\text{logit}\{E(Y|Z)\} = \alpha + \beta Z$$

- *Conditional (on X) model*

$$\text{logit}\{E(Y|X, Z)\} = \alpha_0 + \alpha_1^T X + \phi Z$$

Similarly: *time to event outcome*

- *Unconditional model*

$$\lambda(t|Z) = \lambda_0(t) \exp(\beta Z)$$

- *Conditional (on X) model*

$$\lambda(t|X, Z) = \lambda_0(t) \exp(\alpha^T X + \phi Z)$$

- $\phi \neq \beta \Rightarrow$ *different focus*

Conditional versus unconditional inference

Debate: Which is more *clinically relevant*?

- Most trials: *unconditional primary analysis*
- \Rightarrow We focus on *unconditional* inference

Semiparametric model

Model for the data (Y_i, Z_i) only: Class of all probability densities

$$p_{Y,Z}(y, z; \theta, \eta, \pi) = p_{Y|Z}(y | z; \theta, \eta) p_Z(z; \pi), \quad \theta = (\beta, \alpha)$$

- π is *known*, so $p_Z(z; \pi)$ is *completely specified*
- $p_{Y|Z}(y | z; \theta, \eta)$ is a density *consistent with* the situation of interest
- E.g., a *fully parametric* model (e.g., logistic)
- E.g., a *nonparametric* model (treatment means) or *semiparametric* model (proportional hazards)

4. Semiparametric model

Model for all data (Y_i, X_i, Z_i) : Class of all probability densities

$$p_{Y,X,Z}(y, x, z; \theta, \eta, \psi, \pi) = p_{Y,X|Z}(y, x | z; \theta, \eta, \psi) p_Z(z; \pi),$$

- π is *known*, so $p_Z(z; \pi)$ is *completely specified*
- $Z \perp\!\!\!\perp X$ *by randomization*
- $p_{Y,X|Z}(y, x | z; \theta, \eta, \psi)$ is *consistent with* $p_{Y|Z}(y | z; \theta, \eta)$

Goal: *Consistent and asymptotically normal estimators* for β under this *semiparametric model* for (Y, X, Z)

- Inclusion of $X \Rightarrow$ *covariate adjustment*
- Find the *most precise* such estimator

Approach: Use *semiparametric theory* to find all *unbiased estimating functions* for θ (and hence β) under the *semiparametric model*

Semiparametric theory

Approach: Derive *estimators* by characterizing the class of all *estimating functions* for θ (and hence β) leading to estimators for θ that are *consistent and asymptotically normal* under the semiparametric model

- *Estimating function*: Function of a single observation and parameters that can be used to construct *estimating equations* leading to *estimators* for the parameters
- \Rightarrow We seek *unbiased estimating functions for θ* depending on (Y, Z, X) (lead to *consistent and asymptotically normal estimators*)

Estimating functions without auxiliary covariates

Start by considering unbiased estimating functions depending on (Y, Z) only:

$$m(Y, Z; \theta) \Rightarrow \text{Solve } \sum_{i=1}^n m(Y_i, Z_i; \theta) = 0$$

- *Example 1*: $E(Y | Z) = \alpha + \beta Z$

$$m(Y, Z; \theta) = (1, Z)^T (Y - \alpha - \beta Z)$$

yields *OLS estimator* for $\beta \Rightarrow \hat{\beta}_{OLS} = \text{difference in sample means}$

- *Example 2*: $\text{logit}\{E(Y | Z)\} = \alpha + \beta Z$

$$m(Y, Z, ; \theta) = (1, Z)^T \{Y - \text{expit}(\alpha + \beta Z)\}$$

yields *logistic regression MLE, also log-odds ratio of sample proportions*

Estimating functions without auxiliary covariates

For the *Proportional hazards model* of Example 3, the parameter β is estimated by maximizing the partial likelihood or solving the estimating equation

$$\sum_{i=1}^n \int \{Z_i - \bar{Z}(u, \beta)\} dN_i(u) = 0,$$

where $N_i(u) = I(U_i \leq u, \Delta_i = 1)$ and

$$\bar{Z}(u, \beta) = \frac{\sum Z_i \exp(\beta Z_i) I(U_i \geq u)}{\sum \exp(\beta Z_i) I(U_i \geq u)}$$

Estimating functions using auxiliary covariates

Main result: For a given *semiparametric model* members of the *class of all unbiased estimating functions for θ* using *all of (Y, Z, X)* may be written

$$m^*(Y, Z, X; \theta) = m(Y, Z; \theta) - \{Z - \pi\}a(X)$$

- $m(Y, Z; \theta)$ is a *fixed* unbiased estimating function for θ without auxiliary covariates
- $a(X)$ is an arbitrary function of X
- $a(X) \equiv 0 \Rightarrow$ “*unadjusted estimator*” $\hat{\theta} = (\hat{\beta}, \hat{\alpha})$
- “*Augmentation term*” effects the “*adjustment*”

Estimating functions using auxiliary covariates

$$m^*(Y, Z, X; \theta) = m(Y, Z; \theta) - (Z - \pi)a(X)$$

- By $Z \perp\!\!\!\perp X$, *augmentation term* has *mean zero* \Rightarrow *unbiased*

Adjusted estimator for θ : Solve

$$\sum_{i=1}^n m^*(Y_i, Z_i, X_i; \theta) = 0$$

- *Judicious choice of $a(X)$* \Rightarrow *improved efficiency* over the “*unadjusted*” estimator $\hat{\theta}$

Estimating functions using auxiliary covariates

Optimal estimating function in the class: Elements of the estimator have *smallest asymptotic variance*

- Take $a(X) = E\{m(Y, Z; \theta) \mid X, Z = 1\} - E\{m(Y, Z; \theta) \mid X, Z = 0\}$
- *Optimal estimating equation*

$$\sum_{i=1}^n \left(m(Y_i, Z_i; \theta) - (Z_i - \pi) [E\{m(Y, Z; \theta) \mid X_i, Z = 1\} - E\{m(Y, Z; \theta) \mid X_i, Z = 0\}] \right) = 0$$

- $E\{m(Y, Z; \theta) \mid X, Z = g\}, g = 0, 1$ are *unknown functions of X* \Rightarrow *model them...*

Implementation

Approach: *Adaptive algorithm*

(1) Solve $\sum_{i=1}^n m(Y_i, Z_i; \theta) = 0 \Rightarrow \hat{\theta}$

(2) For *each group* $g = 0, 1$ *separately*, using the “*data*” $m(Y_i, Z_i; \hat{\theta})$ for $Z_i = g$, develop a *regression model*

$$E\{m(Y, g; \hat{\theta}) \mid X, Z = g\} = q_g(X, \zeta_g),$$

$$q_g(X, \zeta_g) = \{1, c_g^T(X)\}^T \zeta_g,$$

and obtain $\hat{\zeta}_g$ by *OLS separately*

(3) For each $i = 1 \dots, n$, form *predicted values* $q_g(X_i, \hat{\zeta}_g)$ for each $g = 0, 1$ and solve in θ with $\hat{\pi} = n^{-1} \sum_{i=1}^n Z_i$

$$\sum_{i=1}^n \left[m(Y_i, Z_i; \theta) - (Z_i - \hat{\pi}) \{q_1(X_i, \hat{\zeta}_1) - q_0(X_i, \hat{\zeta}_0)\} \right] = 0 \Rightarrow \text{“adjusted” } \tilde{\theta}$$

Implementation

Properties: From *semiparametric theory*

- With the *regression models* q_g as above, $\tilde{\theta}$ is *guaranteed relatively more efficient* than $\hat{\theta}$, even if q_g *incorrect*
- $\tilde{\theta}$ is *consistent and asymptotically normal regardless* of q_g
- If the q_g models are *exactly correct* $\Rightarrow \tilde{\theta}$ is *asymptotically equivalent* to the *optimal estimator* if we *knew* $E\{m(Y, Z; \theta) \mid X, Z = g\}$

Standard errors: For $\tilde{\theta}$ and hence $\tilde{\beta}$

- $\tilde{\theta}$ is an *M-estimator*
- \Rightarrow *Sandwich method* for asymptotic variance for $\tilde{\beta}$

Implementation

By-product:

- The “*adjustment*” for X is determined *separately by treatment group*...
- ... *and* regression modeling is carried out *independently of* $\tilde{\beta}$
- \Rightarrow Can develop models *without concerns* over *subjectivity*

“Principled” strategy:

- *Regression modeling* for each $g = 0, 1$ based on data for $i \in g$ *only* may be carried out by *separate analysts for each g*...
- ... *different from* those who calculate $\tilde{\theta}$ (and hence $\tilde{\beta}$)
- \Rightarrow A sponsor could retain *different CROs* to build the models for each treatment

Implementation

Special case: *Example 1* (continuous response Y)

- All estimators for β are *asymptotically equivalent* to

$$\bar{Y}_1 - \bar{Y}_0 - \sum_{i=1}^n (Z_i - \hat{\pi}) \{n_1^{-1} a_1(X_i) + n_0^{-1} a_0(X_i)\},$$

where \bar{Y}_g denotes treatment-specific sample average for treatment $g = (0, 1)$

- *In this class*: ANCOVA, ANCOVA with *treatment-covariate interaction*, Koch et al. (1998)'s “*nonparametric*” estimator,...
- *Optimal estimator* takes

$$a_g(X) = E(Y|X, Z = g), \quad g = 0, 1$$

See Tsiatis et al. (2008)

Simulations

Censored survival data: *Proportional hazards model*

$$\lambda(t|Z) = \lambda_0(t) \exp(\beta Z)$$

In order to generate data where

- the distribution of T given Z follows a proportional hazards model
 - T and X are correlated
 - X and Z are independent
1. We generate bivariate data (V, X) from a bivariate normal density with mean zero, variance 1, and correlation ρ
 2. Independently generate treatment indicator Z as a Bernoulli(π)
 3. Let $T = -\exp(-\beta Z) \log\{1 - \Phi(V)\}$, where $\Phi(\cdot)$ is the cumulative distribution function (CDF) of a standard normal
 4. Censoring was generated as an independent exponential distribution $C \sim \text{Exp}(c)$.

Simulations

- Treatment was assigned with $\pi = .5$
- the correlation of V and X was $\rho = .7$ which resulted in roughly a correlation of 0.6 between T and X
- We took $\beta = 0$ (null hypothesis) and $\beta = .25$
- The value c for the exponential distribution of the censoring variable that would result in roughly 25% of the data being censored
- Sample sizes of 250 and 600 were considered

Simulations

“Estimators considered:”

- $\hat{\beta}_{\text{PH}}$: Unadjusted estimator using MPLE from unconditional model

$$\lambda(t|Z) = \lambda_0(t) \exp(\beta Z)$$

- $\hat{\beta}_{\text{AUG}}$: Augmentation term used $q_g(X, \zeta_g) = \{1, X, X^2\}^T \zeta_g$, fit by OLS
- $\hat{\beta}_{\text{REG}}$: We also considered the estimator $\hat{\phi}$ obtained by considering the Cox regression model

$$\lambda(t|X, Z) = \lambda_0(t) \exp(\alpha_1 X + \alpha_2 X^2 + \phi Z)$$

Note: *This is not the true conditional model*

Simulations $\beta = 0$

	n	$\hat{\beta}_{\text{PH}}$	$\hat{\beta}_{\text{AUG}}$	$\hat{\beta}_{\text{REG}}$
Bias	250	0.002	−0.004	−0.003
	600	0.001	−0.002	−0.001
SE	250	0.148	0.117 (1.60)	0.150 (NA)
	600	0.095	0.075 (1.59)	0.095 (NA)
MCSE	250	0.146	0.120 (1.48)	0.170 (0.74)
	600	0.095	0.076 (1.56)	0.107 (0.79)

Simulations $\beta = .25$

	n	$\hat{\beta}_{\text{PH}}$	$\hat{\beta}_{\text{AUG}}$	$\hat{\beta}_{\text{REG}}$
Bias	250	0.004	-0.002	0.092
	600	-0.008	-0.008	0.091
SE	250	0.149	0.118 (1.60)	0.152 (NA)
	600	0.095	0.076 (1.58)	0.097 (NA)
MCSE	250	0.147	0.121 (1.47)	0.171 (0.74)
	600	0.096	0.077 (1.55)	0.107 (0.80)

Discussion

- General approach to using *baseline auxiliary covariates* to *improve efficiency* of *estimators* and theory can also be applied to *tests*
- General measures of *treatment effect*
- Arises naturally via *semiparametric theory*
- Even when regression adjustment leads to improved estimators of unconditional treatment effect (i.e., linear models) there is a tension between gains in efficiency and compromised analysis
- Incorporation of covariate information *separated from* evaluation of treatment effects
- Impact of model selection
- Can be extended to *k-arm trials* and *missing data*

References

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