Adjusting for covariates in randomized clinical trials for drugs and biological products

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Disclaimer

- This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

Outline

- Motivation for covariate adjustment
- Recommendations in FDA covariate adjustment guidance
- Illustrative simulations
- Selected areas for additional discussion

Motivation

- Incorporating baseline covariates into the analysis leads to a *covariate-adjusted analysis* rather than an *unadjusted analysis*
- Covariate adjustment may be underutilized in clinical trials
- Covariate adjustment can lead to more precise estimation and inference when baseline covariates are prognostic for the outcome
- Moreover, covariate adjustment does not depend on strong statistical assumptions beyond assumptions needed for unadjusted analysis
- Compared to many statistical issues that arise in clinical trials, covariate adjustment is one of the closest to a “free lunch” without major downsides

Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products

Guidance for Industry

- Final guidance in May 2023
- Replaces 2021 revised draft guidance and 2019 draft guidance
- Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adjusting-covariates-randomized-clinical-trials-drugs-and-biological-products

General considerations

- Covariate adjustment is acceptable
- Prespecification
- Covariates to include in adjustment model
- Number of covariates
- Accounting for stratified randomization
- Change from baseline analyses

Considerations for linear models

- Analysis of covariance (ANCOVA): $Y_i = \beta_0+\beta_1 Z_i+\beta_2^T X_i+\varepsilon_i$
  - Use least squares to fit a linear regression of the outcome (Y) on a treatment indicator (Z) and vector of baseline covariates (X) and report the fit of the treatment coefficient (β_1)
- ANCOVA estimates the average treatment effect
- Valid inference even under model misspecification
- Robust standard errors
- Treatment by covariate interactions

Nonlinear models* and collapsibility

- With binary, ordinal, or time-to-event outcomes certain population-level summaries can be non-collapsible even in randomized trials

Non-collapsibility of the odds ratio in a hypothetical target population

	Percentage of target population	Success rate		Odds ratio
		New drug	Placebo	
Biomarker +	50%	80.0%	33.3%	8.0
Biomarker –	50%	25.0%	4.0%	8.0
Combined	100%	52.5%	18.7%	4.8

- It is important to clarify whether the estimand of interest is
  - The conditional treatment effect (8.0 in the table)
  - The unconditional/marginal treatment effect (4.8 in the table)

*Includes generalized linear models with non-identity link functions

Nonlinear models and conditional treatment effects

- Commonly used methods such logistic models, proportional odds models, proportional hazards models
- Advantages
- Disadvantages
- Sponsors should discuss with the relevant review divisions specific proposals in a protocol or SAP containing nonlinear models to estimate conditional treatment effects for the primary analysis

Nonlinear models and unconditional treatment effects

- Sponsors can perform covariate adjusted estimation and inference for an unconditional treatment effect in the primary analysis
- The estimand will be the same as in an unadjusted analysis, but covariate adjustment will typically decrease standard errors and improve power
- The method used should provide valid inference under approximately the same minimal statistical assumptions that would be needed for unadjusted estimation in a randomized trial
  - Such methods exist for continuous, binary, ordinal, time-to-event outcomes
  - Methods depend on fitting a working model (e.g., logistic regression model) in an intermediate step, but final estimator of the treatment effect is robust to model misspecification
- Standard errors or confidence intervals can be formed from an appropriate bootstrap procedure or formulas justified in the statistical literature

Simulations on model misspecification

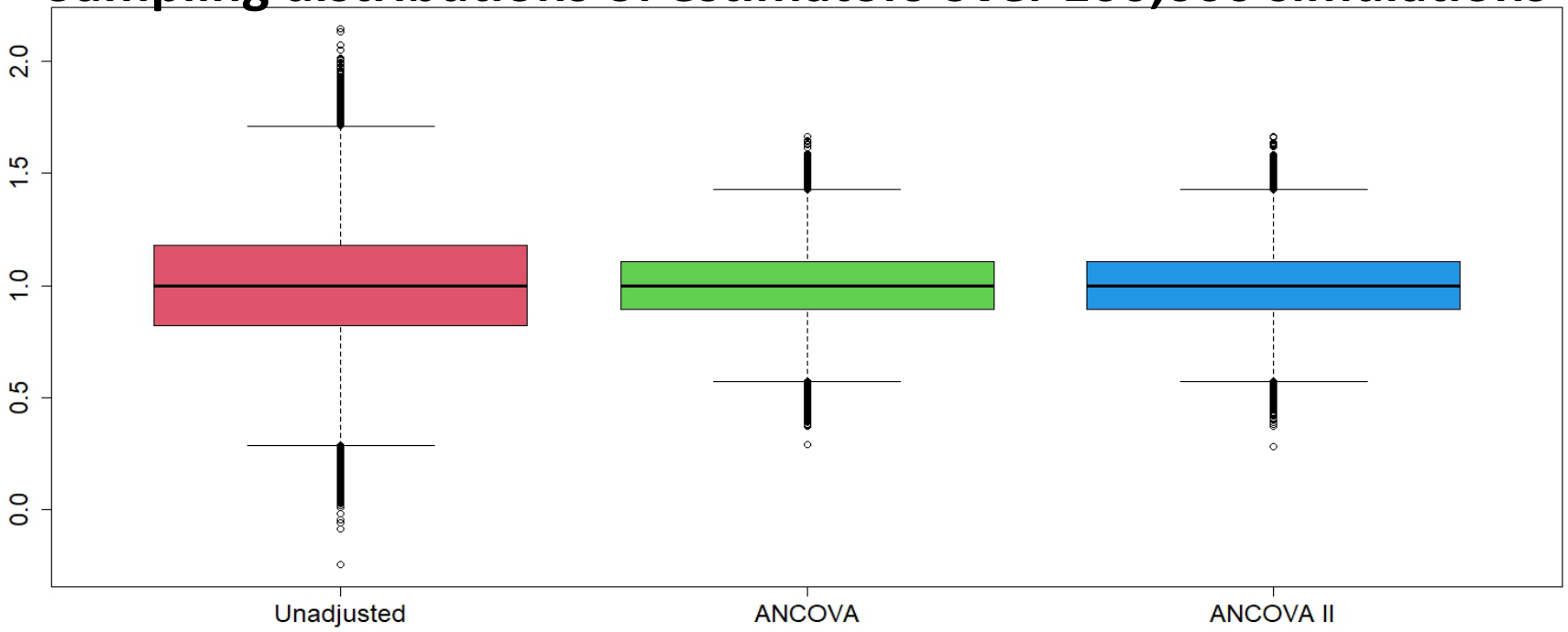
- 100,000 simulated trials
- Each trial has a sample size of n = 200 total participants
- Participant's baseline covariate $W \sim N(0,1)$
- Participant's assignment to treatment (A=1) or control (A=0) through 1:1 randomization
- Participant's independent error $\varepsilon \sim N(0,1)$
- Participant's outcome $Y = W + A + A*W + \varepsilon$
- The average treatment effect, or difference in expected outcomes between treatment and control groups, is 1.0

Simulations on model misspecification

- Compare three estimators of average treatment effect
  - Unadjusted estimator
  - Adjusted estimator 1 (ANCOVA): Linear regression of the outcome on treatment and covariate. The model is incorrectly specified because there is a treatment by covariate interaction.
  - Adjusted estimator 2 (ANCOVA II): Linear regression of the outcome on treatment, covariate, and treatment by covariate interaction. Estimate average treatment effect through G-computation.

Simulations on model misspecification

Sampling distributions of estimators over 100,000 simulations



- All estimators approximately unbiased for the average treatment effect, even though ANCOVA is based on an incorrect model
- ANCOVA and ANCOVA II less variable than unadjusted estimator

Selected areas for additional discussion

- Best practices for use of covariate adjustment in registrational trials with
  - Longitudinal or hierarchical data
  - Adaptive and group sequential designs
  - Covariate adjustment with small sample sizes
  - High-dimensional covariates, regularization, or data-adaptive covariate selection