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

- Changes in new FDA covariate adjustment guidance
- Summary of guidance recommendations
- Data adaptive covariate adjustment

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- Replaces 2021 revised draft guidance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

Main changes in 2023 final guidance from 2021 revised draft guidance

- Additional topics
  - Alignment with estimand framework of ICH
  - Selecting covariates
  - Sample size calculations
  - Permutation tests
  - “Actual” versus “as randomized” strata
  - Covariate adjustment with inverse probability weighting
- Additional details and referenced methods
  - Standard errors and accounting for stratified randomization
  - Estimating average treatment effect in models with interactions
  - Alternatives to g-computation methods
- Various clarifications and corrections

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

- ANCOVA estimates the average treatment effect
- Valid inference even under model misspecification
- Robust standard errors
- Treatment by covariate interactions

Linear models and collapsibility

- With linear models without treatment by covariate interactions the following population-level summary measures are equivalent
  - The “marginal” or “unconditional” average treatment effect, or difference in expected outcomes between the treatment group and the control group
  - The “conditional treatment effect,” or effect conditional on baseline covariate values, which the model assumes is constant

	Percentage of target population	Expected score		Difference
		New drug	Placebo	
Biomarker+	50%	120	110	10
Biomarker-	50%	80	70	10
Combined	100%	100	90	10

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

Data adaptive covariate adjustment

- Guidance comments:
  - "Sponsors should discuss proposals for complex covariate-adaptive randomization, data-adaptive covariate selection, or use of covariate adjustment in an adaptive design with the relevant review division"
- Some literature on regularized covariate adjustment when the number of covariates >> sample size
  - Blonairz et al. Lasso adjustments of treatment effect estimates in randomized experiments. *Proceedings of the National Academy of Sciences* 113, 27 (2016), 7383–7390. https://doi.org/10.1073/pnas.1510506113.
- Suppose machine learning from external study(ies) used to form prognostic index to be used as a covariate in an adjustment model for a new study
  - Inherits property of valid covariate-adjusted inference even if the machine learning method is a "black box"
  - Efficiency gains will depend on the association between the prognostic index and the outcome of interest in the new study