Regulatory perspectives on covariate adjustment in randomized trials

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Outline

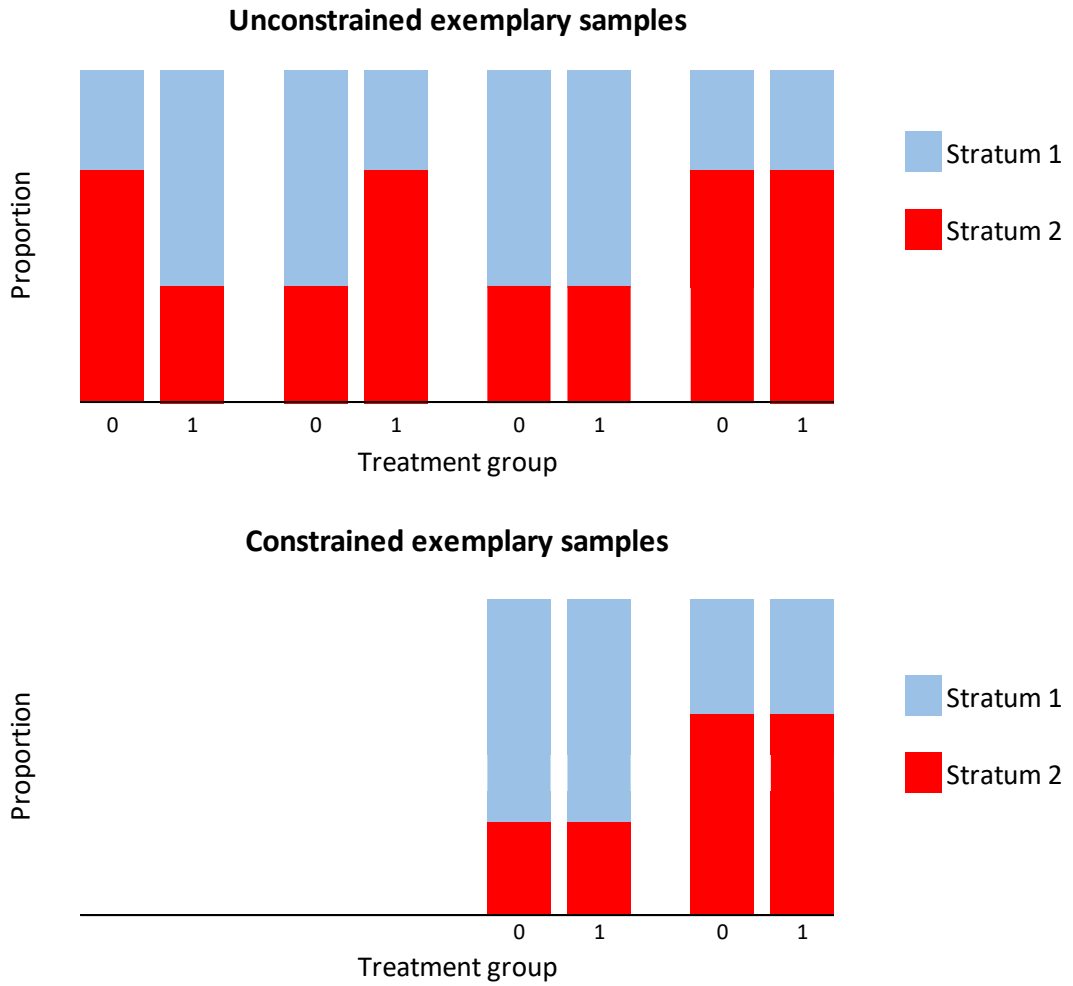
- Role of baseline covariates in randomized controlled trials
- Current guidance on covariate adjustment
- Marginal versus conditional estimands
- Number of covariates and finite sample properties
- Prespecification
- Sample size calculations
- Complex designs

Guidelines

- ICH E9 and addendum on estimands
- EMA Guideline on adjustment for baseline covariates in clinical trials
- FDA Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products

Role of baseline covariates – Design stage

- Constrained randomization (e.g. stratified permuted block)
- Balance covariate distribution between treatment groups
- Reduce variance of observed between group difference: Correlation between the per-group estimates, orthogonal design matrix [Kahan & Morris 2012, Senn et al. 2026]
- Need to account for in analysis to fully harvest efficiency gain)
- Credibility: Imbalance may raise concerns of confounding conditional on given data set
- Constrained randomization biggest impact with small sample sizes



Role of baseline covariates – Analysis stage

- Explain variability, improve precision
- Adjust for imbalance at analysis stage: Minor role, needs model assumptions
- In conditional estimands: Interpret effect as more patient specific, extrapolation to populations with different covariate distribution controversially discussed [Spieker 2022, Van Lancker et al 2024], needs model assumptions
- When stratified randomization uses categorized continuous variables, either version or both may be included as covariate. Continuous version often preferable [Senn et al. 2026].
- It is in general not of interest to analyse the association between covariates and outcome

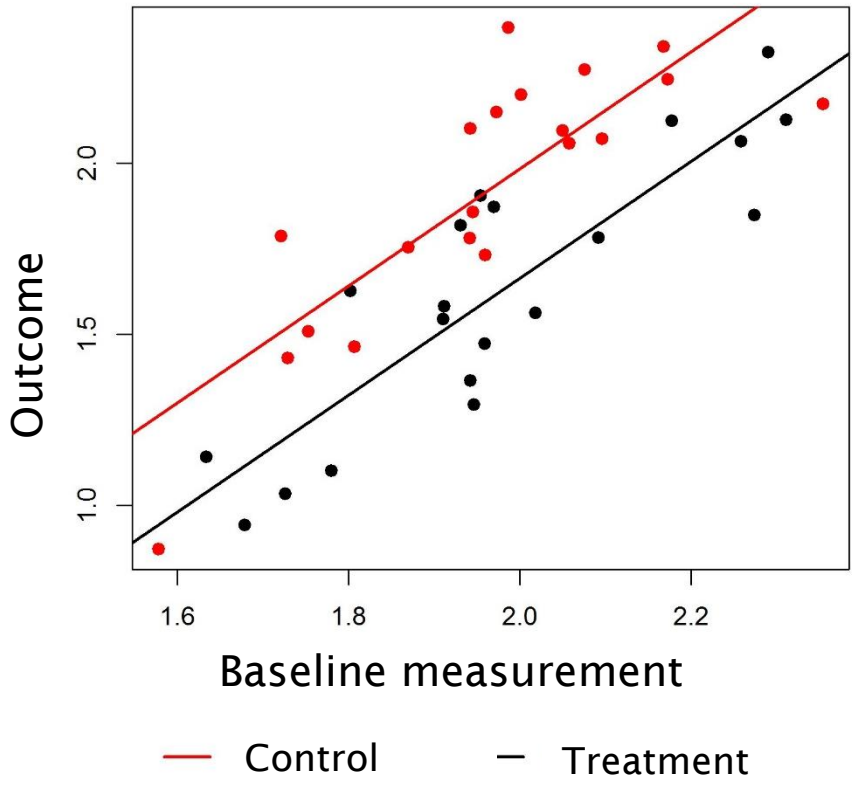


Illustration of ANCOVA explaining variance of outcome through baseline measurments

Traditional focus for covariate adjusted analyses

- Guidelines uniformly recommend utilizing covariates to gain precision
- Caveat in EMA guideline: *„smaller P-values may not be sufficient to produce convincing evidence of a clinically useful effect: the size of the treatment effect and its consistency across levels of covariates will always be important considerations."*
- **Continuous endpoints:**
  - ANCOVA favoured approach
  - No treatment-by-covariate interactions
  - Robust with respect to assumptions (may need sandwich variance for other than 1:1 randomization)
  - Asymptotic efficiency gain over unadjusted analysis
- **Binary and survival endpoints:**
  - Stratified analysis to account for stratified randomization
  - Additional covariates possible in logistic or Cox models
  - Impact on efficiency less obvious
- Common understanding that stratified randomization should be reflected in the analysis, otherwise variability overestimated

„New“ methods focussing on marginal estimands

- General covariate augmentation
- Covariates reduce variability of estimating equation
- Impact on efficiency more obvious than in GLMs
- Asymptotically, efficiency is improved [Bannick et al. 2025]
- Recent proposals to include more complex covariate information
  - ANHECOVA: ANCOVA with treatment by covariate interaction [e.g. Ye et al. 2023]
  - PROCOVA, use supercovariate defined with external data [Schuler et al. 2022]
  - Machine learning to replace linear predictors in general covariate adjustment, need to account for overfitting (e.g. cross fitting) [e.g. Van Lancker et al. 2026]

Potential impact of „new“ methods of marginal adjustment

- Continuous endpoints
  - Typically larger gain from covariate adjustement compared to binary/time-to-event (Shao 2026: median variance reduction of 13.3% for continuous outcomes and 4.6% for binary outcomes in 50 trials)
  - Potential for further improvement by complex models
  - Caveat: Trade-off between sample size and efficiency gain. Small samples may not support estimation of required model parameters.
- Binary endpoints
  - Focus on marginal estimation may facilitate interpretation
  - Compared to logistic regression: May choose summary measure independent of model assumptions
  - Compared to Cochrane-Mantel-Haenszel approach: Use additional/continuous covariates
- Survival
  - Impact less obvious
  - Marginal adjustment for hazard ratio still needs PH assumption for interpretation
  - Methods matching other summary measures (RMST, x-year survival) may be less powerful

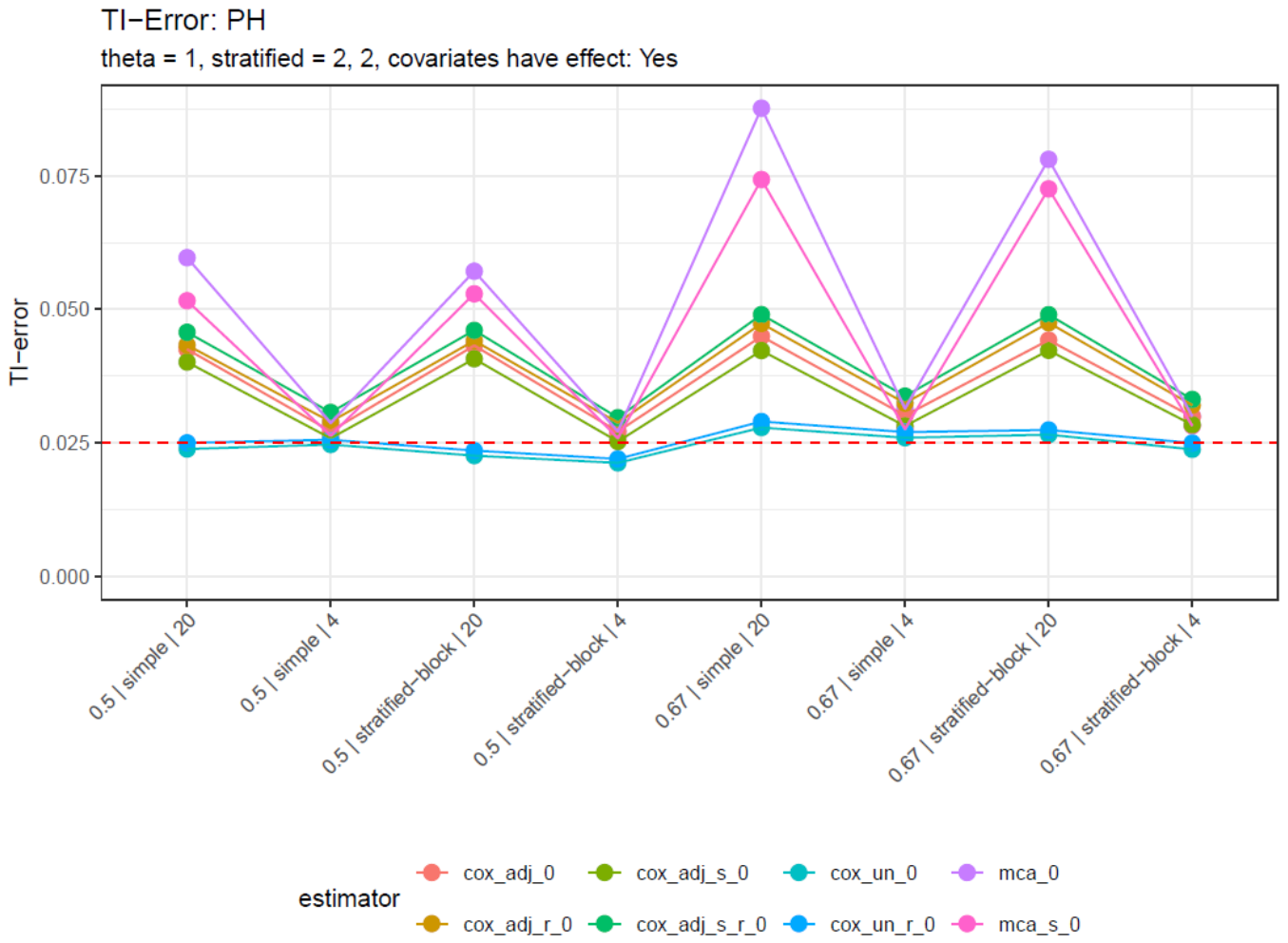
Marginal versus conditional estimands in guidelines

- EMA guideline
  - Focused on traditional models
  - Implies conditional estimands in case of non-linear models
  - Does not rule out marginal estimands
- FDA guideline
  - Both approaches in principle acceptable
  - Detailed guidence on marginal estimands and estimation methods
  - Allows for unadjusted analysis
- Align analysis with estimand

(See, e.g., Daniel et al. 2021 for discussion of marginal vs. conditional estimands and unadjusted vs. adjusted estimation.)

Number of covariates

- Traditional guidance: Few covariates
- ICH E9 and FDA guideline mention unadjusted analysis as viable option
- Methods based solely on large sample asymptotics do not account for uncertainty introduced by additional model parameters
  - Type I error inflation
- With proper finite sample corrections (akin to degrees of freedom in linear models), too many covariates may reduce power
- Few covariates may remain advisable approach



Simulated type I error rates in RCT with time-to-event endpoint and 66 events.
x-axis: Allocation ratio | randomization | number of covariates
Methods: Unadjusted Cox models (cox_un), conditionally adjusted Cox (cox_adj), marginally adjusted Cox (mca) as in Ye et al. 2024. r...robust sandwich variance, s...stratified.

Importance of prespecification

- New methods offer increased complexity
  - Potentially larger covariate space
  - Functional shapes other than linear
  - Arbitrarily composed supercovariates
- More technical parameters to set
  - Decisions when implementing marginal adjusted logrank test proposed by Ye et al. 2024:
    - Use expected or observed group allocation ratio in the variance estimator?
    - Fit internal linear model once, or update while iteratively fitting the hazard ratio?
  - With cross-fitting, which split to choose, how to guarantee reproducible results?
  - Choice between different variance estimators
- Need to prespecify models exactly
- Reviewers need to be aware of modelling options to be able to assess whether prespecification is complete

Sample size calculation

- Should the potential gain in efficiency be accounted for in sample size planning?
  - May lead to smaller (faster, more cost effective) trials
- Traditionally, covariate information is not used in sample size calculations
- Power may be typically larger than planned 80% or 90%
- FDA guideline „*sample size and power calculations can be based on adjusted or unadjusted methods*"
- But: Requires good understanding of impact of covariates on sample size/power
  - Straight forward for ANCOVA, less obvious for general covariate adjustment
  - Risk of too optimistic assumptions on effect of covariates
- Sample size should be sufficient to address other aspects than primary endpoint
  - Safety data base
  - Secondary endpoints
  - Rely on large sample asymptotics
- Conservative sample size planning remains advisable

Complex study designs

- Many trials include interim analyses or sample size reassessment
- Stopping boundaries are traditionally calculated based on independent increment property of group sequential statistics, which implies a certain covariance structure
- This property may not hold with covariate adjustment [Van Lancker et al. 2025, Bannick et al. 2026]
- Methods to adjust decision rules have been proposed [Van Lancker et al. 2025, Backenroth et al. 2026]
  - Based on estimated covariances
  - Small sample properties may warrant further investigations
- Similar concerns may arise in the context of other complex designs, e.g. conditional power calculations for sample size reassessment

Simulation Example: 1:1 simple randomization, survival endpoint, max. 380 events, 3 interim looks, Pocock-type alpha spending, four covariates, Ye‘s marginally adjusted logrank test

Type I error inflated to 2.85% (simulation SE 0.05%)

Covariance matrix of score statistics:

	S1	S2	S3
S1	**29.1**	**27.2**	**25.8**
S2	27.2	55.5	53.0
S3	25.8	53.0	81.3

Apprixomate variance of unadjusted score statistics:

31.7 63.3 95.0

Software

- For new methods, limited availability of software implementations
  - Development of R packages RobinCar, RobinCar2 [Bannick et al. 2026], beeca acknowledged
- Ideally validate software with independent implementation

Summary of regulatory challenges

- For each particular study, need to agree on estimand
  - Marginal vs. Conditional
  - Summary measure
- Concerns regarding finite sample properties:
  - Type I error control?
  - Is a complex model indeed more efficient than simple or traditional model?
  - In supporting simulation studies, need to ensure that the simulation settings cover sufficient deviations from assumptions.
- Proporties in combination with specific study design
  - Randomization procedure
  - Interim analysis
  - Sample size reassessment
- Need to be aware of analysis model options to assess prespecification
- Valid software implementation

Literature

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