

# How low can you go?

Tampering with the ICH-E9 guideline concerning  
covariates

Rogier Donders

George Borm

Radboud University Nijmegen Medical Center



## Outline of presentation

- Why incorporate covariates?
- What is the guideline according to the E9?
- What are the arguments for this guideline?
- An (very) alternative approach
- A convenient classification of covariates
- A new and simple proposal

## Why incorporate covariates?

- Basically a trial should provide an unbiased estimate of the difference between (at least) two groups for a relevant outcome...
- Together with some indication about the trustworthiness of the result.
- Covariates can help to improve the precision of the estimate and the power of the trial.
- We will try to stay clear from most points of (heated) discussion...

## Why incorporate covariates?

- Incorporating covariates in a randomization test context is possible but we will be using a modelling perspective for simplicity here.
- We will not go into the discussion about whether an unconditional (raw) or a conditional treatment effect is to be preferred by only considering the case where the outcome variable is continuous. In this case the (least squares) conditional estimator is consistent for the unconditional population difference.
- We will not go into effects of covariate imbalance.

## Why incorporate covariates?

- Thus, covariates are used in a regression model (ANCOVA) to obtain an unbiased estimate for the effect of a treatment.
- The standard error is a measurement of the precision of the estimated treatment effect.
- We want an unbiased estimator for the treatment effect with a small but reliable standard error so that for example confidence intervals are narrow but have a correct coverage probability.

## The ICH-E9 guideline

- For over 10 years: ICH-E9
- International Conference on Harmonisation
- Uniformity in Europe, USA and Japan
- E9: Statistical Principles for Clinical Trials
- Concerning covariates: pre-specification!

## The ICH-E9 guideline

- *“Pre-trial deliberations should identify those covariates and factors expected to have an important influence on the primary variable(s), and should consider how to account for these in the analysis in order to improve precision and to compensate for any lack of balance between treatment groups.”*
- There is a possibility to change the protocol based on a blind review: *“important covariates identified in other recent research may be added to the model”*.

## Arguments for the ICH guideline

- Controlled clinical trials (2000)



---

### How to Select Covariates to Include in the Analysis of a Clinical Trial

Gillian M. Raab, BSc, PhD, Simon Day, BSc,  
and Jill Sales, BSc, MSc

*Applied Statistics Group, School of Mathematical and Physical Sciences, Napier University,  
Edinburgh, Scotland (G.M.R., J.S.) and Leo Pharmaceuticals, Princes Risborough,  
Buckinghamshire, UK (S.D.)*

---

**ABSTRACT:** The comparisons of treatments in randomized clinical trials may use the analysis of covariance to adjust for patient characteristics. We present theoretical results that describe when such an adjustment would be expected to be beneficial. A distinction is made between covariates that are balanced in the design and those that are assigned

## Arguments for the ICH guideline

- Using a post-hoc selection of covariates on basis of a correlation with the outcome will lead to an underestimation of the residual variance and thus the standard error.
- Using a post-hoc selection of covariates on basis of an imbalance across treatment conditions will overestimate the standard error.
- Incorporating a pre-specified, not relevant covariate is equivalent to reducing the effective sample size by one patient.

## Arguments for the ICH guideline

- Since protocols are recorded, this is a transparent method of assuring that no ‘funny things’ are attempted by researchers.
- There is a fear of data dredging: choose those covariates that make the result most significantly.
- When it comes to bias, there is no need to incorporate covariates given that the randomisation is done properly and the trial size is not too small.

## Why tamper with the ICH E9 guideline?

- One really wants to have effect estimates that are as precise as possible.
- Given the funding and the availability of patients: some/many covariates have not been studied in the patient population that is studied in the trial.
- The literature may suggest covariates that have not been studied simultaneously, thus collinearity might be a problem.

## What does an alternative method need?

- It needs to be a method that cannot be easily manipulated.
- It needs to provide an unbiased estimate of treatment effect.
- It needs to provide a realistic estimate of accuracy.
- It needs to increase the power of the trial.

## A very alternative approach.

- Based on semi-parametric theory and missing data considerations.

STATISTICS IN MEDICINE  
*Statist. Med.* (2007)  
 Published online in Wiley InterScience  
 (www.interscience.wiley.com) DOI: 10.1002/sim.3113



**Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: A principled yet flexible approach**

Anastasios A. Tsiatis<sup>1</sup>, Marie Davidian<sup>1,\*†</sup>, Min Zhang<sup>1</sup> and Xiaomin Lu<sup>2</sup>

<sup>1</sup>*Department of Statistics, North Carolina State University, Raleigh, NC 27695-8203, U.S.A.*  
<sup>2</sup>*Department of Epidemiology and Biostatistics, University of Florida, Gainesville, FL 32611, U.S.A.*

SUMMARY

There is considerable debate regarding whether and how covariate-adjusted analyses should be used in the comparison of treatments in randomized clinical trials. Substantial baseline covariate information is routinely collected in such trials, and one goal of adjustment is to exploit covariates associated with outcome to increase precision of estimation of the treatment effect. However, concerns are routinely

## A very alternative approach.

- Decoupling of development of regression model for the outcome and the evaluation of the treatment effect.
- Different regression models for the outcome are built for each of the treatment groups. For example by different statisticians working independently.
- These models can contain different sets of covariates.
- Regression coefficients will differ between the regression models.

## A very alternative approach.

- Since the models are developed independently no bias can be introduced.
- These models can be used to generate predicted values that can be used to 'correct' the raw estimated treatment effect.
- Tsiatis et al also provide a variance estimator of the thus obtained estimated treatment effect.
- They show that this procedure is theoretically optimal.

## A very alternative approach.

- However, the method is not used that much in practice...
- It is very different from what is in the guideline.
- An extra effort is needed to obtain the two independently estimated regression models.
- It is harder to control whether everything is done 'by the book'.
- Thus, although we really want to advocate this method, we also want to propose an alternative...

## A convenient classification of covariates

- Outcome:  $Y$ ; Baseline measurement of outcome:  $B$ ; Baseline measurement of covariate:  $X$ .
- (When no treatment is given:) Correlation outcome-baseline:  $r_{YB}$ ; correlation outcome-covariate:  $r_{YX}$ ; correlation baseline-covariate:  $r_{BX}$ .
- Suppose:  $r_{YX} = r_{BX} \times r_{YB}$ .
- Such a covariate would not contain additional information when the baseline measurement of the outcome is already in the ANCOVA: a useless covariate.

## A convenient classification of covariates

- Suppose:  $r_{YX} < r_{BX} \times r_{YB}$ .
- Such a covariate would contain additional information when the baseline measurement of the outcome is already in the ANCOVA: it *suppresses* variance in the baseline measurement that is unrelated to the outcome.
- For example: outcome and baseline are blood pressure and covariate is baseline stress level.

## A convenient classification of covariates

- Suppose:  $r_{YX} > r_{BX} \times r_{YB}$ .
- Such a covariate would contain additional information when the baseline measurement of the outcome is already in the ANCOVA.
- For example: a very stable covariate like age.
- For example: a covariate with a lagged effect such as salt intake.

## A convenient classification of covariates

- One thing to note here is that almost all relevant covariates are correlated to the baseline measurement.
- And that almost all covariates that are correlated to the baseline measurement are relevant covariates.

## A new and simple proposal

- Use the baseline measurement to select covariates that cannot be identified on basis of existing research!
- This overcomes problems that arise when selecting covariates on basis of the outcome.
- No inflation of type I error rates, no underestimated standard errors.
- It can be implemented without too much effort.

## A new and simple proposal

- It fits in nicely with the existing guideline: change “*important covariates identified in other recent research may be added to the model*” to “*important covariates identified in other recent research and/or an analysis of the relation with the baseline measurement may be added to the model*”
- The protocol can be changed before the blind is lifted.

## A new and simple proposal

- Simulation results are not that surprising...
- When there are only non-relevant predictors (“ $r_{YX} = r_{BX} \times r_{YB}$ ”), the method is almost as efficient as an analysis without baseline covariates, whilst preserving the type I error rate.
- When there are relevant predictors (“ $r_{YX} \neq r_{BX} \times r_{YB}$ ”), the method is more efficient than an analysis without baseline covariates, whilst preserving the type I error rate.

## A new and simple proposal

- When there are no covariate by treatment interactions, some relevant covariates, and a limited number of non-relevant covariates, the method is almost as efficient as the method of Tsiatis et al.
- When there are covariate by treatment interactions, the method is less efficient than the method of Tsiatis et al. unless (all) covariate by treatment interactions are put in the analysis model.

## Conclusion

- The proposed method ('using the baseline to select the covariates) is simple when an appropriate baseline measurement is available.
- It does not lead to biases.
- It fits in nicely with the existing guidelines.
- It is less flexible than the method of Tsiatis et al but more flexible than the current guidelines.