Adjustment for Baseline Covariates in Clinical Trials

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Guideline on adjustment for baseline covariates in clinical trials

- Minimize bias by adjusting for possible imbalance between treatment groups
- Increase power by reducing the unexplained part of the variation
- Instead of outcome$\sim$f(treatment) we use outcome$\sim$f(treatment,x_i)

Adjustment for baseline variables

- Association with endpoint of interest:
  - Baseline measure of (continuous) endpoint of interest
  - The associations should be known or expected
  - Should be specified in the protocol
- Stratification:
  - Primary analysis should reflect stratification of randomisation
  - Multicentre trials
- Variables measured after randomisation and so potentially affected by the treatment should not be included as covariates in the primary analysis

Baseline imbalance

- Post hoc observed baseline imbalance is not considered an appropriate reason to adjust for a baseline variable
- Statistical testing for baseline imbalance has no role in case of fully satisfactory randomisation
- Conducting exploratory analyses including baseline imbalance observed post hoc might be helpful to assess the robustness of the primary analysis

Pre-specification in a depression trial

"The change from baseline to week 8 in MADRS total score will be analysed by an ANCOVA adjusting for baseline value, grouped site, and treatment"

"All sites contributing by less than 4 patients in the FAS will be merged into a single collective site within each country. If this single collective site still contributes less than 5 patients, it will be further merged with other to small merged or non-merged sites from comparable (geographical/cultural) countries. This will give rise to a new factor, which will be used in the analysis of the primary and key secondary endpoints. The allocation of sites that do not contribute with at least 4 patients will be specified prior to unblinding."

Number of baseline variables to adjust for

- Only a few covariates should be included in a primary analysis. Although larger data sets may support more covariates than smaller ones, justification for including each of the covariates should be provided
- Non-significant covariates must not be removed from the model
  - Even though the effect is not statistically significant there can still be an effect
  - The model must be pre-specified in order for the p-value to be valid

Pre-specification in a COPD trial

"Beside the treatment, the following factors and covariates will be included in the statistical models described in the following sections: baseline value, age, sex, smoking status, concomitant treatment with LABA and country pool. Smoking status and concomitant treatment with LABA are included in the model, as these were used as stratification variables in randomization."

Does adjustment for baseline variables matter?

Analysis	Placebo mean (SE)	Low dose mean (SE)	High dose mean (SE)
Descriptive	-11.20 (0.78)	-15.59 (0.68)	-17.83 (0.57)
Corrected for:			
treatment	-11.20 (0.69)	-15.59 (0.67)	-17.83 (0.66)
treatment, grouped site	-11.79 (0.64)	-15.90 (0.61)	-17.83 (0.60)
treatment, baseline	-11.27 (0.67)	-15.63 (0.65)	-17.72 (0.64)
treatment, baseline, grouped site	-11.86 (0.64)	-16.00 (0.61)	-17.82 (0.60)

Result of the pre-specified analysis

Comparison	Difference	95% CI	p-value
Low dose vs. PBO	-4.14	[-5.90 ; -2.38]	p<0.0001
High dose vs. PBO	-5.97	[-7.71 ; -4.22]	p<0.0001

Adjustment for baseline variables

- Change from baseline analysis:
  - For continuous outcome common choice instead of the raw outcome
  - Whichever of these endpoints is used the baseline measurement should be included as a covariate
  - When including baseline measurement as a covariate, the estimated treatment effects are identical

Instead of change from baseline in MADRS we use MADRS at week 8

Analysis	Placebo mean (SE)	Low dose mean (SE)	High dose mean (SE)
Descriptive	20.19 (0.72)	15.85 (0.66)	13.88 (0.63)
Corrected for:			
treatment	20.19 (0.68)	15.85 (0.66)	13.88 (0.65)
treatment, grouped site	19.50 (0.66)	15.27 (0.63)	13.72 (0.62)
treatment, baseline	20.25 (0.67)	15.88 (0.65)	13.80 (0.64)
treatment, baseline, grouped site	19.66 (0.64)	15.52 (0.61)	13.70 (0.60)

Instead of change from baseline in MADRS we use MADRS at week 8

Comparison	Difference	95% CI	p-value
Low dose vs. PBO	-4.14	[-5.90 ; -2.38]	p<0.0001
High dose vs. PBO	-5.97	[-7.71 ; -4.22]	p<0.0001

It is the same as before !!

Adjustment for interaction terms

- Treatment by covariate interaction:
  - The interaction terms should only be included in the pre-specified analysis if there is reason to suspect such an interaction
  - Treatment by covariate interactions should be explored
  - Test of interaction often lack statistical power - hence absence of statistical evidence is not evidence of no clinically relevance