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Adjustment for Baseline Characteristics in Randomized Clinical Trials

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The purpose of randomization in clinical trials is to ensure that there are no systematic differences between treatment groups with respect to measured and unmeasured baseline characteristics that could influence the outcome of interest. In a randomized clinical trial (RCT) without selection or information bias, an unadjusted analysis (ie, an analysis that does not take baseline characteristics into account) will provide unbiased estimates of treatment effects.

However, adjusting for baseline characteristics in the analysis of RCTs is advised by both the European Medicines Agency and the US Food and Drug Administration because it may improve statistical efficiency, enhancing the ability to draw a reliable conclusion from the available data. Nevertheless, investigators may be unaware of the benefits of adjusting for baseline characteristics or may misinterpret the purpose of adjustment as a correction for chance imbalances between groups to obtain valid results.

In an RCT, Zampieri et al investigated the effect of fluid therapy with a balanced solution compared with a 0.9% sodium chloride solution on 90-day survival among critically ill patients across 75 intensive care units in Brazil. In their primary analysis, the investigators adjusted for the enrollment site and specific baseline patient characteristics.

Use of Baseline Adjustment in the Analysis of RCTs

Description of Adjustment for Baseline Patient Characteristics in RCTs

When considering adjusting for baseline characteristics in the analysis of an RCT, the investigator team must decide when to adjust, which variables to adjust for, what statistical method to use, how to handle missing data, and what to report. Adjustment for baseline variables should generally be considered when stratified randomization is used or when there is a known or anticipated strong association between baseline characteristics and the primary outcome (eg, strong prognostic factors).

Variables included in the adjustment should be selected prospectively, should not be plausibly affected by the treatment (ie, they should generally be characteristics measured prior to randomization), and should be prespecified in the trial protocol. Improved statistical efficiency is achieved only if the included baseline characteristics are strong prognostic characteristics (ie, they are strongly associated with the outcome). This often occurs when the end point is a later measurement of a characteristic measured at baseline.

There is no formal rule for specifying the number of baseline variables that should be adjusted for in the statistical analysis, but the model should generally include a limited number of variables relative to the sample size. Including too many variables may lead to complex and unstable statistical models.

Adjustment is typically achieved by including the variables of interest in a regression model, but other methods are possible (eg, inverse probability of treatment weighting). When baseline variables are adjusted for in a regression model, care should be taken when specifying the model properties if there are few trial participants or rare outcomes because adjustment for an excessive number of variables may lead to unreliable estimates of the treatment effect. Missing data on relevant baseline characteristics can be minimized in the trial design by prespecifying variables for which missing data are expected to be rare and with diligence in data collection. If there are missing data, imputation strategies may be used to address them.

The details of adjustment should be prespecified in the trial protocol or associated statistical analysis plan and reported in the article, including the choice of variables and the justification for including those variables. The precise analytic approach (ie, the mathematical definition of the modeling approach) should generally be included in the statistical analysis plan. Additional analyses may be presented in the article or in the supplementary materials to investigate the robustness of the results (eg, by reporting both the results of the unadjusted and adjusted analyses).

Why Adjust for Baseline Characteristics When Analyzing Results From RCTs?

By accounting for factors influencing the outcome other than the randomly assigned intervention, adjustment leads to increased statistical power (ie, the ability to detect a treatment effect when present) and may increase precision in the estimation of the treatment effect, depending on the type of outcome. Analyses of hypothetical trials have suggested that the relative increase in effective sample size may be up to 20% by adjusting for baseline characteristics, although the actual increase is strongly dependent on the prognostic value of the baseline characteristics included in the model.

Similar benefits can be obtained when stratified randomization is used in the design of the trial and that stratification variable is adjusted for in the statistical analysis. Stratification is commonly used to ensure balance of the trial interventions across 1 or more prognostic groups or trial sites. Failure to adjust for the stratification variable may lead to reduced statistical power.

Limitations of Adjustment for Baseline Characteristics in RCTs

Adjustment for nonprognostic variables will not lead to an increase in statistical efficiency and could potentially decrease precision in the estimation of treatment effects (ie, widen confidence intervals) or decrease the statistical power even compared with an unadjusted analysis. Post hoc selection of variables for adjustment (eg, based on the magnitude of the observed imbalance between treatment groups or on an evaluation of the effect of adjusting for different variables on the results of the analysis) can lead to bias in the estimates of the treatment effects.

For trials that incorporate stratified randomization, adjustment for the stratification variable may be problematic if there are many strata (eg, many trial sites) relative to the sample size. Interpretation of the trial findings may be complicated because the treatment effect being estimated (ie, the treatment estimand) can differ...
based on whether the analyses are unadjusted or adjusted for certain effect estimates.\(^7\)

**How Was Adjustment for Baseline Characteristics Done in the Trial by Zampieri et al?**

Zampieri et al\(^5\) compared the effect of fluid therapy with a balanced solution vs a 0.9% sodium chloride solution on 90-day survival in 10,520 critically ill patients across 75 intensive care units. The enrollment site was included as a stratification variable in the design of the trial and adjusted for in the statistical analysis. The authors also adjusted for 3 prespecified variables collected at baseline that were known or anticipated to be prognostic of 90-day survival including age, Sequential Organ Failure Assessment score, and the type of admission (planned, unplanned with baseline sepsis, or unplanned without baseline sepsis). As recommended by the regulatory agencies, the choice of baseline variables included in the adjusted model was prespecified prior to unblinding of the trial.

**How Should the Adjusted Results Be Interpreted?**

The authors reported an adjusted hazard ratio of 0.97 (95% CI, 0.90-1.05), indicating that there was no substantial difference in 90-day survival in trial participants receiving fluid therapy with a balanced solution compared with a 0.9% sodium chloride solution. By adjusting for predefined prognostic variables, the authors optimized the chance of finding an effect if present and strengthened the negative result.

**REFERENCES**