Please join the Biometric Colloquium

KELLY VAN LANCKER

Department of Applied Mathematics, Computer Science and Statistics, Ghent University

OPTIMIZING RANDOMIZED TRIAL EFFICIENCY: INNOVATIVE APPROACHES TO COVARIATE ADJUSTMENT

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Seminarraum Center for Medical Data Science (previously CeMSIIS),
Spitalgasse 23, Room 88.03.513
Medical University of Vienna, 1090 Wien
Host: Martin Posch und Franz König

Abstract:

In clinical trials, there is potential to improve precision and reduce the required sample size by appropriately adjusting for baseline variables in the statistical analysis. This is called covariate adjustment. Despite recommendations by regulatory agencies in favor of covariate adjustment, it remains underutilized leading to inefficient trials. We address three potential obstacles that make it challenging to use covariate adjustment.

A first challenge is the incompatibility of many covariate-adjusted estimators with standard boundaries in group sequential designs (GSD). GSDs, which involve pre-planned interim analyses for early stopping for efficacy or futility, are commonly used for ethical and efficiency reasons. However, adjusted estimators may lack the independent increments structure (asymptotically) required to directly apply standard stopping boundaries. We address this by applying a linear transformation to the sequence of adjusted estimators across analysis times, resulting in a new sequence of consistent, asymptotically normal estimators with the independent increments property and that either improves or leaves precision unchanged.

Second, we address the practical problem of handling uncertainty about how much (if any) precision gain will result from covariate adjustment. This is important for trial planning, since an incorrect projection of a covariate's prognostic value risks an over- or underpowered trial. We propose using information-adaptive designs, i.e., continuing the trial until the required information level is achieved. This design enables faster, more efficient trials, without sacrificing validity or power.

Third, practical implementation of efficient estimators has been hindered by the regulatory mandate to pre-specify baseline covariates for adjustment, leading to challenges in determining appropriate covariates and their functional forms. By enabling the use of data-adaptive methods, while at the same time guaranteeing a valid inference that is insulated against model misspecification, we indicate how covariate adjustment can be incorporated in an automated manner.