Basel Biometric Society Meeting on Covariate Adjustment in Clinical Trials

Tuesday March 25, 2025

Face to face meeting at Novartis

9:30 – 12:00 CET

Presenters: Stephen Senn (Consultant Statistician), Jack Kuipers (ETH Zurich), Dominic Magirr (Novartis)

Discussant: Tim Morris (UCL)

Venue: Fabrikstrasse 16**,** Novartis Campus, Basel

Registration: LINK TO REGISTRATION

For information regarding registration and/or the scientific content including questions in advance for the speakers, please feel free to contact the organizers:

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Covariate adjustment is well known and common in statistical modelling, but its use in the analysis of clinical trials is still rather limited. This half-day meeting is dedicated to covariate adjustment in clinical trials and will provide a theoretical as well as practical view on the topic. Case studies will be presented and their alignment with FDA and EMA guidance on adjusting for covariates will be discussed.

Arrival at Novartis 09.15	
09.30	Welcome
09.40	**Stephen Senn (Consultant Statistician)** *Why do covariate adjustments blow up?*
Break 10.30 – 10.50	
10.50	**Jack Kuipers (ETH Zurich)** *To adjust or not to adjust: insights from the simplest non-trivial system of discrete variables*
11.10	**Dominic Magirr (Novartis)** *Assumption-lean covariate adjustment for time-to-event endpoints*
11.30	**Tim Morris (UCL)** *Discussion*
11.45	Q&A
12.00	Close

Stephen Senn (Consutant Statistician)
Why do covariate adjustments blow up?

There are three effects on the precision of the treatment estimate when fitting a covariate in a “least squares” analysis of continuous outcome data from a clinical. First, to the extent that the covariate is prognostic, the mean square error will be reduced. Second, to the extent that the covariate is unbalanced, the variance inflation factor will be increased. Third, a degree of freedom will be lost for estimating the residual error. The first two of these are a matter of first-order precision; they affect the variance of the treatment estimate. The third is a matter of second-order precision; it affects the precision with which the variance is estimated.
I shall explain how formulae for the expected values of these three factors may be used to understand more fully the expected effect of covariate adjustment, thus obviating the need for simulations, the results of which can often be inconclusive. I shall pay particular attention to the second, the variance inflation factor, which is especially relevant to choices of design and model.
Among matters that it illuminates are, the value of median stratification, the problems with propensity score adjustment of clinical trials, the potential gains and losses of fitting a prognostic score instead of its component factors and what the consequences are of replacing an ordered categorical classification with a simple linear score.
I also offer some speculative remarks as to what implications there might be for studying rare diseases, particularly as regards exploiting historical studies of prognostic covariates.

Jack Kuipers (ETH Zurich)
To adjust or not to adjust: insights from the simplest non-trivial system of discrete variables

Adjusting for covariates is a well-established method to estimate the total causal effect of an exposure variable on an outcome of interest. Depending on the causal structure of the mechanism under study, there may be different adjustment sets, equally valid from a theoretical perspective, leading to identical causal effects. However, in practice, with finite data, estimators built on different sets may display different precisions. To investigate the extent of this variability, we consider the simplest non-trivial non-linear model of a v-structure on three nodes for binary data. We explicitly compute and compare the variance of the two possible different causal estimators. Further, by going beyond leading-order asymptotics, we show that there are parameter regimes where the set with the asymptotically optimal variance does depend on the edge coefficients, a result that is not captured by the recent leading-order developments for general causal models. As a practical consequence, the adjustment set selection needs to account for the relative magnitude of the relationships between variables with respect to the sample size and cannot rely on purely graphical criteria.

Dominic Magirr (Novartis)
Assumption-lean covariate adjustment for time-to-event endpoints

Heavy use of parametric modelling and an attitude that “all models are wrong, but some are useful” is now frequently criticized within the statistical community. An alternative approach involving ‘model-free’ estimands and assumption-lean analysis methods (such as double-robust estimation and targeted learning) is becoming more popular in many scientific fields. For clinical trials with time-to-event endpoints, however, typical analysis methods still rely on strong modelling assumptions. In this talk, I’ll describe the opportunities and challenges of moving towards more assumption-lean analysis methods for time-to-event endpoints, paying close attention to what is included in the FDA’s 2023 guidance document on covariate adjustment.