Kolloquium „Statistische Methoden in der empirischen Forschung“

Wann: 17. November 2020, 17:00 – 18:30 Uhr

Wo: Online

Regina Stegherr (Universität Ulm)
on behalf of the SAVVY Study Group

Survival analysis for AdVerse events with VarYing follow-up times - Results of the empirical study of the SAVVY project

In the evaluation of new therapies in clinical trials, the analysis of adverse events (AEs) is an important part of the safety assessment. There is general agreement among stakeholders including regulators, payers, industry, healthcare professionals, and patients that improvements in the evaluation of a drug's safety would benefit all. The "Survival analysis for AdVerse events with VarYing follow-up times" (SAVVY) project aims to improve the analyses of AE data in clinical trials through the use of survival techniques appropriately dealing with censoring, competing risks, and varying follow-up times. In the analysis of AEs typically used estimators as the incidence proportion, incidence densities, or a non-parametric Kaplan-Meier estimator either ignore censoring or competing events or rely on a too restrictive assumption of constant hazards. In an empirical study including randomized clinical trials from several sponsor companies, these potential sources of bias are investigated by comparing the before mentioned estimators to the non-parametric Aalen-Johansen estimator. Descriptive quantities, plots, and a more formal assessment using a random-effects meta-analysis are used for the comparisons. Factors influencing the bias are investigated in a meta-regression. The comparisons are not only conducted at the end of follow-up but also at three earlier evaluation times. For group comparisons, relative risks and a comparison of the hazard ratio of the Cox model and the ratio of incidence densities are considered. Thereby, similar methods are applied. In the empirical study, 186 types of AEs from seventeen clinical trials contributed by ten sponsor companies were included. Compared to the Aalen-Johansen estimator the 1-Kaplan-Meier estimator is on average about 1.2-fold larger and a probability transform of the incidence density ignoring competing events overestimates the AE probability even more. The average bias using the incidence proportion is less than 5%. But the bias should not be neglected as its size strongly depends on the amount of censoring. The adequate consideration of non-constant hazards is less an issue in the estimation of the AE probability. But the correct definition of competing events is important. Not only death but all treatment-related terminations of follow-up may be considered as a competing event. This impacts the amount of censoring and competing events which are the leading forces influencing the bias. The choice of the estimator is crucial for the estimation of the AE probability, but also for group comparisons. There is an urgent need to improve the guidelines of reporting AEs by finally replacing the Kaplan-Meier estimator and the incidence proportion by the Aalen-Johansen estimator with an appropriate definition of competing events.