The Impact of Dropouts on the Analysis of Dose-Finding Studies with Recurrent Event Data

Untersuchung der Auswirkungen von fehlenden Daten bei der Analyse von Dosis-Findungs Studien mit Recurrent Event Daten
(Der Vortrag wird auf Deutsch gehalten.)

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This work is motivated by dose-finding studies, where the number of events per subject within a specified study period form the primary outcome. The aim of these studies is to identify the target dose for which the new drug can be shown to be simultaneously safe and as effective as a competitor medication. Given a pain-related outcome, we expect a considerable number of patients to drop out before the end of the study period. The impact of missingness on the analysis and models for the missingness process must be carefully considered.

The recurrent events are modelled as over-dispersed Poisson process data, with dose as regressor. Additional covariates may be included. Constant and time-varying rate functions are examined. Based on these models the impact of missingness on the precision of the target dose estimation is evaluated. Diverse models for the missingness process are considered, including dependence on covariates and number of events. The performances of five different analysis methods are assessed via simulations: a complete case analysis; two analyses using different single imputation techniques; a direct likelihood analysis; and an analysis using pattern-mixture models.

The target dose estimation is robust if the same missingness process holds for the target dose group and the active control group. Furthermore, we demonstrate that this robustness is lost as soon as the missingness mechanisms for the active control and the target dose differ. Of the methods explored, the direct-likelihood approach performs best, even when a missing not at random mechanism holds.