Adverse events with survival outcomes: from clinical questions to methods for statistical analysis

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Introduction and Objective(s) - When studying a novel treatment with a survival time outcome, failure can be defined to include an adverse event (AE) among the endpoints typically considered, for instance relapse. These events act as competing risks, where the occurrence of relapse as first event and the subsequent treatment change exclude the possibility of observing AE related to the treatment itself. In principle, the analysis of AE could be tackled by two different approaches: 1. It requires a competing risk framework for analysis: the clinical question relates to the observed occurrence of AE as first event, in the presence of the event "relapse"; 2. It requires a counterfactual framework for analysis: the clinical question relates to the treatment causing AE occurrence as if relapse could not occur. This work has two aims: the first is to critically review the standard theoretical quantities and estimators with reference to their appropriateness for dealing with approaches 1 or 2 and to the following features: (a) estimators should address for the presence of right censoring; (b) theoretical quantities and estimators should be functions of time. The second aim is to define a strategy to relax the assumption of independence between the potential times to the competing events of the commonly used estimators when counterfactual approach 2 is of interest.

Method(s) and Results - After reviewing the standard methods[1] we clarify the impact of the crucial assumption of independence between potential times to competing events of the standard estimators used in the counterfactual approach. We propose the use of regression models, stratified Kaplan-Meier curves and inverse probability of censoring weighting[2] to relax the assumption of independence by achieving conditional independence given covariates and we develop a simulation protocol to show the performance of the proposed methods.

Conclusions - The proposed methods overcome the problem due to the dependence between the two potential times. In particular, one can handle patients' selection in the risk sets, and thus obtain conditional independence between the two potential times, adjusting for all the observed covariates that induce dependence. The proposed methods can be also extended to the case of repeated adverse events.

References

[1] A. Allignol, J. Beyersmann, C. Schmoor (2016). Statistical issues in the analysis of adverse events in time-to-event data. Pharmaceutical Statistics, 15, 297-305

[2] S.J.W. Willems, A. Schat, M.S. van Noorden, M. Fiocco (2018). Correcting for dependent censoring in routine outcome monitoring data by applying the inverse probability censoring weighted estimator. Biometrical Journal, 62, 836-851