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Methods for Planning and Analyzing Clinical Trials with Composite Endpoints

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Composite endpoints combine several event variables of interest into a single outcome variable. Besides some generally favorable properties of using composite endpoints, planning clinical trials with composite outcomes and the analysis as well as the interpretation of composite results is often challenging. The present work deals with three methods for planning and analyzing composite endpoints encountered in different situations in clinical practice.

In the first part of this work multiple testing procedures are applied in order to improve the interpretation of composite endpoint results. When planning a trial with a composite primary outcome the study is usually powered in order to detect the composite treatment effect. The result is then difficult to interpret as the single components may show varying or even opposite treatment effects. Therefore several clinical trial situations often met in practice are considered and appropriate multiple testing procedures are proposed. Using these procedures can lead to more confirmatory evidence and thus more information about the component effects without an (or only with a slight) increase in sample size based on the arising multiplicity problem.

The second part deals with the uncertainty regarding the treatment effects for the composite endpoint and its components in the planning stage. As the number of parameters to be specified within composite outcomes is substantial and the available information about the component effects is often rather low, clinical trials with composite primary outcomes tend to be over- or underpowered. Group sequential designs allow for stopping a trial early in an interim analysis either for efficacy or for futility. The decision rule to stop a trial early, especially for futility, is often not straightforward. Therefore general optimality criteria are proposed for the choice of suitable futility boundaries which maximize the probability of detecting small or opposite treatment effects while limiting the power loss and the probability of stopping the study ‘wrongly’. The criteria are illustrated on three different group sequential designs including two endpoints, which are motivated by the fact that in many clinical trial applications it is not sufficient to consider only one primary endpoint in order to adequately describe the efficacy of a new treatment. As the properties of futility boundaries are often not considered in practice and unfavorably chosen futility boundaries may have serious consequences with respect to the performance of the study design, it can be recommended to assess the impact of these boundaries according to the proposed admissibility and optimality criteria.

In the third part the situation of a composite endpoint and subsequent occurring events is considered. Composite time-to-first event variables by definition consider only the first occurring event. Subsequent occurring events are generally not investigated and it is therefore recommended to take these into account in the analysis of the single components. However, first and subsequent events do not necessarily follow the same survival distribution and ignoring this would lead to biased effect estimates. Multistate models can be used to analyze

single endpoints and subsequent event types separately, but the often small number of events limits the analysis and yields unvalid results. Therefore a prediction procedure for a specific clinical trial situation (modeled by the illness-death model) is proposed which works by predicting event times and types for originally censored observations. The prediction leads to an increase of the number of evaluable events by preserving the original data structure, strengthens the effects without occurrence of major biases and improves the power in order to detect assumed treatment effects.