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Methods for Subgroup Selection in Biomarker-Based Clinical Trials

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In this thesis, methods for the selection of subgroups in biomarker-based trial designs were devised and investigated. The focus of this thesis were so-called adaptive enrichment designs which are two-stage designs allowing to tailor the target population to a particular subgroup of patients at an interim analysis, and subsequently enrolling solely patients from this subgroup for the second stage of the trial.

Four different situations for the outcome of a biomarker-based trial were investigated. This included the cases of a normally distributed, a binary, and a time-to-event outcome for both the interim and final analysis, and the situation where the interim decision is based on a binary surrogate outcome but the proof of efficacy is conducted based on a correlated time-to-event outcome.

For all four settings, optimal decision rules were derived which take uncertainty about treatment effects into account by the modeling of prior distributions. The optimality criterion was the expected loss under a false decision, which was specified according to a quadratic loss function. For a normally distributed and a time-to-event outcome, normally distributed priors were applied, while continuous uniform and truncated normal priors were applied to the situation of a binary decision criterion. Optimal decision rules could analytically be derived for normally distributed and time-to-event outcomes, while numerical methods were used for the situation of a binary outcome and a surrogate. These rules depended on the distribution of the prior, relevance thresholds defining the loss function, the prevalence of the biomarker, amount of information at the interim analysis reflected by the sample size or the number of events, respectively.

Simulation studies were conducted in order to investigate the performance of decision rules in terms of probability for a correct selection, type I error rate, and power. For the investigated situations, optimal decision rules mostly performed comparably or better as compared to *ad hoc* rules proposed in the literature. The practical applicability of the devised methods was illustrated for all four outcome situations by the use of clinical trial examples.

For the situation of a normally distributed endpoint, the assumption of a perfect identification of the biomarker, i.e. the sensitivity and specificity of the biomarker being equal to 1, was relaxed. It could be shown by means of analytical calculations and simulation studies that the sensitivity and specificity of the biomarker both have a tremendous impact on performance characteristics of the trial design in terms of correct selection probability, type I error rate, and power.

In summary, this thesis illustrates the crucial role of the interim decision rule in adaptive biomarker-based trials and devises a method how to choose a rule in an optimal way given uncertainty about treatment effects. Furthermore, the performance of the bioassay identifying the biomarker is of an utmost importance, since a low sensitivity and specificity will cause severe performance disadvantages. Hence, due to their cruciality, both the correct identification of subgroups and the choice of an appropriate interim decision rule should always be carefully assessed when planning a clinical trial with subgroup selection.