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Flexible Designs in Oncological Clinical Trials Allowing for Inclusion of Prognostic Factors.

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Design and planning of a clinical study rely on assumptions about patients' accrual, data distribution, potential influence factors on the investigated study endpoint and the actual therapeutic effects of the treatment options under examination. The less is known about disease, studied patient population or examined treatments, the greater the uncertainty about the assumptions underlying the study design and the statistical evaluation. If in the course of the study misconceptions become obvious, this is accounted for by protocol amendments or additions. Flexible design procedures ensure that such design changes are performed in a statistically valid way, i.e. under control of the overall type I error.

Three flexible design approaches are considered in this thesis which are allocated in the interim or final analysis and based either on an unblinded or a blinded data review, i.e. with or without knowledge about patients' treatment allocation. Conventional group sequential designs (GSDs) allow for early stopping after an interim analysis either in case of non detectable treatment effect (stopping for futility) or when a strong treatment effect is apparent (stopping for efficacy). Adaptive designs (ADs) provide greater flexibility and more opportunities for design modifications. Sample size recalculation is the most common design adaptation, but other adaptations are also possible. Both, the GSD and the AD base their data-driven modification on the unblinded data in an interim analysis. As a third option allowing data-driven modifications, Edwards' proposal is examined which performs a covariate selection based on the complete, still blinded, study data in the final analysis.

The thesis investigates the applicability of ADs for survival time studies which permit inclusion of relevant covariates. In this thesis the adaptive conditional rejection probability (CRP) principle of Müller and Schäfer is extended for use in proportional hazards models allowing adjustment for the treatment effect as well as the covariate effects. The AD is used to render possible two specific design adaptations during a two-stage trial: (i) sample size adaptation or (ii) covariate selection in an interim analysis. In the case of covariate selection, the CRP principle is additionally extended and combined with Keiding's method: The data from patients recruited in the first stage is left truncated at the time point of the interim analysis, if their data contribute also to the second stage. The ADs are compared to the other flexible designs in the specific context: in scenario (i) to two-stage GSDs allowing for early stopping after an interim analysis and thus modifying the sample size, and in scenario (ii) to Edwards' design allowing for blinded covariate selection in the final analysis.

Operational characteristics such as type I error rate, empirical power, average sample number (ASN) or ability to select relevant covariates are analysed on the basis of Monte Carlo simulations for the AD and the competing designs. The simulations clone the course of randomized two-stage survival trials, which are scheduled to test the treatment difference between two treatment arms.

Firstly, the AD, which performs a sample size recalculation (SSR) in an unplanned interim analysis during a fixed sample trial, is compared to the two-stage GSD allowing for early stopping for efficacy. Simulation studies are performed, implementing either one binary or one normal covariate. The association of covariate information with the power and the efficiency of a clinical trial is ascertained in the simulation studies: The stronger the covariate effect the more power is lost in test decisions when omitting the covariate information. Covariates amplifying the treatment effect on survival lead to reduction of the ASN in the GSD and the AD. Furthermore, for overestimated treatment effect in the planning phase, the SSR results in increased ASN for the AD and such diminishes the loss of power one would experience otherwise. For underestimated treatment effect, the AD reduces an overshooting of the power and such corrects the sample size downwards. Hence, the flexibility of the presented AD provides benefit especially in exploratory situations.

Secondly, the AD (CRP principle and Keiding's approach) is compared to Edwards' approach to perform a data-driven covariate selection. The AD selects the strongest covariates in interim analyses which take place in the middle of the trial or later. Covariates with weak influence on survival often are not detected in the AD, unless in very late interim analyses. However, the left truncation of the data induces a monotonic power decrease of the test in the AD which is the stronger the later the interim analysis takes place. This is due to the increasing information loss when the truncated time span becomes longer. Although Keiding's method provides large flexibility for design adaptations, it also induces a large power loss when applied in late interim analyses. The method should therefore only be implemented in early interim analyses. The simulations show that Edwards' method outperforms the AD in its ability to identify the correct data model as well as in the achieved power. Additionally, an interim analysis implies high financial and logistic efforts. Thus, correcting the data model during an ongoing study is best done in the blinded way applying Edwards' method in the final analysis.

Finally, the AD including SSR is applied for a phase II study with survival endpoint, investigating two treatments for patients suffering from non-clear cell renal cell carcinoma (ncc-RCC). Little knowledge about active treatments in ncc-RCC, few eligible patients and limited funding restricts the study planning. A two-sided hypothesis comparing the two treatment arms is examined where stopping after the first stage is only possible for futility and where continuation depends on the recalculated sample size. The simulation study replicating the whole trial for a large set of possible trial conditions allows the selection of a feasible design under the restrictions of a maximum achievable sample number, very low accrual rate and predetermined trial duration. The implementation of the AD in the ncc-RCC trial thus illustrates the applicability and benefit of the developed AD method in practice.