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Flexible Designs for Single-Arm Phase II Trials in Oncology

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Clinical phase II trials in oncology are conducted to determine whether the activity of a new anticancer treatment is promising enough to merit further investigation. Two-stage designs are commonly used for this situation to allow for early termination. Although there is an ongoing debate on the relative merits of single-arm versus randomized phase II trials, the standard tool in cancer research remain single-arm trials.

Designs proposed in the literature so far have the common drawback that the sample sizes for the two stages have to be specified in the protocol and have to be adhered to strictly during the course of the trial. As a consequence, designs that allow a higher extent of flexibility are desirable. Currently available flexible design methods are tailored to comparative studies with continuous test statistics. We have shown that direct transfer of these methods to discrete test statistics results in conservative procedures and, likewise, in a loss in power. Therefore, special methods are needed for discrete test statistics.

In this thesis, we propose flexible methods that allow an arbitrary modification of the sample size of the second stage using the results of the interim analysis or external information while controlling the type I error rate. We constructed new designs based on a combination test and based on the conditional error function principle that directly account for the discreteness of the outcome. It is shown, further, how both approaches can be combined to construct new phase II designs that are more efficient as compared to currently applied designs and that allow flexible mid-course design modifications. We derived these new flexible and more efficient phase II designs for both a planned fixed second-stage sample size and for the situation that the planned second-stage sample size depends on the interim outcome. Results are tabulated for a wide range of frequently used design parameters.

Taking into account that classical phase II designs in oncology have been deemed to be optimal for decades, the additional decrease in sample size which can be achieved by applying our proposed methods must be regarded as a significant contribution to the field of clinical trial design. As hundreds of phase II oncology trials are performed each year worldwide, the application of our new designs will not only allow for flexibility in the conduct of these trials, but also preclude a considerable number of patients from being included in such trials.

The search algorithms used to identify these designs are computationally intensive. Therefore, ways to improve the search strategy were developed and the implementation of these methods was described in detail. All computer programs are provided and illustrated with examples.

Emphasis was placed on evaluation of the adaptive performance of the developed flexible phase II designs. When adjustments are made, the consequences in terms of increasing/decreasing the sample size have to be weighed against the gain/loss in power. We developed a performance indicator that fits to binary outcomes and satisfactorily addresses recalculation possibilities. Thus, we identified recalculation rules which improved the performance of the designs, if there is uncertainty with respect to the treatment effect.

Application and the rich possibilities of the proposed methods were illustrated with a clinical trial that was planned with methodology described in this thesis.

In summary, the new designs we developed allow the use of mid-course information for planning the second stage of the study, thus meeting practical requirements when performing phase II clinical trials in oncology. The observed reduction in average sample size when applying our new flexible study designs, with no resultant loss in power, is due to the new methodology and the efficient search algorithm.