

Pavel Mozgunov's PhD "Adaptive design for complex dose finding studies"

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Abstract

The goal of an early phase clinical trial is to find the regimen (dose, combination, schedule, etc.) satisfying particular toxicity or (and) efficacy characteristics. Designs for trials studying doses of a single cytotoxic drug are based on the fundamental assumption "the more the better", that is, the toxicity and efficacy increase with the dose. This monotonicity assumption can be violated for novel therapies and for more advanced trials studying drug combinations or schedules. It also becomes common to consider a more complex endpoint rather than a binary one as they can carry more information about the drug. Both the violation of the monotonicity assumption and the complex outcomes give rise to important statistical challenges in designing novel clinical trials which require an extensive attention.

In the first part of this thesis, we consider a specific class of combination trials which involve novel therapies and can benefit from the monotonicity assumption. We also propose a general tool evaluating the performance of novel designs in the context of complex clinical trials. Further, we consider a problem of Bayesian inference on restricted parameter spaces. We propose novel loss functions for parameters defined on the positive real line and on the interval demonstrating their performances in standard statistical problems. Based on the obtained results, we propose a novel allocation criterion for model-based designs that results in a more ethical allocation of patients.

In the second part of this thesis, we consider a more general setting of early phase trials in which an investigator has no (or limited) information about the monotonic orderings of regimens' responses. Using an information-theoretic approach we derive novel regimen selection criteria which allow the avoidance of any parametric or monotonicity assumptions. We propose novel designs based on these criteria and show their consistency. We apply the proposed designs to Phase I, Phase II and Phase I/II clinical trials and compare their performances to currently used model-based methodologies.