A Contribution to the Design and Analysis of Phase III Clinical Trials

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Abstract

Clinical trials are an established methodology for evaluation of the effects of a new medical treatment. These trials are usually divided into several phases, namely phase I through IV. The earlier phases (I and II) are relatively small and have a more exploratory nature. The later phase III is confirmatory and aims to demonstrate the efficacy and safety of the new treatment. This phase is the final one before the treatment is marketed, with phase IV consisting of post-marketing studies.

Phase III is initiated only if the conductors of the clinical study judge that the evidence from earlier stages indicates clearly that the new treatment is effective. However, several studies performed in recent years show that this assessment is not always correct. Two papers written on the subject point out average attrition rates of around 45% and 30%. In other words, it is estimated that only around two thirds of the compounds that enter phase III finish it successfully. This thesis examines some of the possible ways of improving efficiency in phase III clinical trials. The thesis consists of four papers on various topics that touch this subject, these topics being adaptive designs (paper I), number of doses (paper II) and multiplicity correction procedures (papers III and IV).

The first paper examines the properties of the so called dual test, which can be applied in adaptive designs with sample size re-estimation. This test serves as a safeguard against unreasonable conclusions that may otherwise arise if an adaptive design is used. However, there is a price of possible power loss as compared to the standard test that is applied in such situations. The dual test is evaluated by considering several scenarios where its use would be natural. In many cases the power loss is minimal or non-existing.

The second paper considers the optimal number and placement of doses used in phase III, with the probability of success of the trial used as optimality criterion. One common way of designing phase III trials is to divide the patients into two groups, one group receiving the new drug and another a control. However, as is demonstrated in paper II, this approach will be inferior to a design with two different doses and a control if there is enough uncertainty in the dose-response model prior to the initiation of the trial.

The last two papers study possible gain that results from optimization of the multiplicity correction procedure that is applied if more than one hypothesis is tested in the same trial. Two families of such procedures are considered. The first one, examined in paper III, consists of a combination of a weighted Bonferroni test statistic with the principle of closed testing. The second one, examined in paper IV, is based on combining the same principle with a "pooled" test statistic. Paper III demonstrates that optimizing a multiplicity testing procedure can lead to a significant power increase as compared to simpler, non-optimized, procedures. The optimization is performed with respect to expected utility, an approach that originates from decision theory. Paper IV examines the difference between the Bonferroni-based and the pooled-based multiplicity corrections, finding the latter to be superior to the former if the test statistics follow a known multivariate Normal distribution.