Scientific collaboration with African students in mathematics, exemplified for a project to determine the assurance during project planning of clinical development programs

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Background

The African Institute of Mathematical Sciences (AIMS) has been established to foster the mathematical education in this continent. Students can acquire a postgraduate Master in mathematics at 5 AIMS centers following a one year structured education.

The courses shall enable a broad view on mathematical topics related to current applied problems in various disciplines (such as quantum physics or climate change), which are provided by lecturers and supervisors for MSc essays from both Africa and Overseas.

We have supported several students at AIMS Rwanda during the last 2 years, and one of the projects is presented at the workshop. We will explain how the teaching and essay writing is organized, and which directions future projects will take.

Introduction

The assurance is a great communication tool for statisticians during the design stage of a clinical trial. Instead of determining the power of the trial using fixed assumptions e.g. of the expected treatment effect, the expected power is derived using a distribution of the treatment effect, which reflects the current uncertainty about the effect.

During drug development programs, the uncertainty on the treatment effect will be reduced from one trial to the next by gaining information over time. When planning subsequent trials, it is possible to minimize the total sample size of both trials by selecting an optimal sample size for the first trial. Such a method had already been proposed by Whitehead (2016) using deterministic frameworks, based on an assumed (fixed) effect size of the treatment effect. We have applied this idea using the assurance concept.

Methods

The method is illustrated for quantitative (normally distributed) endpoints for trials with a new treatment against a negative control.

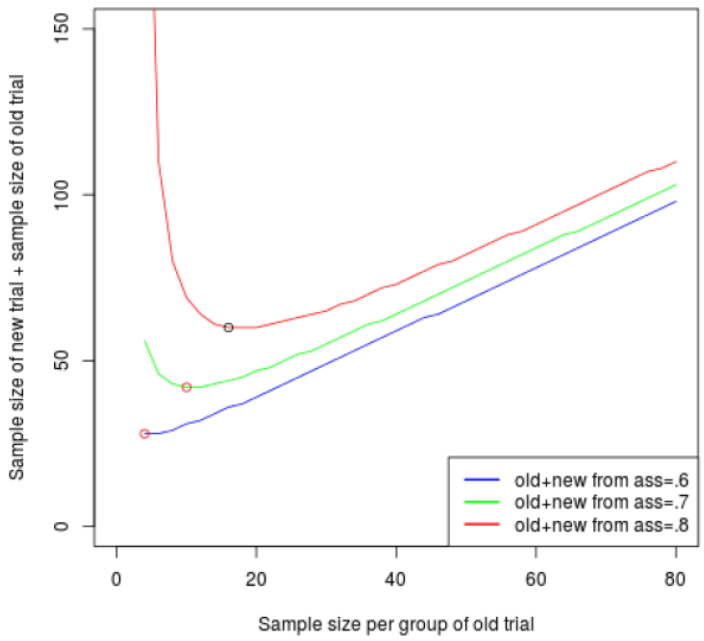
Two subsequent trials are planned simultaneously, in order to minimize the total cost of both trials. The first trial is used to estimate the magnitude of the effect, while the second trial is planned as confirmatory trial. The larger the sample size in the first trial, the smaller the expected confidence interval of the treatment effect, which leads to smaller sample size in the second trial due to a narrower prior distribution.

The concept as shown by Chuang-Stein (2006) is applied to investigate the probability for a successful second trial. This concept has been implemented in R.

Results

The key results can be illustrated in V-shaped curves for given standardized effect sizes. These results are directly comparable to the results of Whitehead (2016). The optimum sample size depends on the assurance for the second trial: The higher the assurance, the larger the sample size in the first trial, which is an expected result. An example is shown in Figure 1.

Figure 1: Optimal sample size for the first of two subsequent trials to achieve an assurance of 0.6, 0.7 and 0.8 for the second trial, given a standardized effect size of 0.75.



Outlook

The method is currently extended to 3 sequential trials, e.g. one phase IIa, one phase IIb and one phase III trial. The first trial has already been performed, which resulted in a preliminary estimate of the effect size and its uncertainty.

Then the derivation of the total costs for the two subsequent IIb + III trials will be based on the resulting prior distribution of the effect size instead of assuming a fixed effect size, otherwise the same concept as above is applied. Further options for future research on project planning will be discussed at the workshop.

References

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Whitehead (2016). Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Meth Med Res. 2016, 25(3) 1057 –1073.