ESR Researcher Project: Non-technical Summary

"Monitoring clinical trials using short-term information when long-term information is missing"

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The use of interim analyses has become popular in drug development. An interim analysis allows us to assess the results of an ongoing trial. During the analysis a trial can be stopped early for efficacy or futility, or some design adaptations such as sample size reassessment or dropping of treatment arms can be performed. Consideration of futility stopping is seen to be important and useful for both ethical and economic reasons, and is therefore widely used [1-3]. Sample size could be also increased in case the interim results are promising in order to make sure that efficacy can be claimed on a treatment being tested.

During interim assessment of the trial, there might be some information available in addition to the outcome on the primary endpoint. It could be beneficial to add such information into the analysis as the number of patients with complete observations on the primary endpoint might be limited. An example of including such additional data could be incorporation of shorter observations on patients. Let us consider a primary outcome of interest in a trial, which is observed after some pre-specified time, for example one year. Then, there could be more patients available at interim with complete observations on a shorter amount of time, which is e.g. 6 months. An example showing such a setting is represented in Figure 1 below, which shows the patient recruitment over time. At some point during the trial an interim analysis is performed. There is a number of patients recruited in the trial, and a fraction of them have already collected response on the long-term primary outcome in the trial, which is denoted by shaded circles. It can be seen that at the same time, there are some additional patients that have completed the shorter observations (denoted by shaded triangles), which could be incorporated into the interim analysis in order to improve the decision-making process.

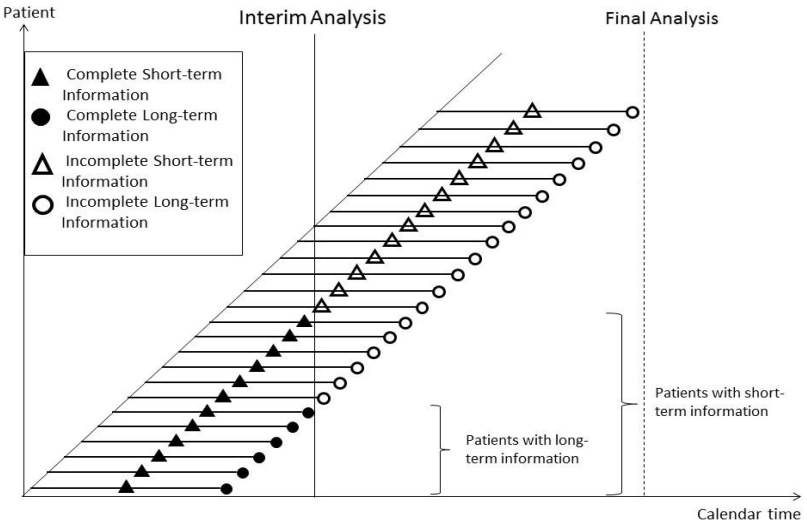

Figure 1: Plot showing recruitment of patients over time and an interim analysis, where some additional short-term information is available on some patients

Therefore, in our research we investigated the impact of inclusion of such groups of patients into interim analyses for clinical trials. At first, we considered a design, which would allow for futility stopping. We compared our approach with one including only long-term information, as well as one in which only the short-term data was used. We looked at different scenarios, taking into account the correlation between the short and long observations or the timing of an interim analysis. We showed that the use of both long- and short-tem endpoints could increase the power of a trial, which would result in a higher chance of claiming efficacy of the treatment being tested. A range of correlations between short- and long-term data was investigated and the higher the correlation the higher was the increase in power.

We further extended our methodology to adaptive designs with sample size reassessment. This means that if the trial would not be stopped for futility, we would also look at the results and see if smaller number of participants would be sufficient to claim efficacy on the treatment. Or, in a case where the results were promising but possibly not good enough for the pre-specified number of patients, we could recruit more patients and then be able to reject the null hypothesis. The methods were based on the well-established combination function [4], which controls the chance of having a false positive. Use of both short- and long-term observation during the interim analysis was shown to increase the power of a trial when compared to the other two approaches. This however resulted in an increased average sample size. Therefore, if the objective of the sample size reassessment is to increase the power, then use of both short- and long-term data is recommended. When, however, the aim is to reduce the average sample size, use of only long-term information is recommended and in such a case, no power increase can be seen.

References

[1] Elsäßer, A., Regnstrom, J., Vetter, T., Koenig, F., and Hemmings, R. J., Greco, M., Papaluca-Amati, M., and Posch, M. (2014). Adaptive clinical trial designs for European marketing authorization: a survey of scientific advice letters from the European Medicines Agency. *Trials* 13:383.

[2] Hatfield, I., Allison, A., Flight, L., Julious, S. A., and Dimairo, M.(2016). Adaptive designs undertaken in clinical research: a review of registered clinical trials. *Trials* 17:150.

[3] Lin, M., Shiowjen, L., Boguang, Z., Scott, J., Horne, A., Solomon, G., and Russek-Cohen, E. (2016). CBERs Experience With Adaptive Design Clinical Trials. *Therapeutic Innovation & Regulatory Science* 50:(2)195-203.

[4] Bauer, P. and Köhne, K. (1994). Evaluation of experiments with adaptive interim analyses *Biometrics* 16:1029-1041

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