Bayesian Methods for Clinical Trials

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24th – 25th of February 2025

Practical 3: Bayesian sequential designs

You are asked to design a Phase II singe-agent PoC clinical trial of a new anti-cancer agent (setting of Practical 2). The team would like to evaluate a particular dose of the new agent in terms of the objective response rate (ORR) at Week 12 after the start of the treatment. The uninteresting response rate that would not suggest a promising activity is $p_0 = 0.30$ and an interesting treatment effect that would trigger the further development of the compound is $p_1 = 0.50$. The currently planned sample size is $N = 40$ patients.
You are asked to design this study using a Bayesian design and consider inclusion of the interim analysis/analyses during the course of the trial.

(a) Firstly, consider a design with no interim analysis. Apply posterior probability criterion to claim the efficacy at the end of the trial. Find the critical probability threshold for the posterior probability that will ensure the control of the type I error at 5%. What power is achieved for the proposed sample size and the found value of the probability threshold? Would you recommend to change the sample size?

(b) Consider now an inclusion of the interim analysis after the half of the total number of patients has been recruited in the trial. At the time of the interim analysis, one can stop the trial earlier for efficacy. Use the same probability threshold found in (a) for the interim and final analysis. What effect will it have on the type I error? Do you need to adjust the critical probability threshold. If yes, find the new value that control the type I error at the desirable level. What is the power of the study now?

(c) Consider now an inclusion of the interim analysis after the half of the total number of patients has been recruited in the trial. At the time of the interim analysis, one can stop the trial earlier for futility only. The decision rule for the futility is based on the posterior probability. Evaluate several design options with different futility bounds and propose a design option that achieves a balance in the operating characteristics. Why have you chosen this design?

(d) Consider now the futility rule based on the conditional power that uses the planned response rate (i.e. assumed under the alternative). Evaluate several design options using different futility bounds. Find a value of the futility bound that would match as closely as possible the operating characteristics of the design in point (c). Have you managed to find one or the operating characteristics could not be matched? Why?

(e) Assume now that there is some prior knowledge about the response rate. Specifically, the most likely value is 40% and we are 80% confident that the response rate is between 20% and 65%. Find the Beta prior matching these characteristics. For the new prior distribution, evaluate the decision rules proposed in (c). How does the new prior change the operating characteristics? Why? Does one need to make any changes to the design under the new prior? Why?