Bias-corrected treatment effect estimators for group-sequential platform trials with non-concurrent controls

Pavla Krotka[1], Martin Posch[2], Marta Bofill Roig[1]

[1]Universitat Politècnica de Catalunya/Department of Statistics and Operations Research; [2]Medical University of Vienna/Center for Medical Data Science

Platform trials enhance drug development by offering increased flexibility and efficiency. They evaluate the efficacy of multiple treatment arms, with the added benefit of permitting treatment arms to enter the trial over time and to stop early based on interim data. Efficacy is usually assessed using a shared control arm. For arms entering later, the control data is divided into concurrent and non-concurrent controls (NCC), referring to control patients recruited while the given treatment arm is in the platform and before it enters, respectively. Including NCC can reduce the sample size and increase power, but also lead to bias in the effect estimates, if there are time trends.

For platform trials with continuous endpoints without interim analyses, a regression model has been proposed that utilizes NCC and adjusts for time trends by including the factor "period" as a fixed effect. Here, periods are defined as time intervals bounded by any treatment arm entering or leaving the platform. It was shown that this model leads to unbiased effect estimates and asymptotically controls the type I error rate regardless of the time trend pattern, if the time trend affects all arms in the trial equally and is additive on the model scale. However, if interim analyses are included, the definition of the factor periods becomes data dependent and the number of periods to adjust for depends on previous results. Furthermore, due to early stopping the sample sizes in different arms become outcome dependent, and therefore the effect estimates are no longer unbiased. This can affect the adjustment for time trends in the linear model, and the type I error rate might no longer be controlled.

In this work, we examine the performance of the currently available model in group-sequential platform trials and show that it leads to a loss of the type I error rate control and bias in the effect estimators. In addition, we describe how the weight of the non-concurrent controls in the treatment effect estimator is stochastically dependent on the outcome in the non-concurrent controls. Moreover, we will investigate adjusted treatment effect estimators that aim to eliminate or reduce the potential bias and resulting type I error rate inflation. Focusing on a simple platform trial with two experimental treatment arms and a continuous endpoint, we will present results from a simulation study, where we evaluate the performance of the considered approaches and compare them to current methods.

Keywords: Platform trials, Interim analysis, Non-concurrent controls, Statistical inference, Statistical modeling.