Statistical modeling to adjust for time trends in platform trials utilising non-concurrent controls

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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. Treatment 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. Analysis using NCC can reduce the required sample size and increase power, but also lead to bias in the effect estimates and hypotheses tests, 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 (T1E) 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 [1]. 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 interim results. Furthermore, due to early stopping the sample sizes in the different arms become outcome dependent, and therefore treatment effect estimates are no longer unbiased. This can affect the adjustment for time trends in the linear model, and the T1E rate might no longer be controlled.

In this talk, we suggest two extensions of this model. First, we propose an alternative definition of the time covariate by dividing the trial into fixed-length data-independent calendar time intervals. Second, we propose alternative models to adjust for time trends. In particular, we consider: accounting for dependency between closer time intervals by adjusting for autocorrelated random effects; and employing spline regression to model time with a smooth polynomial function. We implement the proposals in the `NCC` R-package [2] and evaluate their performance in terms of the T1E rate and statistical power for individual treatment-control comparisons in a simulation study under a wide range of scenarios.

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

References

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