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Abstract

In platform trials.

Platform trials enhance drug development by offering increased flexibility and efficiency as compared to traditional randomized clinical trials. They evaluate the efficacy of multiple treatment arms, with the added benefit of permitting treatment arms to enter and leave the trial over time as new experimental treatments become available. Treatment efficacy is usually assessed using a shared control arm. For arms entering the ongoing trial later, the control data is divided into concurrent and non-concurrent controls. Concurrent controls refer to control patients allocated while the given treatment arm is active in the platform, hence with a strictly positive probability to be randomized to the respective treatment arm. In contrast, non-concurrent controls are trial participants recruited before the given arm joins the platform. Analysis using non-concurrent controls can reduce the required sample size and increase the statistical power, but might also lead to bias in the treatment effect estimates and hypotheses tests, if time trends are present in the trial.

Aiming at utilizing non-concurrent controls for treatment-control comparisons while leading to valid statistical inference, several analysis approaches have been proposed. In particular, a frequentist regression model has been suggested that improves the precision of estimates by using both concurrent and non-concurrent data, while adjusting for potential bias by including the factor "period" as a fixed effect, defining periods as time intervals bounded by any treatment arm entering or leaving the platform. It was shown that this model leads to unbiased treatment 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.

This thesis aims to enhance the frequentist methodology for incorporating non-concurrent controls. We begin by reviewing the current methods proposed in the literature ~~so far~~. Next, we suggest two extensions to the frequentist modelling strategy. First, we introduce an alternative definition of the time covariate by dividing the trial into fixed-length calendar time intervals. Second, we consider more flexible models to adjust for time trends. On one hand, we propose including time as a random effect in mixed models. This allows us to additionally account for dependency between closer time intervals by considering autocorrelated random effects. On the other hand, we employ spline regression to model time with a smooth polynomial function, permitting us to capture potential non-linearities in the underlying time trend function. Finally, we present results from a simulation study, where we evaluate the performance of the proposed approaches in terms of the type I error rate and statistical power under a wide range of scenarios.

We create an R-package, called `NCC`, that implements the considered methods, along with functions for simulating data from ~~flexible~~ platform trials under the presence of time trends. Moreover, the package provides wrapper functions for visualizing the simulated data and efficiently running simulation studies using parallel computing.

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