On the use of non-concurrent controls in platform trials

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Platform trials are multi-arm multi-stage clinical trials that aim at evaluating the efficacy of several treatment arms within a single trial. Experimental treatments are permitted to enter and exit the trial at different times, as new treatments become available, and the total number of newly added treatments is not prespecified. Moreover, the treatment arms may share the control group. While this shared control group offers several benefits, such as reduced sample size and increased statistical power, it may also introduce bias in effect estimators. In particular, the use of non-concurrent control data, i.e., control data from patients that have been recruited before the given treatment arm entered the trial, can be a source of calendar time bias due to possible time trends.

In this work, we assess different methods to adjust for time trends in the comparison of treatment effects of a treatment arm that is added to the ongoing trial compared to a control arm. Especially, we investigated through simulations under which conditions the methods provide valid inference when using non-concurrent controls. Especially, we consider trials with binary and continuous endpoints and linear and stepwise time trends. We investigate regression models where time trends are adjusted using either data from all treatment arms or only data from the new treatment arm and the control group. The performance of these models is evaluated in terms of the type I error rate, statistical power and bias and root mean squared error of the effect estimators of the newly added arm. We show that the validity of inference relies on the assumption that the time trends are equal in all treatment groups on an appropriate scale. We moreover discuss under which circumstances power is increased by incorporating non-concurrent controls.