The resilience of random intercepts and slopes models to violations of the linearity assumption in the treatment group

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Abstract

When planning a clinical trial with a continuous outcome, researchers may know that the trajectory in the control group will be approximately linear. However, they may be less sure of the trajectory in the treatment group. If this is also linear, one possible analysis method is the random intercepts and slopes (RIS) model, which estimates the mean difference in slopes between the treatment and control groups. However, if it is not linear, the assumptions of the RIS do not hold. Other methods which do not assume linearity, such as a mixed model for repeated measures (MMRM) may perform better as they do not assume linearity but estimates the mean difference between groups. We conducted a simulation study to assess the performance of the RIS and other analysis models that relax the linearity assumption in the setting of a linear control-group trajectory and non-linear treatment-group trajectory. We considered a wide range of scenarios, including seven treatment-group trajectories, several between to within-participant variance ratios, and ranging the spacing of follow-up visits.

We found that RIS is relatively robust to small amounts of non-linearity in treatment group trajectories when the between-participant variance is large compared to within-participant, with only small amounts of bias (calculated from the mean difference between groups at final visit) and maintaining statistical power at the expected level. However, in other scenarios we found the RIS had a large amount of bias. We found a two-stage method that first tests for non-linearity before choosing either the RIS or MMRM performs moderately well across a wide range of scenarios. We also present analytic results that support our simulations and consider the implications of these results in the design of clinical trials by applying these methods to real trial data.

Keywords

Random Intercepts and Slopes; Linearity Assumption; Randomised Clinical Trial; Mixed Model with Repeated Measures; Statistical Power

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