Shared parameter models for the analysis of randomized clinical trials whose primary endpoint is a normally distributed longitudinal response

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Introduction: In a randomized clinical trial, it is crucial to adhere to the intent-to-treat principle and handle appropriately missing data. An intercurrent event (ICE) refers to any circumstance that occurs during the study that affects the interpretation and/or observation of the response of interest, such as a participant's decision to discontinue the study medication. Every clinical trial should have a well-defined study estimand, that is, the specific treatment effect that is being estimated. The study estimand can only be well-characterized when all relevant ICEs are identified, and a strategy to handle each of them is pre-specified in the study protocol. It is the responsibility of the study statistician to choose an estimator that properly handles missing data in accordance with the chosen estimand.

Methodology: We examined the performance of shared parameter models (SPM) in analysing normally distributed longitudinal endpoints in the presence of an intercurrent event that needs to be handled with a hypothetical strategy. Using this strategy, we are not interested in using data collected after the ICE as our estimand targets an imaginary world where the ICE has not occurred. With SPM, we modelled the (longitudinal and normally distributed) endpoint of interest together with the time-to-event process associated with the occurrence of the ICE. We compared SPM with the current gold standard methodology in this field, mixed models for repeated measures (MMRM). Using MMRM, the probability distribution of the ICE is ignored as this process is simply considered an underlying generator of missingness. Additionally, we proposed a new methodology to choose between MMRM and SPM by expanding the longitudinal data density (using MMRM) into the likelihood of both longitudinal and time-to-event data by plugging in the likelihood of a survival parametric time-varying covariates model.

Results: The simulation study demonstrated that the SPM approach outperforms MMRM in terms of bias only if the association between the endpoint of interest and the ICE follows the SPM parameterization. However, SPM introduced significant bias when the ICE process depended not only on the random effects but also on the entire last observation (including noise) of the longitudinal response. Additionally, SPM was rather sensitive to the correct specification of the association structure. The simulation experiment also showed that the novel approach proposed to choose between MMRM and SPM accurately selects the optimal tool (MMRM or SPM) with sample sizes typical of phases 2b and 3.

Conclusions: This research has highlighted some limitations associated with the use of SPM for the analysis of longitudinal responses in randomized clinical trials. In particular, we have demonstrated that SPM outperforms standard mixed models only under a narrow set of conditions. However, we have proposed a novel methodology that can accurately select the optimal tool (MMRM or SPM) for a given set of conditions.

Keywords: missing data, estimands, shared parameter models.