Estimating sample size for biomarker-strategy designs with survival endpoints

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Abstract:

Background

In response to the rapid growth of precision medicine and the number of molecules entering the drug development pipeline, several study designs including the biomarker-strategy design (BSD) have been proposed. Contrary to traditional designs, the emphasis here is on the comparison of treatment strategies and not on the treatment molecules as such. Patients are assigned to either a biomarker-based strategy (BBS) arm where biomarker-positive patients receive an experimental treatment or a non-biomarker-based strategy (NBBS) arm where patients receive a treatment regardless of their biomarker status.

Methods

We examined several designs of BSD according to the biomarker assessment and the treatment received in NBBS arm and used frailty survival models to analyse them. Depending on the limits and specificity of each, we proposed statistical models that best described each design. We thus developed a partially clustered frailty model (PCFM) for the (standard) case where the biomarker status is only known in BBS arm. The PCFM allows us to account for the complex structure of BSD that may consider clustering only in one arm. In addition, we proposed an approach to calculate sample size for survival data relying on PCFM. We also proposed statistical tests to measure the overall strategy effect as well as the biomarker-by-strategy interaction effect.

Results

We conducted extensive simulations to assess, for each design, the robustness and performances of the different statistical models. We also performed power analysis and sample size estimation to compare the performance of PCFM to more traditional frailty models, and provided guidelines on the use of BSD in survival analysis.

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Key words: Biomarker-strategy, Sample size, frailty model, heterogeneity, randomized