Biomarker-driven optimal designs for patient enrollment restriction

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Introduction

Medical progress is leading to a transition from traditional practice, based on the belief that treatment effects are homogeneous among all patients, to precision/personalized medicine. In this new context, patients are treated according to their own characteristics, or biomarkers. In the presence of a subpopulation that benefits from a treatment, enrichment designs assume a crucial role. Enrichment refers to the process of selecting specific subgroups for a clinical trial based on subjects' biomarkers. Nevertheless, very often, the effect of biomarkers on treatments is unclear. Thus, adaptive enrichment design methodologies can be applied to identify the most responsive population. While many biomarkers are dichotomous (e.g., male/female, presence/absence), and this clearly simplifies subgroup selection, the situation is complex in the presence of continuous ones (e.g., age, cholesterol). In this setting, standard practice consists of discretizing a continuous biomarker via a pre-determined cutoff/threshold, usually the median. This approach, although widely used, leads to a significant loss of information and may result in severe consequences: e.g. an inappropriate patient recruitment if the threshold is misidentified [1;2]. Despite the progress in biomarker discovery, there is a shortage of studies that estimate the threshold on a continuous scale to accurately distinguish between sensitive (biomarker-positive) and insensitive (biomarker-negative) patients [3].

Objectives

The main goal of this work [4] is to derive the optimal cutoff of a quantitative predictive biomarker, directly on a continuous scale, in binary trials for treatment comparisons. In addition, after the identification of the threshold, we also investigate the ethical impact of discretizing a continuous biomarker through the adoption of a median-based cutoff.

Methods

We take into account a clinical trial where patients are assigned sequentially to one of two competing treatments, T or C. For each subject entering the trial, a quantitative biomarker is observed that is assumed to be a random variable (i.e., the experimenter cannot choose a-priori the biomarker values of the subjects), but it can be measured right before assigning a treatment to a patient. Based on a predetermined randomization rule, patients receive T or C, and their corresponding response is observed.
We determine the optimal design for estimating the biomarker cutoff in order to guide future treatment decisions for individual patients. The treatment-by-covariate approach is used and optimal design theory is applied. More precisely, we minimize appropriate criteria related to the inverse of the Fisher information matrix (i.e. D- and A- optimality), which approximates the variance-covariance matrix of the Maximum Likelihood Estimators. Given that the derived optimal allocation depends on the unknown model parameters and on the patients' biomarker values, we also introduce a novel Covariate-Adjusted Response Adaptive rule to implement the optimum.

Results

Analytical and simulation results show the superiority of our approach in terms of D- and A-efficiency, and variance of the estimated threshold with respect to traditional methods, namely complete randomization and permuted block design. Moreover, our research confirms the strong negative ethical impact arising from the discretization of a continuous biomarker via the median.

Conclusion

Optimal allocations for inference on the threshold of a continuous biomarker for binary trials are provided. Our proposal also ensures that more patients are assigned to the superior treatment based on their biomarker levels, with respect to the median-based approach. It goes without saying that our research aligns with the principles of the International Code of Medical Ethics, which prescribes that every trial partecipant's well-being is always prime. We strongly advise against the discretization of continuous biomarkers and encourage researchers to abandon this practice.

References

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