Statistical design and data monitoring for personalized medicine interventions

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There is currently much interest in pharmacogenetics: determining variation in genes that regulate drug effects, with a particular emphasis on improving drug safety and efficacy. The ability to determine such variation motivates the application of personalized drug therapies that utilize a patient's genetic makeup to determine a safe and effective drug at the correct dose. To ascertain whether a genotype-guided drug therapy improves patient care, a personalized medicine intervention may be evaluated within the framework of a randomized clinical trial. A key consideration in the design of a personalized medicine intervention is an untargeted or targeted design, that is, to include or exclude subjects who are potentially unresponsive to either the drug therapy or the pharmacologic intervention under study. In an untargeted design, statistical power calculations may depend on the distribution of relevant allelic variants in the study population, and whether the pharmacogenetic intervention is equally effective across subpopulations defined by allelic variants. In addition, an untargeted design may employ an alpha allocation approach in which a portion of the overall level of significance is used to test the comparison in the full cohort, and the remaining portion is used to test the comparison in a pre-defined primary subgroup of subjects expected to benefit most from the intervention. We will use the statistical design of an NIH-sponsored trial to introduce and explore these statistical issues. A numerical study will be used to determine whether a sample size modification based on the observed proportion of allelic variants necessitates an increase in the type-1 error rate.

Key words: alpha allocation; pharmacogenetics; randomized controlled trial, targeted design