Statistical inference based on the bootstrap method under covariate adaptive randomization

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Abstract

In randomized clinical trials, if the baseline covariates associated with the outcome are known in advance, it is common to use the covariate adaptive randomization design such as the minimization method (Taves, 1974; Pocock and Simon, 1975) and stratified permuted block design to keep the covariate balance. It is known that when the covariate adaptive randomization is performed, the precision of the effect estimates like the difference of means increases compared to that under complete randomization. However, if we conduct a naive analysis such as the ordinary two sample *t*-test without design consideration, the test becomes overly conservative and the power of the test decreases due to the overestimation of the variance (e.g. Hasegawa and Tango, 2009; Shao, Yu, and Zhong, 2010). For this problem, nonparametric methods such as the permutation test (Simon, 1979) and bootstrap test (Shao, Yu, and Zhong, 2010; Shao and Yu, 2013) have been proposed. However, these methods estimate the distribution of the test statistics under the null hypothesis that there is no difference between groups. Thus, they can only be used for the testing purpose. Therefore, in this research, we propose a new method to estimate the sampling distribution of the test statistics based on the bootstrap with an importance sampling weight. Since the proposed method does not assume the null hypothesis, it is possible to use for the standard error and interval estimation for continuous, discrete, and survival outcomes.

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