ABSTRACT

CAUSAL INFERENCE METHODS FOR RANDOMIZED CONTROLLED TRIALS WITH NONCOMPLIANCE

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It is well established that a randomized controlled trial (RCT) is the gold standard design for medical studies. However, understanding the effect of a treatment based on a clinical trial can be difficult when compliance is not 100%. Even in these circumstances, one of our goals is to estimate the biological effect of the treatment, which we think of as the outcome if a subject takes the treatment versus the outcome if that same subject did not take the treatment. The usual Intent-to-Treat approach does not consider compliance, while the As-Treated and Per-Protocol estimates assume noncompliance is random even when the subjects who comply are different from those who do not. Instead we focus on the Complier Average Causal Effect (CACE) estimand as a more appropriate approach for measuring the biological effect. The first portion of the paper focuses on a two-arm randomized trial with a placebo control. We incorporate principal stratification and instrumental variable assumptions to estimate the CACE. The focus is on demonstrating how CACE estimates can improve measurements of safety since more focus is being placed on properly weighing these risks against the benefits of the treatment. A simulation study and a clinical trial comparing drug therapy following surgery for melanoma versus no additional treatment are used to compare the toxicity estimates.

The second portion of the paper develops a procedure for estimating the CACE in a two-arm randomized trial with an active control. Here we must define parameters that determine the latent relationships among the patients. In cases when the maximum likelihood equations generate infeasible solutions, we develop an Expectation-Maximization algorithm that will maximize the likelihood subject to linear and log-linear constraints. A sensitivity analysis across the possible range of values for the latent parameters is then performed. Data comparing drug therapy with behavioral therapy to placebo with behavioral therapy for alcohol dependence demonstrates this new methodology. In general we believe statistical analyses of RCTs should more consistently measure compliance and estimate the CACE as a supplement to any ITT analyses to better understand efficacy and safety outcomes.