Robust estimation in randomized trials with partial compliance using generalized method of moments applied to g-estimating equations

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Background: Patients in randomized trials may be at best partially compliant to the treatment allocation, by switching the study treatments or by permitting concomitant administration of another standard treatment. G-estimation is a method to estimate the causal parameters in structural nested models (SNMs) with such non-compliance data through estimating equations based on either randomization (i.e., randomized g-estimation) or the “no-unmeasured confounders” assumption (i.e., observational g-estimation). Randomized g-estimation does not rely on the untestable “no-unmeasured confounders” assumption, and since causal-null hypothesis of treatment effect in SNMs is equivalent to intent-to-treat (ITT) null hypothesis, model misspecification does not invalidate the test of null-effect. However, considerable non-compliance to the treatment allocation leads to inefficient estimates with this randomized analysis. Further, the orthogonality condition brought by randomization restricts the number of identifiable parameters to less than the number of treatment arms. Hence for obtaining efficient estimates of richly specified models, analysts may choose observational g-estimation that uses covariates information under the “no-unmeasured confounders” assumption even in randomized trials.

Methods: For compromising these bias-and-variance and model-misspecification-and-unidentifiablity trade-offs between the analyses, we develop the new method to estimate the causal parameters in SNMs in the framework of randomized trials with non-compliance. Specifically, to estimate the causal parameters we simultaneously solve the estimating equations based on randomized g-estimation and those based on observational g-estimation for the same SNMs using the technique of generalized method of moments (GMM; Hansen, L.P. (1982). *Econometrica* **50**, 1029–54). Our GMM overspecifies the models by adding the orthogonality conditions based on randomization to those based on “no-unmeasured confounders” assumption. Simulation studies in cross-sectional settings are conducted; we will also give application of the method to the randomized controlled trials in which a treatment other than study drugs were widely prescribed and in which patients switched the study treatments frequently.

Results: The performance of the proposed GMM estimator is evaluated through simulation studies from the following bias and variance perspectives: sensitivity to “no-unmeasured confounders” assumption; effect of the proportion of non-compliance on the sensitivity above and efficiency in the estimator; sensitivity to misspecification of propensity-score models; and effect of changing weights in the estimating equations of randomized and observational g-estimation.

Conclusion: By incorporating randomization information, our estimators might be robust to the “no-unmeasured confounders” assumption, whereas the assumption retains covariates information that gives efficiency to estimates.

(NOTE: This abstract was originally prepared for the presentation at the ISCB 2013. I will give a presentation at the lab meeting, Shodokukai, in Japanese.)