Bias reduction using auxiliary variables in clinical trial

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Missing data is an awkward problem which can cause a serious bias in statistical inference. In clinical trial, it often happens that the endpoints cannot be measured or are missing, due to the subjects' discontinuation from the study (e.g. dropout). Recently it is becoming more active to apply appropriate statistical methods dealing with missing data as well as several techniques of study design to limit the amount of missing data, following the recommendations by O'Neill and Temple (2012) and National Research Council (NRC) report (2010).

Even when a missing-data mechanism is not missing at random (NMAR), consistent estimators could be obtained if the full-likelihood (Rubin 1976) would be used which involves an appropriate missing-data mechanism in the likelihood. Problems of the approach are difficulty with modeling the missing-data mechanism appropriately and computational difficulty in optimizing the likelihood or even to create identification problems. As a result, the estimation based on the direct-likelihood instead of the full-likelihood is often made. In such cases, it has been suggested that auxiliary variables (Ibrahim et al. 2001, O'Neill and Temple 2012) be added to the model to make up for the lost outcomes to be assessed and to supplement the missing information. In clinical trial, post-treatment information such as surrogate endpoints (Prentice 1989) can be auxiliary variables to be added to the model for the analysis of the clinical (true) endpoint.

The inclusion of auxiliary variables seems to reduce the bias of the direct-likelihood estimator. No theory for the bias reduction has been reported, however. Takagi and Kano (2017) theoretically studied the bias of a direct-likelihood estimator using auxiliary variables and evaluated the possibility to reduce or inflate the bias in the case of several typical correlation structures.

In this talk, we will report some results of applying our theoretical results in Takagi and Kano (2017) to analyze an actual data from a clinical trial in patients with choroidal neovascularization secondary to age-related macular degeneration (Pharmacological Therapy for Macular Degeneration Study Group, 1997).

References

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