Estimations Following Group Sequential Testing in a Clinical Trial with Multivariate Observations

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In many clinical trials in which data accumulate repeatedly over the study period, interim analyses have often been used for many reasons: ethical, scientific, administrative, economic etc.. As group sequential methods make it possible to decide to stop the trials earlier than scheduled, they improve from the conventional fixed sample design when the trials shows early benefits or unexpected toxicity.

With any sequential design the estimation of treatment effect sizes is biased by the choice of stopping rule, so that with early stopping the maximum likelihood estimator overestimates the underlying effect. Many authors have paid attention to the estimation following closed sequential test, and various procedures have also been proposed for constructing confidence intervals following group sequential test. Under the flexible group sequential procedure based on the use function proposed by Lan and DeMets(1983). Most of the estimation procedures work only when the individual measurements are statistically independent. However, this assumption of independence is no longer reasonable when the patients enter the study sequentially and a response variable is measured for each patient at successive follow-up visits. There are many clinical trials in which we are interested in comparing changes in responses between two treatment groups sequentially. Many authors have proposed group sequential methods with repeated measurement data, and Scharfstein, Tsiatis and Robins (1997) have unified many of these methods and showed the general distributional structure for the successive test statistics in both longitudinal and survival clinical trials.

Recently, for the single measurement case, Pinheiro and DeMets(1997) have considered methods for estimating and reducing the bias of treatment difference estimators in groups sequential designs under the Gaussian independent increment structure. Fan(2000-a) proposed a conditional bias adjusting methods to minimize the conditional bias at each possible stopping stage and conditional confidence interval methods were studied which generate confidence intervals with exact coverage probability at any stopping stage as well as in overall(Fan, 2000-b). For the repeated measurements case, Lee and Park(2000) compared the MLE, MUE and the midpoint of 100(1-á)%

exact confidence interval as point estimators for the rates of change based on the linear mixed effects model. Lee, Jo, DeMets and Kim(2001) extended a method by Kim and DeMets(1987) to the repeated measurements case for deriving an exact confidence interval.

In this study, we extend conditional estimation method(Fan, 2000-a) and reducing bias estimation(Pinheiro and DeMets, 1997) to the multivariate measurements case. For the point estimation, we investigate by simulations the properties of the MLE, MUE, and the midpoint estimator (Lee and Park, 2000), the extended bias reducing estimator, and the extended conditional estimator. For the interval estimation, the naive confidence interval, the repeated confidence interval, the unconditional exact confidence interval(Lee, Jo, DeMets and Kim, 2001) and the conditional exact confidence interval (Fan, 2000-b) are also considered by Monte Carlo simulation under various situations.

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RESUME

We compare by simulations both point and interval estimation methods after early stopping of a clinical trial with multivariate observations. For the point estimation, we investigate the properties of the maximum likelihood estimator, median unbiased estimator, and the midpoint of the exact confidence interval, the extended bias reducing estimator and the extended conditional estimator. For the interval estimation, the naive confidence interval, the repeated confidence interval, the unconditional exact confidence interval and the conditional exact confidence interval are considered under various situations.