

ADAPTIVE DESIGN AND STATISTICAL INFERENCE IN CLINICAL TRIALS

For the last decade, the drug development is becoming increasingly expensive, and has a high clinical failure rate. Pharmaceutical companies try to overcome these difficulties in various ways: one is adaptive design of clinical studies. Adaptive design allows us to modify the study design based on the interim results of the ongoing study by predefined decision rules. There are many types of adaptive design: e.g., discontinuing treatment arms, seamless phase 2/3 design, and sample size re-estimation. It is a kind of traditional adaptive design to perform interim analyses for an early termination of clinical trials due to overwhelming drug effects or the futility of trials.

Any adaptive design needs interim analyses. The time of conducting an interim analysis affects the probability of the early termination and the number of subjects enrolled until the interim analysis. We examine the optimal time for conducting interim analyses with a view to minimizing the expected total sample size. We also consider the time for one interim analysis including the sample size adjustment in terms of minimizing the expected total sample size.

Among many types of adaptive design, sample size re-estimation has attracted the attention of many investigators, since it is common that uncertainties remain in the critical assumptions about the effect size and extent of data variation in the planning stage. We address the methodology of sample size re-estimation for survival data which is still in developing phase, and propose an interim hazard ratio estimate that can be used to re-estimate the sample size under those circumstances.

When the sample size re-estimation is implemented, the upper limit of the sample size should be set because huge clinical trials are infeasible and expose many people to study drugs which have perhaps no efficacy benefit. It is recommended to set the upper limit of the sample size based on the clinical importance (Shih, 2001; Hung *et al.*, 2006). We state the roles of minimal clinically important effect in each phase of new drug development and make systematic approaches to establishing that.

We also deal with statistical testing and sample size for a special distribution. Although adaptive design is a hot topic for efficient drug development, it is more essential to choose a statistical method appropriate to the distribution. Our study considers zero-inflated count data as a special distribution because count data with excess zeros are frequently observed. When a test drug is compared to a control, zero-inflated data may be ignored or interest is taken only in the proportion of zero counts. Two-part statistic (Lachenbruch, 2001) can combine the test statistics of the zero part and the non-zero part. We propose methods for calculating the sample size and power for the two-part statistic with zero-inflated Poisson data. Furthermore, we examine the power of the two-part statistic, conventional methods, and the zero-inflated Poisson model.