Sample size re-estimation in Adaptive Trials

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Introduction:

Adaptive designs in clinical trials are becoming more popular in many areas of medical research, because drug development in a clinical trial is more expensive and time consuming process. The use of adaptive design makes possible to reduce the costs and time to the market and such type of design increases the success of the trial. Adaptive design is a design that allows modifications to trials and/or statistical procedures of the clinical trial after its initiation without undermining the validity and integrity of the trial\(^1\). The major difference between the conventional design and adaptive design is that the adaptive design uses accumulating results. Sometimes, multiple adaptations may lead to totally different clinical trial design with more efficient features. However, sometimes, it may also lead to an inefficient clinical trial design due to frequent changes. All adaptations should be planned before starting the study and it should be acceptable for regulatory authorities. The plan for adaptive design must be documented in study protocol. The objective of this paper is to provide an idea about sample size re-estimation in Adaptive design in blinded clinical trials.

Sample Size Re-estimation:

Sample size re-estimation is a type of adaptive design which allows for sample size adjustment or re-estimation based on the observed data at interim analyses. In clinical trial, a sufficient number of subjects are required to achieve some pre-specified power to detect a clinically significant difference if such a difference truly exists. Often the choice of such difference is not straight forward. Generally, the number of subjects to be enrolled into the trial is decided based on the knowledge available at the time of planning the trial. However, there may be an uncertainty about the knowledge such as effect size between two treatment groups and variability of the primary end point. In that situation adaptive design allows us to re-estimate the sample size during the trial period as it progresses.

The requirements for the sample size re-estimation are treatment effect size and its variability as mentioned above. An inaccurate estimation of the effect size and its variability could lead to a study with less statistical power or more statistical power. In case of less statistical power, the sample size requirement is less which may fail to detect a real difference between two treatment groups. On the other hand, a study with high statistical power, the sample size requirement is more which may detect even a small statistically significant difference between two treatment groups that may not be clinically significant. In this situation, the study could lead to unnecessary exposure of many patients to a potentially harmful compound when the drug is, in fact, not effective. Thus, the researcher should design the study in such a way that the statistical power is optimum and meaningful. However, an adaptive design allows re-estimating the sample size based on estimates derived from interim data from a blinded clinical trial.

Blinded sample size re-estimation uses the interim data without breaking the randomization codes at the time of interim analysis to update the sample size of the trial. This method is useful when there is uncertainty in the variability of primary endpoint. However, it is a concern that the actual patient population after the adaptations could deviate from the originally target patient population and consequently the overall type I error rate may not be controlled. Using blinded data we can reduce the significance level (\(\alpha\) inflation. However, a blinded sample size re-estimation does not require adjustment of alpha. Generally, this approach would be used to determine whether a sample size is acceptable as originally planned or needs to be increased based on the interim results.

Consider a randomized parallel group design to compare the test treatment and the control group. Then, the required number of subjects in each group for achieving the pre-specified power (1-\(\beta\)) to detect the clinically meaningful difference (\(\Delta\)) is given by
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\[ n = \frac{2(Z_\alpha + Z_\beta)^2 \sigma^2}{\Delta^2} \]

Where \( \alpha \) is the level of significance and \( \sigma^2 \) is the expected pooled variance. During interim analysis, if the variance of the primary endpoint became larger than the initial variability, we need to re-estimate the sample size without breaking the randomization codes\(^1\). Suppose the observed variance at interim data is \( \sigma'^2 \), then the re-estimated sample size to achieve the desired power \( 1-\beta \) is

\[ N' = N \frac{\sigma'^2}{\sigma^2} \]

Where, \( N \) = planned sample size calculated based on \( \sigma^2 \) and \( N' \) is the re-estimated sample size. The above exercise could be repeated after each interim analysis as per the protocol.

**Conclusion and Recommendation**

In practice, it is often difficult to estimate the effect size and variability because of many uncertainties during protocol development. Thus, it is desirable to have the flexibility to adjust the sample-size in the middle of the trial. This will help the sponsor / Clinical Research Organization (CRO) to reduce cost and faster completion of the trial. This will also help the Pharma Company to bring the new product to the market at the earliest. Finally the targeted patient population will be benefited with the new drug much earlier than from a conventional clinical trial. Hence the authors recommend that the sample size re-estimation adaptive design may be used wherever it is feasible in clinical trial.

References: