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Sample Size Reassessment for Continuous Data in Clinical Trials

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1 Introduction

When planning a clinical trial, investigators can specify a meaningful effect that they wish to detect with a high power with greater certainty than they can specify certain parameters, as the variance, necessary for the the sample size calculation. Most of the time, this variability is guessed or comes from previous studies that may involve different patients or may be conducted in different conditions. In both cases the assessment of the variance of the outcome variable has great chance to be imprecise. However, misspecification of the variance can have substantial impact on the power of the newly planned trial.
Underestimating the true variance means that the sample size will be too small and then the trial will not reach the intended power for detecting the required treatment effect, leading to the risk of an inconclusive trial. Furthermore, an inconclusive trial is a waste of time and money, and exposes patients to unnecessary risk.
On the other hand, overestimating the true variance means that too many patients will be enrolled in the study which will take more time than necessary and will also lead to excessive cost. Moreover, the power will be higher than required.
These ethical and economic reasons motivate the introduction of the concept of sample size reassessment.

The reason for undertaking sample size re-estimation is to preserve the power of a trial to detect a specified alternative hypothesis without compromising the type I error. In this way, interim data may be used to see if the trial has accumulated sufficient information upon completion to provide adequate power for detecting the required treatment effect. In practice, if the variance from the accumulated observations at an interim stage is not too different from the value used at the protocol development stage to compute the sample size, then the trial can go on to completion without any change to the sample size. Otherwise, the sample size could be adjusted to assure that the trial will be sensitive enough to provide definitive conclusions.

However sample size reassessment methods aiming at adjusting the sample size of ongoing trials are not substitute methods for careful planning of trial. The trial's design should always reflect the best available knowledge of the variability. In addition, expanding an ongoing trial introduces a substantial number of potential administrative problems. Investigators/patients entering into the study at a later stage are not necessary the same as those entered early. Moreover, reactivating the machinery to select more investigators and/or enter more patients may be fairly complicated and expensive. For the same reason, in general, it is not advisable to consider more than one interim sample size adjustment during the trial.

In the literature, numerous methods for sample size reassessment have been described [1] [14], blinded as well as unblinded methods, some of these based on conditional power, on fully sequential or on quasi-sequential procedures,etc...

Blinded sample size reassessment procedures rely on re-estimates of the within-group variability of the outcome variables based on interim data without revealing the treatment identity. For unblinded sample size reassessment procedures, the treatment code needs to be broken.

This report will mainly describe blinded sample size reassessment methods for continuous data. The reasons for focusing on blinded techniques are that treatment assignments don't have to be necessary unblinded to apply reassessment method and secondly that "blindning" is the key to the scientific validity of trial. Indeed, keeping the treatments' identity blinded will limit the occurrence of conscious and unconscious bias during the conduct of the clinical trial. Unblinding of treatments' identity may influence the further recruitment of patients, patients'care, the data collection process, the data analysis process,etc...

In this report several methods for sample size adjustment during the course of the trial are presented. Before getting to the heart of the matter, it could be useful to understand the concept of a pilot study. Two kinds of pilot studies are presented in the next section.
As normally distributed outcome variables are frequently used in clinical trials, sample size reassessment procedures for normally distributed outcome variables restricted to the case of a two-sided superiority trial will be presented in section 3.
These procedures then will be extended to the case of equivalence and non-inferiority.

The first method described in section 3 is the Wittes and Brittain procedure [6] [11] [12]. It is an unblinded sample size reassessment procedure which necessitates the establishment of an Independent Data Monitoring Committee (IDMC) in order to avoid conscious and unconscious bias during the trial.
The second procedure for sample size re-estimation is a blinded one, the Gould and Shih method [2] [3] [24]. They propose two different methods for blinded variance estimation for the case of normally distributed outcome variables. An adjusted version of the one-sample variance estimator is first presented, but as mentioned by Zucker, [16] [25], the Gould and Shih method doesn't take into account the discrepancy between the clinically minimum difference and the true treatment difference. Hence, a refined version of this simple adjustment variance estimate is described as well as its effect on the type I error and power. Before going to the second method, the influence of a possible bias in the refined version proposed by Zucker [16] on the

sample size re-estimation is studied.
The second method proposed by Gould and Shih uses the EM algorithm to provide an estimate of the within-group variance. Impact on the type I error and the power, will be discussed [18]. Finally, some serious deficits observed for the EM algorithm, will be exposed using SAS macro's [23] [24], which are displayed in appendix 2.
In section 4, after having introduced the notion of non-inferiority and equivalence trial, the Wittes and Brittain, and Gould and Shih procedures are extended to non-inferiority/equivalence trials with normally distributed outcome variables and research hypotheses phrased in terms of differences of means.