SAMPLE SIZE RE-ESTIMATION FOR ADAPTIVE SEQUENTIAL DESIGN IN CLINICAL TRIALS

Short title: Sample size re-estimation

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ABSTRACT
There is considerable interest in methods that use accumulated data to modify trial sample size. However, sample size re-estimation in group sequential designs has been controversial. We describe a method for sample size re-estimation at the penultimate stage of a group sequential design that achieves specified power against an alternative hypothesis corresponding to the current point estimate of the treatment effect.

Key words: adaptive design; sequential design; conditional power; sample size reestimation; Brownian motion; Markov process; transition function

1. INTRODUCTION
When designing clinical trials, investigators often estimate the sample size from limited information about the variance of the response and the size of the treatment effect. The reliability of sample size estimation can be limited by several factors: the prior information may have been derived from small trials that do not provide robust estimates of the treatment effect and its variance; changes in medical practice may alter the treatment effect; the patient population in the current trial may differ from that in earlier trials; or the effect size estimate may have been derived from clinical trials of other drugs in the same class as the test drug. In such circumstances, it would be desirable to have the ability to modify the sample size during the course of the study to achieve desired power against an alternative hypothesis derived from the accumulating data. Different approaches have been proposed in the literature (e.g., Proschan and Hunsberger, 1995; Fisher, 1998; Cui et al., 1999; Jennison and Turnbull, 2003; and Liu et al., 2008). Mu□ller and Schäfer describe a general method for modifying sequential designs based on the principle of preservation of conditional rejection probabilities (Mu□ller and Schäfer, 2001, 2004). Their approach is both general and flexible. However, in the typical situation, it requires further specification of the revised sequential design and numerical integration to determine the stopping boundaries.

In some special situations, including two-stage adaptive designs (Fisher, 1998) and sequential analysis (Cui et al., 1999), methods for sample size re-estimation with closed form solutions have been described. These methods have, however, been controversial. In particular, the method proposed by Cui et al. (1999) has been understood to require "down3 weighting" of the data acquired after the sample size re-estimation, thus raising concerns about both the appropriateness and the efficiency of the method (Fleming, 2006).

In this paper, we employ the properties of Brownian motion to derive a method of sample size re-estimation at the penultimate analysis in a group-sequential design. We show that

the proposed adaptive design is a conventional group-sequential design with the feature that the timing of the last analysis is determined stochastically. The method is thus similar in spirit to the methods proposed by Lan and DeMets (1983) for modifying the timing of interim analyses. The proposed method is shown to be an extension of the variance spending function proposed by Fisher (1998) to the group-sequential setting. The method preserves the conditional type I error, thus conforming to the general principle described by Mu□ller and Schäfer (2001, 2004). We show that, in the special case with only one interim analysis, the proposed method is a two-stage adaptive design of the type described by Proschan and Hunsberger (1995), with a "linear error function". We also show that the method is equivalent to the method proposed by Cui et al. (1999), and that both are special cases of the method of Mu□ller and Schäfer (2001, 2004). There have been debates about whether the "down-weighting" in Cui et al. is ethical or efficient (e.g. Jennison and Turnbull, 2003). The equivalence of the three methods demonstrates that the sample size re-estimation method of Cui et al. is valid and does not truly down-weight any portion of the data.

2. A GROUP-SEQUENTIAL DESIGN WITH SAMPLE SIZE ADJUSTMENT

3. ADJUSTING THE FINAL CRITICAL VALUE AFTER SAMPLE SIZE ADJUSTMENT

4. CONDITIONAL POWER UNDER THE ALTERNATIVE HYPOTHESIS

5. COMPARISON WITH FISHER (1998) AND CUI ET AL. (1999)

6. TIMING OF SAMPLE SIZE MODIFICATION

7. COMPARISON WITH PROSCHAN AND HUNSBERGER (1995)

8. EXAMPLE

9. A SIMULATION EXPERIMENT

10. BEHAVIOR OF C'_K AS A FUNCTION OF STATISTICS AT LOOK K-1

11. DISCUSSION

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