SAMPLE SIZE DETERMINATION FOR GROUP SEQUENTIAL CLINICAL TRIALS WITH IMMEDIATE RESPONSE

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SUMMARY

The use function approach to group sequential methods has been explored previously.\textsuperscript{1,2} Any group sequential design requires specifying the frequency and times of repeated analyses, but only the use function approach allows deviations from those specified in the design, without affecting the type I error in the analysis. This article illustrates how the use function provides a simple and flexible design procedure and how the initially projected maximum sample size can be calculated for randomized clinical trials in which responses are known relatively soon after patient entry and for which there is an early stopping rule built into the study protocol. Also the consequence of using the proposed design procedure is investigated in terms of the operating characteristics of the subsequent group sequential analyses.

\textbf{KEY WORDS}  Group sequential method  Information time  Interim analysis  Statistical information  Use function
1 Introduction

For ethical and economic reasons, clinical trials may be terminated prematurely when strong evidence emerges that one treatment is clearly superior to the other or that treatments are equally ineffective. Group sequential methods are known to be practical and suitable for monitoring accumulating data, while preserving the type I error probability at a desired significance level despite repeated application of significance tests. These methods are particularly useful for guiding early termination of a study when there is a significant treatment difference.

There are three types of large-scale randomized clinical trials where accumulating data are analyzed periodically. In one type, the patient’s response to treatment is available relatively soon after entry, and data may be analyzed in sequential groups of patients. In another type of clinical trial, one follows patients to the time of a certain event, such as death, treatment failure, or relapse from remission, and data are analyzed in sequential groups of such events. In a third type of clinical trial, one measures the patient’s outcome repeatedly over time.

For monitoring clinical trials with relatively immediate outcome data, group sequential designs with predetermined boundaries can be used. While these designs are relatively straightforward to implement, the amount of accumulating data, referred to as the statistical information, has to be identical between repeated analyses, and the frequency of such analyses has to remain fixed as prespecified. However, in many clinical trials, interim analyses are conducted at times dictated by the scheduling of data monitoring committee meetings, and thus the requirement of equal increments of statistical information is often not feasible. As an alternative, Lan and DeMets proposed a flexible group sequential method based on the use function approach. It generalizes the previous methods and does not require equal amounts of statistical information between repeated analyses, a prespecified number of repeated analyses, or that the frequency of repeated analyses remain fixed.

In this article, we illustrate how to design a clinical trial when a particular use function is
proposed for data monitoring and investigate the consequence of the use function approach in terms of the operating characteristics. A brief summary of the use function approach to group sequential design is provided in Section 3 and may be skipped if the reader is familiar with the method. Examples for continuous and binary outcome data are provided.

2 Summary of the Design Procedure

For a fixed sample size design, a null and an alternative hypothesis are specified as well as the desired type I and type II error probabilities. Given the distribution of a test statistic, a value of the parameter of interest under the alternative hypothesis is specified, and from this the necessary sample size can be computed. In addition, for the group sequential design, the number of equally spaced interim analyses must also be specified. Pocock\(^2\) and O'Brien and Fleming\(^4\) provide details for the design of group sequential studies.

As already indicated, Lan and DeMets\(^1\) do not require that the exact times of repeated analyses nor the number of such analyses be specified in advance. However, in order to determine the operating characteristics of the subsequent analysis, some approximate times must be specified in advance, recognizing that these times may not be strictly adhered to in the actual analyses. To do this, we have two choices. We can specify equally spaced information times and, using the methods described by Kim and DeMets\(^2\), determine the value of the drift parameter corresponding to the specified use function. Alternatively, for Pocock or O'Brien-Fleming-type use functions, we can specify equal intervals of time and use directly the published values of the parameter in those articles. Thus, for design, the use function approach to group sequential monitoring requires some specification of the interim analyses in advance. The flexibility is gained in the actual analysis, not in the design.

The major issue in this article is to evaluate the impact on operating characteristics if the analyses do not follow the prespecified information times exactly. That is, how discrepant in time or in frequency can the real interim analyses be from those assumed in the design without adversely affecting the desired power of the trial? As seen in earlier work by Lan
and DeMets\textsuperscript{5} and DeMets and Gail\textsuperscript{6} and from further evaluation here, moderate changes in the planned interim analyses have negligible impact on the power. Thus, the approach to design group sequential studies based on the use function is to 1) prespecified equally spaced anticipated analysis times, 2) determine the value of the drift parameter, or use those provided here and in other articles, and 3) compute the projected maximum sample size of the trial. The following example illustrates the steps involved in determining sample size in group sequential clinical trials. The details of this example will be discussed later.

Recently the drug, tamoxifen, was evaluated at the University of Wisconsin-Madison as a potential chemoprevention agent in women with early stage breast cancer and compared with a placebo in a double blind clinical trial.\textsuperscript{7} In addition to evaluating the recurrence of cancer, this study measured the effect the drug might have on the lipid cholesterol level. If the level were decreased, a reduction in cardiovascular risk would be induced. If the cholesterol level were increased, the drug might be increasing the risk of heart disease and thus diminish the potential benefit. For women eligible for this study, the mean cholesterol level on the placebo was expected to be 220 mg/dl with a standard deviation of 30 mg/dl. A clinically significant change induced by the drug was thought to be a 20 mg/dl decrease or increase in mean cholesterol level.

Suppose we wish to design this trial, using a 5\% significance level for a two-sided test of hypothesis with 90\% power to distinguish between mean cholesterol levels of 220 mg/dl vs. 200 mg/dl or 240 mg/dl. Assuming that the measurement of cholesterol level is normally distributed, the standardized difference in mean cholesterol level is \( \frac{20}{30 \sqrt{2}} = 0.471 \). If we specify five equally spaced repeated analyses, then the drift parameter is 3.281 (see Table 1) for a design based on the O’Brien-Fleming-type use function. This value is calculated by recursive numerical integration. The maximum sample size per treatment is calculated as \( (3.281/0.471)^2 = 48.5 \).
3 The Use Function and Group Sequential Designs

For a group sequential clinical trial, let the value of the information time \( t \) correspond to the proportion of total statistical information anticipated by the end of the trial. We specify a use function \( \alpha^*(t) \) that is a non-decreasing function in \( t \) with \( \alpha^*(0) = 0 \) and \( \alpha^*(1) = \alpha \), the significance level. This function allocates the amount of type I error probability that one can "use" or "spend" at each analysis. In other words, a use function specifies how the overall type I error probability is spent as a function of the amount of accumulating statistical information.

More specifically, for a one-sided test of hypothesis, a use function is defined by

\[
\alpha^*(t) = \Pr(\tau \leq t) \text{ for } 0 < t \leq 1
\]

where \( \tau \) is the first time a standard Brownian motion process \( W_t \) crosses a specified boundary \( b_t \) that guarantees a type I error probability of \( \alpha \). The recursive numerical integration procedure for the partial sum of normal random variables by Armitage, McPherson and Rowe\(^8\) can be easily modified for the standard Brownian motion process to determine group sequential boundaries. Use functions that approximate the group sequential procedures of O'Brien and Fleming\(^4\) and of Pocock\(^3\) have been specified as

\[
\alpha_1^*(t) = 2\{1 - \Phi(z_{1-\alpha/2}/\sqrt{t})\}
\]

and

\[
\alpha_2^*(t) = \alpha \log\{1 + (e - 1)t\},
\]

respectively, where \( z_\gamma \) is the \( \gamma \) quantile of the standard normal distribution.\(^1\)

Rather than requiring equal increments of statistical information or a prespecified frequency of repeated analyses, the use function approach requires specifying a use function, \( \alpha^*(t) \). Once it is specified, we may monitor accumulating data after equal increments of calendar
time, after equal increments of statistical information, or even sporadically. The operating characteristics and early stopping properties of group sequential tests are not very different whether you analyze the data five times, 10 times, or more often. For this reason the use function approach is especially flexible and well-suited for planning group sequential designs and analyses in clinical trials.

For design considerations, let $X_1, X_2, \ldots$ denote a sequence of independent and identically distributed normal random variables with unknown mean $\zeta$ and unit variance, and let $S_k = X_1 + \cdots + X_k$. Consider a group sequential test of $H_0 : \zeta = 0$ using a group sequential boundary generated by a use function. In randomized clinical trials, each $X_i$ can be thought of as a measure of treatment difference. Then $S_{nk} \sim N(n_k \zeta, n_k)$ where $n_k$ is the accumulated sample size by the $k$th repeated analysis. A group sequential procedure for the partial sum $S_{nk}$ based on a use function is equivalent to a discrete boundary-crossing problem for a Brownian motion process $W_t$ with drift parameter $\xi$, that is, $W_{t_k} \sim N(t_k \xi, t_k)$, where $t_k$ is the information time of the $k$th repeated analysis.

Let $n_K$ be the projected maximum sample size to be achieved at the last ($K$th) repeated analysis. If the value of the standardized test statistic is $z_c$, the maximum likelihood estimators of the mean and the drift parameter are $\hat{\zeta} = z_c/\sqrt{n_k}$ and $\hat{\xi} = z_c/\sqrt{t_k}$, respectively, so that $\hat{\xi}/\hat{\zeta} = \sqrt{n_k/t_k}$. Then, the maximum sample size $n_K$ becomes

$$n_K = \left(\frac{\hat{\xi}}{\hat{\zeta}}\right)^2,$$

under the assumption that $n_k/t_k \equiv n_K$, which simply implies that the information time $t_k$ of the $k$th repeated analysis is proportional to the accumulated sample size $n_k$. It should be noted that the magnitude of the drift parameter depends implicitly on the magnitude of the treatment difference, the number of repeated analyses, the amount of information at each repeated analysis, as well as the use function. For a fixed sample size design with a level $\alpha$ one-sided test of hypothesis and power $1 - \beta$, the drift parameter is simply
\[ \xi = z_{1-\alpha} + z_{1-\beta}. \]

Given \( \zeta, K, n_K, \) and \( \alpha, \) one can apply recursive numerical integration similar to McPherson and Armitage\(^9\) to compute the attainable power \( 1 - \beta, \) i.e.,

\[ 1 - \beta = pr_\xi(\tau \leq 1). \]

During the design, it is often more useful to know the value of the drift parameter corresponding to particular \( \alpha, K, \zeta, \) and \( \beta. \) Thus, given any group sequential boundary, one can determine by a search method the drift parameter of the equivalent Brownian motion process which would attain a desired power by solving the above formula for \( \xi. \) In order to determine the value of the drift parameter, we need to specify anticipated information times in advance, just as in other group sequential procedures. Unless indicated otherwise, equally spaced information times may be satisfactory for the purposes of design. The values of the parameter \( \xi \) for \( \alpha = 0.05, 0.025, 0.01, 0.005, K = 1, 2, 3, 4, 5, \) and \( 1 - \beta = 0.75, 0.8, 0.85, 0.9, 0.95 \) are given in Tables 1 and 2 for one-sided tests of hypothesis using the O'Brien-Fleming-type use function \( \alpha_1^*(t) \) and the Pocock-type use function \( \alpha_2^*(t) \), respectively, with equal increments of information time. For two-sided level \( \alpha \) tests, one can use the values of the drift parameter \( \xi \) corresponding to the one-sided level \( \alpha/2 \) tests.

4 Designs for Immediate Outcome Data

Whether the response to treatment is normal or binary, the difference in treatment effect can be expressed as a standardized difference of means or of probabilities. For a specified magnitude of the anticipated treatment difference, the maximum sample size \( n_K \) per treatment can be determined numerically. The results for normal and binary outcome data are first summarized in this section. We then show how to implement the proposed procedure for
determining the maximum sample size of group sequential clinical trials. We use two recent clinical trials for illustration. We consider designing new trials, using the same response variables and similar assumptions about the levels of response, variability, significance level, and power as in those two clinical trials.

4.1 Normal Data

Suppose that the treatment responses are normally distributed with means, $\mu_e$ and $\mu_c$, for the experimental and the control treatments, respectively, and with common variance $\sigma^2$; that is, $Y_{1e}, Y_{2e}, \ldots$ and $Y_{1c}, Y_{2c}, \ldots$ are independently and identically distributed as $N(\mu_e, \sigma^2)$ and $N(\mu_c, \sigma^2)$, respectively. Then, at the $k$th analysis, the test statistic

$$S_{n_k} = \frac{\sum_{i=1}^{n_k} Y_{ie} - \sum_{i=1}^{n_k} Y_{ic}}{\sigma \sqrt{2}} \sim N(n_k \zeta, n_k)$$

where $\zeta = (\mu_e - \mu_c)/(\sigma \sqrt{2})$ is a standardized difference of means. Therefore, using the result in Section 3, the maximum sample size per treatment necessary to detect $\delta_\mu = \mu_e - \mu_c$ with power $1 - \beta$ is

$$n_K = \frac{2\sigma^2 \zeta^2}{\delta_\mu^2}.$$ 

When $K = 1$, that is, for a fixed sample size design, this formula becomes the familiar sample size formula for normal data,

$$n_K = \frac{2\sigma^2(z_{1-\alpha} + z_{1-\beta})^2}{\delta_\mu^2}.$$ 

For a group sequential procedure by Pocock$^3$ for which the frequency of repeated analyses is fixed at $K$ and the number of observations per treatment between repeated analyses is equal to $m$, the power of detecting the difference $\delta_\mu = \mu_e - \mu_c$ is a function of $\Delta = (\delta_\mu \sqrt{m})/(\sigma \sqrt{2})$, the values of which are given in Table 2 of Pocock$^3$ for various values of $\alpha$, $1 - \beta$, and $K$. 

9
Since the number of observations per treatment between repeated analyses can be expressed as \(2(\Delta \sigma / \delta_\mu)^2 = (\Delta / \zeta)^2\) and since \(n_K = mK\), the drift parameter of the Brownian motion process corresponding to a Pocock group sequential boundary is related to \(\Delta\) by

\[\xi = \Delta \sqrt{K}.\]

Again it should be noted that the magnitude of the drift parameter depends on the magnitude of the treatment difference, the number of repeated analyses, and the amount of information at each repeated analysis.

### 4.1.1 Example 1: A Cancer Chemoprevention Trial

We described a recent clinical trial to evaluate the potential chemoprevention agent, tamoxifen, in women with early stage breast cancer and showed how to determine the maximum sample size per treatment in Section 2. The details of that sample size determination are given below.

Suppose we wish to design this trial, using a 5% significance level two-sided test with 90% power to distinguish between cholesterol levels of 220 mg/dl vs. 200 mg/dl or 240 mg/dl. Then \(\mu_c = 220\), \(\mu_e = 220 \pm 20\), and \(\delta_\mu = 20\) with size \(\alpha = 0.05\) and power \(1 - \beta = 0.90\). Also assume that the measurement on the cholesterol level is normally distributed with a common standard deviation \(\sigma = 30\). Using recursive numerical integration, the drift parameter is \(\xi = 3.281\) (see Table 1) for a design based on the O'Brien-Fleming-type use function, \(\alpha_1^*(t) = 2\{1 - \Phi(z_{1-\alpha/2}/\sqrt{t})\}\), with equal increments between five repeated analyses, \(K = 5\). Since \(\zeta = 20/(30\sqrt{2}) = 0.471\), the maximum sample size per treatment becomes \(n_K = (3.281/0.471)^2 = 48.5\). The corresponding fixed sample size is \((z_{0.975} + z_{0.9})/\zeta)^2 = (3.242/0.471)^2 = 47.4\).
4.2 Binary Data

The design procedure for binary outcome data follows the same argument as above except that the normal distribution for the partial sum is only approximate. Suppose that the responses to treatments have Bernoulli distributions with probabilities of success, \( p_e \) and \( p_c \), for the experimental and the control treatments, respectively; that is, \( Y_{1e}, Y_{2e}, \ldots \) and \( Y_{1c}, Y_{2c}, \ldots \) are independently and identically distributed as \( B(1, p_e) \) and \( B(1, p_c) \). Then, the summary statistic at the \( k \)th analysis

\[
S_{n_k} = \frac{\sum_{i=1}^{n_k} Y_{ie} - \sum_{i=1}^{n_k} Y_{ic}}{p_e(1 - p_e) + p_c(1 - p_c)} \sim N(n_k \zeta, n_k)
\]

asymptotically, where \( \zeta = (p_e - p_c)/\sqrt{p_e(1 - p_e) + p_c(1 - p_c)} \) is a standardized difference of probabilities of success. Therefore, the maximum sample size necessary to detect \( \delta_p = p_e - p_c \) with power \( 1 - \beta \) is

\[
n_K = \frac{\{p_e(1 - p_e) + p_c(1 - p_c)\} \zeta^2}{\delta_p^2}
\]

per treatment for testing \( H_0 : p_e = p_c \) at a significance level \( \alpha \). Again, for a fixed sample size design, the sample size is

\[
n_K = \frac{\{p_e(1 - p_e) + p_c(1 - p_c)\}(z_{1-\alpha} + z_{1-\beta})^2}{\delta_p^2},
\]

a familiar sample size formula for binary data.

4.2.1 Example 2: A Thrombolytic Intervention Trial

In recent years, cardiologists have been studying a class of agents which rapidly break down fresh blood clots in heart vessels that are blocking or restricting blood flow. This blockage can lead to heart attacks and muscle damage. Reperfusing or reopening these vessels is
believed to be effective in reducing the severity of heart attacks. The recent Thrombolytic Intervention in Myocardial Infarction (TIMI) Trial\(^{10}\) studied the ability of two such agents to reperfuse closed coronary vessels. With the standard agent, 40% of the patients had their vessels reperfused. With the new agent, 60% were expected to have vessels reperfused.

For this trial, we can specify \(p_c = 0.4\), \(p_s = 0.6\), and \(\delta_p = 0.2\) so that \(\zeta = (0.6 - 0.4)/2(0.4)(0.6) = 0.289\). Suppose we were to design the trial with \(K = 5\), using a 5% level one-sided test with 90% power based on the Pocock-type use function,\(^1\) \(\alpha^*_s(t) = \alpha \log\{1 + (\epsilon - 1)t\}\). Then, by recursive numerical integration, the drift parameter of the Brownian motion process becomes \(\xi = 3.211\) (see Table 2), and \(n_K = (3.211/0.289)^2 = 123.4\) is the maximum sample size per treatment. The corresponding fixed sample size is \((2.926/0.289)^2 = 102.5\).

5 Operating Characteristics

While the proposed design procedure is useful, a number of practical issues need to be resolved. First, for many clinical trials, repeated analyses are conducted at fixed intervals of calendar time corresponding to meetings of the data monitoring committee. Therefore the numbers of patients between repeated analyses will not be exactly the same. Secondly, there will be often changes in the frequency of repeated analyses. In this section, the consequence of using the design procedure proposed in this paper is investigated in terms of the operating characteristics of the subsequent group sequential analyses. The operating characteristics can be studied quite simply by exact probability computations similar to Armitage, McPherson and Rowe\(^8\) and McPherson and Armitage.\(^9\)

In Example 1, if the maximum sample size is \(2(50) = 100\) so that the drift parameter \(\xi = \zeta \sqrt{n_K} = 0.471 \sqrt{50} = 3.330\), the group sequential analysis based on the O'Brien-Fleming-type use function at the information time \(\{0.2, 0.4, 0.6, 0.8, 1.0\}\) would attain power of 0.909. Suppose, instead, that the sample sizes at five repeated analyses are \(\{10, 20, 30, 60, 100\}\) and \(\{30, 60, 80, 90, 100\}\), so that the the actual information times are \(\{0.1, 0.2, 0.3, 0.6, 1.0\}\) and \(\{0.3, 0.6, 0.8, 0.9, 1.0\}\), respectively. Then the group sequential analysis based on the use
function approach will achieve power of 0.913 and 0.906 for detecting $\delta = 20$, respectively, while still maintaining the type I error probability at 0.05. If the predetermined O'Brien-Fleming group sequential boundaries are used for the analysis without adjustment for the change in the information time, however, the chances of detecting the specified difference become 0.910 and 0.906 with type I error probabilities of 0.0576 and 0.0458, respectively.

Suppose, in Example 2, that the patient accrual is expected to be 100 per year. Assume that the monitoring committee is scheduled to meet every 6 months for five times so that the maximum sample size is 250, instead of $2(124) = 248$. If the number of patients at the time of interim and final analyses is $\{50, 100, 150, 200, 250\}$, then the information time is $\{0.2, 0.4, 0.6, 0.8, 1.0\}$ and the group sequential test would attain power of 0.903.

If the accrual rate turns out to be 50 instead of 100, the actual information time will be $\{0.1, 0.2, 0.3, 0.4, 0.5\}$ at the scheduled repeated analyses. If the committee decides to continue accruing patients until the maximum sample size of 250 is obtained, the frequency of repeated analyses needs to be increased to 10 and, consequently, the study duration also increases from 2.5 years to 5 years. Under this situation, the use function approach to group sequential analysis at the information time $\{0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0\}$ will have power of 0.896 with type I error probability of 0.05. However, if one proceeds with the predetermined Pocock group sequential boundaries without adjustment for the change in the frequency of repeated analyses, the power of the group sequential tests for detecting $\delta = 0.2$ becomes 0.896 while the type I error probability becomes 0.0444.

If the accrual rate is 125 per year instead, the maximum sample size will be achieved only after 2 years of accrual. The information time at the first four committee meetings becomes $\{0.25, 0.5, 0.75, 1.0\}$, and the power actually achieved becomes 0.907 with type I error probability of 0.05. If one proceeds with the predetermined Pocock group sequential boundaries, the chance of detecting the difference becomes 0.911; however, the type I error probability becomes 0.0702.
6 Discussion

The proposed design procedure allows for various combinations of the significance level, power, and frequency and times of repeated analyses, whereas there is only a limited number of tables available for the group sequential designs with predetermined boundaries.

For design purpose, the proposed procedure, just like any other group sequential method, requires that the frequency and times of repeated analyses be specified in advance, even though neither may or can be followed exactly. If the prespecified plan is adhered to, the operating characteristics of the subsequent group sequential analysis will be exactly the same as specified during the design. The advantage then is that, while both procedures require specification of the frequency and times of repeated analyses during the design, the proposed use function approach provides greater flexibility during the analysis. The flexibility of the use function approach is achieved by using the actual information times during the monitoring of the clinical trial, rather than the prespecified information times.

If the analysis plan is altered or if the actual information times are not as specified at any or all interim analyses, the use function approach allows this flexibility and still preserves the exact significance level. The power will not be preserved exactly. However, major departures are required either from equal increments or in frequency before serious change in power is noted. Thus, the trade-off for the flexibility in conducting interim analyses at unequal increments in statistical information or at unscheduled but necessary time does not jeopardize the design in terms of power while preserving the significance level exactly. If the information times of interim analyses are altered, the power can either increase or decrease from what has been prespecified during the design. If the frequency of repeated analyses is increased or decreased, the power is decreased or increased, respectively, as a consequence of the necessary adjustment in the nominal significance to maintain the significance level. In both situations, the examples presented indicate that the change in power is rather minor.

A situation quite different from those considered in Section 5 and discussed above occurs
when extra unplanned interim analyses are conducted because the observed data suggest that a significant treatment difference exists. As was investigated by Lan and DeMets\textsuperscript{5}, if the frequency of future interim analyses is affected by a large, yet nonsignificant test statistic, in other words, data-driven, then the type I error probability will not be preserved even with the use function approach.
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REFERENCES


Table 1: Values of the drift parameter $\xi$ for a one-sided test using $\alpha_1(t)$

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Table 2: Values of the drift parameter $\xi$ for a one-sided test using $\alpha^*_2(t)$

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