GROUP SEQUENTIAL DESIGN FOR REDUCING AVERAGE SAMPLE NUMBER

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ABSTRACT

The study is to propose a group sequential design which reduces the average sample number in the repeated group significance tests to compare the efficacy between two treatments. As the impractical problems of clinical trials, we often need a large number of sample size when the difference between two population means is small. Thus it is necessary to devise the group sequential design for reducing the average sample number from an ethical point of view. We construct the group sequential design which has the inner boundaries intending to accept the null hypothesis at an early stage. We compare our group sequential design with the usual group sequential design in terms of the average sample number in the simulations.

1 INTRODUCTION

Pocock (1977) proposed the group sequential procedure in order to compare the efficacy between two treatments based on the accumulated data in clinical trials when a response variable is normal (or binary). Other group sequential procedures have been proposed by many authors like O'Brien and Fleming (1979), DeMets and Ware (1980), Whitehead (1983), and Fleming Harrington and O'Brien (1984). Lan and DeMets (1983) constructed the repeated confidence boundaries by using error spending function in the repeated significance tests. The group sequential procedure is characterized by the group sequential design based on the repeated confidence boundaries constructed for realizing the test. The group sequential procedure is usually used to reduce the average sample number or to terminate early the decision in the repeated group significance test. However, some impractical problems about clinical trials still exist, e.g. we need a large number of sample size, especially when the difference between two population means is small.

In this study we propose a group sequential design that enables us to reduce the average sample number based on the probability of Type II error specified in advance.

The usual group sequential design is possible to accept the null hypothesis at the final stage only. We device the group sequential design which has the inner boundaries, the inner upper and inner lower boundaries, for accepting the null hypothesis at the intermediate stage. Regarding the calculations of the repeated boundaries under the null hypothesis and alternative hypothesis, we use the recursive formulae of numerical integrations referred to Armitage *et al.* (1969). Finally we compare our group sequential design with the usual group sequential design in terms of the average sample number in the simulations.

2 GROUP SEQUENTIAL PROCEDURE

We consider a group sequential procedure for testing the difference in efficacy between a new treatment (treatment A) and a standard treatment (treatment B). Total number of test K, the probabilities of Type I error (significance level) α and Type II error β are specified in advance. We suppose that each group of patients arrives successively and that each group has sample size $2g$. In a group, g patients are treated with treatment A and the other g patients with treatment B. In this case the treatments are allocated to the patients at random. The responses on treatment A, B are denoted by random variables X_A, X_B, and they are independent normal $N(\mu_A, \sigma^2)$, $N(\mu_B, \sigma^2)$ respectively, where μ_A, μ_B are mean and σ^2 is a known variance. Thus $2g$ observations obtained at the kth stage, $x_{A,n_{k-1}+1}, x_{A,n_{k-1}+2}, \cdots, x_{A,n_k}$ and $x_{B,n_{k-1}+1}, x_{B,n_{k-1}+2}, \cdots, x_{B,n_k}$ are samples from $N(\mu_A, \sigma^2)$ and $N(\mu_B, \sigma^2)$ respectively, where $n_k = gk$. Now we test the null hypothesis

$$H_0 : \mu_A = \mu_B \quad \textit{against alternative } H_1 : \mu_A \neq \mu_B. \tag{2.1}$$

If we let

$$\bar{x}_{A,k} = \frac{\sum_{i=1}^{n_k} x_{A,i}}{gk}, \quad \bar{x}_{B,k} = \frac{\sum_{i=1}^{n_k} x_{B,i}}{gk},$$

$\bar{x}_{A,k} - \bar{x}_{B,k}$ is distributed according to $N(\mu_A - \mu_B, \frac{2\sigma^2}{gk})$. We write the distribution as

$$\bar{x}_{A,k} - \bar{x}_{B,k} \sim N\left(\mu_A - \mu_B, \frac{2\sigma^2}{gk}\right). \tag{2.2}$$

Thus

$$y_k = \frac{k\sqrt{g}(\bar{x}_{A,k} - \bar{x}_{B,k})}{\sqrt{2\sigma^2}} \sim N\left(\frac{k\sqrt{g}\delta}{\sqrt{2\sigma^2}}, k\right), \tag{2.3}$$

where $\delta = \mu_A - \mu_B$.

2.1 Construction of repeated confidence boundaries

The group sequential procedure is realized by constructing the repeated confidence boundaries under the null hypothesis $H_0 : \mu_A - \mu_B = 0$. Let $X_i (i = 1, 2, \cdots, K)$ be a variable according to $N(0, 1)$ independently. Then

$$S_k = \sum_{i=1}^{k} X_i$$

is distributed according to $N(0, k)$. Here we must determine the repeated confidence boundaries $b_1, b_2, \cdots, b_K$ so as to satisfy the following relations

$$P(\mid S_1 \mid > b_1) = \alpha_1^*,$$

$$\cdots$$

$$P(\mid S_1 \mid \leq b_1, \cdots, \mid S_{k-1} \mid \leq b_{k-1}, \mid S_k \mid > b_k) = \alpha_k^*, \tag{2.4}$$

$$\cdots$$

$$P(\mid S_1 \mid \leq b_1, \cdots, \mid S_{K-1} \mid \leq b_{K-1}, \mid S_K \mid > b_K) = \alpha_K^*,$$

where α_k^* is the probability that the test terminates by accepting H_1 at the kth stage under H_0. Furthermore, α_k^* must satisfy $\alpha = \alpha_1^* + \cdots + \alpha_K^*$ for a specified significance level α. The repeated confidence boundary $b_i (i = 1, 2, \cdots, K)$ in (2.4) can be obtained by using the integrations (cf. Armitage *et al.* (1969))

$$\alpha_1^* = 1 - \int_{-b_1}^{b_1} f_1(u) du, \tag{2.5}$$

$$\alpha_k^* = 2 \int_{b_k}^{\infty} \int_{-b_{k-1}}^{b_{k-1}} f_{k-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} du dv, k = 2, \cdots, K \tag{2.6}$$

where $f_{k-1}(u)$ is the probability density function of S_{k-1} at the $(k-1)$th stage. Thus we call $b_1, b_2, \cdots, b_K$ the upper boundaries and $-b_1, -b_2, \cdots, -b_K$ the lower boundaries in the group sequential design.

The group sequential procedures are characterized by the way to construct the repeated confidence boundaries. We adopt Lan-DeMets' procedure in which the repeated confidence boundaries are determined by using the formulae (2.5) and (2.6). Here the significance level α_k^* at the kth stage is given by $\alpha_k^* = \alpha(k) - \alpha(k-1)$, where $\alpha(k) = \alpha \cdot \frac{k}{K} (k = 1, 2, \cdots, K)$ is the error spending function.

When the repeated confidence boundaries $b_1, b_2, \cdots, b_K$ are determined, the decision rules of the group sequential procedure in terms of y_k defined in (2.3) are as follows:
(a) If $y_k (k \leq K-1)$ at the kth stage reaches the upper boundary b_k or the lower boundary $-b_k$, that is $\mid y_k \mid \geq b_k$, then one accepts the hypothesis H_1. Otherwise, one tests again in terms of y_{k+1} at the $(k+1)$th stage.
(b) If y_K at the Kth stage reaches the upper boundary b_K or the lower boundary $-b_K$, that is $\mid y_K \mid \geq b_K$, then one accepts the hypothesis H_1. Otherwise, one accepts the hypothesis H_0.

3 GROUP SEQUENTIAL DESIGN HAVING INNER BOUNDARIES

The group sequential design is possible to accept the null hypothesis at the final stage only. Here we propose the group sequential design which has the inner boundaries at the intermediate stage for accepting early the null hypothesis. The inner boundaries are constructed based on the Type II error under the alternative hypothesis after constructing the repeated confidence boundaries in **2.1**.

3.1 Construction of inner boundaries

First we will constructe the repeated confidence boundaries under the alternative hypothesis $H_1 : \mu_A - \mu_B = \delta > 0$. If we let

$$\Delta = \frac{\sqrt{g}\delta}{\sqrt{2\sigma^2}}, \tag{3.1}$$

y_k in (2.3) is written by

$$y_k = \frac{k\sqrt{g}(\bar{x}_{A,k} - \bar{x}_{B,k})}{\sqrt{2\sigma^2}} \sim N(\Delta k, k). \tag{3.2}$$

Next we allocate the Type II error β each stage by using Lan-DeMets' the error spending function, i.e. the probability β_k^* at the kth stage is given by $\beta_k^* = \beta(k) - \beta(k-1)$, $\beta(K) = \beta$.

The repeated confidence boundary $c_i (i = 1, 2, \cdots, K)$ under H_1 can be obtained by using the integrations

$$2\beta_1^* = 1 - \int_{-c_1}^{c_1} f_1(u)du, \tag{3.3}$$

$$2\beta_k^* = 2\int_{c_k}^{\infty}\int_{-c_{k-1}}^{c_{k-1}} f_{k-1}(u)\frac{1}{\sqrt{2\pi}}e^{-\frac{(v-u-\Delta)^2}{2}}dudv, k = 2, \cdots, K \tag{3.4}$$

where $f_{k-1}(u)$ is the probability density function of S_{k-1} at the $k-1$th stage. If c_k at the mth stage takes first a positive number, we construct a group sequential design having the inner upper boundaries since the kth stage. Thus the inner upper boundaries are $c_k, c_{k+1}, \cdots, c_K$ under the alternative hypothesis $H_1 : \mu_A - \mu_B = \delta > 0$.

Futhermore we use $-c_k, -c_{k+1}, \cdots, -c_K$ as the inner lower boundaries under the alternative hypothesis $H_2 : \mu_A - \mu_B = -\delta$. Thus the inner boundaries, the inner upper and inner lower boundaries, are $(-c_m, c_m), (-c_{m+1}, c_{m+1}) \cdots, (c_K, c_K)$ respectively.

3.2 Probabilities

In the group sequential design whether the inner boundary at the intermediate stage appear or not depend on the values of β and Δ. Here we define the probability for accepting H_0, for rejecting H_0 and for continuation to test again at the next stage in the following cases.

(i) 1st stage

The upper probability for rejecting H_0 and the probability for continuation

$$\frac{\alpha_1^*}{2} = \int_{b_1}^{\infty} f_1(u)du, \quad \gamma_1^* = \int_{-b_1}^{b_1} f_1(u)du. \tag{3.5}$$

(ii) 2nd stage$-(m$-1)th stage

The upper probability for rejecting H_0,

$$\frac{\alpha_i^*}{2} = \int_{b_i}^{\infty}\int_{-b_{i-1}}^{b_{i-1}} f_{i-1}(u)\frac{1}{\sqrt{2\pi}}e^{-\frac{(v-u)^2}{2}}dudv, \quad i = 2, \cdots, m-1. \tag{3.6}$$

The probability for continuation

$$\gamma_i^* = \int_{-b_i}^{b_i}\int_{-b_{i-1}}^{b_{i-1}} f_{i-1}(u)\frac{1}{\sqrt{2\pi}}e^{-\frac{(v-u)^2}{2}}dudv, \quad i = 2, \cdots, m-1. \tag{3.7}$$

(iii) mth stage

The upper probability for rejecting H_0,

$$\frac{\alpha_m^*}{2} = \int_{b_m}^{\infty}\int_{-b_{m-1}}^{b_{m-1}} f_{m-1}(u)\frac{1}{\sqrt{2\pi}}e^{-\frac{(v-u)^2}{2}}dudv. \tag{3.8}$$

The upper probability for continuation

$$\gamma_m^* = \int_{c_m}^{b_m} \int_{-b_{m-1}}^{b_{m-1}} f_{m-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} du dv. \tag{3.9}$$

The probability for accepting H_0

$$\delta_m^* = \int_{-c_m}^{c_m} \int_{-b_{m-1}}^{b_{m-1}} f_{m-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} du dv. \tag{3.10}$$

(iv) $(m+1)$th$-K$th stage

The upper probability for rejecting H_0,

$$\begin{aligned} \frac{\alpha_i^*}{2} &= \int_{b_i}^{\infty} \left(\int_{-b_{i-1}}^{-c_{i-1}} f_{i-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} du \right. \\ &\quad \left. + \int_{c_{i-1}}^{b_{i-1}} f_{i-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} du \right) dv, i = m+1, \cdots, K. \end{aligned} \tag{3.11}$$

The upper probability for continuation

$$\begin{aligned} \gamma_i^* &= \int_{c_i}^{b_i} \left(\int_{-b_{i-1}}^{-c_{i-1}} f_{i-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} du \right. \\ &\quad \left. + \int_{c_{i-1}}^{b_{i-1}} f_{i-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} du \right) dv, i = m+1, \cdots, K. \end{aligned} \tag{3.12}$$

The probability for accepting H_0

$$\begin{aligned} \delta_i^* &= \int_{-c_i}^{c_i} \left(\int_{-b_{i-1}}^{-c_{i-1}} f_{i-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} du \right. \\ &\quad \left. + \int_{c_{i-1}}^{b_{i-1}} f_{i-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} du \right) dv, i = m+1, \cdots, K. \end{aligned} \tag{3.13}$$

Next we define the average sample size for a treatment as

$$E(n_i) = \sum_{i=1}^{m-1} n_i \alpha_i^* + \sum_{i=m}^{K-1} n_i (\alpha_i^* + \delta_i^*) + n_K \{1 - (\alpha_{K-1} + \delta_{K-1})\} \tag{3.14}$$

where $\alpha_{K-1} = \alpha_1^* + \cdots + \alpha_{K-1}^*$, $\delta_{K-1} = \delta_m^* + \cdots + \delta_{K-1}^*$.

4 SIMULATIONS

The purpose of the simulations is to compare our group sequential design with the usual group sequential design in terms of the average sample number. First, we specify Type I error $\alpha = 0.05$, Type II error $\beta = 0.05$, total number of test $K = 4$. We divide α and β at each stage by the error spending function as preparation. We calculate the boundaries (upper boundaries(b_i) and inner upper boundaries(c_i)), the probabilities (upper probability for rejecting H_0 $(\alpha_i^*/2)$, probability for continuation(γ_i^*), upper probability for continuation(upper γ_i^*), probability for accepting $H_0(\delta_i^*)$) and the average sample number$(E(n_i))$.

After constructing the usual group sequential design for $\delta = 0$, we set up the group sequential design having inner boundaries for $\delta = 1.8$. Table 4.1 and 4.2 show the boundaries and the probabilities at each stage, the average sample number.

Table 4.1 Boundaries, Probabilities and Average sample number for $\delta = 0.0$

Stage	Boundaries		Probability				$E(n_i)$
	b_i	c_i	$\alpha_i^*/2$	Upper γ_i^*	γ_i^*	δ_i^*	
1	2.48	—	0.0066	—	0.9870	—	
2	3.42	—	0.0061	—	0.9751	—	
3	4.02	—	0.0064	—	0.9625	—	
4	4.49	—	0.0063	—	—	0.9500	39.2

Table 4.2 Boundaries, Probabilities and Average sample number for $\delta = 1.8$

Stage	Boundaries		Probability				$E(n_i)$
	b_i	c_i	$\alpha_i^*/2$	Upper γ_i^*	γ_i^*	δ_i^*	
1	2.48	—	0.0066	—	0.9870	—	
2	3.42	0.93	0.0061	0.2443	—	0.4922	
3	4.02	2.49	0.0063	0.0537	—	0.3680	
4	4.49	4.14	0.0050	0.0035	—	0.0900	25.7

Thus we can confirm that $E(n_i)$ in Table 4.1 takes smaller than $E(n_i)$ in Table 4.2.

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