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Comparative Study on Group Sequential Procedure

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Abstract

The group sequential procedures have used to reduce the average sample size and to terminate early the decision in the repeated significance test for comparing the efficacy between two treatments. The group sequential procedure is characterized by the group sequential design based on the repeated confidence boundaries for realizing the test. In this study we compare the representative methods to construct the repeated confidence boundaries in the group sequential procedure in terms of the average sample size in the simulation studies.

Key Words and Phrases : average sample size; some group sequential procedures; repeated confidence boundaries; simulation study

1. Introduction

The group sequential procedure is the method to test sequentially the hypothesis of no difference between two treatments based on the accumulated data in clinical trials when a response variable is normal(or binary). Pocock(1977) proposed first the group sequential procedure based on the repeated confidence boundaries constructed by the use of recursive fomulae of numerical integrations in Armitage *et al.*(1969). Many authors like O'Brien and Fleming(1979), DeMets and Ware(1980), Whitehead(1983), Fleming Harrington and O'Brien(1984) and so on, have presented the different methods which obtain the repeated confidence boundaries under the probability of Type I error specified in advance. Lan and DeMets(1983) proposed an unique method to construct the repeated confidence boundaries by using α spending function. In general we use the group sequential procedure to reduce the average sample size and to terminate early the decision in the repeated significance test from the ethical point of view in clinical trials. In the simulation studies, we compare five representative methods in

group sequential procedures in terms of the average sample size after constructing the repeated confidence boundaries.

2. Group Sequential Procedure

We consider a group sequential procedure that tests the hypothesis of no difference in efficacy between a new treatment(treatment A) and a standard treatment(treatment B). In advance we specify the total number of test K and the probabilities of Type I error(significance level) α. We suppose that each group of patients arrives successively and the $k(k = 1, \cdots, K)$th stage has sample size $2g$. In a group, g patients are randomly allocated to receive treatment A and the other g patients are randomly allocated to receive treatment B. Each response on treatment A and B is denoted by random variables X_A and X_B, and they are independently distributed according to normal distribution $N(\mu_A, \sigma^2), N(\mu_B, \sigma^2)$ respectively, where μ_A, μ_B are means 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 $N(\mu_A, \sigma^2), N(\mu_B, \sigma^2)$ respectively, where $n_k = gk$.

Table 2.1 Group of observations

Stage	Group of observations			
1	$x_{A,1}$	$x_{A,2}$	$\cdots$	x_{A,n_1}
	$x_{B,1}$	$x_{B,2}$	$\cdots$	x_{B,n_1}
2	x_{A,n_1+1}	x_{A,n_1+2}	$\cdots$	x_{A,n_2}
	x_{B,n_1+1}	x_{B,n_1+2}	$\cdots$	x_{B,n_2}
$\vdots$		$\vdots$		
K	$x_{A,n_{K-1}+1}$	$x_{n_{A,K-1}+2}$	$\cdots$	x_{A,n_K}
	$x_{B,n_{K-1}+1}$	$x_{B,n_{K-1}+2}$	$\cdots$	x_{B,n_K}

Now we give the null hypothesis H_0 against the alternative hypothesis H_1 as

$$H_0 : \mu_A = \mu_B, \quad H_1 : \mu_A \neq \mu_B. \tag{2.1}$$

Here we let

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

then $\bar{x}_{A,k} - \bar{x}_{B,k}$ is distributed according to $N(\mu_A - \mu_B, \frac{2\sigma^2}{gk})$. We will 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 $\delta = \mu_A - \mu_B$.

3. Repeated Confidence Boundaries

The group sequential procedure is characterized by the repeated confidence boundaries under the null hypothesis H_0 by Armitage *et al.*(1969).

Let $X_1, \cdots, X_K$ be series of random variables distributed according to $N(0,1)$ independently. Then

$$S_k = \sum_{i=1}^{k} X_i \sim N(0, k).$$

Here we need determine the repeated confidence boundaries $b_1, \cdots, b_K$ so as to satisfy the following relations

$$\begin{aligned}
&\Pr(|S_1| > b_1) = \alpha_1^*, \\
&\vdots \\
&\Pr(|S_1| \le b_1, \cdots, |S_{k-1}| \le b_{k-1}, |S_k| > b_k) = \alpha_k^*, \\
&\vdots \\
&\Pr(|S_1| \le b_1, \cdots, |S_{K-1}| \le b_{K-1}, |S_K| > b_K) = \alpha_K^*,
\end{aligned} \tag{3.1}$$

where α_k^* is the probability that the test terminates first by rejecting H_0 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 $b_i (i = 1, \cdots, K)$ in (3.1) can be obtained by using the following integrations by Armitage *et al.*

$$\alpha_1^* = 1 - \int_{-b_1}^{b_1} f_1(u)du, \quad where\ f_1(u) = \frac{1}{\sqrt{2\pi}} e^{-\frac{u^2}{2}}, \tag{3.2}$$

$$\alpha_k^* = 2\int_{b_k}^{\infty} \int_{-b_{k-1}}^{b_{k-1}} f_{k-1}(u) \frac{1}{\sqrt{2\pi}} e^{-\frac{(v-u)^2}{2}} dudv, \quad k = 2, \cdots, K, \tag{3.3}$$

where $f_{k-1}(u)$ is the probability density function of S_{k-1} at $(k-1)$th stage. Thus we call $b_1, \cdots, b_K$ the upper boundaries and $-b_1, \cdots, -b_K$ the lower boundaries in the repeated confidence boundaries. Then we define the necessary average sample size $E(n_k)$ for treatment A and treatment B as

$$E(n_k) = 2g\left[\sum_{k=1}^{K-1} k\alpha_k^* + K\left\{1 - \left(\sum_{k=1}^{K-1} \alpha_k^*\right)\right\}\right] \tag{3.4}$$

When the repeated confidence boundaries $b_1, \cdots, b_K$ are determined, the decision rules in the group sequential procedure are as follows:

(i) The case of the $k(k = 1, \cdots, K-1)$th stage.

If $|y_k| \geq b_k$, then one accepts the hypothesis H_1. Otherwise, one tests again in terms of y_{k+1} at the $(k+1)$th stage.

(ii) The case of the Kth stage.

If $|y_K| \geq b_K$, then one accepts the hypothesis H_1. Otherwise, one accepts the hypothesis H_0.

Here we show the repeated confidence boundaries in the group sequential procedure in Fig. 3.1.

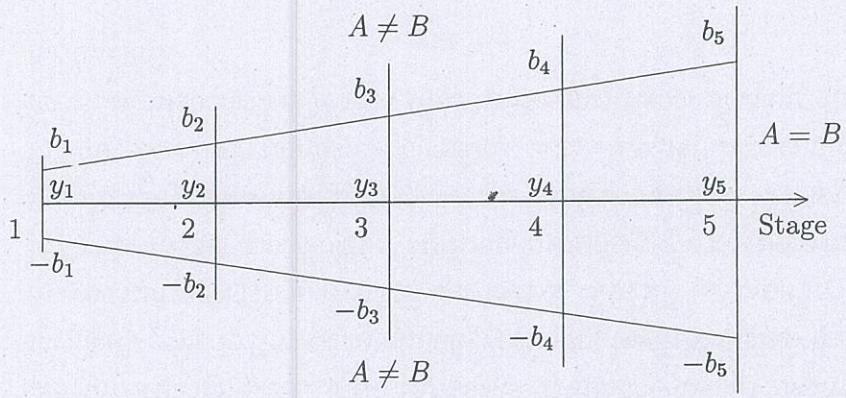

Fig.3.1: Repeated confidence boundaries

4. Representative Methods

We introduce three representative methods for deciding the repeated confidence boundaries.

(1) Pocock's method(1977)

This method is to adopt the repeated confidence boundaries

$$b_k = Z \cdot \sqrt{k}, \quad k = 1, \cdots, K, \tag{4.1}$$

when $\sum_{i=1}^{K} \alpha_i^*$ is equal to the significance level α by using the common value of Z through all the stages.

(2) O'Brien and Fleming's method(1979)

This method is to adopt the repeated confidence boundaries

$$b_k = U\sqrt{\frac{K}{k}}\sqrt{k} = U \cdot \sqrt{K}, \quad k = 1, \cdots, K, \tag{4.2}$$

when $\sum_{i=1}^{K} \alpha_i^*$ is equal to the significance level α by using the value of $U\sqrt{K/k}$ through all the stages. The value of U is decided by Monte Carlo simulation.

(3) Lan and DeMets' method(1983)

The method is to define the following three α spending functions. We assign the significance level α for each stage and decide the repeated confidence boundaries based on the Armitage's method.

(a) Normal method

In this method, α spending function is defined by

$$\alpha(k) = 2\left\{1 - \Phi\left(Z_{\frac{\alpha}{2}}\sqrt{\frac{K}{k}}\right)\right\}, \quad k = 1, \cdots, K, \tag{4.3}$$

where Φ is the standard normal distribution and $Z_{\frac{\alpha}{2}}$ is the $\frac{\alpha}{2}$ point of standard normal distribution.

(b) Log method

In this method, α spending function is defined by

$$\alpha(k) = \alpha \times \log\left\{1 + (e-1)\frac{k}{K}\right\}, \quad k = 1, \cdots, K. \tag{4.4}$$

(c) αt method

In this method, α spending function is defined by

$$\alpha(k) = \alpha \times \frac{k}{K} = \alpha t, \quad k = 1, \cdots, K. \tag{4.5}$$

By the above methods, we calculate $\alpha(k)$ and decide α_k^* for each stage by $\alpha_k^* = \alpha(k) - \alpha(k-1)$. Then α_k^* must satisfy the following equation.

$$\alpha = \sum_{k=1}^{K} \alpha_k^*. \tag{4.6}$$

5. Simulation Studies

The purpose of the simulation studies is to compare the representative methods in the group sequential procedure in terms of the average sample size. First we calculate the value of $\alpha(k)(k = 1, \cdots, 5)$ at each stage on five methods in Section 4 after constructing the repeated confidence boundaries under $K = 5$ and $\alpha = 0.05$.

Table 5.1 shows the values of $\alpha(k)$ on five methods. In Table 5.1, Pocock's method and Log method take larger values at the first stage and increase slightly with the change of k. Normal method and O'Brien- Fleming's method take smaller values at early stage and increase largely with the change of k. The αt method shows that a rate of increase is equal through all the stages. Fig.5.1 illustrates the change of $\alpha(k)$ for each five methods in Table 5.1.

In Fig.5.1, Pocock's method and Log method take the large values at the first stage and show the increasing curve with the change of k. Normal method and O'Brien and Fleming's method increase loosely at early stage and increase largely with the change of k. The αt method shows a straight line.

Table 5.1 The value of $\alpha(k)$

Stage (k)	1	2	3	4	5
Pocock's method	0.01552	0.02718	0.03614	0.04341	0.04953
Log method	0.01477	0.02616	0.03543	0.04324	0.05000
αt method	0.01000	0.02000	0.03000	0.04000	0.05000
Normal method	0.00001	0.00194	0.01139	0.02843	0.05000
O-F's method	0.00001	0.00128	0.00899	0.02582	0.05043

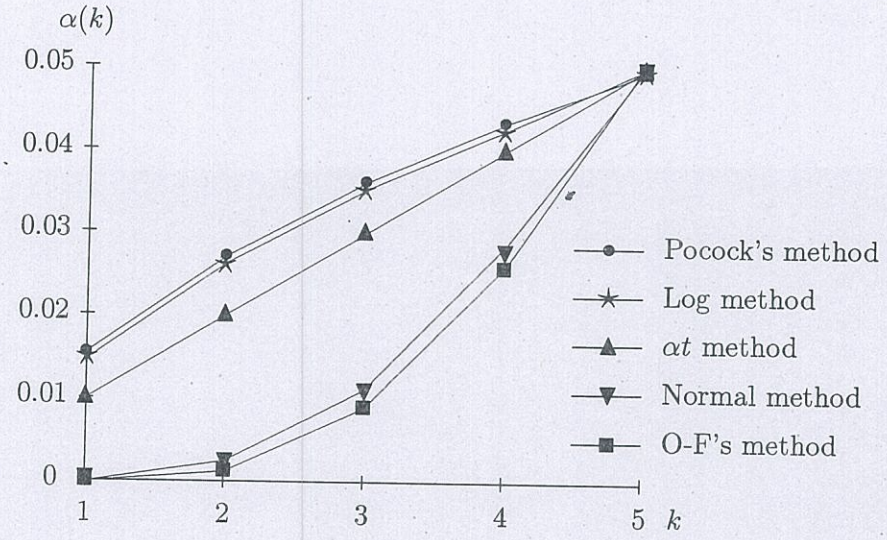

Fig.5.1 Comparison of the value of $\alpha(k)$

In Table 5.2 we show the average sample size $E(n_k)$ of two treatments A and B on five methods under $g = 20, \alpha = 0.05$ and $K = 3, 5$. From Table 5.2, $E(n_k)$ of Pocock's method and Log method take the small values than $E(n_k)$ of the other methods. But $E(n_k)$ of Normal method and O'Brien-Fleming's method take the large values than $E(n_k)$ of the other methods. $E(n_k)$ of αt method take intermediate values among these methods.

Fig.5.2 shows the comparison of the value of $E(n_k)$ on five methods based on Table 5.2. Thus we confirm Pocock's method and Log method are available because $E(n_k)$ of these methods take the small values.

Table 5.2 Average sample size $E(n_k)$

Methods	Pocock	Log	αt	Normal	O-F
$K = 3$	118.48	118.47	118.67	119.35	119.43
$K = 5$	195.11	195.22	196.00	198.33	198.56

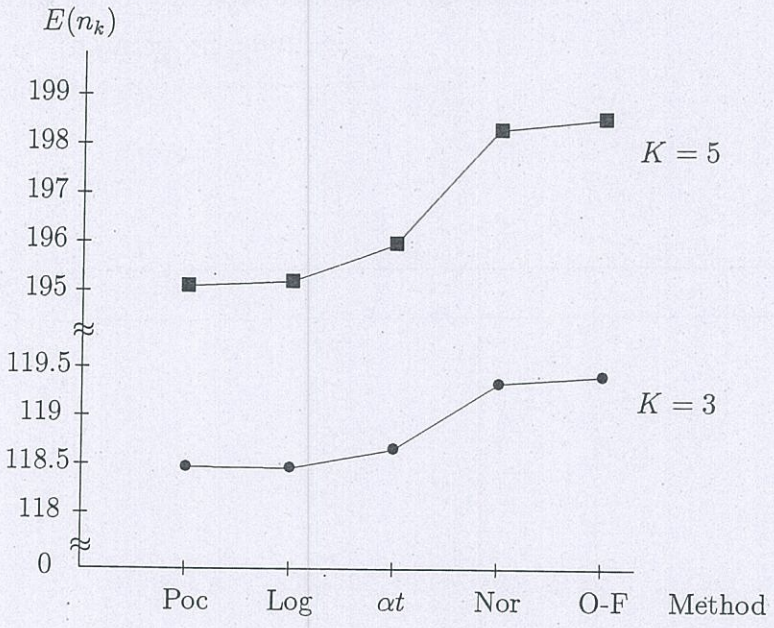

Fig.5.2 Comparison of the value of $E(n_k)$

6. Conclusions

In this study, we focus the comparative studies of the average sample size on five methods in the group sequential procedure from the ethical point of view in clinical trials. In the simulation studies we can see that $E(n_k)$ take the small value, when $\alpha(k)$ take larger values at the early stage. Thus we confirm that Pocock's method and Log method can reduce effectively the average sample size. Furthermore we will develop the group sequential design for reducing the average sample size in the future.

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