ON SEQUENTIAL DESIGN BASED ON MARKOV CHAINS FOR SELECTING ONE OF TWO TREATMENTS IN CLINICAL TRIALS WITH DELAYED OBSERVATIONS

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ABSTRACT

A truncated sequential design for selecting the better of two medical treatments is constructed by using a fundamental relation of Markov chains, with delayed observations based on a time lag of response time. The design is practical and applicable to a wide range of sequential clinical trials. The iterative formula of Markov chains is based on the trinomial random walk on a lattice diagram which adopts the untied and the tied pairs on the double-dichotomous responses. The study is to determine an optimum sequential design based on the evaluation of minimum expected loss.

1. Introduction

The truncated sequential procedures for selecting the better of two medical treatments are introduced by Armitage(1957) for testing the difference between the means of two binomial distributions. These procedures have been applied to sequential clinical trials for deciding the superiority between two treatments by using the double-dichotomous responses. These procedures only employ the untied pairs on the double-dichotomous responses such that each patient pair is tested sequentially by treatment *A* and *B*, and then, each response of the patient is immediately available. However, in the practical clinical trials we must frequently deal with delayed observations where there exists a time lag between the administration of the treatment and the availability of the response. The statistical studies associated with the delayed observations are already presented by Anderson(1964), Choi and Clark(1970), Langenberg and Sirinivasan(1981). Anderson, Choi and Clark have dealt the probabilities of error associated with the terminal decision by using the delayed observations, after making a tentative decision. Langenberg and Sirinivasan have studied a fixed sample size plan for clinical trials with delayed observations.

Sequential procedures have been developed by modification of Wald's sequential probability ratio test, but our sequential designs are realized from minimizing the expected loss function based on Colton's criterion. Colton(1963) proposes that the only loss involved for attempting to design an optimal clinical trial is the consequence of being treated by the inferior among two treatments and that all other losses may be disregarded from the ethical point of view. On the other hand, Choi(1968) has presented a new type of sequential design for clinical trials by using a fundamental relation of Markov chains. Sugimura, Goto and Asano(1969,1971) have already developed some types of open and closed optimum sequential

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designs based on Colton's decision theory which uses the fundamental equation of Markov chains without using delayed observations.

In the study we incorporate a sequential design based on Markov Chains for selecting one of two medical treatments in clinical trials by using delayed observation pairs. Here the procedure is constructed according to the following fundamental scheme.

(1) Firstly, during the trial period, a clinical trial will be performed sequentially on patient pairs with treatment A on one member of the pair and treatment B on the other. At a certain point in time, one of two treatments will be tentatively decided to be superior to the other according to a tentative decision rule.

(2) Secondly, immediately after the trial period, the better of the two treatments will be performed on all patient pairs arriving during the waiting period of d unit times. At the end of the waiting period, the better treatment will be ultimately decided according to a final decision rule.

(3) Finally, based on the final decision rule, the treatment period will be performed as the better treatment for all the remaining patients.

Under the above mentioned scheme, we shall further decide an optimum statistical design utilizing an evaluation based on Colton's criterion. Since we deal with the untied and tied pairs on the responses, this is formulated by using general iterative formulas of Markov Chains, based on the trinomial random walk on a lattice diagram. Thus, we will consider the expected loss function, which is proportional to an average patient number of being treated with the inferior treatment. Then, our criterion will be to minimize the overall expected loss over a priori distribution of parameter.

An object of this study is to determine the optimum statistical design from the evaluation based on Colton's criterion and to compare the superiority between the following two sequential designs numerically. Specifically, the first design (Design 1) will be constructed according to the above mentioned procedure and the second design (Design 2) will consist of the trial period and the treatment period without the waiting period. Thus, the second design is that the better of the two treatments will be decided at the end of the trial period. Based on results from the trial period, the treatment period will be performed as the better treatment for all the remaining patients.

2. Assumptions

The assumptions which pertain throughout this paper are as follows:

Firstly, suppose a new treatment A and standard treatment B in clinical trials. Let p_A be the probability of effectiveness with treatment A , and p_B be of effectiveness with treatment B . Then we will consider the following hypotheses for comparing the superiority or inferiority of A against B .

$$H_2 : \delta = 0 \text{ against } H_1 : \delta = \Delta \ (\Delta > 0) \quad (2.1)$$

$$H_2 : \delta = 0 \text{ against } H_3 : \delta = -\Delta \quad (2.2)$$

where $\delta = p_A - p_B$. Let N be the total number of patients who are treated with one of two treatments, A and B for a disease, where N is fixed and large. Next, a patient pair who arrives successively for treatment during the interval of unit time, will participate in the clinical trial by being administered A on one patient and B on the other in a patient pair allocated at random. Let n be the number of allocated patient pairs. There is a time lag d between the administration of the treatment and the availability of the response. Then, the result of effectiveness on a treatment is denoted by "1" and the result of ineffectiveness

is denoted by "0". If treatment A is effectiveness and treatment B is ineffectiveness, the delayed observation pair is denoted by $(1, 0)$. The untied pairs on the double-dichotomous responses are denoted by $(1, 0)$, $(0, 1)$, and tied pairs are denoted by $(1, 1)$, $(0, 0)$. Thus the m -th observation pairs are denoted by one of four different pairs, $(1, 0)$, $(0, 1)$, $(1, 1)$ and $(0, 0)$. Let m_1 be the number of pairs $(1, 0)$, m_3 the number of pairs $(0, 1)$, and m_2 the number of pairs $(1, 1)$ and $(0, 0)$ in the sequence obtained up to m -th observation pair. Next the set of three variables $\{m_1, m_2, m_3\}$ is distributed according to the trinomial distribution in which the number of trials is $m = \sum_{i=1}^3 m_i$, and each probability is

$$p_1 = P_r\{(a, b) = (1, 0)\} = p_A(1 - p_B),$$

$$p_2 = P_r\{(a, b) = (1, 1) \text{ or } (0, 0)\} = p_A p_B + (1 - p_A)(1 - p_B),$$

$$p_3 = P_r\{(a, b) = (0, 1)\} = (1 - p_A)p_B.$$

Here a parameter expressing a discrepancy of the effects among treatments A and B shall be given by δ . Then, we can measure the superiority of effects among the two treatments by using a value of δ . Namely, " $\delta > 0$ " is equivalent to " $p_A > p_B$ ", " $\delta = 0$ " equivalent to " $p_A = p_B$ ", and " $\delta < 0$ " equivalent to " $p_A < p_B$ ".

Secondly, we must assume that the only loss involved is the result of being treated with the inferior among two treatments and all other loss may be disregarded from the ethical point of view. Moreover, it is assumed that the cost is directly proportional to the true values of $|\delta|$. Namely, in terms of the expected loss formulation, if a patient is treated with the inferior treatment, a positive loss which is proportional to $|\delta|$ is scored for him.

Finally, we shall assume that a priori distribution $g(\delta)$ for the parameter δ which is assumed as a random variable instead of a priori two-dimensional distribution for two parameters p_1 and p_3 may be given as a probability distribution. It seems that the assumptions are reasonable in the practical clinical problem. In section 3, we shall also detail the following statistical designs in order to incorporate the procedure.

3. Truncated sequential design 1

3.1. Decision rules

The sequential design 1 for the equivalence test on (2.1) and (2.2) consists of trial period, waiting period and treatment period with the following decision rules. Namely, the design is constructed by the above mentioned fundamental scheme of procedure and the following stopping rules. Then we finally accept one of three hypotheses by use of delayed observation pairs, that is, treatment A is superior to treatment B , B is superior to A , and there is no difference between the two treatments. Here M is the maximum time limit of trial period. Figure 3.1 illustrates the truncated sequential design 1 by coordinate representation, a number of allocated patient pair as the n coordinate axis, and $y_m = m_1 - m_3$ as the y_m coordinate axis, where $n = m + d$. The fixed upper and lower boundary lines for accepting H_1 and H_3 are represented on the graph in Figure 3.1., $U (y_m = c)$ and $L (y_m = -c)$ respectively. The middle boundary line for accepting H_2 takes the form of a virtual line at M , where $d \geq 2c$ and $M \geq d + c$ are the necessary relations to be mentioned later. Figure 3.1 shows that when a sequence is given as $\{(1, 0), (0, 1), (1, 0), (1, 0), (0, 0), (1, 0)\}$ with $d = 6$ under $c = 3$ and $M = 20$, a point of 1-st observation pair $(1, 0)$ is plotted as the coordinates $(n, y_m) = (7, 1)$, and the other points of the sequence are plotted successively in the same way. Then the sequence reaches the upper boundary first in Figure 3.1, thus the tentative decision H_1 is accepted.

We give more detail in the next sequential procedure by adopting tentative and final decision rules. The procedure is classified from the following cases, that is, case 1-1 and case 1-2 (see Figure 3.1) are that the tentative decision is carried out before the $(M - d)$ -th observation pair is observed, and case 2 (see Figure 3.2) is that the tentative decision is carried out just at the $(M - d)$ -th observation pair without previously reaching both boundaries.

(Case 1-1)

If a sequence reaches the upper boundary at the m -th discrete step corresponding to m -th observation pair, where $c \leq m \leq M - d$, (i.e., if $m_1 - m_3 = c$ firstly at the m -th step, where $m = m_1 + m_2 + m_3$, m_1 is the number of $(1, 0)$ pairs, m_2 is the number of $(1, 1)$ or $(0, 0)$ pairs, and m_3 is the number of $(0, 1)$ pairs), then one accepts the tentative decision H_1 at the end of the trial period, and d patients pairs arriving during the waiting period are assigned to A treatment. Here we give the final decisions as follows:

(1) now, let d_1 be the number of $(1, 0)$ pairs, and d_3 be of $(0, 1)$ pairs, and d_2 be of $(0, 0)$ or $(1, 1)$ during the waiting period, $d = d_1 + d_2 + d_3$, if $d_1 - d_3 \geq 0$, then assign A for the remaining patients $N - 2m - 4d$ during the treatment period, as one accepts the terminal decision H_1 ,

(2) if $0 > d_1 - d_3 > -2c$, then assign treatment A to half of the remaining patients $N - 2m - 4d$ and treatment B to the other half, as the terminal decision H_2 ,

(3) if $d_1 - d_3 \leq -2c$, then assign B for the remaining patients $N - 2m - 4d$, as the terminal decision H_3 , where $d \geq 2c$.

Figure 3.1 Sequential design 1 for Case 1-1 ($M = 20, c = 3, d = 6$)

(Case 1-2)

If a sequence reaches the lower boundary at the m -th step, where $c \leq m \leq M - d$, then one accepts the tentative decision H_3 and d patients pairs arriving during the waiting period are assigned to B treatment. Moreover the terminal decisions are as follows:

(1) if $d_1 - d_3 \leq 0$ at the end of the waiting period, then assign B for the remaining patients $N - 2m - 4d$, as one accepts the terminal decision H_3 ,

(2) if $0 < d_1 - d_3 < 2c$, then assign treatment A at half of the remaining patients $N - 2m - 4d$ and treatment B at the other half, as the terminal decision H_2 ,

(3) if $d_1 - d_3 \geq 2c$, then assign A for the remaining patients $N - 2m - 4d$, as the terminal decision H_1 , where $d \geq 2c$.

(Case 2)

There are the path points l , $l = 2, \dots, 2c$, which are the ordinate value of the lattice points for accepting H_2 at $(M-d)$ -th observation pair, denoted by $(2), (3), \dots, (6)$ in case of Figure 3.2. If a sequence reaches neither the upper or lower boundary before the $(M-d)$ -th observation pair is observed, and arrives at the l -th path point at the $(M-d)$ -th step, (i.e., if $c > m_1 - m_3 > -c$ at the $(M-d)$ -th step without previously reaching both boundaries), then one accepts the tentative decision H_2 at the end of the trial period, and assigns treatment A to half of the patient pairs d arriving during the waiting period and treatment B to the other half.

Figure 3.2 Sequential design 1 for Case 2 ($M = 20, c = 3, d = 6$)

Here the terminal decisions are as follows:

(1) if $d_1 - d_3 \geq l - 1$ at the end of the waiting period, then assign A for the remaining patients $N - 2M - 2d$ during the treatment period, as one accepts the terminal decision H_1 ,

(2) if $l - 1 > d_1 - d_3 > l - (2c + 1)$, then assign treatment A to half of the remaining patients $N - 2M - 2d$ and treatment B to the other half, as the terminal decision H_2 ,

(3) if $d_3 - d_1 \geq (2c + 1) - l$, then assign B for remaining patients $N - 2M - 2d$, as the terminal decision H_3 .

3.2. Construction of overall expected loss function

The sequential designs based on the above mentioned decision rules are characterized by the probabilities of tentatively accepting one of the three hypotheses of H_i , α_i , $i = 1, 2, 3$, the conditional probabilities that one accepts the terminal decision H_j , given that one accepts the tentative decision H_i , are α_{ij} , $i = 1, 3$, $j = 1, 2, 3$, and the joint probabilities that one accepts the tentative decision H_2 and accepts the terminal decision H_j , are $\alpha^{2,j}$, $j = 1, 2, 3$.

Here y_m becomes a trinomial random walk on a lattice diagram. And the absorption probabilities where a sequence crosses upper, lower and middle boundary point, can be calculated exactly by using the general iterative formulas of Markov Chains. Then we shall show the average patient pair number and the over all expected loss function by the following way.

Let $s_0(p_1, p_3) = (s_1, s_2, \dots, s_l, \dots, s_{2c+1})$ be a $(2c + 1)$ dimensional row vector which arranges the initial probabilities, where the l -th component s_l , $l = 1, 2, \dots, 2c + 1$, is the probability of reaching the l -th path point at the c -th step. It follows that for each

$$s_l = \sum_{(m_1, m_2, m_3)} c! / m_1! m_2! m_3! \cdot p_1^{m_1} p_2^{m_2} p_3^{m_3}, \quad (3.1)$$

where the symbol $\sum$ denotes the summation of all combinations (m_1, m_2, m_3) of three integers m_1, m_2 and m_3 which satisfy three conditions

$$\sum_{i=1}^3 i m_i = c + l - 1, \quad \sum_{i=1}^3 m_i = c, \quad c \geq m_1, m_2, m_3 \geq 0, \quad (3.2)$$

for the fixed values of p_1, p_3 and c . It should be noted that the sum of all components s_l in $s_0(p_1, p_3)$ is equal to the expansion formula of $(p_1 + p_2 + p_3)^c$, where $\sum_{l=1}^{2c+1} s_l = 1$.

Here, $T(p_1, p_3)$ is the $(2c + 1) \times (2c + 1)$ transition probability matrix from each path point at the $(c + j)$ -th step to these points at the $(c + j + 1)$ -th $j = 0, 1, \dots, M - d - c - 1$ as,

$$T(p_1, p_3) = \begin{bmatrix} 1 & 0 & \dots & \dots & \dots & \dots & 0 \\ p_1 & p_2 & p_3 & 0 & \dots & \dots & 0 \\ 0 & p_1 & p_2 & p_3 & 0 & \dots & 0 \\ \cdot & & & & & & \cdot \\ \cdot & & & & & & \cdot \\ \cdot & \dots & \dots & \dots & \dots & \dots & \cdot \\ \cdot & & & & & & \cdot \\ \cdot & & & & & & \cdot \\ 0 & \dots & \dots & p_1 & p_2 & p_3 & 0 \\ 0 & \dots & \dots & \dots & p_1 & p_2 & p_3 \\ 0 & \dots & \dots & \dots & \dots & 0 & 1 \end{bmatrix} \quad (3.3)$$

Let $\mathbf{s}_j(p_1, p_3) = (s_1^j, s_2^j, \dots, s_i^j, \dots, s_{2c+1}^j)$ be a $(2c+1)$ dimensional vector, where the i -th component represents the probability of reaching the i -th path point at the $(c+j)$ -th step ($i = 1, 2, \dots, 2c+1; j = 0, 1, \dots, M-d-c$). Then, by a fundamental relation of Markov chains,

$$\mathbf{s}_j(p_1, p_3) = \mathbf{s}_0(p_1, p_3) \cdot T^j(p_1, p_3), \quad (3.4)$$

where $T^0(p_1, p_3)$ is defined as a $(2c+1) \times (2c+1)$ unit matrix. Let $\mathbf{e}_i$ be a $(2c+1)$ dimensional row vectors such that the i -th component is 1 and the others are all zeros, that is,

$$\mathbf{e}_i = (0, \dots, 0, 1, 0, \dots, 0), \quad i = 1, 2, \dots, 2c+1. \quad (3.5)$$

$\dots, i, \dots$

Since the 1-st and $(2c+1)$ -th path point are absorbing barriers, it can be shown that

$$\begin{aligned} \alpha_1^j &= P_r\{\text{accepting tentatively } A \text{ until } (c+j) \text{-th step} \mid p_1, p_3; c, M, d\} \\ &= \mathbf{s}_0 \cdot T^j \cdot \mathbf{e}'_1 = \mathbf{s}_j(p_1, p_3) \cdot \mathbf{e}'_1, \quad j = 0, 1, 2, \dots, h, \end{aligned} \quad (3.6)$$

where $\mathbf{s}_0 = \mathbf{s}_0(p_1, p_3)$, $T = T(p_1, p_3)$ and $h = M - c - d$.

$$\begin{aligned} \alpha_3^j &= P_r\{\text{accepting tentatively } B \text{ until } (c+j) \text{-th step} \mid p_1, p_3; c, M, d\} \\ &= \mathbf{s}_j(p_1, p_3) \cdot \mathbf{e}'_{2c+1}, \quad j = 0, 1, 2, \dots, h, \end{aligned} \quad (3.7)$$

Then, $\alpha_i, i = 1, 2, 3$, is denoted as,

$$\alpha_1 = \alpha_1^h, \quad \alpha_3 = \alpha_3^h, \quad \alpha_2 = 1 - \alpha_1 - \alpha_3.$$

The conditional probabilities that one accepts the terminal decision H_j , given that one accepts the tentative decision H_i , are $\alpha_{ij}, i = 1, 3, j = 1, 2, 3$.

$$\begin{aligned} \alpha_{11} &= P_r\{\text{accepting } H_1 \text{ finally} \mid \text{acceptance of } H_1 \text{ tentatively}\} \\ &= \Sigma_1 d! / d_1! d_2! d_3! \cdot p_1^{d_1} p_2^{d_2} p_3^{d_3}, \end{aligned}$$

where the notation Σ_1 represents the summation overall triples (d_1, d_2, d_3) under the condition $d_1 \geq d_3$ and $d_1 + d_2 + d_3 = d$.

$$\begin{aligned} \alpha_{12} &= P_r\{\text{accepting } H_2 \text{ finally} \mid \text{acceptance of } H_1 \text{ tentatively}\} \\ &= \Sigma_2 d! / d_1! d_2! d_3! \cdot p_1^{d_1} p_2^{d_2} p_3^{d_3}, \end{aligned}$$

where the notation Σ_2 represents the summation overall triples (d_1, d_2, d_3) under $0 < d_3 - d_1 < 2c$ and $d_1 + d_2 + d_3 = d$.

$$\begin{aligned} \alpha_{13} &= P_r\{\text{accepting } H_3 \text{ finally} \mid \text{acceptance of } H_1 \text{ tentatively}\} \\ &= \Sigma_3 d! / d_1! d_2! d_3! \cdot p_1^{d_1} p_2^{d_2} p_3^{d_3}, \end{aligned}$$

where the notation Σ_3 represents the summation overall triples (d_1, d_2, d_3) under $d_3 - d_1 \geq 2c$ and $d_1 + d_2 + d_3 = d$. Now, $\alpha_{31} = \alpha_{13}^*$, where α_{13}^* represents the function obtained by

exchanging p_1 and p_3 at α_{13} . Similarly, $\alpha_{32} = \alpha_{12}^*$, and $\alpha_{33} = \alpha_{11}^*$, where α_{12}^* and α_{11}^* represent respectively the function obtained by exchanging p_1 and p_3 at α_{12} , and at α_{11} .

The joint probabilities that one accepts the tentative decision H_2 and accepts the tentative decision $H_j, j = 1, 2, 3$, are $\alpha^{2,j}, j = 1, 2, 3$.

$$\alpha^{21} = \sum_{l=2}^{2c} \Sigma_4 d! / d_1! d_2! d_3! \cdot p_1^{d_1} p_2^{d_2} p_3^{d_3} \cdot s_h(p_1, p_3) \cdot e'_l,$$

where second summation Σ_4 is over $\{d_1 - d_3 \geq l - 1, d_1 + d_2 + d_3 = d\}$.

$$\alpha^{22} = \sum_{l=2}^{2c} \Sigma_5 d! / d_1! d_2! d_3! \cdot p_1^{d_1} p_2^{d_2} p_3^{d_3} \cdot s_h(p_1, p_3) \cdot e'_l,$$

where second summation Σ_5 is over $\{l - 1 > d_1 - d_3 > l - (2c + 1), d_1 + d_2 + d_3 = d\}$.

$$\alpha^{23} = \sum_{l=2}^{2c} \Sigma_6 d! / d_1! d_2! d_3! \cdot p_1^{d_1} p_2^{d_2} p_3^{d_3} \cdot s_h(p_1, p_3) \cdot e'_l,$$

where second summation Σ_6 is over $\{d_3 - d_1 \geq (2c + 1) - l, d_1 + d_2 + d_3 = d\}$.

Let $E(n \mid p_1, p_3; M, c, d)$ be the average patient pair number during the trial period. $E(n \mid p_1, p_3; M, c, d)$ can be obtained by the following equation,

$$\begin{aligned} E(n) &= (d+c)(\alpha_1^0 + \alpha_3^0) + (d+c+1)(\alpha_1^1 - \alpha_1^0 + \alpha_3^1 - \alpha_3^0) \\ &\quad + (d+c+2)(\alpha_1^2 - \alpha_1^1 + \alpha_3^2 - \alpha_3^1) \\ &\quad + \dots + (d+c+h)(\alpha_1^h - \alpha_1^{h-1} + \alpha_3^h - \alpha_3^{h-1}) + M\alpha_2 \\ &= (d+c)s_0 e' + (d+c+1)(s_1 - s_0)e' \\ &\quad + (d+c+2)(s_2 - s_1)e' \\ &\quad + \dots + M(s_h - s_{h-1})e' \\ &\quad + M\{1 - s_h e'\} \\ &= M - \sum_{k=0}^{h-1} s_k e', \end{aligned}$$

where $e = e_1 + e_{2c+1}$. If treatment A is inferior to treatment B , then the expected loss function due to performing the treatment A , denoted by $[E \text{ Loss}]_A$, is obtained from the assumption in §2 as follows,

$$\begin{aligned} [E \text{ Loss}]_A &= |\delta \mid G [E(n) \\ &\quad + 2d\alpha_1 + \alpha_1\{(N - 2E(n) - 2d)\alpha_{11} + (N/2 - E(n) - d)\alpha_{12}\} \\ &\quad + \alpha_3\{(N - 2E(n) - 2d)\alpha_{31} + (N/2 - E(n) - d)\alpha_{32}\} \\ &\quad + d\alpha_2 + (N - 2M - 2d)\alpha^{21} + (N/2 - M - d)\alpha^{22}]. \end{aligned} \quad (3.9)$$

where G is a constant of positive proportionality. In the same manner, if treatment B is inferior to treatment A , then the expected loss function due to performing the treatment B , denoted by $[E \text{ Loss}]_B$, is obtained as follows,

$$\begin{aligned}
[E \text{ Loss}]_B &= | \delta | G [E(n) \\
&\quad + 2d\alpha_3 + \alpha_3 \{(N - 2E(n) - 2d)\alpha_{33} + (N/2 - E(n) - d)\alpha_{32}\} \\
&\quad + \alpha_1 \{(N - 2E(n) - 2d)\alpha_{13} + (N/2 - E(n) - d)\alpha_{12}\} \\
&\quad + d\alpha_2 + (N - 2M - 2d)\alpha^{23} + (N/2 - M - d)\alpha^{22}]. \tag{3.10}
\end{aligned}$$

By integration (3.9) and (3.10) over a priori distribution for δ , the over all expected loss function (i.e., the average risk), denoted by $\overline{E \text{ Loss}}/NG$, is then constructed.

$$\overline{E \text{ Loss}}/NG = \left\{ \int_{-1}^0 [E \text{ Loss}]_A g(\delta) d\delta + \int_0^1 [E \text{ Loss}]_B g(\delta) d\delta \right\} / NG, \tag{3.11}$$

where $g(\delta)$ denotes the probability density function of a priori distribution for the parameter δ . If $g(\delta)$ is a discrete probability function, the above integrations are replaced by summations in the following way:

$$\overline{E \text{ Loss}}/NG = \left\{ \sum_{\{i|-1 \leq \delta_i < 0\}} [E \text{ Loss}]_A g(\delta_i) + \sum_{\{i|0 < \delta_i \leq 1\}} [E \text{ Loss}]_B g(\delta_i) \right\} / NG. \tag{3.12}$$

4. Truncated sequential design 2

The sequential design 2 for the equivalence test on (2.1) and (2.2) is constructed by trial period and treatment period with the following decision rules. Namely, the procedure is that the treatment period is performed as the better treatment for all the remaining patients, after the better treatment is decided at the end of trial period. The design is incorporated in a similar manner to the sequential design 1, and is shown in Figure 4.1. The truncated sequential procedure is given as follows.

(Case 1-1)

If a sequence reaches the upper boundary at the m -th step, where $c \leq m \leq M - d$, as one accepts the decision H_1 , then assign A for the remaining patients $N - 2m - 2d$ during the treatment period.

(Case 1-2)

If a sequence reaches the lower boundary at the m -th step, where $c \leq m \leq M - d$, as one accepts the decision H_3 , then assign B for the remaining patients $N - 2m - 2d$.

(Case 2)

If a sequence reaches neither the upper or the lower boundary before the $(M - d)$ -th observation pair is observed, as one accepts the decision H_2 , then assign treatment A to half of the remaining patients $(N - 2M)/2$ and treatment B to the other half.

 Figure 4.1 Sequential design 2 for Case 1-1 ($M = 20, c = 3, d = 6$)

Three probabilities of accepting H_1, H_2 and H_3 , $\alpha_i, i = 1, 2, 3$, and the average patient pair number during the trial period, $E(n)$, equal to those of design 1. The expected loss functions are,

$$[E \text{ Loss}]_A = |\delta| G [E(n) + \alpha_1(N - 2E(n)) + \alpha_2(N/2 - M)], \quad (4.1)$$

and

$$[E \text{ Loss}]_B = |\delta| G [E(n) + \alpha_3(N - 2E(n)) + \alpha_2(N/2 - M)]. \quad (4.2)$$

The overall expected loss function, $\overline{E \text{ Loss}}/NG$, has the same form of (3.11)(or (3.12)). The object of statistical design is to determine an optimum value c which minimizes the overall expected loss function for each value of d under $N, M, d, \delta, g(\delta)$ given.

5. Numerical Examples

We shall deal with some numerical examples in the various types of pair (p_A, p_B) with a priori distribution $g(\delta)$ in Table 5.1. To investigate the values of $\overline{E \text{ Loss}}/NG$ for each of d , Table 5.2 and Table 5.3 show respectively the values of $\overline{E \text{ Loss}}/NG$ with c for each of value d on Type 3 under $M = 30$ and $N = 1000$ on design 1 and design 2. Here the optimum value of $\overline{E \text{ Loss}}/NG$ for each of d is denoted by EL^* and the value of c corresponding to EL^* is denoted by c^* . The results are shown as follows:

- (1) The values of c^* take $c = 2, 3$ for design 1 and design 2.
- (2) The value of EL^* on design 2 has smaller value than the value of EL^* on design 1 for each of value d when $d \leq 8$, but the value of EL^* on design 1 has smaller value than it on design 2 when $d \geq 10$.

Then, we can see that the other type of (p_A, p_B) has a similar result. To compare the results for each of the types on design 1 and design 2, Table 5.4 and Table 5.5 show the

probabilities $\overline{\alpha}_i$ of accepting finally the hypotheses of H_i , EL^* and c^* for $d = 18$. Here $\overline{\alpha}_i = \alpha_1\alpha_{1i} + \alpha_2^{2i} + \alpha_3\alpha_{3i}$, $i = 1, 2, 3$ on design 1, and $\overline{\alpha}_i = \alpha_i$, $i = 1, 2, 3$ on design 2.

In Table 5.4 and Table 5.5, $\overline{\alpha}_1$ for any (p_A, p_B) takes a large value except $(p_A, p_B) = (0.7, 0.6)$. Moreover Type 1 has lower values of EL^* , because each of δ on Type 1 takes a large value, while Type 3 has higher values of EL^* , because each of δ on Type 3 takes a small value.

Table 5.6 gives the relation between $\overline{\alpha}_1$ and M for each of three types under $N = 1000$, $d = 18$ on design 1. Furthermore, Figure 5.1 shows the comparison of curve of $\overline{\alpha}_1$ for the selected (p_A, p_B) in each of three types, i.e., $(p_A, p_B) = (0.7, 0.4)$ on Type 1, $(p_A, p_B) = (0.7, 0.5)$ on Type 2 and $(p_A, p_B) = (0.7, 0.6)$ on Type 3. It becomes clear as follows:

- (3) The curve for Type 3 increases as M increases, while the curve for Type 1 is almost flat.

Table 5.7 and Table 5.8 give the relation between EL^* and M for the above three types on design 1 and design 2 under $N = 1000$, $d = 18$, and Figure 5.2 shows the comparison of curve of EL^* among three types. It is mentioned as follows:

- (4) As to design 1, the curve of EL^* for Type 3 decreases as M increases, however the curve for Type 1 is almost unchangeable as M increases. As to design 2, the curves of EL^* for all Types decrease monotonously.
 (5) As to Type 2 and Type 3, the value of EL^* on design 1 has a smaller value than the value of EL^* on design 2 for each of value M when $M \leq 50$, but the value of EL^* on design 2 has a smaller value than the value of EL^* on design 1 when $M \geq 60$.

Table 5.9 and Table 5.10 give the relation between EL^* and N for the above three types on design 1 and design 2 under $M = 30$, $d = 18$. It is mentioned as follows:

- (6) The values of EL^* increase as N increases, specially the value on design 2 increases remarkably, because EL^* is influenced by the design without waiting period.

From the above results, it becomes clear that the superiority among two designs depends on the values of M and d .

6. Further discussions

The study is concerned with two sequential designs for selecting one of two treatments with delayed observations in clinical trials. In practice, when an analyzer wishes to use the sequential designs, the procedure is as follows:

- (1) The probabilities (p_A, p_B) , a priori distribution $g(\delta)$ and the time lag d should be set up by preliminary trials and clinical knowledge.
- (2) The total number of patients N must be estimated from a preliminary survey by restricting region and period.
- (3) We can find out the value of M corresponding to $\overline{\alpha}_i$ to be satisfied by the specified error probability in the Table which shows the relation between M and $\overline{\alpha}_i$.
- (4) The values of EL^* between design 1 and design 2 are compared under the given M , the better of two designs can be selected and the value of c^* is obtained.
- (5) Thus the analyzer can use the sequential design based on observation pairs under M and c^* obtained.

However, regarding use of the design, there are still several difficulties as follows:

- (6) In this study, the time lag d is taken by some fixed values, however if the

time lag will show a variation by the differences among individuals from practical and clinical aspects, we should deal with it as a random variable.

(7) When M is chosen in terms of the precision of test, the average patient pair number $E(n)$ often takes a large value. Then we will again set up an adequate value M from the economical point of view.

(8) It is difficult to decide the total number N of patients on a disease in clinical trials, so we will suggest estimating the value of N from a sample survey.

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Table 5.1 The types for each (p_A, p_B)

p_B	0.4					0.5					0.6				
	p_1	p_2	p_3	δ	$g(\delta)$	p_1	p_2	p_3	δ	$g(\delta)$	p_1	p_2	p_3	δ	$g(\delta)$
p_A	Type 1					Type 2					Type 3				
0.7	.42	.46	.12	.3	.2	.35	.50	.15	.2	.2	.28	.54	.18	.1	.2
0.8	.48	.44	.08	.4	.6	.40	.50	.10	.3	.6	.32	.56	.12	.2	.6
0.9	.54	.42	.04	.5	.2	.45	.50	.05	.4	.2	.36	.58	.06	.3	.2

Table 5.2 $\overline{E Loss}/NG$ (Design 1, Type 3)

d	4	6	8	10	12	14	16	18
1	3.965	3.428	3.017	2.699	2.453	2.260	2.109	1.991*
2	2.926*	2.723*	2.527*	2.357*	2.218*	2.112*	2.036*	1.991*
3		2.733	2.600	2.686	2.692	2.718	2.767	2.838
4			3.600	3.769	3.962	4.167	4.374	4.565
c				5.137	5.535	5.938	6.303	6.567
6					7.013	7.511	7.923	8.156
7						8.664	8.998	9.128
8							9.588	9.623
9								9.844

($N = 1000, M = 30$) The value with asterisk means optimum value of $\overline{E Loss}/NG$ for each d

Table 5.3 $\overline{E Loss}/NG$ (Design 2, Type 3)

d	4	6	8	10	12	14	16	18
1	4.977	4.997	5.017	5.038	5.058	5.079	5.101	5.125
2	2.468*	2.530	2.605	2.701	2.826*	2.996*	3.229*	3.559*
3		2.153*	2.378*	2.654*	2.995	3.419	3.952	4.625
4			3.143	3.581	4.102	4.722	5.456	6.315
c				4.853	5.502	6.233	7.036	7.881
6					6.897	7.618	8.335	8.992
7						8.681	9.207	9.613
8							9.686	9.883
9								9.974

($N = 1000, M = 30$) The value with asterisk means optimum value of $\overline{E Loss}/NG$ for each d

Table 5.4 $\overline{\alpha}_i$, EL^* and c^* (Design 1)

p_B	0.4			0.5			0.6		
	$\overline{\alpha}_1$	$\overline{\alpha}_2$	$\overline{\alpha}_3$	$\overline{\alpha}_1$	$\overline{\alpha}_2$	$\overline{\alpha}_3$	$\overline{\alpha}_1$	$\overline{\alpha}_2$	$\overline{\alpha}_3$
p_A	Type 1			Type 2			Type 3		
0.7	0.957	0.038	0.005	0.844	0.125	0.031	0.618	0.261	0.121
0.8	0.994	0.006	0.000	0.965	0.032	0.003	0.863	0.114	0.023
0.9	1.000	0.000	0.000	0.997	0.002	0.001	0.980	0.019	0.001
	$EL^* = 1.164$			$EL^* = 1.465$			$EL^* = 1.991$		
	$c^* = 2$			$c^* = 2$			$c^* = 2$		

($N = 1000, M = 30, d = 18$)

Table 5.5 $\bar{\alpha}_i$, EL^* and c^* (Design 2)

p_B	0.4			0.5			0.6		
	$\bar{\alpha}_1$	$\bar{\alpha}_2$	$\bar{\alpha}_3$	$\bar{\alpha}_1$	$\bar{\alpha}_2$	$\bar{\alpha}_3$	$\bar{\alpha}_1$	$\bar{\alpha}_2$	$\bar{\alpha}_3$
p_A	Type 1			Type 2			Type 3		
0.7	0.864	0.066	0.070	0.740	0.125	0.135	0.571	0.193	0.236
0.8	0.946	0.028	0.026	0.872	0.073	0.055	0.743	0.153	0.104
0.9	0.987	0.007	0.005	0.960	0.029	0.011	0.889	0.086	0.025
	$EL^* = 2.494$ $c^* = 2$			$EL^* = 3.207$ $c^* = 2$			$EL^* = 3.559$ $c^* = 2$		

 $(N = 1000, M = 30, d = 18)$ Table 5.6 Comparison of three types on $\bar{\alpha}_1$ (Design 1)

M		30	40	50	60	70	80	90	100
(p_A, p_B)									
Type 1	0.7 0.4	0.957	0.961	0.962	0.962	0.962	0.962	0.962	0.962
	0.8 0.4	0.994	0.995	0.995	0.995	0.995	0.995	0.995	0.995
	0.9 0.4	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Type 2	0.7 0.5	0.844	0.857	0.860	0.869	0.872	0.873	0.873	0.904
	0.8 0.5	0.965	0.970	0.974	0.976	0.976	0.976	0.976	0.983
	0.9 0.5	0.997	0.998	0.999	0.999	0.999	0.999	0.999	0.999
Type 3	0.7 0.6	0.618	0.636	0.612	0.629	0.638	0.645	0.658	0.666
	0.8 0.6	0.863	0.881	0.884	0.896	0.900	0.913	0.917	0.918
	0.9 0.6	0.980	0.986	0.988	0.990	0.990	0.992	0.992	0.992

 $(N = 1000, d = 18)$ Figure 5.1 Comparison of three types on $\bar{\alpha}_1$ (Design 1)
 $(N = 1000, d = 18)$ Table 5.7 Comparison of three types on EL^* (Design 1)

M		30	40	50	60	70	80	90	100
Type 1	EL^*	1.164	1.128	1.161	1.161	1.161	1.161	1.161	1.161
	c^*	2	2	2	2	2	2	2	2
Type 2	EL^*	1.465	1.369	1.344	1.312	1.303	1.301	1.300	1.299
	c^*	2	2	3	3	3	3	3	4
Type 3	EL^*	1.991	1.824	1.766	1.679	1.648	1.592	1.562	1.548
	c^*	2	2	3	3	3	4	4	4

 $(N = 1000, d = 18)$

Table 5.8 Comparison of three types on EL^* (Design 2)

M		30	40	50	60	70	80	90	100
Type 1	EL^*	2.494	1.472	1.282	1.197	1.179	1.175	1.174	1.174
	c^*	2	3	4	4	4	4	4	4
Type 2	EL^*	3.207	1.950	1.504	1.262	1.173	1.141	1.129	1.118
	c^*	3	3	3	4	4	4	4	5
Type 3	EL^*	3.559	2.536	1.910	1.619	1.405	1.397	1.233	1.175
	c^*	2	3	3	4	4	4	5	5

($N = 1000, d = 18$)

Figure 5.2 Comparison of three types on EL^* (Design 1)
($N = 1000, d = 18$)

Table 5.9 Comparison of three types on EL^* (Design 1)

N		1000	1500	2000	2500	3000	3500	4000	4500	5000
Type 1	EL^*	1.164	1.274	1.384	1.494	1.604	1.713	1.824	1.932	2.044
	c^*	2	2	2	2	2	2	2	2	2
Type 2	EL^*	1.465	1.830	2.195	2.560	2.925	3.290	3.655	4.020	4.385
	c^*	2	2	2	2	2	2	2	2	2
Type 3	EL^*	1.991	2.751	3.510	4.270	5.030	5.790	6.750	7.310	8.069
	c^*	2	2	2	2	2	2	2	2	2

($d = 18, M = 30$)

Table 5.10 Comparison of three types on EL^* (Design 2)

N		1000	1500	2000	2500	3000	3500	4000	4500	5000
Type 1	EL^*	2.494	3.332	4.170	5.048	5.847	6.685	7.523	8.361	9.199
	c^*	2	2	2	2	2	2	2	2	2
Type 2	EL^*	3.207	4.529	5.850	7.171	8.493	9.814	11.135	12.456	13.778
	c^*	2	2	2	2	2	2	2	2	2
Type 3	EL^*	3.559	5.181	6.803	8.426	10.048	11.670	13.292	14.915	18.537
	c^*	2	2	2	2	2	2	2	2	2

($d = 18, M = 30$)

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