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On A Fixed Point Adaptation Problem for Ordinal Clinical Responses

G. Chattopadhyay
Bureau of Applied Economics and Statistics,
Government of WB, India

A. Chatterjee
Department of Statistics,
University of Burdwan,Golapbag
Burdwan, 713104, WB, India
e-mail: ac_bustat1@yahoo.co.in

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Abstract

In clinical trials often treatment responses are evaluated at certain fixed point after completion of a certain course of treatment. Analysis of such type of data towards studying the efficacy of one drug to the other is always very challenging. Moreover, if the treatment difference is large and the end point of the study is potentially dangerous, it does not seem appropriate to expose the large number of study patients in the inferior arm. To circumvent such situation, implementation of data-dependent treatment allocation techniques among sequentially entering patients have already made its place in medical statistics literatures. Randomized-Play-the-Winner (RPW) rule is one such technique. While adopting RPW rule, it is usually assumed that the treatment responses are instantaneous and dichotomous (or at least can be dichotomized based on some threshold value). The present paper deals with a technique based on the RPW rule for comparing two treatments in a situation when treatment responses are ordinal in nature and patients are evaluated after certain fixed point (time). Here adaptation is based on grouped data already accrued. The proposed procedure is based on 'ridit'analysis. Different asymptotic results related to the proposed technique from a frequentist point of view are studied. Extensive simulation studies have also been performed to study the power of the test and saving in sample from being treated by the inferior treatment. The diagnostic feature of the procedure as indicated by the loss-in-power owing to the implementation of the adaptive design is compared with the 50-50 randomization scheme. The loss have been found to be well compensated by the savings in sample size in not exposing the study patients to the inferior arm.

Keywords and Phrases: Categorical data, clinical trial, consistency, fixed point, adaptive design, nonparametric, play-the-winner rule, sequential, simulation, urn model.

AMS Classification: Primary 62G10, Secondary 62L10.

1 Introduction

Clinical trial is undoubtedly very important for progress towards development of more effective treatments. However, as mentioned by Weinstein (1974) the ethical side of a trial is also a very important issue to be considered, especially when lawyers, sociologists, economists, theologians and physicians have articulated the case that randomized trial presents severe legal, social and ethical problems. In support of necessity of addressing ethical issues in clinical trial Kadane (1996, p-3) mentioned "...it is a challenge to our collective applied cleverness to see if we can somehow devise alternatives that are both arguably better for patients and scientifically responsible". In view of this, many researchers are now interested in adaptive design, which is essentially a data dependent allocation technique of treatments among sequentially entering patients. The literature of adaptive design is replete with concepts and philosophy. Herbert Robbins (see, in particular, Robbins, 1952, 1956) is perhaps the progenitor of adaptive design, and his work was followed by a flurry of activity in the 1960s, beginning with Anscombe (1963) and Colton (1963). To safeguard the ethical imperative of a trial and / or to protect the study patients from paying a handsome price for the benefit of future patients, Zelen (1969) introduced the concept of play-the-winner rule for dichotomous treatment responses based on Robbin's (1952) idea. This rule has been studied extensively in selection and ranking theory. Sobel and Weiss (1970, 1971, 1972), Fushimi (1973) are few among them. A good summary is given by Hoel et. al. (1975). Weinstein (1974) recommended that adaptive designs should be used more often both from statistical and ethical issues. Wei and Durham (1978) and Wei (1979) modified the idea of Zelen (1969) and introduced randomized-play-the-winner rule. The rule can be described through the following urn model:
Start with an urn having two types of balls A and B corresponding to two treatments A and B. Let a be the number of balls of either type. When a patient enters into a system it is assigned a treatment by drawing a ball at random (with replacement). If the response is success (or failure) we add an additional b number of balls of the same (or opposite) kind in the urn. The rule for given (a, b) is denoted by RPW (a, b). On an average this RPW (a, b) scheme allows more patients to be treated by the better treatment in the course of taking treatment decision.

From the above urn model it is clear that the treatment responses need to be binary and instantaneous to apply the RPW rule. Following Wei (1979) many authors (Rosenberger (1996)) have studied this RPW rule. Those studies are restricted for binary treatment outcome, or for continuous treatment outcome after being dichotomized based on some threshold value. Wei (1988) developed a permutation test based on this rule. RPW rule has been used in at least three clinical studies: the Michigan ECMO Trial (Cornell et. al. (1986)) and two anti-depression drug trials sponsored by Eli Lilly (Tamura et. al. (1994)). Although the results of such trials are not very encouraging, several authors (Yao and Wei (1996)) have shown that had RPW rule been used in several other trials, where actually 50-50 allocation rules have

been followed, the ethical aspect could have been better preserved.

In many clinical trials the treatment responses are measured on an ordinal scale (Marlowe et.al. (1989), Sun et. al.(1992), Lauretti et. al. (1996)). Rosenberger (1996) highlighted the importance of considering polytomous, as opposed to dichotomous, responses in case of dose-response studies. Kadane (1996) mentioned that the application of data-determined sequential designs to clinical trials with non-binary end points requires either an arbitrary definition of a dichotomy (success or failure) or a re-expression of a and b of the urn model, as (integer- valued) functions of the data already accrued. Further the treatment responses may not always be instantaneous. In real life, non-binary (particularly ordinal) and non-instantaneous treatment responses are quite common. Many times the patients are evaluated after certain fixed days since administering the treatment. Specially, this is true for outdoor patients (say, for a fever, a clinician may prescribe a dose of three antibiotics a day for four days and then desire to evaluate the patient on the fifth day, i.e., the pre-specified fixed day). It may be noted that in such cases the effect of the treatment might have occurred before the time of evaluation but actually measured at the time of evaluation.

The present paper aims to develop a RPW rule where the treatment responses are ordinal in nature and are not ascertainable immediately before the next patient is randomized. For the same we modify the urn model suitably. The paper comprises of 7 sections. In section 2 we shall describe the motivation of the problem. The test will be formulated in the light of the proposed requirement in section 3. Section 4 deals with some useful results. Several asymptotic properties of the test procedure have been discussed in section 5. A comprehensive simulation study has been done in section 6. The paper ends up with some concluding remarks in section 7 and an appendix.

2 Motivation of the Problem

In the previous section, it has been noted that the conventional RPW rule is applicable only when the treatment response are binary and instantaneous in nature. Rosenberger (1993) considered a permutation test statistics for general but 'instantaneous'outcomes. Chattopadhyay (2004) considered a RPW rule for ordered categorical data modifying the conventional urn model suitably to accommodate the option of more than two treatment responses. However, the method proposed by Chattopadhyay is applicable only when the treatment responses are instantaneous. Rosenberger and Lachin (2002, p-204) stressed upon considering problems when the patient responses are not ascertainable immediately before the next patient is randomized. In fact they also noted that 'instantaneous' responses are used only to simplify the probabilistic properties of the response-adaptive randomization. They mentioned that one might consider two different setups in practice when the responses are not instantaneous.

One can 'adapt'at certain fixed points using grouped data already accrued, or one can factor in a delayed response through updating the urn as each patient responds. Motivated by the comments of Rosenberger and Lachin (2002), we shall consider a fixed-point adaptation technique (i.e., the first setup) for ordinal non-instantaneous (delayed) clinical data by modifying the urn model suitably.

Technique for analysis of ordinal data always received due attention from researchers. Many authors in past decades have considered such techniques. There have been many developments in model-based approaches for such type of data. However, simpler approaches have a long history. Those approaches consist of scoring or assigning values or weights to categories in some way, prior to analysis by methods more familiar in the context of interval scale variable or modifications of them. They have the advantage of being more familiar to researchers who lack the expertise to be fully acquainted with model based approaches and/or do not have adequate computer software to handle them. A very interesting review of literature for such type of data analysis is available in Fielding (1997).

Bross (1958) introduced a simple scoring system called "ridit"(also see Agresti (1984), pp. 167-168 and Fleiss (1973), pp. 102-108). In ridit analysis, instead of arbitrarily selecting scores, the researcher uses cumulative probability scores. Brockett and Levine (1977) noticed that the ridit scores, estimated from the data, have the interesting property that if we combine two adjacent categories and redefine the scores by the same method, then the scores for the remaining categories remain unchanged. The most common category scores viz., equal-interval scores, do not have this property. 'Ridit'stands for "relative to an identified distribution". Ridit analysis has been applied to the study of automobile accident (Bross (1960)), cancer (Wynder et. al. (1960)), schizophrenia (Spitzer et. al. (1965)), preference studies (Pouplard et. al.(1997)). A mathematical study of ridit analysis was made by Kantor et. al. (1968). Fay and Gennings (1996) developed a nonparametric two-sample test for repeated ordinal responses using ridits.

For the preference group, we estimate the proportion of all individuals below a particular category (say j) plus half the proportion in that category, which is the jth ridit. Given the distribution of any other group over the same categories, the mean ridit for that group can be calculated. The mean ridit for a group is simply the sum of the products of observed frequencies times the corresponding ridits divided by the total frequency. It is interesting to note that the jth ridit is nothing but a linear combination of the jth mid rank (Agresti (1984), p-178) and as such the mean ridit may be interpreted as a discrete version of a rank based statistic. The adaptation technique is ultimately based on the mean ridit of grouped data already accrued.
Consider two treatments (say treatment A and treatment B) and assume that the treatment responses are ordinal in nature. Let us also assume that each patient is

evaluated after certain time period (say T days) from the date of administering the treatment. Now, we modify the urn model as follows:
Start with an urn having a number of balls of type A and a number of balls of type B. First T days, draw a ball at random (with replacement) from the urn and treat the entering patient by treatment A provided the type of ball drawn is A else treat the patient by treatment B. Before treating any patient on $(T+t)^{th}$ day $(t \geq 1)$, we calculate sample mean ridit of treatment B with respect to treatment A based on the treatment responses received from the patients treated on day t (say $R_E^{(t)}$) and add additional number of balls in the urn according to the following rule:
For suitably chosen C_t^0 $(C_t^0 > 0)$, add b number of balls of type A provided $R_E^{(t)} > \frac{1}{2} + C_t^0$ or, add b number of balls of type B provided $R_E^{(t)} < \frac{1}{2} - C_t^0$ or, add $\frac{b}{2}$ number of balls of type A and $\frac{b}{2}$ number of balls of type B provide $\frac{1}{2} - C_t^0 \leq R_E^{(t)} \leq \frac{1}{2} + C_t^0$ (b is any even number). Draw a ball at random (with replacement) from the urn and allocate treatment to the entering patients on $(T+t)^{th}$ day noting down the type of ball drawn. On an average this rule also allows more patients to be treated by better treatment in course of decision-making.
Note that, when $\frac{1}{2} - C_t^0 \leq R_E^{(t)} \leq \frac{1}{2} + C_t^0$, addition of $\frac{b}{2}$ number of balls of each kind increases the proportion of balls for the kind that has less representation.

But it has some important features. In the long run if the situation continues (which is almost equivalent to the fact that the two treatments are identical) then the difference between the proportions of balls of the two kinds converges to zero. This means that if, in majority of the cases, treatment A and B are equivalent there is no reason to favor either of the treatment due to its few initial better performance over the other. This appeals to be more practical than maintaining the gain. Secondly, the mathematical complexity and/or intractability can be avoided if during each adaptation totally 'b' new balls are added in the urn. As such, when $\frac{1}{2} - C_t^0 \leq R_E^{(t)} \leq \frac{1}{2} + C_t^0$, we are adding $\frac{b}{2}$ number of balls of each type in the urn.
It is important to observe here that we have assumed that lower treatment response indicates better treatment output and in the sequel we shall derive all results based on this assumption. Otherwise the addition pattern of balls may have to be reversed.

3 Formulation of the Test Procedure

Let X_A and X_B denote the random variables corresponding to the responses of treatment A and B respectively. Now define,

$$\Delta = P(X_A > X_B) - P(X_A < X_B). \tag{3.1}$$

We assume that each treatment when it is applied to a patient has L possible outcomes, viz. $1, 2, .., L$. Define

$$\pi_{kj} = \textit{ Probability that a patient's response is } j \textit{ when}$$

$$\textit{the } k^{th} \textit{ treatment is applied to the patient, } j = 1, 2, .., L, \ k = A, B. \tag{3.2}$$

Based on the observations, our object is to test whether treatment A and B are equivalent in performance or treatment B is better than treatment A. To mean treatment B to be better than treatment A in performance, when lower response indicates better treatment outcome, we can use the measure Δ to be positive. It is important to note here that, one may also be interested in considering the statement that $X_A > X_B$ to mean treatment B to be better than treatment A. But this will needlessly be restrictive (and clinically dubious). For example let X_A and X_B take values 1, 2 , 3 with probabilities 0.1,0.1, 0.8 and 0.04, 0.21 , 0.75 respectively. Then X_A is not stochastically higher than X_B although $\Delta > 0$. Again, $\Delta = 0$ need not necessarily mean the distributions are identical. This is clear from the counter example where X_A and X_B take values 1, 2 , 3 with probabilities 0.25, 0.00 , 0.75 and 0.1, 0.2 , 0.7 respectively. So our problem of interest is,

$$H : \pi_{Aj} = \pi_{Bj}, \ j = 1, 2, .., L \textit{ against } H_a : \Delta > 0. \tag{3.3}$$

Let us observe the treatment responses of n pre-fixed number of patients treated either by treatment A or treatment B through the modified urn model. Then for each patient, on t th day, we have the pair $(\delta_i^{(t)}, Z_{ij}{}^{(t)})$ of random variables as follows:

$$\delta_i^{(t)} = 1 \textit{ or } 0 \textit{ according as the } i^{th} \textit{ patient is treated by } A \textit{ or } B \textit{ on } t^{th} \textit{ day}, \tag{3.4}$$

$$Z_{ij}{}^{(t)} = 1 \textit{ or } 0 \textit{ according as the } i^{th} \textit{ patient, treated on day } t, \textit{ responded } j \textit{ or not.} \tag{3.5}$$

For every j, we also set

$$R_{kj} = \pi_{k1} + \pi_{k2} + .. + \pi_{kj-1} + 0.5\pi_{kj}, k = A, B. \tag{3.6}$$

and get the mean ridit as

$$R = \sum_{j=1}^{L} R_{Aj}\pi_{Bj} \tag{3.7}$$

Observe that R satisfies

$$R = P(X_B > X_A) + 0.5P(X_B = X_A) \tag{3.8}$$

$$= 0.5 - 0.5\Delta. \tag{3.9}$$

This R has a major implication in clinical trials. It measures the effectiveness of one treatment over another. In this connection it is also important to note that $R = 0.5$ under H and $R < 0.5$ under H_a, where H and H_a are as defined in (3.2). Let us now

denote by

$$m = \textit{ Total number of days required to accumulate } n \textit{ number of patients.} \quad (3.10)$$

$$n_t = \textit{ Number of patients treated on day } t,\ t = 1, 2, .., m. \quad (3.11)$$

$$N_A^{(t)} = \sum_{i=1}^{n} \delta_i^{(t)} = \textit{ Number of patients treated by treatment } A \textit{ on day } t. \quad (3.12)$$

$$N_B^{(t)} = \sum_{i=1}^{n} (1 - \delta_i^{(t)}) = \textit{ Number of patients treated by treatment } B \textit{ on day } t. \quad (3.13)$$

$$N_A^{(t)}(j) = \sum_{i=1}^{n} \delta_i^{(t)} Z_{ij}^{(t)} = \textit{ Number of patients in } j \textit{ th response category among patients treated by treatment } A \textit{ on day } t. \quad (3.14)$$

$$N_B^{(t)}(j) = \sum_{i=1}^{n} (1 - \delta_i^{(t)}) Z_{ij}^{(t)} = \textit{ Number of patients in } j \textit{ th response category among patients treated by treatment } B \textit{ on day } t. \quad (3.15)$$

$$p_{kj}^{(t)} = \frac{N_k^{(t)}(j)}{N_k^{(t)}} = \textit{ Proportion of patients in } j^{th} \textit{ response category, on day } t, \textit{ out of the patients treated by treatment } k,\ k = A, B. \quad (3.16)$$

$$N_A = \sum_{t=1}^{m} N_A^{(t)}, N_B = \sum_{t=1}^{m} N_B^{(t)} \quad (3.17)$$

$$N_A(j) = \sum_{t=1}^{m} N_A^{(t)}(j), N_B(j) = \sum_{t=1}^{m} N_B^{(t)}(j) \quad (3.18)$$

$$p_{kj} = \frac{N_k(j)}{N_k}, k = A, B. \quad (3.19)$$

Then based on the outcomes of n_t such patients on day t, we can set an estimate of R as

$$R_E^{(t)} = \sum_{j=1}^{L} r_{Aj}^{(t)} p_{Bj}^{(t)} \quad (3.20)$$

where

$$r_{kj}^{(t)} = p_{k1}^{(t)} + p_{k2}^{(t)} + \ + p_{kj-1}^{(t)} + 0.5 p_{kj}^{(t)}, k = A, B. \quad (3.21)$$

We shall show in subsequent section that $R_E^{(t)}$ tends to R for large n_t and thus smaller under H_a than under H. As such it is always possible to construct a suitable test

based on $R_E = (R_E^{(1)}, , R_E^{(m)})$.
In the next section, we shall show that there exists a positive definite matrix

$$\Lambda = \sigma^2 Diag(1, 1, .., 1), \tag{3.22}$$

such that, for large n, the null distribution of $(\sqrt{n_t}(R_E^{(t)} - \frac{1}{2}, t = 1, 2, , m)'$ can be approximated by $N_m(0, \Lambda)$. Let $S = Diag(s_1^2, s_2^2, .., s_m^2)$, be a consistent estimator of Λ. Then, we construct the test statistic:

$$U_n = \frac{1}{\sqrt{m}} \sum_{t=1}^{m} \sqrt{n_t} \frac{(R_E^{(t)} - 1/2)}{s_t} \tag{3.23}$$

Note that for large n, U_n will tend to be smaller under H_a than under H and thus we reject H at an approximate level of significance α iff

$$U_n < C, \tag{3.24}$$

where C is to be determined from the in-equation

$$P_H(U_n < C) \leq \alpha. \tag{3.25}$$

$\alpha \in (0, 1)$ being the prefixed level of significance.

4 Some Useful Results

In this section we shall deal with some useful asymptotic results corresponding to the proposed sampling scheme. For this we shall first assume that, as $n \to \infty$,

$$n_t \to \infty, t = 1, 2, .., m \; but \; \frac{n_t}{n} \to \lambda_t \in (0, 1) \; is \; such \; that \sum_{t=1}^{m} \lambda_t = 1 \tag{4.1}$$

In the sequel we shall make (4.1) as our basic assumption. Now define the random variables $W_t, t = 1, 2, , m$, as follows:

$$W_t = 0 \; if \; R_E^{(t)} < \frac{1}{2} - C_t^0$$

$$= \frac{1}{2} \; if \; \frac{1}{2} - C_t^0 \leq R_E^{(t)} \leq \frac{1}{2} + C_t^0$$

$$= 1 \; if \; R_E^{(t)} > \frac{1}{2} + C_t^0 \tag{4.2}$$

From the urn model, it is obvious that

$$P(\delta_i^{(t)} = 1) = \frac{1}{2} \; for \; i = 1, 2, .., n_t \; and \; t = 1, 2, .., T. \tag{4.3}$$

Now, following Wei (1988), the conditional probability of $\delta_i^{(T+t)}$ =1 given $(W_1, W_2, .., W_t)$ is given by

$$P(\delta_i^{(T+t)} = 1 | W_1, ..., W_t) = \frac{a + b\sum_{j=1}^{t} W_j}{2a + bt}, i = 1, .., n_{(T+t)}. \tag{4.4}$$

Hence, the unconditional probability is given by

$$P(\delta_i^{(T+t)} = 1) = \frac{a + b\sum_{j=1}^{t} E(W_j)}{2a + bt}, i = 1, .., n_{(T+t)}. \tag{4.5}$$

From (4.1), we have

$$E(W_t) = P(R_E^{(t)} > \frac{1}{2} + C_t^0) + \frac{1}{2}P(\frac{1}{2} - C_t^0 \leq R_E^{(t)} \leq \frac{1}{2} + C_t^0)$$

$$= \frac{1}{2} - \frac{1}{2}[P(R_E^{(t)} < \frac{1}{2} - C_t^0) - P(R_E^{(t)} > \frac{1}{2} + C_t^0)]. \tag{4.6}$$

Noting the fact that $R_E^{(t)}, t = 1, 2, .., m$ are identically distributed and letting

$$\theta_1 = P(R_E^{(t)} < \frac{1}{2} - C_t^0), \theta_2 = P(R_E^{(t)} > \frac{1}{2} + C_t^0), \tag{4.7}$$

we have,

$$\lim_{n\to\infty} P(\delta_i^{(t)} = 1) = \frac{1}{2} - h_t, \; i = 1, 2, .., n_t, \; t = 1, 2, .., m. \tag{4.8}$$

where

$$h_t = 0 \; for \; t = 1, 2, .., T,$$

$$= \frac{1}{2}\frac{(t-T)b}{2a + (t-T)b}(\theta_1 - \theta_2), \; t = T + 1, .., m.$$

We now have the following lemma:
Lemma 4.1: As $n \to \infty$,

$$\frac{N_A^{(t)}(j)}{n_t} \xrightarrow{P} (\frac{1}{2} - h_t)\pi_{Aj}, \frac{N_B^{(t)}(j)}{n_t} \xrightarrow{P} (\frac{1}{2} + h_t)\pi_{Bj} \tag{4.9}$$

$$\frac{N_A(j)}{n} \xrightarrow{P} \pi_{Aj} \sum_{t=1}^{m}(\frac{1}{2} - h_t), \frac{N_B(j)}{n} \xrightarrow{P} \pi_{Bj} \sum_{t=1}^{m}(\frac{1}{2} + h_t) \tag{4.10}$$

and

$$\frac{N_A}{n} \xrightarrow{P} \sum_{t=1}^{m}(\frac{1}{2} - h_t), \frac{N_B}{n} \xrightarrow{P} \sum_{t=1}^{m}(\frac{1}{2} + h_t) \tag{4.11}$$

where h_t is as defined in (4.8).
Proof: Proof of the lemma is given in the appendix.

Corollary 4.1: As $n_t \to \infty, R_E^{(t)}$ converges in probability to R. (4.12)

Proof: Re-writing $R_E^{(t)}$ as

$$R_E^{(t)} = \sum_{j=1}^{L} \frac{N_A^{(t)}(1) + ... + N_A^{(t)}(j-1) + \frac{1}{2}N_A^{(t)}(j)}{N_A^{(t)} N_B^{(t)}} \tag{4.13}$$

and using the above lemma, we have the proof of the corollary.

Corollary 4.2: Under $H, \theta_1 = \theta_2 = 0$, i.e. $h_t = 0, t = 1, 2, .., m$ and under $H_a, \theta_1 \geq 0, \theta_2 = 0$, i.e. $h_t = 0, t = 1, 2, .., T$ and $h_t = \frac{1}{2}\frac{(t-T)b}{2a+(t-T)b}\theta_1 \geq 0, t = T+1, .., m$, where θ_1 and θ_2's are as defined in (4.7). (4.14)

Proof: Proof of the result is obvious from the result of corollary 3.1 and noting the fact that $R = \frac{1}{2}$ under H and $R < \frac{1}{2}$ under H_a.

Note 1: From the above result, we have, under H, as $n \to \infty$,
$\frac{N_A^{(t)}}{n_t}$, $\frac{N_B^{(t)}}{n_t}$, $\frac{N_A}{n}$, $\frac{N_B}{n}$ converges in probability to $\frac{1}{2}$.

Note 2: As $n \to \infty, h_m \geq h_{m-1} \geq .. \geq h_{T+1} \geq h_T = h_{T-1} = .. = h_1$. (4.15)

From the above note 2 it is clear that, when the sample size is large, the chance of treating a patient by the inferior treatment decreases as day proceeds on, serving the ethical imperative of the clinical trial, i.e. allocating lesser number of patients in the inferior arm.

5 Asymptotic Properties

Asymptotic null distributions: In this section our aim is to establish asymptotic null distributions of the test statistics and U_n. This may be noted here that Beder and Heim (1990) studied the asymptotic distribution of test statistic based on sample ridit. Prior to that Agresti (1984) proposed to develop asymptotic results of the same through delta method. But in both cases the sample observations were of fixed size. In the present set up we have to deal with sample mean ridit based on random number of sample observations from both the arm. As such to develop asymptotic null distribution, we have to first prove some special probabilistic results following Billingsley (1979) and thereafter delta method to be invoked as proposed by Agresti (1984).

Theorem 5.1: Under H , as $n_t \to \infty$,

$$\sqrt{n_t}(R_E^{(t)} - \frac{1}{2}) \xrightarrow{D} N(0, \sigma^2) \tag{5.1}$$

where

$$\sigma^2 = 4\sum_{j=1}^{L} R_{Aj}^2 \pi_{Aj} - 1 \tag{5.2}$$

and $X_n \xrightarrow{D} X$ denotes that X_n converges in distribution to X.
Proof of the theorem depends on the following lemma:
Lemma 5.1: Suppose, for each $n_t (t \geq 1)$, there exist two positive integers $\nu_A^{(t)} = \nu_A^{(t)}(n_t)$ and $\nu_B^{(t)} = \nu_B^{(t)}(n_t)$,such that $\nu_A^{(t)} + \nu_B^{(t)} = n_t$ and as $n_t \to \infty, \nu_A^{(t)}, \nu_B^{(t)} \to \infty, \frac{\nu_A^{(t)}}{n_t}, \frac{\nu_B^{(t)}}{n_t} \to \frac{1}{2}$. Then, under H, as $n_t \to \infty$,

$$\frac{1}{\sqrt{n_t}}[\sum_{i=1}^{N_A^{(t)}} Z_{ij}^{(t)0} - \sum_{i=1}^{\nu_A^{(t)}} Z_{ij}^{(t)0}] \xrightarrow{P} 0. \tag{5.3}$$

$$\frac{1}{\sqrt{n_t}}[\sum_{i=1}^{N_B^{(t)}} Z_{ij}^{(t)0} - \sum_{i=1}^{\nu_B^{(t)}} Z_{ij}^{(t)0}] \xrightarrow{P} 0 \tag{5.4}$$

where

$$Z_{ij}^{(t)0} = Z_{ij}^{(t)} - \pi_{Aj} \tag{5.5}$$

Proof: Under H, $Z_{ij}^{(t)0}$'s are iid with mean 0 and variance $\pi_{Aj}(1 - \pi_{Aj})$. Hence using the above lemma and by the well-known standard technique (see problem 27.14 of Billingsley (1979, p-320)), the results (5.3) and (5.4) can easily be established.

Proof of the theorem: Let us re-write $R_E^{(t)}$ as

$$R_E^{(t)} = \sum_{j=1}^{L}(p_{A1}^{(t)} + ... + p_{Aj-1}^{(t)} + \frac{1}{2}p_{Aj}^{(t)})p_{Bj}^{(t)} \tag{5.6}$$

Let $i_m, m = 1, 2, .., N_A(t)$ be those suffixes for which $\delta_{i_m}^{(t)} = 1$, and $l_m (l_m \neq i_m), m = 1, 2, .., N_B(t)$ be those for which $\delta_{l_m}^{(t)} = 0$. Then, under H, as $Z_{ij}^{(t)}$'s are iid and are distributed independently of $\delta_i^{(t)}$'s, without any loss of generality, we assume that first $N_A^{(t)}$ δ's to be 1 and remaining $N_B^{(t)} (= N(t) - N_A^{(t)})$ δ's to be 0. So, under H, we have

$$p_{Aj}^{(t)} \overset{D}{\approx} \frac{\sum_{i=1}^{N_A^{(t)}} Z_{ij}^{(t)}}{N_A^{(t)}} \tag{5.7}$$

where "$X_n \overset{D}{\approx} Y_n$"implies that X_n is asymptotically equivalent in distribution to Y_n. Thus,

$$\sqrt{n_t}(p_{Aj} - \pi_{Aj}) \overset{D}{\approx} \frac{\nu_A^{(t)}}{N_A^{(t)}} \frac{\sqrt{n_t}}{\nu_A^{(t)}} \sum_{i=1}^{\nu_A^{(t)}} Z_{ij}^{(t)0}$$

$$+ \frac{\sqrt{n_t}}{N_A^{(t)}} [\sum_{i=1}^{N_A^{(t)}} Z_{ij}^{(t)0} - \sum_{i=1}^{\nu_A^{(t)}} Z_{ij}^{(t)0}] \tag{5.8}$$

By lemma 5.1, the second term from the R.H.S. of (5.8) tends to zero in probability. Now from (4.9) noting the fact that $\frac{N_A^{(t)}}{n_t}$ converges in probability to $\frac{1}{2}$ under H (observing that in Lemma 5.1, as $n_t \to \infty$, $\frac{\nu_A(t)}{n_t} \to \frac{1}{2}$ i.e. $\frac{N_A^{(t)}}{\nu_A^{(t)}}$ converges in probability to 1), (5.8) gives

$$\sqrt{n_t}(p_{Aj} - \pi_{Aj}) \overset{D}{\approx} \sqrt{\frac{2}{\nu_A^{(t)}}} \sum_{i=1}^{\nu_A^{(t)}} Z_{ij}^{(t)0} \tag{5.9}$$

Similarly, without any loss of generality assuming that first $N_B^{(t)} (= N(t) - N_A^{(t)})$ δ's to be 0 and the remaining δ's to be 1 we have under H,

$$\sqrt{n_t}(p_{Bj} - \pi_{Bj}) \overset{D}{\approx} \sqrt{\frac{2}{\nu_B^{(t)}}} \sum_{i=1}^{\nu_B^{(t)}} Z_{ij}^{(t)0} \tag{5.10}$$

By applying multivariate CLT, we get, as $n \to \infty$,

$$(\sqrt{n_t}(p_{Aj} - \pi_{Bj}, j = 1, .., L; \sqrt{n_t}(p_{Bj} - \pi_{Bj}, j = 1, .., L) \xrightarrow{D} N(0, 2\Lambda), \tag{5.11}$$

where

$$\Lambda = Diag(\Lambda_{11}, \Lambda_{11}) \; and \; \Lambda_{11} = Diag(\pi_{11}, \pi_{12}, , \pi_{1L}) - \pi\pi'. \tag{5.12}$$

$$\pi' = (\pi_{11}, \pi_{12}, , \pi_{1L})'. \tag{5.13}$$

Invoking the delta method, it follows that, under H, as $n \to \infty$,

$$\sqrt{n_t}(R_E^{(t)} - \frac{1}{2}) \xrightarrow{D} N(0, 2\Gamma'\Lambda\Gamma), \tag{5.14}$$

where

$$\Gamma = (1 - r_{A1}, 1 - r_{A2}, , 1 - r_{AL}, r_{A1}, r_{A2}, , r_{AL})'.$$

Observe that

$$\Gamma'\Lambda\Gamma = [1'\Lambda_{11}1 \;\; + \;\; 2r_A'\Lambda_{11}r_A \;\; - \;\; 2r_A'\Lambda_{11}1], \tag{5.15}$$

where

$$1 = (1, 1, , 1)', r_A = (r_{A1}, r_{A2}, , r_{AL})'.$$

Also observe the fact that

$$1'\Lambda_{11} = 0 \; and \; r_A'\Lambda_{11}r_A = \sum_{j=1}^{L} r_{Aj}^2\pi_{Aj} - 1/4. \tag{5.16}$$

Thus using (5.14) and (5.15), the required result follows.
In practice σ^2 is unknown and based on data on t^{th} day a consistent estimator of σ^2 is obtained as

$$s_t{}^2 = \frac{N_A{}^{(t)}S_A(t)^2 + N_B{}^{(t)}S_B^{(t)^2}}{n_t} \tag{5.17}$$

where

$$S_k{}^{(t)^2} = 4\sum_{j=1}^{L} r_{kj}{}^{(t)^2}p_{kj}{}^{(t)}, k = A, B.$$

It is obvious that, under H, as $n \to \infty$,

$$\sqrt{n_t}\frac{(R_E^{(t)} - \frac{1}{2})}{s_t} \xrightarrow{D} N(0,1) \tag{5.18}$$

A reasonable choice of C_t^0 as defined in section 1, may be given by

$$C_t^0 = \tau_{\frac{\beta}{2}} \frac{s_t}{\sqrt{n_t}} \tag{5.19}$$

where $\tau_{\frac{\beta}{2}}$ is upper $\frac{\beta}{2}$ - point of a standard normal deviate (β may be chosen to be different from α defined in (3.25)).
Let us now define

$$\nu_A = \sum_{t=1}^{m} \nu_A^{(t)}, \nu_B = \sum_{t=1}^{m} \nu_B^{(t)} \tag{5.20}$$

then

$$\frac{\nu_A}{n} = \sum_{t=1}^{m} \frac{\nu_A^{(t)}}{n_t}\frac{n_t}{n} \xrightarrow{P} \frac{1}{2}, \frac{\nu_B}{n} = \sum_{t=1}^{m} \frac{\nu_B^{(t)}}{n_t}\frac{n_t}{n} \xrightarrow{P} \frac{1}{2} \tag{5.21}$$

Then proceeding in the same way as in the proof of theorem 5.1, we have the following theorem:

Theorem 5.2: Under H , as $n \to \infty$, $\frac{1}{\sqrt{m}} \sum_{t=1}^{m} \sqrt{n_t}(\frac{R_E^{(t)} - \frac{1}{2}}{s_t}) \xrightarrow{D} N(0,1)$. (5.22)

Proof: Proof is obvious from (5.18) and the fact that $R_E^{(t)}$'s are independent under H.

Consistency: To prove the consistency of the test it is sufficient to show that there exists a function $g = g(\pi_{kj}, j = 1, 2, , L, k = A, B)$, such that , as $n \to \infty$,

$$\frac{1}{\sqrt{n}} U_n \to g, \tag{5.23}$$

where $g = 0$ *or* < 0 according as H or H_a is true. Now, taking $g = \frac{1}{\sqrt{m}} \frac{R - \frac{1}{2}}{\sigma} \sum_{t=1}^{m} \frac{1}{\sqrt{\lambda_t}}$ and using the representations (3.8) and (3.2), we have the following theorem:

Theorem 5.3: The proposed test is consistent against those alternatives for which $\Delta > 0$.

6 Simulation Study

To study, how far the proposed procedure fulfills the objective of preserving the ethical imperative, simulation studies were performed for calculating limiting allocation

proportion corresponding to the inferior treatment (here treatment A). This has been computed through $\frac{ASN(A)}{n}$, where $ASN(A)$ is the average number of patients corresponding to treatment A in a set of 's ' number of simulations (after rounding off to the nearest integer) and is denoted by P_A. The corresponding standard deviation, denoted by S_A has also been simulated. In addition to that the simulated power of the test are obtained under various alternatives. Power of the test has been determined as the proportion of U_n, out of 's ' number of simulations, less than τ_α, τ_α being the upper α -point of a normal deviate. Table 6.1 and 6.2 provides results of some such studies, for 10000 simulations, under different null and alternative hypotheses. From the results of the P_A and S_A it is evident that the main purpose of implementation of RPW rule has been served satisfactorily. Moreover, here we like to refer to Note 2 of section 4, where it has been pointed out that the asymptotic probability of treating a patient by the inferior treatment decreases gradually as day proceeds on. But the same result could not be established analytically for small sample. This is quite evident from the results tabulated in Table 6.1, that the proportion of patients treated by the inferior treatment (treatment A) on t th day given by p_{At} gradually decreases as soon as the first set of patients appear for evaluation in the clinic, i.e, from the $(T+1)^{st}$ day. This is a normal expectation from RPW rule. However the picture is not so clear from such values tabulated in Table 6.2. This is because, in Table 6.1 we have deliberately imputed moderately large number of patients in each day compared to that in Table 6.2. Further, from Table 6.1 and Table 6.2, it is observed that the power of the test increases as the value of R is away from $\frac{1}{2}$, i.e. the treatment difference is large.

To investigate how far the present procedure perform in comparison with the equal sample allocation under various choices of design parameters (a, b), simulation studies are made and tabulated in Tables 6.3 and 6.4. Proportion of savings in sample size for the1st sample (the inferior one) is calculated as $\frac{\frac{n}{2}-ASN(A)}{\frac{n}{2}}$. It is seen that the power of the test under equal allocation (i.e when $b = 0$) is slightly higher compared to that when $b > 0$. However the loss-in-power is well compensated by the reasonably satisfactory proportion of savings in the 1st sample size, i.e., protecting the ethical aspect of the clinical trial. At the same time the diagnostic feature of the test is not hampered to a great extent owing to the minor loss in power compared to the 50-50 equal allocation rule. It is further observed that the proportion of savings increases when R is smaller (i.e. the treatment difference is large) and $\frac{b}{a}$ is higher. However, this should in no way be the guiding feature towards the choice of a and b. Some further discussion on this issue is given in the next section. Note that, simulated size is not expected to be exactly equal to the theoretical size condition. This happened in the present study also. However the departure of the simulated size is not very high compared to α, the theoretical size.

Table 1: Simulation study results of P_A , S_A and Power (P_{ab}) of the test for design parameters (a, b) $(n = 250, m = 5, T = 2, n_1 = 40, n_2 = 60, n_3 = 50, n_4 = 30, n_5 = 70, \alpha = 0.05, \beta = 0.05)$

L	$\pi_{Aj}, j = 1, .., L$	$\pi_{Bj}, j = 1, .., L$	R	$p_{At}, t = T + 1, ..., m$	P_A	S_A	P_{12}	P_{10}
3	.1,.3,.6	.2,.4,.4	.39	.43,.40,.38	.438	.059	.945	.968
3	.1,.3,.6	.1,.5,.4	.41	.45,.42,.41	.454	.056	.875	.875
3	.1,.3,.6	.1,.3,.6	.5	.50,.50,.50	.5	.044	.047	.047
4	.2,.2,.2,.4	.3,.3,.2,.2	.38	.43,.39,.37	.437	.058	.957	.969
4	.2,.2,.2,.4	.2,.3,.3,.2	.42	.46,.44,.43	.466	.054	.726	.734
4	.2,.2,.2,.4	.2,.2,.2,.4	.5	.50,.50,.50	.5	.045	.056	.059
5	.2,.2,.2,.2,.2	.3,.3,.2,.1,.1	.38	.43,.39,.37	.439	.058	.961	.965
5	.2,.2,.2,.2,.2	.2,.3,.3,.1,.1	.42	.46,.44,.43	.466	.053	.722	.734
5	.2,.2,.2,.2,.2	.2,.2,.4,.1,.1	.44	.47,.46,.45	.475	.052	.55	.546
5	.2,.2,.2,.2,.2	.2,.2,.2,.2,.2	.5	.50,.50,.50	.5	.046	.055	.055

Table 2: Simulation study results of P_A, S_A and Power (P_{ab}) of the test for design parameters $(a, b)(n = 200, m = 10, T = 2, n_i = 20, i = 1, 2, .., 10, \alpha = 0.05, \beta = 0.05,)$

L	$\pi_{Aj}, j = 1, .., L$	$\pi_{Bj}, j = 1, .., L$	R	$p_{At}, t = T + 1, ..., m$	P_A	S_A	P_{12}	P_{10}
3	.1,.3,.6	.3,.3,.4	.37	.43,.43,.41,.41,.41,.40, .40,.40	.429	.070	.981	.984
3	.1,.3,.6	.2,.4,.4	.39	.44,.44,.42,.42,.42,.41, .42,.41	.440	.069	.937	.957
3	.1,.3,.6	.1,.5,.4	.41	.45,.45,.43,.43,.43,.43, .43,.42	.450	.068	.84	.84
3	.1,.3,.6	.2,.31,.49	.43	.46,.47,.46,.46,.46,.46,.46,.46	.469	.062	.613	.624
3	.1,.3,.6	.15,.36,.49	.44	.46,.47,.46,.46,.46,.46, .46,.46	.471	.060	.519	.523
3	.1,.3,.6	.1,.3,.6	.5	.50,.50,.50,.50,.50,.50, .50,.50	.501	.052	.055	.055
4	.2,.2,.2,.4	.3,.3,.2,.2	.38	.43,.44,.43,.42,.42,.41, .42,.40	.440	.069	.922	.941
4	.2,.2,.2,.4	.3,.2,.3,.2	.4	.45,.46,.44,.44,.42,.44, .44,.43	.454	.064	.863	.871
4	.2,.2,.2,.4	.2,.3,.3,.2	.42	.45,.47,.45,.45,.45,.45, .45,.45	.463	.064	.694	.699
4	.2,.2,.2,.4	.2,.2,.3,.3	.47	.47,.45,.48,.48,.48,.48, .48,.48	.487	.054	.179	.199
4	.2,.2,.2,.4	.2,.2,.2,.4	.5	.50,.50,.50,.50,.50,.50, .50,.50	.501	.054	.063	.063
5	.2,.2,.2,.2,.2	.35,.25,.2,.1,.1	.37	.43,.43,.42,.42,.41,.41, .41,.40	.434	.07	.961	.969
5	.2,.2,.2,.2,.2	.3,.3,.2,.1,.1	.38	.44,.44,.43,.42,.43,.42, .42,.41	.443	.068	.922	.934
5	.2,.2,.2,.2,.2	.35,.2,.2,.15,.1	.39	.44,.45,.44,.43,.44,.43, .43,.42	.449	.066	.879	.898
5	.2,.2,.2,.2,.2	.2,.3,.3,.1,.1	.42	.46,.47,.46,.45,.46,.45, .45,.45	.466	.062	.659	.675
5	.2,.2,.2,.2,.2	.25,.25,.2,.2,.1	.43	.46,.47,.47,.46,.47,.47,.46,.46	.473	.058	.558	.561
5	.2,.2,.2,.2,.2	.2,.2,.4,.1,.1	.44	.46,.47,.47,.46,.47,.47, .47,.46	.474	.056	.471	.487
5	.2,.2,.2,.2,.2	.2,.2,.2,.2,.2	.5	.48,.50,.50,.50,.50,.50, .50,.50	.498	.047	.047	.039

Table 3: Comparative study with equal sample allocation based on simulation in respect of power (P_{ab}) and savings (S_{ab}) in first sample size for design parameters (a, b) $(n = 250, m = 5, T = 2, n_1 = 40, n_2 = 60, n_3 = 50, n_4 = 30, n_5 = 70, \alpha = 0.05, \beta = 0.05)$

L	$\pi_{Aj}, j = 1, .., L$	$\pi_{Bj}, j = 1, .., L$	R	P_{10}	P_{12}	P_{14}	P_{16}	S_{12}	S_{14}	S_{16}
3	.1,.3,.6	.2,.4,.4	.39	.968	.945	.945	.937	.12	.152	.16
3	.1,.3,.6	.1,.5,.4	.41	.875	.875	.875	.875	.09	.112	.12
3	.1,.3,.6	.1,.3,.6	.5	.047	.047	.055	.059	0	0	0
4	.2,.2,.2,.4	.3,.3,.2,.2	.38	.969	.957	.953	.957	.13	.152	.16
4	.2,.2,.2,.4	.2,.3,.3,.2	.42	.734	.726	.710	.707	.064	.08	.09
4	.2,.2,.2,.4	.2,.2,.2,.4	.5	.059	.066	.063	.063	0	0	0
5	.2,.2,.2,.2,.2	.3,.3,.2,.1,.1	.38	.965	.961	.953	.949	.12	.152	.16
5	.2,.2,.2,.2,.2	.2,.3,.3,.1,.1	.42	.734	.722	.703	.707	.072	.08	.09
5	.2,.2,.2,.2,.2	.2,.2,.4,.1,.1	.44	.546	.550	.558	.55	.048	.064	.064
5	.2,.2,.2,.2,.2	.2,.2,.2,.2,.2	.5	.055	.055	.063	.063	0	0	0

Table 4: Comparative study with equal sample allocation based on simulation in respect of power (P_{ab}) and savings (S_{ab}) in first sample size for design parameters $(a, b)(n = 200, m = 10, T = 2, n_i = 20, i = 1, 2, .., 10, \alpha = 0.05, \beta = 0.05)$

L	$\pi_{Aj}, j = 1, .., L$	$\pi_{Bj}, j = 1, .., L$	R	P_{10}	P_{12}	P_{14}	P_{16}	S_{12}	S_{14}	S_{16}
3	.1,.3,.6	.3,.3,.4	.37	.984	.981	.977	.977	.14	.16	.17
3	.1,.3,.6	.2,.4,.4	.39	.957	.937	.930	.937	.12	.13	.15
3	.1,.3,.6	.1,.5,.4	.41	.840	.84	.844	.824	.10	.11	.12
3	.1,.3,.6	.2,.31,.49	.43	.624	.614	.629	.625	.06	.07	.08
3	.1,.3,.6	.15,.36,.49	.44	.523	.519	.538	.538	.06	.07	.07
3	.1,.3,.6	.1,.3,.6	.5	.055	.055	.052	.055	0	0	0
4	.2,.2,.2,.4	.3,.3,.2,.2	.38	.941	.922	.918	.926	.12	.14	.15
4	.2,.2,.2,.4	.3,.2,.3,.2	.4	.871	.863	.867	.866	.09	.10	.11
4	.2,.2,.2,.4	.2,.3,.3,.2	.42	.699	.694	.702	.691	.07	.08	.09
4	.2,.2,.2,.4	.2,.2,.3,.3	.47	.199	.179	.199	.195	.03	.03	.04
4	.2,.2,.2,.4	.2,.2,.2,.4	.5	.063	.063	.058	.055	0	0	0
5	.2,.2,.2,.2,.2	.35,.25,.2,.1,.1	.37	.969	.961	.957	.953	.13	.15	.16
5	.2,.2,.2,.2,.2	.3,.3,.2,.1,.1	.38	.934	.922	.902	.903	.11	.13	.14
5	.2,.2,.2,.2,.2	.35,.2,.2,.15,.1	.39	.898	.879	.883	.879	.10	.11	.12
5	.2,.2,.2,.2,.2	.2,.3,.3,.1,.1	.42	.675	.659	.659	.655	.07	.08	.08
5	.2,.2,.2,.2,.2	.25,.25,.2,.2,.1	.43	.561	.558	.550	.554	.05	.06	.07
5	.2,.2,.2,.2,.2	.2,.2,.4,.1,.1	.44	.487	.471	.472	.484	.05	.06	.07
5	.2,.2,.2,.2,.2	.2,.2,.2,.2,.2	.5	.039	.047	.047	.047	0	0	0

7 Concluding Remarks

Tamura et. al. (1994) rightly felt that adaptive designs represents a middle ground between the community benefit and the individual benefit and will always be subject to attack from either side. Thus in one-side when the potential benefits of adaptive allocation for clinical trials was recognized by many researchers (Cornfield et. al. (1969), Weinstein (1974)), others advocated strongly against any form of adaptive design (Royall (1991)). Kadane (1996, p-310) mentioned "..although the ethical and especially the legal materials are American in orientation, the same general considerations apply in Europe but perhaps less so to Japan ". Though many papers have been published on the methodology of adaptive sampling, there are few examples of its implementation in practice. Both logistical and ethical issues have been cited for this lack of usage. Rosenberger and Lachin (2002, p-208) mentioned that although an adaptive design does not eliminate the ethical problems of randomizing patients to the inferior treatment, it mitigates by making the probability of assignment to the inferior treatment smaller. The proposed method may be considered to be an attractive alternative to the usual 50:50 randomization for certain clinical trials. Kadane (1996, p-310) deserve adaptive technique to be one of the options considered in designing clinical trial. He further mentioned "...ethical ideas change (and, we hope advanced) over time. A result of our increased sensitivity to ethical issues can be a wish to conduct clinical trials differently". Rosenberger (1999) discussed conditions under which response adaptive randomization is reasonable. Some of them are (1) the therapies have been evaluated previously for toxicity, (2) delay in response is moderate, allowing the adaptation to take place, (3) the experimental therapy is expected to have significant benefits to the public health, (4) modest gain in terms of treatment successes are desirable from an ethical standpoint, (5) duration of the trial is limited and recruitment can take place during most or all of the trial. The applicability of the present method, being an adaptive technique, is thus restricted by the conditions of Rosenberger (1999) as well.

This is interesting to observe here that in the proposed technique upto certain fixed time (here T-days), prior to the start of adaptation, equal allocation technique has been implemented. In the subsequent days chance of treating a patient has been changed to be different from half through the change in urn model but remains same for all patients treated on that day, i.e., the fixed-point adaptation has been invoked and the adaptation is based on grouped data. Thus the chance of allocating a very few number of patients in the inferior arm, as happened in ECMO trial (Cornell et. al. (1986)) can be controlled in the proposed technique.

The proposed test on an average successfully tackles the ethical imperative to provide best possible medical care to the patients in the context of a clinical trial when the treatment responses are measured on a ordinal scale. At the same time, owing to the imbalance between the sample sizes there is a loss in power, which might be taken

to be marginal. This loss of power feature has been noted in the previous studies on randomized play-the-winner rule (Rosenberger et. al.(2001), Stallard and Rosenberger (2002), Hu and Rosenberger (2003)). Ivanova (2003) mentioned that high variability of adaptive designs has made them somewhat impractical even though they are appealing from an ethical point of view. One reason is that these random allocation schemes are based on random responses from patients and hence highly variable.

The optimum choices of the design parameters viz. a and b may be a major issue while considering the ethical aspect, as for different choices of the design parameters, the proportion of savings as well as powers are different. Hardwick and Stout (1995) reviewed several criteria that one may wish to optimize, including expected number of treatment failures, expected number of success lost, expected number of patients assigned to the inferior treatment, the total expected sample size, the probability of correct selection, or total expected cost. Of course, the first two criteria are valid for binary responses only. The general optimization approach derives from the approach of Jennison and Turnbull (2000), and can be traced back to ideas of Hayre (1979). The idea is to fix the variance of the test statistic to be constant and then to find an optimal allocation ratio. Hayre and Turnbull (1981) considered the general formulation with binary response in the context of sequential estimation. Melfi and Page (1998) showed that a change in the allocation proportion might also serve to increase efficiency of the estimation. Rosenberger et. al. (2001) also dealt with binary data. In a very recent study Hu and Rosenberger (2003) established a precise link between power and the variability of design. There they have compared four adaptive designs, viz, sequential maximum likelihood procedure (SMLE), doubly adaptive biased coin design (DBCD) of Eisele (1994), randomized play-the-winner (RPW) rule and drop-the-loser (DL) rule of Ivanova (2003). DBCD, which is designed to sequentially target the optimal allocation, has been seen to be quite powerful but the power is less compared to DL rule. Hu and Rosenberger (2003) favored DBCD rule because it is flexible in terms of targeting any desired allocation. DL rule is superior if one is interested only in the urn limiting allocation. However the recent studies on DL rule and DBCD rule are restricted to binary treatment responses only. The non-binary case with responses being instantaneous or delayed require due attention.

One notable feature of the present test is its applicability when the treatment responses are not instantaneous. An experimenter only need to adjust the clinic time in the manner to get the opportunity of evaluating the performance of the patients treated earlier before taking treatment decision regarding patients on the current day. The case of updated control group, where the responses of all the previously treated patients who have been evaluated are taken into account; has not been considered here as this will give rise to dependent set up and as such will be much more complex to derive analytic solutions. Moreover, there may be missing patients, which may be interpreted as censored data. Repeated measures on a single patient at different time

points are quite common in clinical trials. In such situations the present method has to be updated in the light of the longitudinal ordered categorical data. Further, there may be bio-markers available to assess the prognostic factors for the patients, or the general health condition of the patients have to be taken into account which may well be translated in terms of choice of appropriate co-variates while allocating treatments to the patients. The responses may be multivariate in nature, some of which are ordered categorical and the rest may be continuous. In clinical trials, sometimes it is logical and rational to adopt a crossover trial, when a particular treatment fails to give reasonable response up to a given time point. There may be multi-site as well as multi-arm clinical trials where treatment responses are to be evaluated respectively on the basis of trials conducted simultaneously at several locations or for trials involving more than two treatments. Some progress in these regards has already been made and the authors propose to address these issues in subsequent communications.

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Appendix

In this section, we shall give detail proof of the Lemma 4.1 stated in this article.

Proof of Lemma 4.1: Note that, $\frac{N_A^{(t)}(j)}{n_t} = \frac{1}{n_t}\sum_{i=1}^{n_t}\delta_i^{(t)}$ and so from (4.8), we have, as $n_t \to \infty$,

$$\frac{E(N_A^{(t)}(j)}{n_t} \to (\frac{1}{2} - h_t). \tag{A.1}$$

Again, from the urn model, it is trivial that for a particular t and any $i' \neq i$,
$Cov(\delta_i^{(t)}, \delta_{i'}^{(t)}) = 0$ *and as* $n_t \to \infty$

$$\frac{Var(N_A^{(t)}(j)}{n_t} = \frac{1}{n_t^2}\sum_{i=1}^{n_t} V(\delta_i^{(t)}) \leq \frac{1}{4n_t} \to 0. \tag{A.2}$$

Hence (A.1) and (A.2) together implies that, as $n_t \to \infty$,

$$\frac{N_A^{(t)}(j)}{n_t} \xrightarrow{P} (\frac{1}{2} - h_t). \tag{A.3}$$

Similarly, it can be shown that, as $n_t \to \infty$,

$$\frac{N_A^{(t)}(j)}{n_t} \xrightarrow{P} (\frac{1}{2} + h_t). \tag{A.4}$$

Noting the fact that $\frac{N_k}{n} = \sum_{t=1}^{m}\frac{n_t}{n}\frac{N_k^{(t)}}{n_t}$, k = A, B and using (A.3), (A.4) and (4.1), we have the result (4.11). Further, observe that

$$N_A^{(t)}(j) - N_A^{(t)}\pi_{Aj} = \sum_{i=1}^{n}\delta_i^{(t)}(Z_{ij}^{(t)} - \pi_{Aj}) = \sum_{i=1}^{n} V_i(say) \tag{A.5}$$

It is easy to show that (A.5) is a zero mean martingle satisfying the condition that as $n_t \to \infty, \sum_{i=1}^{n_t} E(V_i^2) \xrightarrow{P} 0$. Hence by (13.13) of Rosenberger and Lachin (2002), we have, as $n_t \to \infty$,

$$\frac{1}{n_t}\sum_{i=1}^{n_t} E(V_i) \xrightarrow{P} 0. \tag{A.6}$$

Thus, as $n_t \to \infty$,

$$\frac{[N_A^{(t)}(j) - N_A^{(t)}\pi_{Aj}]}{n_t} \xrightarrow{P} 0 \tag{A.7}$$

Similarly, it can be shown that, as $n_t \to \infty$,

$$\frac{[N_B^{(t)}(j) - N_B^{(t)}\pi_{Bj}]}{n_t} \xrightarrow{P} 0 \tag{A.8}$$

Hence, using (A.3) and (A.4) respectively in (A.7) and (A.8), we have the result (4.9). The result (4.10) can be obtained using (4.1) and as an obvious extension of (4.9).