CHAPTER-6
RANDOMIZED PLAY-THE-WINNER RULE FOR ORDERED
CATEGORICAL DATA

6.1 INTRODUCTION

In chapter 4 of the present dissertation it has been mentioned that randomized
play-the-winner (RPW) rule, more generally adaptive designs, gained its popularity as
the classical sequential trials do not resolve the ethical dilemma posed by the
increasingly available information during the course of the trial. Such informations
may suggest that the new therapy is preferred, but prior to reaching a pre-chosen level
of "statistical significance" the control will still be assigned to every other patient
entering such trial. To safeguard the ethical dilemma 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. Subsequently Wei and Durham (1978) and Wei (1979) modified this idea
and introduced randomized-play-the-winner rule. Wei (1988) developed a
permutation test based on this rule. This RPW rule has been used in at least three
clinical studies: the Michigan ECMO Trial (cf. Cornell et. al. (1986)) and two anti-
depression drug trials sponsored by Eli Lilly (cf. Tamura et. al. (1994)). The design
may well be illustrated through an urn model and has already been discussed in
section 1.2 of chapter 1. A good number of works, based on this randomized play-the-
winner rule, have also been developed. Among those are Yao and Wei (1996),
Bandyopadhyay and Biswas (1997a, 1997b), Biswas and Basu (2001). But all the
previous works are pertaining to dichotomized responses or continuous responses
after being dichotomized using some threshold value. Rosenberger (1993) developed
a permutation test statistic using ranks for general outcome based on randomized
play-the-winner rule. However, in the previous chapter, we have seen that in clinical
trials polychotomous treatment responses are quite common. Those are measured on
an ordinal scale rather than on a continuous scale. There we have discussed a partially
sequential test procedure for such type of ordinal treatment responses. In the present
chapter our aim is to discuss a RPW rule, proposed by Chattopadhyay (2003), for
polychotomous treatment responses measured on an ordinal scale and a suitable
technique for testing identity of two treatments after allocating treatments among the
sequentially entering patients through RPW rule. Let there be two treatments A and B and outcome of each treatment may be one of 1, 2, ..., L. Throughout this article, let us further assume that a smaller value of response category represents a better treatment outcome. Hence we have to modify the urn model. The modified urn model is as under:

Start with an urn having two types (type A and type B) of ball. 'a' number of balls of each type. Draw a ball at random (with replacement) from the urn. Note down the type of the ball drawn. Treat the entering patient by the corresponding treatment (treatment A for type A ball and B for type B ball). Now, if the entering patient is having response in category j, we add an additional (L-j)b balls of the same kind and (j-1)b balls of opposite kind in the urn before we take the treatment decision of the next patient. On an average this rule also allows more patients to be treated by better treatment in course of decision making. Let us denote this rule by RPWO(a, b) (here 'O' stands for 'ordinal' data whereas RPW has usual sense). In section 6.2 of this chapter the proposed test has been formulated. Section 6.3 deals with relevant probability distributions. The asymptotic null distribution of the test statistic as well as several asymptotic properties have been discussed in sections 6.4 and 6.5. An extensive simulation study has been done in section 6.6 to find the power along with average sample number corresponding to both the treatments of the proposed test by following RPW rules with various parameter combinations. These values have been compared with 50-50 allocation scheme. It has been observed that, a moderate saving in terms of not exposing the patients to the inferior arm may, well compensate the marginal loss of power in each case. In section 6.7 a real life data set (with some modifications to fit in the present set up), as mentioned in the case of the first investigator of Boos and Brownie (1992), has also been analyzed in the light of the present RPWO (5,2) scheme to ensure the preservation of ethical aspect of the clinical trial. The chapter ends up with some conclusions and recommendations provided in section 6.8.

6.2. FORMULATION OF THE TEST PROCEDURE

Let on the basis of the observations corresponding to treatments A and B our object is to test

\[ H: A = B \text{ against } H_a: B > A, \]  

(6.2.1)
where the symbol '>', is used to represent "better than".

Let us write

\[ \pi_{kj} = \text{Probability that a patient's response is } j \text{ when the } k\text{-th treatment is applied to the patient, } j=1,2,\ldots,L, k = A, B. \quad (6.2.2) \]

and use the variable \( X_A \) and \( X_B \) to denote the response corresponding to treatment A and B respectively. Like in Boos and Brownie (1992), let us now define two measures as follows:

\[ \mu_d = E(X_A) - E(X_B) \quad \text{and} \quad \Delta = P(X_A > X_B) - P(X_A < X_B) \]

where \( E(X_k) = \sum_{j=1}^{L} j \pi_{kj} \), \( k = A, B \).

To mean treatment B to be better than treatment A in performance, when lower response indicates better treatment outcome, we can either use the measure \( \mu_d \) to be positive or that the measure \( \Delta \) to be positive. However, in case of ordinal data \( \Delta > 0 \) does not always imply that \( \mu_d > 0 \) and vice versa (e.g. \( X_A \) and \( X_B \) equal to 1,2,3 with the \( X_A \) probabilities being .1,1,8 and \( X_B \) probabilities being .04,.21 and .75. Here \( \Delta > 0 \) but \( \mu_d < 0 \) and if \( X_A \) probabilities are 0.2, 0.4, 0.4 and \( X_B \) probabilities are 0.32, 0.18 and 0.5 then \( \Delta < 0 \) but \( \mu_d > 0 \). Further neither \( \Delta = 0 \) nor \( \mu_d = 0 \) implies that the distributions are identical (e.g. \( X_A \) and \( X_B \) taking values 1,2,3 with \( X_A \) -probabilities 0.2, 0.4, 0.4 and \( X_B \)-probabilities 0.3, 0.2, 0.5 respectively implies \( \mu_d = 0 \) but \( X_A \) and \( X_B \) are not identical. Similarly when \( X_A \) and \( X_B \) take values 1,2,3 with \( X_A \) -probabilities 0.25, 0, 0.75 and \( X_B \) -probabilities 0.1, 0.2, 0.7 respectively then \( \Delta = 0 \) but \( X_A \) and \( X_B \) are not identically distributed). Thus at present by (6.2.1) we shall mean

\[ H: \pi_{Aj} = \pi_{Bj} \text{ for all } j = 1,\ldots,L \text{ against } H_a: \mu_d > 0. \quad (6.2.4) \]

(The testing problem of \( H \) against restricted alternative \( H_a^*: \mu_d > 0, \Delta > 0 \) will be discussed in a later section). Let us consider that we observe the treatment responses of \( n \) pre-fixed number of patients treated either by treatments A or B through RPWO (a, b) sampling scheme. Then for each patient we have the pair \( (\delta_i, \zeta_{i,j}) \) of random variables as follows:

\[ \delta_i = 1 \text{ or } 0 \text{ according as the } i\text{ th patient is treated by A or B.} \quad (6.2.5) \]
\[ Z_{ij} = 1 \text{ or } 0 \text{ according as the } i \text{ th patient's treatment response is } j \text{ or not.} \quad (6.2.6) \]

\[ N_A = \sum_{j=1}^{a} \delta_j = \text{Number of patients treated by treatment A.} \quad (6.2.7) \]

\[ N_B = \sum_{j=1}^{a} (1 - \delta_j) = \text{Number of patients treated by treatment B.} \quad (6.2.8) \]

\[ N_A(j) = \sum_{j=1}^{a} \delta_j Z_{ij} = \text{Number of patients in } j \text{-th response category among patients treated by treatment A.} \quad (6.2.9) \]

\[ N_B(j) = \sum_{j=1}^{a} (1 - \delta_j) Z_{ij} = \text{Number of patients in } j \text{-th response category among patients treated by treatment B.} \quad (6.2.10) \]

\[ p_{kj} = \frac{N_k(j)}{N_k} = \text{Proportion of patients in } j \text{-th response category out of the patients treated by treatment } k, k=A,B. \quad (6.2.11) \]

We now have the estimate of \( E(X_A) \) and \( E(X_B) \) as:

\[ \overline{X}_A = \sum_{j=1}^{l} j p_{A,j} \quad \text{and} \quad \overline{X}_B = \sum_{j=1}^{l} j p_{B,j} \]

respectively. As smaller response indicates better treatment outcome \( T_n = (\overline{X}_A - \overline{X}_B) \) will tend to be larger under \( H_1 \) than under \( H \). Thus a right tailed test based on \( T_n \) can be used as an approximate test for the problem \((6.2.1)\). We reject \( H \) if and only if

\[ T_n > C \quad (6.2.12) \]

where, \( C \) is determined from the size condition

\[ P_H \left( T_n > C \right) \leq \alpha, \quad (6.2.13) \]

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

### 6.3 RELEVANT PROBABILITY DISTRIBUTIONS

In this section we shall deal with several probability distributions corresponding to RPWO \((a,b)\) sampling scheme. For this we first observe that, corresponding to the treatment outcome \( j \), addition of \((L-j)b\) balls of the same kind and \((j-1)b\) balls of the opposite kind is equivalent to the addition of \( W_ib \) balls of the same kind and \((L-1-W_i)b\) balls of the opposite kind, where \( Z_{ij} \)'s are as defined in \((6.2.6)\) and

\[ W_i = \sum_{j=1}^{l} (L-j)Z_{ij} \quad (6.3.1) \]

Now, following Wei (1988), the conditional probability of \( \delta_{Z+1} = 1 \) given \((\delta_1, \delta_2, \ldots, \delta_a, Z_{11}, \ldots, Z_{1L}, \ldots, Z_{a1}, \ldots, Z_{aL}) \) is given by
\[ P_{2+1} = \frac{a + b(2 \sum_{m=1}^{L} W_i \delta_i + (L-1) \lambda - (L-1) \sum_{m=1}^{L} \delta_i - \sum_{m=1}^{L} W_i)}{2a + b(L-1) \lambda} \]  

(6.3.2)

From the urn model, it is clear that

\[ P_1 = P(\delta_1 = 1) = 1/2, \quad E(\delta_1) = 1/2 \]  

(6.3.3)

and using (6.2.2), we have for any \( i \) and \( j \)

\[ E(Z_{ij}) = \pi_{A_i} P(\delta_i = 1) + \pi_{B_j} P(\delta_j = 0). \]  

(6.3.4)

Denoting

\[ \Pi_k = \sum_{j=1}^{k} (L - j) \pi_{sj} = L - E(X_k), \quad k = A, B, \]  

(6.3.5)

we obtain the marginal distributions successively as follows:

\[ P_2 = P(\delta_2 = 1) = E[ P(\delta_2 = 1| \delta_1, Z_{11}, ..., Z_{1L})] = E[ \frac{1}{2} (2W_1 \delta_1 + (L-1) \delta_1 - W_1)] (2a + (L-1)b) = \frac{1}{2} - d_2 \]  

(say) (6.3.6)

where

\[ d_2 = \frac{1}{2} (\Pi_B - \Pi_A) \left( \frac{b}{2a + (L-1)b} \right) = \frac{1}{2} b \mu_{\delta_i}/(2a + (L-1)b). \]

In general, it can be shown that

\[ P_n = P(\delta_n = 1) = \frac{1}{2} - d_n \]  

(6.3.7)

where

\[ d_n = \left[ \sum_{j=2}^{n-1} d_j \right] (\Pi_B - \Pi_A)(-(L-1)) + (n-1)(\Pi_B - \Pi_A)/2 \left( \frac{b}{2a + (n-1)(L-1)b} \right). \]  

(6.3.8)

We shall now observe the following properties of \( d_n \).

**Lemma 6.3.1** For any \( n > 2 \), \( d_n \leq 2d_{n-1} \) provided \( d_{n-1} \geq d_2 \).  

(6.3.9)

**Proof**: Using the representation (6.3.8), we have

\[ d_n = \frac{d_{n-1}((\Pi_B + \Pi_A)b + 2a + (n-3)(L-1)b) + b(\Pi_B - \Pi_A)/2}{2a + (n-1)(L-1)b} \]

\[ = \frac{d_{n-1}((\Pi_B + \Pi_A)b + 2a + (n-3)(L-1)b) + (2a + (L-1)b)d_2}{2a + (n-1)(L-1)b} \]  

(6.3.10)

So, using the assumption \( d_{n-1} \geq d_2 \) as in (6.3.9),

\[ d_n / d_{n-1} \leq 1 + \left[ \frac{(\Pi_B + \Pi_A - (L-1))b + 2a}{(n-1)(L-1)b + 2a} \right]. \]  

(6.3.11)
Observe that $W_i$'s defined in (6.3.1) are bounded by $(L-1)$ and hence $\Pi_B, \Pi_A$ are bounded by $(L-1)$. Thus

$$\Pi_B + \Pi_A - (L-1) < L-1$$

and

$$d_n / d_{n-1} \leq 2.$$  \hfill (6.3.13)

Lemma 6.3.2: Let 'a' and 'b' be chosen in such a way that

$$b/a \leq 2/(L-1)$$ \hfill (6.3.14)

then

$$d_n \geq d_{n-1} \geq \ldots \geq d_2 \geq 0.$$ \hfill (6.3.15)

Proof: Rewriting $\Pi_B$ and $\Pi_A$ as

$$\Pi_B = L - E(X_B), \quad \Pi_A = L - E(X_A)$$ \hfill (6.3.16)

and noting the fact that under $H_a$, $E(X_A) > E(X_B)$ we get

Now,

$$d_2 = (\Pi_B - \Pi_A)b / 2(2a + (L-1)b) \geq 0.$$ \hfill (6.3.17)

$$d_3 = \left[ d_2(\Pi_A + \Pi_B - (L-1)) + (\Pi_B - \Pi_A) \right] b/(2a+2(L-1)b)$$

$$= \left[ d_2(\Pi_A + \Pi_B - (L-1))b + 2d_2(2a + (L-1)b) \right] / (2a+2(L-1)b)$$

$$= d_3 [ 1 + (2a + (\Pi_A + \Pi_B - (L-1))b)/(2a+2(L-1)b) ].$$ \hfill (6.3.18)

Observing the fact that $E(X_A) \leq L$, $E(X_B) \leq L$ and using (6.3.12), (6.3.16) it can be shown that $2a + (\Pi_A + \Pi_B - (L-1))b \geq 2a - (L-1)b$. Now using the condition (6.3.14), we have

$$d_3 \geq d_2.$$ \hfill (6.3.19)

Again, using (6.3.13), we have

$$d_3 \leq 2d_2.$$ \hfill (6.3.20)

For general $n$, $d_n$ can be written as

$$d_n = [(2a + (n-2)(L-1)b) d_{n-1} + (\Pi_B + \Pi_A - (L-1)) \ b d_{n-1} +$$

$$(2a + (L-1)b) d_2 \ ] / (2a + (n-1)(L-1)b).$$ \hfill (6.3.21)

Let us now assume that

$$d_{n-1} \geq \ldots \geq d_2.$$ \hfill (6.3.22)

Then using (6.3.9) repeatedly, we have

$$d_{n-1} \leq 2d_{n-1} \leq \ldots \leq 2^{n-3} d_2.$$ \hfill (6.3.23)
Now applying (6.3.23) in (6.3.21) we have
\[
\begin{align*}
&d_n \geq d_{n-1} + d_{n-1} \left[ 2a / 2^n + (\Pi_B + \Pi_A - (L-1)b(2^{n-2} - 1) / 2^{n-3}) \right] / \\
&(2a + (n-1)(L-1)b),
\end{align*}
\]
which implies
\[
d_n \geq d_{n-1} \text{ provided } b/a \leq (2/(L-1)) / (2^{n-2} - 1).
\]
As \(1/(2^{n-2} - 1) < 1\) for any \(n \geq 3\), the condition in (6.3.25) is realized if (6.3.14) holds.

Q.E.D

Note that in practice it is always possible to choose 'a' and 'b' satisfying condition (6.3.14) and the above lemma tells us that \(P_n \leq P_{n-1} \leq \ldots \leq P_2 \leq P_1 (=1/2)\), i.e. the chance of treating a patient by the inferior treatment gradually decreases as more patients enter into the study.

### 6.4 ASYMPTOTIC NULL DISTRIBUTION

In this section our aim is to establish asymptotic null distribution of the test statistic \(T_n\):

**Theorem 6.4.1:** Under \(H\), as \(n \to \infty\),
\[
n^{1/2} T_n \xrightarrow{d} \mathcal{N} (0, \sigma^2)
\]  \hspace{1cm} (6.4.1)

where
\[
\sigma^2 = 4 \left[ \sum_{j=1}^{l} j^2 \pi_{aj} - \left( \sum_{j=1}^{l} j \pi_{aj} \right)^2 \right].
\]  \hspace{1cm} (6.4.2)

Proof of the theorem depends on the following lemmas:

**Lemma 6.4.1:** Under \(H\), as \(n \to \infty\),
\[
N_A / n \xrightarrow{p} \chi_2, \ nB / n \xrightarrow{p} \chi_2.
\]  \hspace{1cm} (6.4.3)

**Proof:** Note that under \(H\), \(\Pi_A = \Pi_B\), where \(\Pi_A\) and \(\Pi_B\) are as defined in (6.3.5).

Now following (10.10) of Rosenberger and Lachin (2002), P-180) and noting that the urn's generating matrix in this case to be
\[
\begin{pmatrix}
\Pi_A & (L-1) - \Pi_A \\
(L-1) - \Pi_A & \Pi_A
\end{pmatrix}
\]  \hspace{1cm} (6.4.4)

we have,
\[
\lim_{n \to \infty} \frac{N_A}{n} = 1 - \lim_{n \to \infty} \frac{N_B}{n} = \left[ (L-1) - \Pi_A \right] / \left[ (L-1) - \Pi_A + (L-1) - \Pi_A \right] = \tfrac{1}{2}.
\]

So, we have the result (6.4.3).

**Q.E.D.**

**Lemma 6.4.2:** Suppose, for each \( n \geq 1 \), there exist two positive integers, \( v_A = v_A(n) \) and \( v_B = v_B(n) \), such that \( v_A + v_B = n \) and as \( n \to \infty \), \( v_A \to \infty \), \( v_B \to \infty \), \( v_A/n, v_B/n \to \frac{1}{2} \).

Then, under \( H \), as \( n \to \infty \),

\[
n^{-1/2} \left( \sum_{i=1}^{v_A} Z_{ij}^0 - \sum_{i=1}^{v_B} Z_{ij}^0 \right) \overset{p}{\to} 0
\]

and

\[
n^{-1/2} \left( \sum_{i=1}^{v_A} Z_{ij}^0 - \sum_{i=1}^{v_B} Z_{ij}^0 \right) \overset{p}{\to} 0
\]

where

\[
Z_{ij}^0 = Z_{ij} - \pi_{Aj}.
\]

**Proof:** Under \( H \), \( Z_{ij}^0 \)'s are iid with mean 0 and variance \( \pi_{Aj} (1-\pi_{Aj}) \). Hence using the above lemma and by a standard technique (cf. problem 27.14 of Billingsley ((1979), P-320)), the results (6.4.6) and (6.4.7) can easily be established.

**Q.E.D.**

**Proof of the theorem:** Let \( i_m, m=1,2,\ldots,N_A \) be those suffixes for which \( \delta_{i_m} = 1 \), and \( \lambda_m (\neq i_m), m=1,2,\ldots,N_B \) be those for which \( \delta_{\lambda_m} = 0 \). Then, under \( H \), as \( Z_{ij} \)'s are iid and are distributed independently of \( \delta_{i_m} \)'s, without any loss of generality, we assume that first \( N_A \delta \)'s to be 1 and remaining \( N_B (=N-N_A) \delta \)'s to be 0. Then we have

\[
p_{Aj} = \frac{N_A}{N_A + N_B} \sum_{i=1}^{N_A} Z_{ij} / N_A, \quad p_{Bj} = \frac{N_B}{N_A + N_B} \sum_{i=N_A+1}^{N_A+N_B} Z_{ij} / N_B
\]

(6.4.9)

Thus,

\[
n^{1/2} \left( p_{Aj} - \pi_{Aj} \right) \overset{d}{=} \frac{\sqrt{n}}{N_A} \sum_{i=1}^{N_A} Z_{ij} - \frac{\sqrt{n}}{N_A} \sum_{i=1}^{N_B} Z_{ij} + \frac{\sqrt{n}}{N_A} \sum_{i=1}^{N_A} Z_{ij} - \frac{\sqrt{n}}{N_A} \sum_{i=1}^{N_B} Z_{ij}
\]

(6.4.10)

By Lemma 6.4.2, the second term from the R.H.S. of (6.4.10) tends to zero in probability and hence (6.4.10) gives
\[ n^{1/2} (p_{A} - \pi_{A}) \overset{D}{\approx} (2/\nu_{A})^{1/2} \sum_{i=1}^{v_{A}} Z_{ij}^{0} \quad (6.4.11) \]

Similarly, we have
\[ n^{1/2} (p_{B} - \pi_{B}) \overset{D}{\approx} (2/\nu_{B})^{1/2} \sum_{i=1}^{v_{B}} Z_{v_{A}^*i,j}^{0} \quad (6.4.12) \]

By applying multivariate CLT, we get, as \( n \to \infty \),
\[ n^{1/2} (p_{A} - \pi_{A}, j=1,2,..L, p_{B} - \pi_{B}, j=1,2,..L) \overset{D}{\to} N (0, \Lambda) \quad (6.4.13) \]

where
\[ \Lambda = 2 \text{Diag} (\Lambda_{11}, \Lambda_{11}), \Lambda_{11} = \text{Diag} (\pi_{A1}, \pi_{A2}, ..., \pi_{AL}) - \pi' \quad (6.4.14) \]

and
\[ \pi' = (\pi_{A1}, \pi_{A2}, ..., \pi_{AL})'. \quad (6.4.15) \]

By delta method, it follows that, under \( H \), as \( n \to \infty \),
\[ n^{1/2} T_{n} \overset{D}{\to} N (0, \text{D}' \text{A} \text{D}) \quad (6.4.16) \]

where
\[ \text{D} = (1, 2, ..., L, -1, -2, ..., -L)'. \]

Now, observe that
\[ \text{D}' \text{A} \text{D} = 4 [ (1, 2, ..., L) \Lambda_{11} (1, 2, ..., L)' ] = \sigma^2. \quad (6.4.17) \]

Q.E.D.

In practice \( \sigma^2 \) is unknown and the proposed test can be performed by using the following consistent estimator:
\[ S^2 = (N_{A} S_{A}^2 + N_{B} S_{B}^2) / n \quad (6.4.18) \]

where
\[ S_{k}^{2} = 4 \left[ \sum_{j=1}^{L} j^2 p_{kj} - \left( \sum_{j=1}^{L} j p_{kj} \right)^2 \right], \quad k = A, B. \]

Thus it is obvious that, under \( H \), as \( n \to \infty \),
\[ n^{1/2} T_{n} / S \overset{D}{\to} N (0,1). \quad (6.4.19) \]

6.5 ASYMPTOTIC PROPERTIES

In this section we shall study the consistency property of the test statistic. For the same, we shall take the help of the following two lemmas:

**Lemma 6.5.1**: Let \( a \) and \( b \) be such that the condition (6.3.14) holds. Then, as \( n \to \infty \),
\[ d_{n} \to d, \quad \text{where } d \text{ is given by} \]
\[ d = \frac{1}{2} \left( \Pi_B - \Pi_A \right) / \left( 2(L-1) - \Pi_B - \Pi_A \right). \]  

(6.5.1)

**Proof**: From (6.3.8)

\[ d_n = \left[ \left( \sum_{j=2}^{n-1} d_j \right) (\Pi_B + \Pi_A - (L-1)) + (n-1) \left( \Pi_B - \Pi_A \right) / 2 \right] \left( b / (2a + (n-1)(L-1)b) \right) \]

\[ = \left( 1 / (n-1) \right) \left( \left( \sum_{j=2}^{n-1} d_j \right) b (\Pi_B + \Pi_A - (L-1)) / (2a(n-1) + (L-1)b) + \frac{1}{2} (\Pi_B - \Pi_A) b / (2a(n-1) + (L-1)b) \right). \]  

(6.5.2)

Now noting the fact that \( d_n, n \geq 1 \) are bounded above by \( \frac{1}{2} \) and using Lemma 6.3.2 we have the convergent sequence \( \{ d_n \} \). Then writing \( \lim d_n = d \) and using Toeplitz's Lemma (taking limit on both side), as \( n \to \infty \), we have

\[ d = d \left( \Pi_B + \Pi_A - (L-1) \right) / (L-1) + \frac{1}{2} \left( \Pi_B - \Pi_A \right) / (L-1). \]  

(6.5.3)

So (6.5.1) hold. **Q.E.D**

**Lemma 6.5.2**: Let \( a \) and \( b \) such that the condition (6.3.14) holds. Then, as \( n \to \infty \),

\[ N_A(j)/n \xrightarrow{p} \left( \frac{1}{2} - d \right) \pi_{Aj}, \quad N_B(j)/n \xrightarrow{p} \left( \frac{1}{2} + d \right) \pi_{Bj} \]  

(6.5.4)

and

\[ N_A/n \xrightarrow{p} \frac{1}{2} - d, \quad N_B/n \xrightarrow{p} \frac{1}{2} + d. \]  

(6.5.5)

**Proof**: Following (10.10) of Rosenberger and Lachin (2002), P-180 and noting that the urn's generating matrix in this case to be

\[
\begin{pmatrix}
\Pi_A & (L-1) - \Pi_A \\
(L-1) - \Pi_B & \Pi_B
\end{pmatrix}
\]  

(6.5.6)

we have,

\[
\lim_{n \to \infty} N_A / n = 1 - \lim_{n \to \infty} N_B / n
\]

\[
= \left[ (L-1) - \Pi_A \right] / \left[ (L-1) - \Pi_A + (L-1) - \Pi_B \right]
\]

\[
= \frac{1}{2} - d. \]  

(6.5.7)

where \( \Pi_A \) and \( \Pi_B \) are as defined in (6.3.5) and 'd' is as defined in (6.5.1). As such from (6.5.7), we have the result (6.5.5). To prove (6.5.4), we first note that

\[ N_A(j) - N_A \pi_{Aj} = \sum_{i=1}^{\infty} S_i (Z_{ij} - \pi_{Aj}) = \sum_{i=1}^{\infty} U_i \text{ (say)}. \]  

(6.5.8)

It is easy to show that (6.5.8) is a zero mean martingales satisfying the condition that as \( n \to \infty \),
\[
\sum_{i=1}^{n} E(U_{i}^2) \xrightarrow{p} 0 \quad (6.5.9)
\]

So, by (13.13) of Rosenberger and Lachin (2002), we have as \( n \to \infty \),
\[
\sum_{i=1}^{n} U_{i} \xrightarrow{p} 0 \quad (6.5.10)
\]

Thus,
\[
\frac{[N_A(j) - N_A \pi_{A_j}]}{n} \xrightarrow{p} 0, \quad \frac{[N_B(j) - N_B \pi_{B_j}]}{n} \xrightarrow{p} 0. \quad (6.5.11)
\]

So we have the result (6.5.4) from (6.5.11).

**Q.E.D.**

**Consistency:** To prove the consistency of the test it is sufficient to show that there exist a function \( g = g (\pi_{kj}, j=1,2, \ldots, L, k = A, B) \), such that, as \( n \to \infty \),
\[
T_n \xrightarrow{p} g \quad (6.5.12)
\]

where \( g = 0 \) or \( > 0 \) according as \( H \) or \( H_a \) is true. By using the Lemma 6.5.2, we have \( g = \mu_{\nu} \) and hence by using the representation (6.2.4) we have the following theorem:

**Theorem 6.5.1:** The test is consistent against those alternatives for which \( \mu_{\nu} > 0 \).

### 6.6 SIMULATION STUDY AND DISCUSSION

The main purpose of the proposed test is to reach a statistical conclusion by treating lesser number of patients by the inferior treatment, that is to serve the ethical imperative of a clinical trial. At the same time it is also desirable that owing to the imbalance between the sample sizes of the two treatment groups in an adaptive design, the loss of power to detect the treatment differences should only be marginal.

To study, how far the proposed procedure fulfill our purpose, simulation studies were performed to calculate the limiting allocation proportion of patients in the inferior arm (here treatment A) and powers of the test. Asymptotic powers of the test have been simulated at various alternatives. Simulated powers of the proposed test (say \( P_1^* \)) is also compared with that of the competitor test based on NB (say \( P_2^* \)), i.e. the number of patients treated by treatment B, which simply follows a Bin \((n, \pi)\) under H. Note that RPWO \((a,0)\) scheme means the equal allocation scheme. Under equal allocation scheme, the power of the test based on \( T_n \) (say \( P_{10}^* \)) have also been simulated and results are tabulated in Table 6.1 to study the merits and demerits of the adaptive design with respect to the equal allocation scheme. The limiting allocation proportion
corresponding to treatment A, i.e. \( N_A/n \) has been simulated as \( \text{ASN}(A)/n \) where \( \text{ASN}(A) \) is the average sample number of patients treated by treatment A in a set of 's' number of simulations under the adaptive scheme. We denote the same by \( \Pi_A \) and it's standard deviation by \( \delta_A \). Values of \( \Pi_A \) and \( \delta_A \) under various alternatives have been tabulated in Table 6.1. Each simulation study consists of 10000 simulations. As in Yao and Wei (1996), here also it is seen that \( P_{10}^* \) is negligibly higher compared to \( P_1^* \). But the negligible loss-in-power is heavily compensated by observing the \( \Pi_A \) - values much lower than 0.5 with moderate standard deviations. Thus, the ethical aspect of treating lesser number of patients by the inferior treatment has been reasonably safeguarded. It has also been observed that \( P_1^* \) is superior compared to \( P_2^* \). This may also be noted that \( (1-\Pi_A) \), \( P_{10}^* \), \( P_1^* \), \( P_2^* \) increases as \( \mu_d \) increases, i.e., when the treatment difference is large. Further as mentioned in section 6.2, that in case of ordinal data \( \Delta > 0 \) need not always imply that \( \mu_d > 0 \) and vice versa. Thus one may be interested in testing \( H \) against the restricted alternative \( H_a^* : \mu_d > 0 \) and \( \Delta > 0 \). Sample estimate of population Ridit \( (R = R_A + (X_A - X_B) + 0.5 \, P \, (X_A = X_B)) \), as introduced by Bross (1958) (also see Agresti (1984), page 167-168, Fleiss (1973), page 102-108), may be suggested as another test statistic for such type of restricted alternative along with \( T_n \). Mathematically ridit of treatment B with respect to treatment A can be expressed as \( R = R_{A1} \pi_{B1} + \ldots + R_{AL} \pi_{BL} \), where \( R_{A1} = \pi_{A1} + \ldots + \pi_{A1-1} + 0.5 \, \pi_{A1} \) and a sample estimate of the same by \( R_E = r_{A1} \pi_{B1} + \ldots + r_{AL} \pi_{BL} \), where \( r_{A1} = p_{A1} + \ldots + p_{A1-1} + 0.5 \, p_{A1} \). A detailed discussion on ridit relevant to the present setup has been given in section 5.1. Proceeding in the same way as in section 6.4, it can be shown that, under \( H \), as \( n \rightarrow \infty \), \( n^{1/2}(R_n - 1) \) converges in distribution to

\[
N(0, 4 \sum_{j=1}^{L} R^2_{Aj} \pi_{Aj} - 1) \]

and a left sided test based on the same may be suggested for the testing problem \( H \) against \( H_a^* \). This proposed test is also consistent. Under restricted alternatives, simulated powers corresponding to this test (say \( P_3^* \)) has also been calculated and compared with the power of the test based on \( T_n \) (say \( P_1^* \)). Under equal allocation scheme, the powers of the test based on \( T_n \) (say \( P_{10}^* \)) and test based on \( R_E \) (say \( P_{30}^* \)) have been simulated and the results are tabulated in Table 6.2. Here also, like \( \Pi_A \) and \( \delta_A \), the limiting allocation proportion and the corresponding
standard deviation have been simulated and are denoted by \( P_A^* \) and \( S_A^* \) and the results are tabulated in Table 6.2 under various alternatives. As before each simulation study consists of 10000 simulations. The results of power calculation shows that as \( \mu_d \) (or \( \Delta \)) is in the extreme sides, the power of the test based on \( R_{E} \), is some time slightly superior to that based on \( T_n \); otherwise the test based on \( T_n \) is slightly superior to that based on \( R_{E} \). The powers under equal allocation scheme are negligibly higher compared to that under the adaptive allocation scheme, but the negligible loss-in-power have been compensated to a great extent by observing values of \( P_A^* \) much lower than 0.5 with reasonably small \( S_A^* \), confirming the findings of Yao and Wei (1996) once again. Thus the purpose of implementing RPW rule has been served satisfactorily. It may also be noted that in some of the simulation studies the theoretical size condition has been violated. But this is only due to inherent randomness of the underlying study.

Table 6.1: Simulation study results of powers and proportion of savings in first sample size under various alternatives (\( \alpha = 0.05 \)).

<table>
<thead>
<tr>
<th>n</th>
<th>L</th>
<th>Cell(1...L) Probabilities of ( \mu_d )</th>
<th>Simulation Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment A</td>
<td>Treatment B</td>
</tr>
<tr>
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<td>5,4,1</td>
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<td>5,4,1</td>
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<td></td>
<td>1,4,5</td>
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<th>Simulation Study Results</th>
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<td>Allocation Proportion</td>
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Table 6.2: Simulation study results of powers and proportion of savings under various restricted alternatives($\alpha = 0.05$).

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<th>Cell(1...L) Probabilities of</th>
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<th>$\mu_d$</th>
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<td>Treatment B</td>
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<td>Allocation Proportion</td>
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<td></td>
<td></td>
<td></td>
<td>$a=L$, $b=2$</td>
</tr>
<tr>
<td>50</td>
<td>3</td>
<td>2, 4, 4</td>
<td>5, 4, 1</td>
<td>.42, .06</td>
<td>.33, .067</td>
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<td>.40, .069</td>
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<td>.5, .07</td>
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<td>.39, .063</td>
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<td>.42, .064</td>
</tr>
<tr>
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<td>4</td>
<td>2, 2, 2, 4</td>
<td>6, 2, 1, 1</td>
<td>.46, .10</td>
<td>.31, .06</td>
</tr>
<tr>
<td>60</td>
<td>4</td>
<td>2, 2, 2, 4</td>
<td>6, 2, 1, 1</td>
<td>.46, .10</td>
<td>.31, .06</td>
</tr>
</tbody>
</table>
6.7 AN ILLUSTRATIVE EXAMPLE

Sequential clinical trial is a prospective trial. Due to non-availability of such prospective trial data, in this section we would like to demonstrate a trial by generating responses from the treatments hypothetically through random numbers using the data (slightly modified) corresponding to the first investigator of Boos and Brownie (1992). The motivation of doing this is same as in the tune of Yao and Wei (1996) while considering the efficacy of RPW rule in connection with the ACTG 076 trial. The basic idea is to compare in "what would have happened if" spirit. In practice every thing will remain same except that in place of hypothetical treatment responses we have to record original observed treatment responses. Here, as we have assumed lower response indicates better treatment outcome towards the development of the proposed procedure; we have reverted the score pattern and denoted the same by treatment response. The data are tabulated in Table 6.3. The first investigator of Boos and Brownie (1992) treated 20 patients of psoriasis. 10 patients each in placebo and new treatment arms and obtained the treatment responses. Assuming that the probability structure of the data set to be the population probability structure we now
treat 20 patients sequentially by the present RPWO (5,2) scheme, satisfying the condition (6.3.10). The allocation pattern of treatments among 20 sequentially entering patient is provided in Table 6.4. Here \( T_n = 1.972 > \tau_{0.05} \), where \( \tau_n \) is the upper \( \alpha \)-point of a normal deviate. Hence it can be concluded that, at 5% level of significance, the new treatment is better than the placebo treatment. From Table 6.4 it is found that 8 patients have been assigned treatment A (palcebo) and 12 patients have been given treatment B (new) instead of 10 patients in each arm. Thus saving twenty-percent patients from getting inferior treatment and serving the ethical aspect of implementing the RPW rule.

Table 6.3: Frequency distribution of clinical trial data of the first investigator of Boos and Brownie (1992)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response</th>
<th>Total no. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0 2 4 3 1</td>
<td>10</td>
</tr>
<tr>
<td>New</td>
<td>0 4 5 1 0</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 6.4: Allocation pattern, after implementing RPWO (5,2) scheme, of treatments among sequentially entering patients using data of Boos and Brownie (1992)
6.8 CONCLUDING REMARKS

The proposed test satisfactorily tackles the ethical aspect of a clinical trial when the treatment responses are measured on a polychotomous ordinal scale. At the same time, owing to imbalance between the sample size there is a power loss, which might be taken to be marginal. The technique discussed being an adaptive design is not applicable for all types of clinical trials and the conditions under which this technique will be valid mentioned in section 1.4 of chapter 1 of the present dissertation. The optimum choice of the design parameters may be a major issue while considering the ethical aspect as for every choice the proportion of savings as well as powers are different. Moreover the test can be applied only when the treatment responses are instantaneous, i.e., before treating a patient the treatment responses of all patients treated earlier are available with the clinician. This may not always be possible and the patients need to be evaluated after certain time since administering the drug. Again, there may be repeated measures on a single patient at different time points. In this situation the present method has to be updated in the light of the longitudinal ordered categorical data. Moreover, there may be bio-markers available to assess the prognostic factors for the patients, or the general health condition of the patients have to taken into account which may well be translated in terms of choice of appropriate co-variates while allocating treatment to the patients. This is also to mention here that the testing problem for the alternative $\Lambda > 0$ is not a direct application of the present model. The optimum choice of design parameters seems to be an interesting problem, as while considering the adaptive design one has to strike a balance between the savings in sample size and loss in power. At the same time the small sample version of RPW rule is also another point of interest.