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DELAYED RESPONSE IN RANDOMIZED PLAY-THE-WINNER RULE REVISITED

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ABSTRACT

In the context of comparing two treatments in a clinical trial, Wei and Durham (1978) and Wei (1979), assuming instantaneous responses of patients, introduced a sampling design for allocating more patients to the better treatment. Wei (1988) also proposed a model appropriate for delayed responses of patients. But this model is mathematically intractable. Bandyopadhyay and Biswas (1996), possibly sacrificing some efficiencies, suggested an alternaive model which is mathematically simple and convenient. The present study is a comparison of the above two models by considering some exact and asymptotic results.

1. INTRODUCTION

Consider a clinical trial experiment for comparing two treatments A and B and suppose there is a sequential entrance of patients for the experiment. Then the problem of allocating the entering patients among the two treatments is of importance. If the subjects are human beings then, from the ethical point of view, it is essential to have a sampling scheme which allocates a larger number of patients to the better treatment. A major breakthrough towards this direction was first made by Zelen (1969). He introduced a concept called 'play-the-winner rule' for dichotomous responses in a clinical trial. Later Zelen's idea was modified by Wei and Durham (1978) and Wei (1979) by adopting a rule called 'randomized play-the-winner rule'. Let us illustrate the rule by an urn model as follows :

Start with an urn having two types of balls A and B, α balls of each type. When a patient enters in the system it is assigned to a treatment by drawing a ball from the urn with replacement. When a response is obtained we add an additional β balls in the urn in the following way : If the response is a success we add an additional β balls of the same kind, and on the other hand, if the response is a failure we add an additional β balls of the opposite kind in the urn. For a given (α,β), this rule is denoted by $RPW(\alpha,\beta)$.

Suppose the responses by treatment A and B are respectively denoted by the real-valued random variables X and Y, and assume that $X \sim F_1$ independently of $Y \sim F_2$, where F_1 and F_2 are both unknown continuous distribution functions (d.f.'s). Suppose μ_0 is a threshold response, whose choice is in the experimenter's hand and which depends largely on the particular disease concerned. Then, denoting by $p_1 = 1 - F_1(\mu_0)$ and $p_2 = 1 - F_2(\mu_0)$, the probabilities of success by treatment A and B respectively, the object is to accept any of the three possible decisions :

$$a_1 : p_1 = p_2, \qquad a_2 : p_2 > p_1, \qquad a_3 : p_2 < p_1. \tag{1.1}$$

If we assume $F_2(x) = F_1(x-b)$ and $F_1(x)$ is strictly increasing at μ_0, then (1.1) can be equivalently written as

$$a_1 : b = 0, \qquad a_2 : b > 0, \qquad a_3 : b < 0. \tag{1.2}$$

In section 2, we discuss the possibility of delayed response and the corresponding probability models that are available in literature. Section 3 provides some exact results associated with these existing models making suitable orders of approximations. Some asymptotics are also discussed in section 4.

2. DELAY IN RESPONSE : TWO DIFFERENT MODELS

In most of the works on clinical trials the authors have assumed instantaneous patient responses, i.e., a patient's response is either immediate or it is obtained before the entrance of the next patient. The paper by Tamura, Faries, Andersen and Heiligenstein (1994) describes an actual clinical trial with delayed response. Considering instantaneous responses of patients, RPW rule was used for different problems by Wei (1988) and Bandyopadhyay and Biswas (1997a, 1997b). An appropriate model for possible application in delayed response is also given in Wei (1988). This is as follows :

At first, corresponding to the i-th entering patient, we define a set $\{\delta_i, Z_i, \in_{1i}, \in_{2i}, \ldots, \in_{i-1i}\}$ of indicator variables, where

$\delta_i = 1$ or 0 according as treatment A or B is applied following a delayed response $RPW(\alpha, \beta)$ scheme of sampling,

$Z_i = 1$ or 0 according as the i-th patient results in a success or a failure and

$\in_{ji} = 1$ or 0 according as the response of the j-th patient is obtained or not before the entry of the i-th patient, $j = 1(1)i-1$.

Let p_{i+1} be the conditional probability that $\delta_{i+1} = 1$ given all the previous assignments $\{\delta_j, 1 \le j \le i\}$, responses $\{Z_j, 1 \le j \le i\}$ and all the indicator response statuses $\{\in_{ji+1}, 1 \le j \le i\}$. Then, following Wei (1988) we have

$$p_{i+1} = \{\alpha + \beta[2\sum_{j=1}^{i} \in_{ji+1} \delta_j Z_j + \sum_{j=1}^{i} \in_{ji+1} - \sum_{j=1}^{i} \in_{ji+1} \delta_j - \sum_{j=1}^{i} \in_{ji+1} Z_j]\} / (2\alpha + \beta \sum_{j=1}^{i} \in_{ji+1}). \tag{2.1}$$

Observe that the denominator of p_{i+1} is random. So, although this model can easily be used in practice, it is not theoretically tractable in a straightforward way. Hence, to overcome this situation, Bandyopadhyay and Biswas (1996) (BB for subsequent reference) have introduced a delayed response RPW sampling scheme. The scheme can be illustrated by an urn model as follows : Start with an urn having two types of balls A and B, α balls of each type. When a patient enters in the system, the patient is assigned to a treatment by drawing a ball from the urn with replacement. When a patient is assigned to a treatment we add $\beta/2$ balls of each kind. When the response is obtained we withdraw these $\beta/2$ balls of each kind from the urn and add β balls according to the following way : If the response is a success we add β balls corresponding to the patient's assignment. On the other hand, if the response is failure, we add β balls of the opposite kind. Here, without loss of generality, β is taken as even. Note that the proposal to add $\beta/2$ balls to the urn is similar, in principal, to the idea of adding fractional balls which can be attributed originally to Andersen, Faries and Tamura (1994). Let $\tilde{p}_{i-1}$ be the conditional probability that $\delta_{i+1}=1$ given all the previous assignments, responses and indicator response statuses. Then from BB(1996), we have

$$\tilde{p}_{i+1}=\{\alpha+\beta[2\sum_{j=1}^{i}\in_{ji+1}\delta_j Z_j+\frac{1}{2}(i+\sum_{j=1}^{i}\in_{ji+1})-\sum_{j=1}^{i}\in_{ji+1}\delta_i \\ -\sum_{j=1}^{i}\in_{ji+1}Z_j]\}/(2\alpha+i\beta), \tag{2.2}$$

which gives a non-random denominator. In BB(1996) it is assumed that

$$P(\in_{jk}=1)=\pi_{k-j}, \tag{2.3}$$

where $\{\pi_t, t\geq 1\}$ is a non-decreasing sequence with

$$\pi_t \to 1 \text{ as } t\to\infty, \tag{2.4}$$

i.e., when the time lag is infinitely large we are certain to get a response, which is quite logical. Some possible functional forms of π_t may be

(i) $\pi_t = 1-ae^{-bt}$, $0<a\leq 1$, $b>0$.

(ii) $\pi_t = 1-\left(\frac{b}{a+b}\right)^t$, $a>0$, $b>0$.

The marginal distributions of the δ_i 's are obtained as :

$$P(\delta_{i+1} = 1) = \frac{1}{2} - d_{i+1},$$

where

$$d_{i+1} = \frac{\rho}{2+i\rho}(p_2 - p_1)\left[\sum_{j=2}^{i} \pi_{i-j+1}\, d_j + \frac{1}{2} \sum_{j=1}^{i} \pi_j\right] + \frac{\rho(2p_1 - 1)}{2+i\rho} \sum_{j=2}^{i} \pi_{i-j+1} d_j . \tag{2.5}$$

with $\rho = \beta / \alpha$ and p_1, p_2 are defined in section 1.

One point to note is that, the model (2.2), although it is mathematically tractable, ignores the true combination of the urn at any stage. For example, suppose, at the $(i+1)$st stage, out of the previously treated i-patients, j-responses are obtained . But, for the remaining $(i-j)$ patients whose responses are not obtained, we have to add $(i-j)\beta$ balls, $(i-j)\beta / 2$ balls of each kind. These are not due to any observed response. To circumvent this difficulty we look at Wei's (1988) model which is studied in the subsequent sections.

3. SOME EXACT PERFORMANCE CHARACTERISTICS

Following Wei (1988), we can write

$$p_{i+1} = \left[\tilde{p}_{i+1} - \frac{\frac{\beta}{2}\left(i - \sum_{j=1}^{i} \in_{ji+1}\right)}{2\alpha + i\beta} \right] \text{x} \frac{2\alpha + i\beta}{2\alpha + \beta \sum_{j=1}^{i} \in_{j+1}} \tag{3.1}$$

$$= \frac{1}{2} + \left[\tilde{p}_{i+1} - \frac{1}{2}\right] \text{x} \left[1 + \frac{\beta \sum_{j=1}^{i}\left(1 - \in_{ji+1}\right)}{2\alpha + i\beta} + \frac{\beta^2 \left(\sum_{j=1}^{i}\left(1 - \in_{ji+1}\right)\right)^2}{(2\alpha + i\beta)^2} + \ldots \right]. \tag{3.2}$$

From (3.2), neglecting the (k+1) st and higher order terms $(k = 1, 2, \ldots)$, the successive approximations of p_{i+1} are as follows :

$$p_{i+1}^{(1)} = \frac{1}{2} + \left[\tilde{p}_{i+1} - \frac{1}{2}\right] \text{x} \left[1 + \frac{\beta \sum_{j=1}^{i}\left(1 - \in_{ji+1}\right)}{2\alpha + i\beta} \right], \tag{3.3}$$

$$p_{i+1}^{(2)}=\frac{1}{2}+\left[\tilde{p}_{i+1}-\frac{1}{2}\right]\mathrm{x}\left[1+\frac{\beta\sum_{j=1}^{i}\left(1-\epsilon_{ji+1}\right)}{2\alpha+i\beta}+\frac{\beta^{2}\left(\sum_{j=1}^{i}\left(1-\epsilon_{ji+1}\right)\right)^{2}}{(2\alpha+i\beta)^{2}}\right], \quad (3.4)$$

and so on. Hence we get

$$E(p_{i+1}^{(1)})=\frac{1}{2}-d_{i+1}-d_{i+1}^{(1)}=\frac{1}{2}-d_{i+1}^{*(1)}, \quad (3.5)$$

where

$$d_{i+1}^{(1)}=\left(\frac{\rho}{2+i\rho}\right)^{2}(p_2-p_1)\left[\sum_{j=2}^{i}\sum_{j'=1}^{i}\pi_{i+1-j}(1-\pi_{i+1-j'})d_j+\frac{1}{2}\sum_{j=1}^{i}\sum_{j'=1}^{i}\pi_{i+1-j}(1-\pi_{i+1-j'})\right]$$

$$j\neq j'$$

$$+\left(\frac{\rho}{2+i\rho}\right)^{2}(p_2-p_1)(2p_1-1)\sum_{j=2}^{i}\sum_{j'=1}^{i}\pi_{i+1-j}(1-\pi_{i+1-j'})d_j, \quad (3.6)$$

$$j\neq j'$$

and

$$E(p_{i+1}^{(2)})=\frac{1}{2}-d_{i+1}-d_{i+1}^{(1)}-d_{i+1}^{(2)}=\frac{1}{2}-d_{i+1}^{*(2)}, \quad (3.7)$$

where

$$d_{i+1}^{(2)}=\left(\frac{\rho}{2+i\rho}\right)^{3}(p_2-p_1)\left[\sum_{j_1=2}^{i}\sum_{j_2=1}^{i}\sum_{j_3=1}^{i}\pi_{i+1-j_1}(1-\pi_{i+1-j_2})(1-\pi_{i+1-j_3})d_{j_1}\right.$$

$$j_1\neq j_2\neq j_3$$

$$+\sum_{j_1=2}^{i}\sum_{j_2=1}^{i}\pi_{i+1-j_1}(1-\pi_{i+1-j_2})d_{j_1}+\frac{1}{2}\sum_{j_1=1}^{i}\sum_{j_2=1}^{i}\sum_{j_3=1}^{i}\pi_{i+1-j_1}(1-\pi_{i+1-j_2})(1-\pi_{i+1-j_3})$$

$$j_1\neq j_2 \qquad\qquad j_1\neq j_2\neq j_3$$

$$\left.+\sum_{j_1=1}^{i}\sum_{j_2=1}^{i}\pi_{i+1-j_1}(1-\pi_{i+1-j_2})\right]$$

$$j_1\neq j_2$$

$$+\left(\frac{\rho}{2+i\rho}\right)^{3}(p_2-p_1)(2p_1-1)\left[\sum_{j_1=2}^{i}\sum_{j_2=1}^{i}\sum_{j_3=1}^{i}\pi_{i+1-j_1}(1-\pi_{i+1-j_2})(1-\pi_{i+1-j_3})d_{j_1}\right.$$

$$j_1\neq j_2\neq j_3$$

$$\left.+\sum_{j_1=2}^{i}\sum_{j_2=1}^{i}\pi_{i+1-j_1}(1-\pi_{i+1-j_2})d_{j_1}\right]. \quad (3.8)$$

$$j_1\neq j_2$$

In this way we can make an approximation of appropriate order to get the desired degree of accuracy.

For the problem (1.2), BB(1996) proposed two decision rules based on $S_k = \sum_{i=1}^{k} \delta_i$ and $T_k = k - S_k$. Our object is to see whether these decision rules can be adopted by using Wei's (1988) model. For this, as in BB(1996), writing $\theta = (p_1, p_2)$, we concentrate on the following performance characteristics :

(i) Average sample number (ASN) denoted by $A(\theta)$ for early stopping where $A(\theta) = E(N|\theta)$, and $N(\leq n)$ is a random variable denoting the number of patients required to make a decision.

(ii) Expected number of patients treated by treatment A. It is denoted by $A^*(\theta) = E(S_n|\theta)$ or $E(S_N|\theta)$ for the two rules.

(iii) The total proportion of treatment failures denoted by $F(\theta)$. This performance characteristic is used by Rosenberger and Sriram (1997).

(iv) Risk function denoted by $R(\theta)$. Considering the following general type loss function

	a_1	a_2	a_3
$b = 0$	0	1	1
$b > 0$	1	0	$L(\geq 1)$
$b < 0$	1	$L(\geq 1)$	0

the risk funciton becomes

$$R(\theta) = R(L,\theta) = P\left\{S_n < \frac{n}{2} - c|\theta\right\} + P\left\{T_n < \frac{n}{2} - c|\theta\right\} \quad \text{for } \theta{:}b = 0,$$

$$= L.P\left\{T_n < \frac{n}{2} - c|\theta\right\} + P\left\{\frac{n}{2} - c \leq S_n \leq \frac{n}{2} + c|\theta\right\} \quad \text{for } \theta{:}b > 0,$$

$$= P\left\{\frac{n}{2} - c \leq S_n \leq \frac{n}{2} + c|\theta\right\} + L.P\left\{S_n < \frac{n}{2} - c|\theta\right\} \quad \text{for } \theta{:}b < 0,$$

(3.9)

TABLE I

$R(L,\theta)$ for Rules 1 and 2 for normal parent corresponding to the Wei (1988) and the BB(1996) procedure. Results for the BB procedure are in parantheses.

b	$R(1,\theta)$	$R(5,\theta)$	$R(10,\theta)$
0	0.2406 (0.2326) 0.2371 (0.2256)	0.2406 (0.2326) 0.2371 (0.2256)	0.2406 (0.2326) 0.2371 (0.2256)
0.4	0.6458 (0.6483) 0.6448 (0.6538)	0.8519 (0.8564) 0.8549 (0.8579)	1.1096 (1.1166) 1.1176 (1.1131)
0.8	0.4197 (0.4282) 0.4297 (0.4407)	0.5038 (0.5043) 0.5158 (0.5208)	0.6088 (0.5993) 0.6233 (0.6208)
1.6	0.1481 (0.1521) 0.1506 (0.1571)	0.1681 (0.1721) 0.1686 (0.1751)	0.1931 (0.1971) 0.1911 (0.1976)
2.4	0.1006 (0.1036) 0.1006 (0.1076)	0.1166 (0.1196) 0.1186 (0.1256)	0.1366 (0.1396) 0.1411 (0.1481)

TABLE II

Performance characteristics $(A(\theta), A^*(\theta), F(\theta))$ for Rules 1 and 2 for normal parent corresponding to the Wei (1988) and the BB(1996) procedure. Results for the BB procedure are in parantheses.

b	$A^*(\theta)$ for Rule 1	$A(\theta)$ for Rule 2	$A^*(\theta)$ for Rule 2	$F(\theta)$ for Rule 1	$F(\theta)$ for Rule 2
0	24.9665	43.7604	21.8359	0.5000	0.5000
	(24.9885)	(43.6368)	(21.8754)	(0.5000)	(0.5000)
	24.9950	43.6368	21.8019	0.5000	0.5000
	(25.0130)	(43.8114)	(21.8659)	(0.5000)	(0.5000)
0.4	21.0115	43.8704	18.7564	0.4099	0.4110
	(21.0905)	(43.9905)	(18.7944)	(0.4101)	(0.4110)
	21.0085	44.0220	18.8644	0.4099	0.4111
	(21.1536)	(43.9445)	(19.0780)	(0.4103)	(0.4121)
0.8	17.3752	43.3282	15.3833	0.3120	0.3142
	(17.5068)	(43.4662)	(15.5838)	(0.3127)	(0.3152)
	17.4532	43.4207	15.2426	0.3124	0.3130
	(17.6868)	(43.4702)	(15.5988)	(0.3138)	(0.3153)
1.6	11.5038	40.7769	10.2966	0.1572	0.1672
	(11.8449)	(40.8874)	(10.4687)	(0.1603)	(0.1688)
	11.6233	40.7014	10.2951	0.1583	0.1674
	(12.1416)	(41.1346)	(10.8034)	(0.1629)	(0.1717)
2.4	9.1301	39.3437	8.3382	0.0980	0.1124
	(9.6903)	(39.8464)	(8.9710)	(0.1035)	0.1189
	9.2976	39.4072	8.5333	0.0996	0.1147
	(10.1211)	(40.0615)	(9.2836)	0.1077	0.1224

TABLE III

$R(L,\theta)$ for Rules 1 and 2 for a double exponential parent corresponding to the Wei (1988) and the BB(1996) procedure. Results for the BB procedure are in parantheses.

b	$R(1,\theta)$	$R(5,\theta)$	$R(10,\theta)$
0	0.2406 (0.2326) 0.2371 (0.2256)	0.2406 (0.2326) 0.2371 (0.2256)	0.2406 (0.2326) 0.2371 (0.2256)
0.4	0.6273 (0.6303) 0.6283 (0.6368)	0.8254 (0.8304) 0.8344 (0.8339)	1.0730 (1.0805) 1.0920 (1.0825)
0.8	0.4407 (0.4502) 0.4512 (0.4642)	0.5288 (0.5323) 0.5453 (0.5543)	0.6388 (0.6348) 0.6628 (0.6668)
1.6	0.2016 (0.2156) 0.2096 (0.2231)	0.2396 (0.2396) 0.2376 (0.2471)	0.2871 (0.2696) 0.2726 (0.2771)
2.4	0.1266 (0.1386) 0.1226 (0.1421)	0.1426 (0.1586) 0.1446 (0.1661)	0.1626 (0.1836) 0.1721 (0.1961)

TABLE IV

Performance characteristics ($A(\theta)$, $A^*(\theta)$, $F(\theta)$) for Rules 1 and 2 for a double exponential parent corresponding to the Wei (1988) and the BB(1996) procedure. Results for the BB procedure are in parantheses.

b	$A^*(\theta)$ for Rule 1	$A(\theta)$ for Rule 2	$A^*(\theta)$ for Rule 2	$F(\theta)$ for Rule 1	$F(\theta)$ for Rule 2
0	24.9665	43.7604	21.8359	0.5000	0.5000
	(24.9885)	(43.6368)	(21.8754)	(0.5000)	(0.5000)
	24.9950	43.6368	21.8019	0.5000	0.5000
	(25.0130)	(43.8114)	(21.8659)	(0.5000)	(0.5000)
0.4	20.7429	44.0465	18.6563	0.4470	0.4478
	(20.8264)	(44.1261)	(18.7439)	(0.4471)	(0.4479)
	20.7539	44.1136	18.4847	0.4470	0.4473
	(20.9040)	(43.9260)	(18.5138)	(0.4473)	(0.4476)
0.8	17.7454	43.4267	15.4502	0.3937	0.3938
	(17.8749)	(43.6793)	(15.9480)	(0.3941)	(0.3953)
	17.8219	43.4122	15.7874	0.3939	0.3951
	(18.0560)	(43.5508)	(16.0265)	(0.3947)	(0.3958)
1.6	13.2331	41.6068	11.5653	0.2975	0.3012
	(13.6598)	(41.7154)	(11.7229)	(0.2999)	(0.3020)
	13.4282	41.8589	11.9590	0.2986	0.3033
	(13.8479)	(41.9910)	(12.2721)	(0.3009)	(0.3051)
2.4	10.4792	39.9365	9.1246	0.2238	0.2304
	(11.2666)	(40.6540)	(10.1226)	(0.2293)	0.2376
	10.5013	40.0650	9.3537	0.2240	0.2322
	(11.6218)	(40.8514)	(10.3172)	0.2318	0.2388

where 'c' is given in the decision rule (see BB(1996)). The following tables (I-IV) show the comparative figures between Wei (1988) and BB(1996) taking $\rho=1$, $a=0.5$, $b=1$, $n=50$, $c=6$, μ_0 = the median of F_1. Here 10000 simulations are done. The values within parentheses correspond to the BB(1996) procedure. In each cell the first two values correspond to functional from (i) and the last two values correspond to functional form (ii) of π_t.
The following table gives the values of d_i, $d_i^{(1)}$ and $d_i^{(2)}$ for different i. The two values in each cell correspond to the two functional forms of π_t.

TABLE V
Values of d_i, $d_i^{(1)}$, $d_i^{(2)}$ for different i.

	$p_1=0.4, p_2=0.8$			$p_1=0.3, p_2=0.9$		
i	d_i	$d_i^{(1)}$	$d_i^{(2)}$	d_i	$d_i^{(1)}$	$d_i^{(2)}$
6	0.1448	0.0050	0.0070	0.2172	0.0076	0.0012
	0.1371	0.0083	0.0012	0.2057	0.0126	0.0019
20	0.2058	0.0029	0.0001	0.3087	0.0045	0.0002
	0.2025	0.0050	0.0002	0.3037	0.0076	0.0004
60	0.2311	0.0012	0.0000	0.3467	0.0018	0.0000
	0.2297	0.0020	0.0000	0.3446	0.0032	0.0001
100	0.2374	0.0007	0.0000	0.3561	0.0012	0.0000
	0.2365	0.0013	0.0000	0.3547	0.0020	0.0000

4. SOME ASYMPTOTIC RESULTS

In section 3, we have made a comparison of the two models through exact computations. Here we give some theoretical results concerning the Wei (1988) model. The first result is that the asymptotic distribution of S_n under b = 0 is the same as (4.8) of BB(1996). To obtain the limiting value of the risk when $b \neq 0$ we first prove the following Lemma :

Lemma 4.1 : $E(p_{i+1} - \tilde{p}_{i+1}) \to 0$ as $i \to \infty$.

Proof: By (3.1), we have

$$\left(p_{i+1} - \frac{1}{2}\right) = \left(\tilde{p}_{i+1} - \frac{1}{2}\right) \frac{2 + i\rho}{2 + is_i},$$

where $s_i = \sum_{j=1}^{i} \epsilon_{ji+1}$. Then

$$p_{i+1} - \tilde{p}_{i+1} = \frac{\rho(i - s_i)}{2 + \rho s_i} \left(\tilde{p}_{i+1} - \frac{1}{2}\right),$$

whence we get

$$0 \le p_{i+1} - \tilde{p}_{i+1} \le \frac{\rho\left(1 - \frac{s_i}{i}\right)}{\left(\frac{2}{i} + \rho \frac{s_i}{i}\right)} \left|\tilde{p}_{i+1} - \frac{1}{2}\right| \le \frac{\rho\left(1 - \frac{s_i}{i}\right)}{2\left(\frac{2}{i} + \rho \frac{s_i}{i}\right)} . \qquad (4.1)$$

It can easily be shown that, as $i \to \infty$, $s_i / i \to 0$ in probability, and hence, the right hand side of (4.1) converges in probability to zero as $i \to \infty$. Thus, since $\{p_{i+1} - \tilde{p}_{i+1}\}$ is bounded, the required result follows.

Q.E.D.

At this stage we also observe the following : By Toeplitz's lemma, it can be easily shown that, as $j \to \infty$,

$$d_j^{(k)} \to 0, \qquad d_j^{(k+1)} / d_j^{(k)} \to 0. \qquad (4.2)$$

and by Lemma 4.1, it is clear that, as $j \to \infty$,

$$\sum_{k=1}^{\infty} d_j^{(k)} \to 0. \qquad (4.3)$$

Now we prove the following Lemma :

Lemma 4.2 : $\frac{1}{n} \sum_{i=1}^{n} \delta_i \to \mu^*$ (in probability), as $n \to \infty$,

where

$$0 < \mu^* < \frac{1}{2} - d_2.$$

The proof, by using Lemma 4.1, is immediate from Lemma 4.1 of BB(1996). Hence, as in BB(1996), we have the following theorem :

Theorem 4.1 : $\lim_{n\to\infty} R_n(\theta) = 0$ for any $\theta : b \neq 0$.

We also have the following theorem which gives the limiting proportion of allocation :

Theorem 4.2 : Under the assumption (2.4), the limiting proportion of patients treated by treatment A is

$$(1-p_2)/(2-p_1-p_2).$$

Proof : By Lemma 4.2, when all the n patients receive treatment A or B, the proportion of patients treated by treatment A is $\frac{1}{n}\sum_{i=1}^{n}\delta_i$, which, by (4.3) and using the fact that the sequence $\{d_i,\ i \geq 1\}$ is monotone and bounded, converges in probability to

$$\lim_{n\to\infty} \frac{1}{n} E\left(\sum_{i=1}^{n} \delta_i\right) = \frac{1}{2} - d,$$

where $\lim_{n\to\infty} d_i = d$ (exists). Again, as $\pi_t \to 1$ if $t \to \infty$, the Cauchy product $\frac{1}{n}\sum_{i=1}^{n} \pi_{n-i}\,\delta_i$ converges to d. Hence, from (2.5), we get

$$d = (p_2 - p_1)\left(d + \frac{1}{2}\right) + (2p_1 - 1)d,$$

which implies

$$d = (p_2 - p_1)/(2(2 - p_1 - p_2)). \tag{4.4}$$

Thus the limiting proportion of patients receiving treatment A is

$$\frac{1}{2} - d = (1 - p_2)/(2 - p_1 - p_2).$$ **Q.E.D.**

Clearly, this limiting proportion is independent of any choice of $\rho = \beta / \alpha$.

5. CONCLUDING REMARKS

From tables I-IV we see that there is no significant improvement by employing Wei's (1988) method over the BB(1996) method. From table V it is clear that the $d_j^{(k)}$'s converges to zero very quickly. This is easily understandable from section 4 where the asymptotic equivalence of the two methods is established.

Delayed response occurs in most practical situations and fits nicely into a survival analysis context. Some recent results in connecting these areas are due to Yao and Wei (1996), Hallstrom, Brooks and Peckova (1996), Rosenberger and Seshaiyer (1997).

An exact expression of $V(\sum_{i=1}^{n} \delta_i)$ in the case of a delayed response is obtained in BB(1996). The limiting distribution of the proportion of allocation to treatment A can be found using Smythe and Rosenberger (1995). This, along with some further asymptotic results is the subject of a future communication.

In the present paper it is assumed that the ϵ_{ji}'s are independent of the treatment used or any other covariate. But, in practice, the response time can be correlated with treatment assignment (A or B), with response (success or failure) and other covariates including entry time. Some more complicated models under these assumptions are under study.

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