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ALLOCATION BY RANDOMIZED PLAY-THE-WINNER RULE IN THE PRESENCE OF PROGNOSTIC FACTORS

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SUMMARY. In the clinical trial randomized play-the-winner (RPW) rule is used with a goal of allocating more patients to the better treatment in course of sampling. The present paper provides an application of RPW sampling scheme in the presence of prognostic factors. Both the cases of non-stochastic and stochastic prognostic factors are discussed. Some decision rules are provided for comparing two treatments. Limiting proportions of allocations by the two treatments are obtained.

1. **Introduction**

The problem of comparison of two treatments A and B, say, in a clinical trial is considered recently by many authors. Most of the available works in the literature are based on equal number of patients to the two treatments. But if the patients enter in a system sequentially then the problem of allocation of the entering patients among the two treatments gets much importance. If the subjects are human beings, then from ethical point of view, it is required to carry out the decision making procedure with the smallest possible number of patients being treated by the worse treatment in course of sampling. Several data-dependent adaptive designs are used for this purpose.

Zelen (1969), for this purpose, introduced a concept called play-the-winner rule for dichotomous responses in clinical trials. As a modification of Zelen's play-the-winner rule, Wei and Durham (1978) and Wei (1979) introduced the idea of randomized play-the-winner (RPW) rule. Further works in this direction are due to Wei, Smythe and Mehta (1989), Wei (1988), Begg (1990), Bandyopadhyay and Biswas (1996, 1997a, 1997b), among others. Some real life applications of RPW rule are done by Bartlett *et al.* (1985) and Tamura *et al.* (1994).

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In all the above works and in almost all the works available in the literature on clinical trials it is assumed that the entering patients are homogeneous. But, in practice, there may be many prognostic factors like age, sex, blood pressure, heart beat, blood sugar etc. Treatment allocation problem in the presence of prognostic factors are considered by Begg and Iglewicz (1980). They use optimum design theory to suggest a deterministic design criterion, which is then modified for computational convenience. Presence of prognostic factors is also considered by Atkinson (1982) to use optimum design theory to provide a procedure of the biased coin type for an arbitrary number of treatments.

In the present paper we want to incorporate the presence of prognostic factors to introduce an adaptive RPW rule, abbreviated as ARPW rule. We consider both the cases where the prognostic factors are non-stochastic and stochastic. A decision making procedure is indicated. We find the exact and limiting (proportion of) allocations to the two treatments.

Note that, if a distribution is assumed on the prognostic factors, the proposed scheme fits into a generalization of the framework of Wei *et al.* (1990), and some subsequent works by Smythe and Rosenberger (1995) and Smythe (1996). But in those works also, the authors have not thought about the possibility of prognostic factors.

2. Decision Rules Using ARPW Scheme of Sampling

In this section we assume that there is only one prognostic factor C, which is non-stochastic, and the corresponding variable is either discrete or can be easily transformed to a discrete variable with $(G+1)$ ordered grades $0, 1, \cdots, G$, defined by consulting a clinician. Grade 0 is for the least favourable condition and grade G for the most favourable condition. Clearly, the response of the i-th patient depends not only on the treatment (A or B) by which it is treated, but also the grade $u_i \in \{0, 1, \cdots, G\}$ of the i-th patient. Using this prognostic factor C and its $(G+1)$ grades, we now introduce an APRW rule using an urn model.

Start with an urn having two types of balls A and B, α balls of each type. For an entering patient of grade u_j we treat him by drawing a ball from the urn with replacement. If success occurs we add an additional $(G - u_j + t)\beta$ balls of the same kind and $u_j\beta$ balls of the opposite kind in the urn. On the other hand, if a failure occurs we add an additional $(G - u_j)\beta$ balls of the same kind and $(t + u_j)\beta$ balls of the opposite kind in the urn. Thus, for every entering patient, $(G+t)\beta$ balls are added in total, $G\beta$ for the grade and $t\beta$ for a success or failure. For a given (α, β, t) we denote this by ARPW(α, β, t).

Suppose we are interested to accept any one of the following decisions:

$$H_1 : A \succ B, \qquad H_2 : B \succ A, \qquad \ldots (2.1)$$

where '$\succ$' means 'better than'. Suppose we have a sequential chain of patient's entrance upto a maximum of n patients. Corresponding to the i-th entering patient with grade u_i we set a pair of indicator variables $\{\delta_i, Z_i\}$ as follows:

$\delta_i = 1$ or 0 according as the treatment A or treatment B is applied following an ARPW(α, β, t) procedure, and

$Z_i = 1$ or 0 according as the i-th patient response is a success or failure.

Here we make the following assumption:

$$P(Z_i = 1|\delta_i = h, u_i) = p_{2-h} a^{G-u_i}, \quad h = 0, 1, \qquad \ldots (2.2)$$

where $a \in (0, 1)$, called the prognostic factor index, is either known from past experience or can be estimated from past data and $p_1, p_2 \in (0, 1)$, the success probabilities by treatment A and B respectively at grade G, are unknown. It is easy to check that, under equivalence of treatment effects (i.e., when $p_1 = p_2 = p$), δ_i's are identically distributed Bernoulli (1/2), and Z_i's are independently distributed with $P(Z_i = 1) = 1 - P(Z_i = 0) = pa^{G-u_i}$, and δ_i's are independent of Z_i's. Under H_1, we have $p_1 > p_2$. Define the statistics

$$\begin{aligned} T_{An} &= \sum_{i=1}^{n} a^{u_i} Z_i \delta_i, \quad T_{Bn} = \sum_{i=1}^{n} a^{u_i} Z_i (1 - \delta_i), \\ N_{An} &= \sum_{i=1}^{n} \delta_i = \text{ Number of allocations by treatment A}, \\ N_{Bn} &= \sum_{i=1}^{n} (1 - \delta_i) = \text{ Number of allocations by treatment B}, \end{aligned}$$

and hence

$$g_{kn} = T_{kn} / N_{kn}, \quad k = A, B. \qquad \ldots (2.3)$$

For a particular treatment, T_{kn} not only accounts for the total number of successes, but also the grades from which the successes have occurred as a^{u_i} is inversely proportional to the success probability at grade u_i. Then, we set our decision rules as follows:

Rule 1 : This is a terminal decision rule. The rule is:

$$\begin{array}{l} \text{Accept } H_1 \text{ if } g_{An} > g_{Bn} \text{ and } H_2 \text{ if } g_{An} < g_{Bn}. \\ \text{If } g_{An} = g_{Bn}, \text{ accept } H_1 \text{ with probability } 1/2. \end{array} \qquad \ldots (2.4)$$

Rule 2 : This rule is obtained by modifying Rule 1 with the provision of early stopping. For this we consider the random variables:

$$P_{ks}(v) = \frac{T_{ks} + v}{N_{ks} + v}, \quad Q_{ks}(v) = \frac{T_{ks}}{N_{ks} + n - s - v}, \ k = A, B,$$

where $v = 0, 1, \cdots, n - s$. In case $N_{ks} = 0$, we take $P_{ks}(0) = Q_{ks}(n - s) = 0$. Here $P_{ks}(v)$ represent a possible value of g_{kn} where among the future $(n - s)$

incoming patients (after the s-th one) exactly v patients each of grade 0 will be treated by treatment k and for all of them the result will be success. Similarly, $Q_{ks}(v)$ is a possible value of g_{kn} where among the $(n-s)$ remaining patients $(n-s-v)$ will be treated by treatment k and for each of them the result will be failure. We then stop sampling and accept A or B at the s-th stage if

$$\min_v(Q_{As}(v)-P_{Bs}(v))>0 \quad \text{or} \quad \min_v(Q_{Bs}(v)-P_{As}(v))>0.$$

Let $\tilde{p}_{i+1}$ be the conditional probability of $\delta_{i+1}=1$ given all the previous assignments $\{\delta_1,\cdots,\delta_i\}$, and all the previous responses $\{Z_1,\cdots,Z_i\}$. Then, it can be easily shown that

$$\begin{aligned}\tilde{p}_{i+1} \quad = \quad & \left\{\alpha+\beta\left[2t\sum_{j=1}^{i}\delta_j Z_j+\sum_{j=1}^{i}(u_j+t)-\sum_{j=1}^{i}(t+2u_j-G)\delta_j\right.\right. \\ & \left.\left.-t\sum_{j=1}^{i}Z_j\right]\right\}\Big/(2\alpha+i(G+t)\beta), \quad i\geq 1.\end{aligned} \qquad \ldots(2.5)$$

From the urn model it is clear that $\tilde{p}_1=\frac{1}{2}$. Now, from (2.5), the marginal distributions of δ_i's are obtained successively as:

$$P(\delta_1=1)=\frac{1}{2}, \qquad \ldots(2.6)$$

and for $i\geq 1$,

$$P(\delta_{i+1}=1)=\frac{1}{2}-d_{i+1}, \qquad \ldots(2.7)$$

where, by the method of induction,

$$\begin{aligned}d_{i+1} \quad = \quad & \frac{\beta}{2\alpha+i(G+t)\beta}t(p_2-p_1)\sum_{j=1}^{i}a^{G-u_j}\left(\frac{1}{2}+d_j\right) \\ & +\frac{\beta}{2\alpha+i(G+t)\beta}\sum_{j=1}^{i}\left[2tp_1a^{G-u_j}-(t+2u_j-G)\right]d_j.\end{aligned} \qquad \ldots(2.8)$$

Now we consider some performance characteristics. First we take the risk function, denoted by $R(\theta)$, the probability of a wrong decision. Note that, if the two treatments are equivalent, i.e., $p_1=p_2$, then there is no loss of accepting any one as the winner, and hence $R(\theta)=0$ in this case. For the second decision rule the average sample number (ASN) of patients required to get a decision is also used as a performance characteristic. We denote it by $S(\theta)$. It is noted that for both the decision rules risk function are the same. Now, as our initial goal of this sampling design is to allocate more patients to the better treatment, the number of patients treated by treatment A in course of sampling is also used as a performance characteristic. This is denoted by $S_A(\theta)$ and is given by $S_A(\theta) = \sum_{i=1}^{n}(\frac{1}{2} - d_i)$ for Rule 1 and $S_A(\theta) = E(\sum_{i=1}^{N} \delta_i)$ for Rule 2, where N is the ASN-value. The computations of $R(\theta)$, $S(\theta)$ and $S_A(\theta)$ by simulations at different $\theta = (p_1, p_2)$ are given in Table 2.1. 9998 simulations are done. Here we take $n = 50,\ \alpha = \beta = 1,\ t = 5,\ G = 3$ and $a = 0.8$. Here u_j's are generated in such a way that in the long run we have same frequencies for all 4 grades of the prognostic factor.

Table 2.1 : Performance characteristics of the proposed decision rule

(p_1, p_2)	$R(\theta)$	$S_A(\theta)$ for Rule 1	$S(\theta)$ for Rule 2	$S_A(\theta)$ for Rule 2
(0.6,0.2)	0.0022	31.0360	42.2254	25.4354
(0.6,0.3)	0.0176	29.7075	43.7292	25.3381
(0.6,0.4)	0.0904	28.4016	45.4718	25.0690
(0.6,0.5)	0.2566	26.7577	47.0236	24.0690
(0.7,0.2)	0.0004	32.8633	40.0889	25.4944
(0.7,0.3)	0.0032	31.6096	41.4368	25.5380
(0.7,0.4)	0.0270	30.3311	43.1578	25.4758
(0.7,0.5)	0.0839	28.7135	45.1888	25.2447
(0.7,0.6)	0.2473	27.1899	46.9676	24.6663
(0.8,0.2)	0.0000	35.0540	37.5166	26.1909
(0.8,0.3)	0.0008	33.9924	39.3959	26.0184
(0.8,0.4)	0.0024	32.6281	41.0039	25.9704
(0.8,0.5)	0.0188	31.0232	42.8368	25.8317
(0.8,0.6)	0.0742	29.3081	45.1680	25.8013
(0.8,0.7)	0.2351	27.3159	47.0506	24.9902

From the above table it is clear that Rule 2, as it requires fewer sample observations, is definitely better than Rule 1.

3. Some Asymptotic Results

We first make the following assumptions:

$$(i)\frac{1}{n}\sum_{j=1}^{n} u_j \to u, \quad \text{as} \quad n \to \infty. \qquad \ldots(3.1)$$

$$(ii)\frac{1}{n}\sum_{j=1}^{n} a^{G-u_j} \to a_0, \quad \text{as} \quad n \to \infty. \qquad \ldots(3.2)$$

$$(iii)\frac{1}{n}\sum_{j=1}^{n} a^{u_j} \to a_1, \quad \text{as} \quad n \to \infty. \qquad \ldots(3.3)$$

Now we have the following Lemmas:

LEMMA 3.1. *As $n \to \infty$,*

$$\frac{1}{n}\sum_{i=1}^{n}\delta_i \xrightarrow{P} \mu^*, \qquad \ldots(3.4)$$

where $\mu^* \in (0,1)$.

PROOF. See the appendix. □

COROLLARY. *When $p_1 = p_2$, we have $\mu^* = \frac{1}{2}$.*

LEMMA 3.2. *As $n \to \infty$, under $p_1 = p_2$,*

$$\frac{1}{n}\sum_{i=1}^{n}a^{u_i}\delta_i \xrightarrow{P} \frac{a_1}{2}. \qquad \ldots(3.5)$$

PROOF. Note that a^{u_i} is bounded by 1 and hence the follows from Lemma 3.1. □

Now we find the asymptotic distribution under equivalence. Here we have the following theorem:

THEOREM 3.1. *Under equivalence (i.e., when $p_1 = p_2 = p$), as $n \to \infty$,*

$$n^{1/2}\left(g_{An} - pa^G\right) \stackrel{d}{=} n^{1/2}\left(g_{Bn} - pa^G\right) \xrightarrow{d} N\left(0, \sigma^2\right),$$

where

$$\sigma^2 = 2pa^G\left(a_1 - pa^G\right).$$

PROOF. '$\stackrel{d}{=}$' part of the theorem is trivial. For the other part we rewrite T_{An} as

$$T_{An} = \sum_{i=1}^{n}a^{u_i}Z_i\delta_i = \sum_{i=1}^{n}U_i,$$

where $U_i = a^{u_i}Z_i\delta_i$. Note that, for each n and under equivalence, the conditional distribution of U_i given $\boldsymbol{\delta} = (\delta_1, \cdots, \delta_n)$ are independent and δ_i is distributed independently of Z_i. Hence, since $\delta_i^s = \delta_i,\ s = 1, 2, \cdots$, we get, as in Hajek and Sidak (1967, p. 194),

$$\begin{array}{rcl} m_{ni} & = & E(U_i|\boldsymbol{\delta}) = \delta_i pa^G, \\ s_{ni}^2 & = & V(U_i|\boldsymbol{\delta}) = \delta_i a^{G+u_i}p\left(1 - pa^{G-u_i}\right), \end{array} \qquad \ldots(3.8)$$

and hence

$$s_n^2 = \sum_{i=1}^{n}s_{ni}^2 = pa^G\sum_{i=1}^{n}\delta_i a^{u_i} - p^2a^{2G}N_{An} \geq a^{2G}p(1-p)N_{An}. \qquad \ldots(3.9)$$

Then, for every $\epsilon > 0$, we have

$$\begin{aligned} & s_n^{-2} \sum_{i=1}^{n} \int_{|u-m_{ni}|>\epsilon s_n} (u-m_{ni})^2 dP(U_i < u|\boldsymbol{\delta}) \\ \leq \quad & \frac{1}{\epsilon^2 s_n^4} \sum_{i=1}^{n} E\left[(U-m_{ni})^4|\boldsymbol{\delta}\right] \leq \frac{1}{\epsilon^2 a^{4G} p^2 (1-p)^2} \frac{N_{An}}{N_{An}^2}, \end{aligned} \qquad \ldots (3.10)$$

which, by Lemma 3.1, converges to zero in probability, as $n \to \infty$. Hence, using Lemmas 3.1, 3.2 and Hajek and Sidak (1967, ch. V, pp. 194-195), we have

$$\frac{n^{1/2}}{\sigma}\left(g_{An} - pa^G\right) \stackrel{P}{\simeq} \frac{\left(\dfrac{T_{An}}{N_{An}} - pa^G\right)}{\sqrt{\dfrac{pa^G}{N_{An}^2}\left(\displaystyle\sum_{i=1}^{n} \delta_i a_{u_i} - pa^G N_{An}\right)}} \xrightarrow{d} N(0,1), \qquad \ldots (3.11)$$

which completes the proof. $\square$

Next we find the limiting value of the risk function. Here we prove the following theorem:

THEOREM 3.2. *For any* $\theta = (p_1, p_2) : p_1 \neq p_2$, $R(\theta) \to 0$ *as* $n \to \infty$. PROOF. Suppose, $\theta : p_1 > p_2$. If $p_1 < p_2$, the proof follows similarly. Then

$$R(\theta) = P_\theta\{g_{An} < g_{Bn}\} + \frac{1}{2} P_\theta\{g_{An} = g_{Bn}\}. \qquad \ldots (3.11)$$

It is always possible to have two sequences of positive integers $\{\nu_{An}\}$ and $\{\nu_{Bn}\}$ such that, as $n \to \infty$,

$$\nu_{kn} \to \infty,\ k = A, B, \quad \text{and} \quad \frac{\nu_{An}}{n} \to \mu^* \quad \text{and} \quad \frac{\nu_{Bn}}{n} \to 1 - \mu^*. \qquad \ldots (3.12)$$

Then, by Lemma 3.1, we have

$$N_{kn} \stackrel{P}{\simeq} \nu_{kn},\ k = A, B, \qquad \ldots (3.13)$$

and hence

$$g_{kn} = T_{kn} / N_{kn} \stackrel{P}{\simeq} T_{kn} / \nu_{kn} = g_{kn}^* \quad \text{(say)}, \quad k = A, B. \qquad \ldots (3.14)$$

Now

$$E\left(g_{kn}^*\right) = EE\left(g_{kn}^* | \boldsymbol{\delta}\right) = p_1 a^G E\left(\frac{N_{An}}{\nu_{An}}\right) \qquad \ldots (3.15)$$

and

$$\begin{aligned} V\left(g_{kn}^{*}\right) &= EV\left(\frac{N_{An}}{\nu_{An}}\bigg|\boldsymbol{\delta}\right) + VE\left(\frac{N_{An}}{\nu_{An}}\bigg|\boldsymbol{\delta}\right) \\ &= \frac{1}{\nu_{An}^{2}} E\left[pa^{G}\sum_{i=1}^{n}\delta_i a_{u_i} - p^2 a^{2G} N_{An}\right] + p^2 a^{2G}\nu_{An}^{-2} V(N_{An}) \\ &\leq \left(\frac{n}{\nu_{An}}\right)^{2}\left[pa^{G}\frac{1}{n^2}\sum_{i=1}^{n} a_{u_i} + V\left(\frac{N_{An}}{n}\right)\right]. \end{aligned} \quad \ldots (3.16)$$

By (3.12) and Lemma 3.1, as $n \to \infty$, the right hand members of (3.15) and (3.16) converge respectively to $p_1 a^G$ and 0. This, by (3.14), implies

$$g_{An} \xrightarrow{P} p_1 a^G. \quad \ldots (3.17)$$

Similarly, we get

$$g_{Bn} \xrightarrow{P} p_2 a^G. \quad \ldots (3.18)$$

Then, using (3.17) and (3.18) in (3.11), $R(\theta)$ tends to 0 as $n \to \infty$. $\square$

The initial goal of our sampling design was to allocate a larger number of patients to the better treatment in course of sampling. Now we are intended to find the limiting proportions of allocations by the two treatments if ARPW is advocated for a large number of patients. Here we note that for any θ, the sequence $\{d_i,\ i \geq 1\}$ is either increasing or decreasing depending on the values of p_1 and p_2 (see the appendix) and it is bounded above and below (as $0 \leq \frac{1}{2} - d_i \leq 1\ \forall\ i$). Hence writing $\lim_{i\to\infty} d_i = d$, we have by Toeplitz's lemma,

$$E\left(\frac{1}{n}\sum_{i=1}^{n}\delta_i\right) = \frac{1}{2} - \frac{1}{n}\sum_{i=1}^{n} d_i \to \frac{1}{2} - d, \quad \ldots (3.19)$$

which shows that N_{An}/n converges to $\frac{1}{2} - d$, and this is the limiting proportion of patients treated by treatment A. To find d, using assumptions (3.1) and (3.2), we have

$$\frac{1}{n}\sum_{j=1}^{n} u_j d_j - ud = \frac{1}{n}\sum_{j=1}^{n} u_j(d_j - d) + d\left[\frac{1}{n}\sum_{j=1}^{n} u_j - u\right],$$

which tends to zero, as $n \to \infty$. This implies,

$$\frac{1}{n}\sum_{j=1}^{n} u_j d_j \to ud, \quad \text{as} \quad n \to \infty. \quad \ldots (3.20)$$

Similarly, we get,

$$\frac{1}{n}\sum_{j=1}^{n} a^{G-u_j} d_j \to a_0 d, \quad \text{as} \quad n \to \infty. \qquad \ldots (3.21)$$

Using (3.1), (3.2), (3.20) and (3.21) we get from (2.8),

$$d = \frac{t}{G+t}(p_2 - p_1)\left(\frac{a_0}{2} + a_0 d\right) + \frac{1}{G+t}[2tp_1 a_0 - (t + 2u - G)]d,$$

which gives

$$d = \frac{t(p_2 - p_1)a_0}{2[2(t+u) - t(p_2 - p_1)a_0 - 2ta_0 p_1]}. \qquad \ldots (3.22)$$

It is interesting to note that the limiting proportions do not depend on the choice of α and β, but it depends on t. If $a_0 = 1$ and $u = 0$ (which implies the absence of prognostic factor), we get the limiting proportions of allocations in an RPW scheme of sampling (see Wei (1979)).

4. Discussions

So far we have assumed the prognostic factor to be non-stochastic. Now we consider the case when it is stochastic. Suppose the variable U corresponding to the prognostic factor has the distribution function (d.f.) $H(u),\ u = 0, 1, \cdots, G$. If we write $\psi_l(a) = E\left(a^{G-U}.U^l\right)$ (provided it exists) and $P_U(w)$, the probability generating function (p.g.f.) of U, then the marginal distribution of δ_i's can be obtained from (2.6)-(2.8) by replacing $a^{G-u_j}.u_j^l$ and a^{G-u_j} respectively by $\psi_l(a)$ and $a^G P_U(a^{-1})$ at every stage. Subsequent analysis can be similarly done. We consider the simplest case where $G = 1$. Then U follows a Bernoulli (q) distribution. In this case we have $E(a^{G-U}) = (1 - q + qa)$ and $E(a^{G-U}.U^l) = q$ for each l.

All the analyses in this paper are done by considering only one prognostic factor. If there are more than one prognostic factors we can proceed in the following direction. Suppose there are s prognostic factors $C_1, C_2, \cdots, C_s$ with grades $0, 1, \cdots, G_l$ for the l-th factor. First, we consider $G + 1 = \prod_{l=1}^{s}(G_l + 1)$ factor combinations. We can arrange these $G+1$ combinations according to the favourable conditions as $0, 1, \cdots, G$ and carry out the same procedure discussed in this paper. If G is moderately large the revised grading may be a difficult job as it involves combination of different grades. In that case for an entering patient with grade u_{lj} of the factor $C_l,\ l = 1(1)s$, we have

$$P(Z_j = 1|\delta_j = h, u_{lj}, l = 1(1)s) = p_{2-h}\prod_{l=1}^{s} a_l^{G_l - u_{ls}},\ h = 0, 1, \qquad \ldots (4.1)$$

where we have ideas about the prognostic factor indices $a_1, a_2, \cdots, a_s$ from the past experience. Then the same procedure can be carried out. However, it requires more modeling and knowledge about parameters. This is actually a routine generalization and hence we are not proceeding for further study.

In section 2, (2.2) is proposed heuristically. Actually this, at least in theory, could be built up starting from more basic data. Suppose the responses are continuous which are converted to dichotomous responses by setting a threshold response $c \in (0, \infty)$. Let, for grade u, the response variable X_i (for $\delta_i = 1$) have the d.f. $F_u,\ u = 0(1)G$. Writing $\bar{F}_u(x) = 1 - F_u(x)$, we assume that

$$\bar{F}_u(c) \big/ \bar{F}_{u+1}(c) = a. \qquad \ldots (4.2)$$

Note that success probability by X_i with grade u is $\bar{F}_u(c)$. Then denoting $p_1 = \bar{F}_G(c)$, we have

$$\bar{F}_u(c) = a^{G-u} \bar{F}_G(c) = p_1 a^{G-u}.$$

Similarly, $P(Z_i = 1 | \delta_i = 0, u_i) = p_2 a^{G-u}$ can be established. Note that the relationship (4.2) is satisfied by the Weibull family and hence by the exponential distribution as a special case. If $F_u(x) = 1 - e^{-(G+1-u)x}$, we have $a = e^{-c}$. Clearly $a \in (0, 1)$.

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Appendix

Result 1. The sequence $\{d_i\}$ is bounded and is either increasing or decreasing depending on the values of $(p_1, p_2, \alpha, \beta, G, t)$.

PROOF. It is easy to note that for $(p_1, p_2) : p_2 > p_1$, we have

$$d_1 = 0 \quad \text{and} \quad d_2 > 0. \qquad \ldots (A.1)$$

As the choice of design parameters (α, β, t) is in the experimenter's hand, we can choose them in such a way that

$$d_2 \le D(0), D(1), \cdots, D(G),$$

where

$$D(j) = \frac{t(p_2 - p_1)a^{G-j}}{2[2(t+j) - t(p_1 + p_2)a^{G-j}]}.$$

Here we will prove the result by the following steps :

1. $d_{i+1} > 0 \ \ \forall\, i \geq 2$.
2. The sequence $\{d_i\}$ is bounded.
3. $d_{i+1} \geq d_i \ \ \forall\, i \geq 2$.

Step 1. From (2.11) we can write for $i \geq 2$,

$$\begin{aligned} d_{i+1} &= \frac{\beta}{2\alpha + i(G+t)\beta} t(p_2 - p_1) \sum_{j=1}^{i} a^{G-u_j} \left(\frac{1}{2} + d_j \right) \\ &\quad + \frac{\beta}{2\alpha + i(G+t)\beta} \sum_{j=1}^{i} \left[2tp_1 a^{G-u_j} - (t + 2u_j - G) \right] d_j, \end{aligned}$$

which implies

$$\begin{aligned} &(2\alpha + i(G+t)\beta) d_{i+1} \\ &= \beta t(p_2 - p_1) \sum_{j=1}^{i} a^{G-u_j} \left(\frac{1}{2} + d_j \right) + \beta \sum_{j=1}^{i} \left[2tp_1 a^{G-u_j} - (t + 2u_j - G) \right], \\ &= \left\{ \beta t(p_2 - p_1) \sum_{j=1}^{i-1} a^{G-u_j} \left(\frac{1}{2} + d_j \right) + \beta \sum_{j=1}^{i-1} \left[2tp_1 a^{G-u_j} - (t + 2u_j - G) \right] d_j \right\} \\ &\quad + \beta t(p_2 - p_1) a^{G-u_i} \left(\frac{1}{2} + d_i \right) + \beta \left[2tp_1 a^{G-u_i} - (t + 2u_i - G) \right] d_i \\ &= (2\alpha + (i-1)(G+t)\beta) d_i \\ &\quad + \beta t(p_2 - p_1) a^{G-u_i} \left(\frac{1}{2} + d_i \right) + \beta \left[2tp_1 a^{G-u_i} - (t + 2u_i - G) \right] d_i, \end{aligned}$$

implying

$$\begin{aligned} d_{i+1} &= \left(\frac{2\alpha + (i-1)(G+t)\beta}{2\alpha + i(G+t)\beta} \right) d_i \\ &\quad + \frac{\beta}{2\alpha + i(G+t)\beta} t(p_2 - p_1) a^{G-u_i} \left(\frac{1}{2} + d_i \right) \qquad \ldots (A.2) \\ &\quad + \frac{\beta}{2\alpha + i(G+t)\beta} \left[2tp_1 a^{G-u_i} - (t + 2u_i - G) \right] d_i, \end{aligned}$$

and hence

$$\begin{aligned} \frac{d_{i+1}}{d_i} &= \frac{2\alpha + \beta \left\{ (i-1)(G+t) + t(p_2 - p_1) a^{G-u_i} + 2tp_1 a^{G-u_i} - (t + 2u_i - G) \right\}}{2\alpha + i(G+t)\beta} \\ &\quad + \frac{\beta t(p_2 - p_1) a^{G-u_i}}{2\alpha + i(G+t)\beta} \frac{1}{2d_i} \qquad \ldots (A.3) \end{aligned}$$

$$= \frac{2\alpha + \beta\left\{(i-2)(G+t) + t(p_1+p_2)a^{G-u_i} + 2(G-u_i)\right\}}{2\alpha + i(G+t)\beta} + \frac{\beta t(p_2-p_1)a^{G-u_i}}{2\alpha + i(G+t)\beta}\frac{1}{2d_i}. \qquad \ldots (A.4)$$

Using (A.1), it is easy to observe that for $i \geq 2$,

$$d_{i+1}/d_i > 0,$$

implying

$$d_{i+1} > 0 \quad \forall\ i \geq 2.$$

Step 2. For $i \geq 2$,

$$\begin{aligned}
d_i \quad &\leq \quad D(u_i) = \frac{t(p_2-p_1)a^{G-u_i}}{2[2(t+u_i) - t(p_1+p_2)a^{G-u_i}]} \\
&\Longleftrightarrow \quad \left[2\alpha + \beta\left\{(i-2)(G+t) + t(p_1+p_2)a^{G-u_i} + 2(G-u_i)\right\}\right] d_i \\
&\leq \quad \frac{t(p_2-p_1)a^{G-u_i}}{2[2(t+u_i) - t(p_1+p_2)a^{G-u_i}]}\left[2\alpha + \beta\{(i-2)(G+t)\right. \\
&\qquad \left. + t(p_1+p_2)a^{G-u_i} + 2(G-u_i)\}\right] \\
&= \quad \frac{1}{2}t(p_2-p_1)a^{G-u_i}\left[\frac{2\alpha + i(G+t)\beta}{2(t+u_i) - t(p_1+p_2)a^{G-u_i}} - \beta\right] \\
&\Longleftrightarrow \quad \left(\frac{2\alpha + \beta\left\{(i-2)(G+t) + t(p_1+p_2)a^{G-u_i} + 2(G-u_i)\right\}}{2\alpha + i(G+t)\beta}\right) d_i \\
&\qquad + \frac{\beta t(p_2-p_1)a^{G-u_i}}{2(2\alpha + i(G+t)\beta)} \leq \frac{t(p_2-p_1)a^{G-u_i}}{2[2(t+u_i) - t(p_1+p_2)a^{G-u_i}]} \\
&\Longleftrightarrow \quad d_{i+1} \leq \frac{t(p_2-p_1)a^{G-u_i}}{2[2(t+u_i) - t(p_1+p_2)a^{G-u_i}]}.
\end{aligned} \qquad \ldots (A.5)$$

As u_i is a variable, it can take any of the values $0, 1, \cdots, G$. Hence for $j = 0, 1, \cdots, G$,

$$d_2 \leq D(u_2 = j) \Longleftrightarrow d_3 \leq D(j).$$

In a similar manner we can obtain

$$d_i \leq D(0), D(1), \cdots, D(G), \quad \forall\ i \geq 2.$$

Step 3. From (A.4), we get,

$$\frac{d_{i+1}}{d_i} \geq 1 \Longleftrightarrow d_i \leq D(u_i) = \frac{t(p_2-p_1)a^{G-u_i}}{2[2(t+u_i) - t(p_1+p_2)a^{G-u_i}]},$$

where the RHS is ensured by Step 2 for all possible values of u_i.

REMARK. Note that if we write

$$P(\delta_i = 1) = \frac{1}{2} - d_i \quad \text{for} \quad (p_1, p_2) = (a, b),$$

and

$$P(\delta_i = 1) = \frac{1}{2} - d_i^* \quad \text{for} \quad (p_1, p_2) = (b, a),$$

then $d_i^* = -d_i$, as the roles of treatments A and B are interchanged. Thus Result 1 can be easily proved for $p_1 > p_2$, as in that case we are to deal with the sequence $\{-d_i,\ i \geq 2\}$.

If $p_1 = p_2$, then from (2.8), in a recursive manner it can be easily seen that

$$d_i = 0 \ \ \forall\ i.$$

Result 2. As $n \to \infty$,

$$\frac{1}{n}\sum_{i=1}^{n} \delta_i \xrightarrow{P} \mu^*,$$

where $\mu^* \in (0,1)$.

PROOF. It can be easily shown that

$$\begin{aligned}
& P(\delta_{i+1} = 1 | \delta_i = 1) = \frac{1}{2} - \frac{\beta}{2\alpha + i(G+t)\beta} t(p_2 - p_1) \sum_{j=1}^{i-1} a^{G-u_j} \left(\frac{1}{2} + d_j\right) \\
& - \frac{\beta}{2\alpha + i(G+t)\beta} \sum_{j=1}^{i-1} \left[2tp_1 a^{G-u_j} - (t + 2u_j - G)\right] d_j \\
& - \frac{\beta}{2\alpha + i(G+t)\beta} \left[\frac{1}{2}(t + 2u_i - G) - tp_1 a^{G-u_i}\right] \\
= \ & \frac{1}{2} - \bar{d}_{i+1}^{(i)} \qquad \text{(say)},
\end{aligned} \qquad \ldots (A.6)$$

$$\begin{aligned}
& P(\delta_{i+2} = 1 | \delta_i = 1) \\
= \ & \frac{1}{2} - \frac{\beta}{2\alpha + (i+1)(G+t)\beta} t(p_2 - p_1) \\
& \times \left[\sum_{j=1}^{i-1} a^{G-u_j} \left(\frac{1}{2} + d_j\right) + a^{G-u_{i+1}} \left(\frac{1}{2} + \bar{d}_{i+1}^{(i)}\right)\right] \\
& - \frac{\beta}{2\alpha + (i+1)(G+t)\beta} \left[\sum_{j=1}^{i-1} \left(2tp_1 a^{G-u_j} - (t + 2u_j - G)\right) d_j \right. \qquad \ldots (A.7) \\
& \left. + \left(2tp_1 a^{G-u_{i+1}} - (t + 2u_{i+1} - G)\right) \bar{d}_{i+1}^{(i)}\right] \\
& - \frac{\beta}{2\alpha + (i+1)(G+t)\beta} \left[\frac{1}{2}(t + 2u_i - G) - tp_1 a^{G-u_i}\right] \\
= \ & \frac{1}{2} - \bar{d}_{i+2}^{(i)} \qquad \text{(say)},
\end{aligned}$$

and, in general, for $i < k$,

$$\begin{aligned}
& P(\delta_k = 1|\delta_i = 1) \\
= \quad & \frac{1}{2} - \frac{\beta}{2\alpha + (k-1)(G+t)\beta} t(p_2 - p_1) \\
& \times \left[\sum_{j=1}^{i-1} a^{G-u_j} \left(\frac{1}{2} + d_j \right) + \sum_{j=i+1}^{k-1} a^{G-u_j} \left(\frac{1}{2} + \bar{d}_j^{(i)} \right) \right] \\
& - \frac{\beta}{2\alpha + (k-1)(G+t)\beta} \left[\sum_{j=1}^{i-1} \left(2tp_1 a^{G-u_j} - (t + 2u_j - G) \right) d_j \right. \\
& \left. + \sum_{j=i+1}^{k-1} \left(2tp_1 a^{G-u_j} - (t + 2u_j - G) \right) \bar{d}_j^{(i)} \right] \\
& - \frac{\beta}{2\alpha + (k-1)(G+t)\beta} \left[\frac{1}{2}(t + 2u_i - G) - tp_1 a^{G-u_i} \right] \\
= \quad & \frac{1}{2} - \bar{d}_k^{(i)} \qquad \text{(say).}
\end{aligned} \qquad \ldots (A.8)$$

Here, for each i, it can be easily shown that, as $k \to \infty$,

$$\bar{d}_k^{(i)} - d_k \to 0.$$

Hence,

$$\begin{aligned}
& P(\delta_k = 1|\delta_i = 1) - P(\delta_k = 1) \\
= \quad & \frac{\beta}{2\alpha + (k-1)(G+t)\beta} t(p_2 - p_1) \sum_{j=i+1}^{k-1} a^{G-u_j} \left(d_j - \bar{d}_j^{(i)} \right) \\
& + \frac{\beta}{2\alpha + (k-1)(G+t)\beta} \sum_{j=i+1}^{k-1} (t + 2u_j - G) \left(\bar{d}_j^{(i)} - d_j \right) \\
& - \frac{\beta}{2\alpha + (k-1)(G+t)\beta} \left[\frac{1}{2}(t + 2u_i - G) - tp_1 a^{G-u_i} \right] \qquad \ldots (A.9) \\
\leq \quad & \frac{\beta}{2\alpha + (k-1)(G+t)\beta} t|p_2 - p_1| \sum_{j=i+1}^{k-1} a^{G-u_j} |d_j - \bar{d}_j^{(i)}| \\
& + \frac{\beta}{2\alpha + (k-1)(G+t)\beta} \sum_{j=i+1}^{k-1} |t + 2u_j - G||d_j - \bar{d}_j^{(i)}| \\
& + \frac{\beta}{2\alpha + (k-1)(G+t)\beta} |\frac{1}{2}(t + 2u_i - G) - tp_1 a^{G-u_i}| \\
= \quad & c_{ik} \qquad \text{(say),}
\end{aligned}$$

which, by Toeplitz's lemma, tends to zero as $k \to \infty$.

Thus, as $P(\delta_i = 1) = \frac{1}{2} - d_i \leq \frac{1}{2}$ for $p_2 > p_1$, we have

$$
\begin{aligned}
& V\left(\frac{1}{n}\sum_{i=1}^{n}\delta_i\right) \\
& = \frac{1}{n^2}\sum_{i=1}^{n}V(\delta_i)+\frac{1}{n^2}\sum_{i\neq k}cov(\delta_i,\delta_k) \\
& = \frac{1}{n^2}\sum_{i=1}^{n}\left(\frac{1}{2}-d_i\right)\left(\frac{1}{2}+d_i\right) \\
& \quad +\frac{1}{n^2}\sum_{i\neq k}P(\delta_i=1)(P(\delta_k=1|\delta_i=1)-P(\delta_k=1))
\end{aligned}
$$

$$
\begin{aligned}
\leq \quad & \frac{1}{4n}+\frac{1}{n^2}\sum_{k=1}^{n}\frac{(k-1)\beta}{2\alpha+(k-1)(G+t)\beta}t|p_2-p_1| \\
& \sum_{j=i+1}^{k-1}a^{G-u_j}|d_j-\bar{d}_j^{(i)}| \\
& +\frac{1}{n^2}\sum_{k=1}^{n}\frac{(k-1)\beta}{2\alpha+(k-1)(G+t)\beta}{}^{k-1}_{j=i+1}|t+2u_j-G||d_j-\bar{d}_j^{(i)}| \\
& +\frac{1}{n^2}\frac{(k-1)\beta}{2\alpha+(k-1)(G+t)\beta}|\frac{1}{2}(t+2u_i-G)-tp_1a^{G-u_i}|,
\end{aligned}
\qquad \ldots(A.10)
$$

which, by Toeplitz's lemma, tends to zero as $n\to\infty$. Hence the result follows using the fact that the sequence $\{d_i\}$ is monotonic and bounded.

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