Comparison of two treatments with heterogeneous experimental units

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Abstract

The present paper, based on a newly introduced sampling scheme called 'Multi-stage randomized play-the-winner rule', provides a decision theoretic solution for comparing two treatments in a clinical trial experiment. Some numerical computations related to the performance of the proposed solution are obtained. Further some asymptotic results are established. A related estimation problem is also considered.

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1. Introduction

The problem of comparison of two treatments, A and B, say, in a clinical trial is considered by many authors in the recent years. If the patients enter in a system sequentially, the problem of allocating the entering patients between the two treatments gets much importance. If the subjects are human beings then, from the ethical point of view, it is required to have a decision with the smallest number of patients being treated by the worse treatment. Towards this Zelen (1969) proposed a sampling design called play-the-winner rule and, as a modification of the rule Wei and Durham (1978) and Wei (1979) introduced an idea called randomized play-the-winner (RPW) rule which can be interpreted by means of an urn. Some further works in this regard are done by different authors (see, for example, Wei, 1988, Bandyopadhyay and Biswas, 1996, 1997).

The available literatures on clinical trials are mostly based on the assumption that the incoming patients are homogeneous. But, in practice, this is seldom true. Because the entering stages of patients may be distinguished with respect to the intensity of the disease and, at the same time, there may be several possible outgoing stages. All these possibilities are incorporated in the present study by introducing a scheme of sampling called 'multi-stage randomized play-the-winner' (MSRPW) rule. Using this rule, a decision theoretic solution for comparing two treatments is provided in the next section. Some performance characteristics are studied numerically. Further, some asymptotic results are obtained in Section 3, and assuming a simple probability model, an estimation problem is considered in Section 4. Section 5 ends with numerical computations.

2. Proposed decision rule and relevant probability distributions

Our object in the present investigation is to accept any of the following three decisions:

$$a_1 : A \equiv B, \quad a_2 : A > B, \quad a_3 : B > A, \tag{2.1}$$

where the symbol '$>$' is used to mean that one treatment is better than the other one. We consider the case when a patient may have $(k+2)$ stages: $0,1,\ldots,k,k+1$. The stage '0' is for death and the stage $(k+1)$ is for complete cure. The possible entering stages of a patient are $1,2,\ldots,k$ (in total k in number) and the possible outgoing stages are $0,1,2,\ldots,k,k+1$ (in total $(k+2)$ in number). The distinction between different stages is done by the experimenter by consulting a clinician.

Suppose there is a sequential chain of patient's entrance upto a maximum of n patients. The patients are treated by treatment A or B by using an MSRPW rule which can be described by using an urn model as follows: Start with an urn having two types of balls A and B, α of each type. For an entering patient of stage x we treat him/her by drawing a ball from the urn with replacement. If the outgoing stage is y, we add an additional $(y-x+q)\beta$ balls of the same kind and $(k+1-y+q)\beta$ balls of the opposite kind in the urn. This procedure is repeated. Here $(y-x)$ may be negative. Hence q is so choosen that at every moment $y-x+q \geqslant 0$. Keeping this in mind we set q to be equal to k.

Now, for each of the entering patients we define the following variables: $\delta_i = 1$ or 0 according as the ith patient is treated by treatment A or B; $\eta_{xi} = 1$ or 0 according as the ith patient enters with stage x or not. Clearly, $\sum_{i=1}^{k} \eta_{xi} = 1 \ \forall i$. Then our proposed decision rule can be based on the statistics

$$T_1 = \sum_{i=1}^{n} \delta_i (y_i - x_i + k), \quad T_2 = \sum_{i=1}^{n} (1-\delta_i)(y_i - x_i + k).$$

To avoid negative values of T_1 and T_2 both, we use $(y_i - x_i + k)$ instead of $y_i - x_i$ in the summand. Note that under equivalence T_1 and T_2 have the same distribution and hence our proposed decision rule would be:

Take action a_1 if $|T_1 - T_2| \leqslant c$. Take action a_2 or a_3 according as $T_1 - T_2 > c$ or $< -c$.

The choice of 'c' is at the hand of the experimenter. For example 'c' can be chosen by fixing the probability of accepting a_1 when a_1 is true at a pre-assigned level.

Several performance characteristics we consider here are: (i) the probability of correct selection (PCS), and (ii) the proportion of patients treated by treatment A ($\pi(A)$) in course of sampling. These performance characteristics are computed by 10 000 simulations and by making some particular model assumption and these are considered in Section 5. Here one could possibly employ early stopping retaining the same PCS, but exposing smaller number of patients to get a decision. But such a routine study is not done here.

Next we define the concept of outgoing probability matrix. An outgoing probability matrix, when a patient is treated by A, is a $k \times (k+2)$ matrix $P^A = ((p^A_{xy}))$, $x = 1(1)k$, $y = 0(1)k+1$, where the (x, y)th element p^A_{xy} is the probability that a patient of entering stage 'x' has the outgoing stage 'y' when it is treated by treatment A. Clearly, $\sum_{y=0}^{k+1} p^A_{xy} = 1 \ \forall x$. Similarly, we have an outgoing probability matrix $P^B = ((p^B_{xy}))$ for treatment B.

The conditional probability of $\delta_{i+1} = 1$ given all the previous entries, responses and assignments is

$$p_{i+1} = \frac{\alpha + \beta[(k+1+q)i + 2\sum_{j=1}^{i} \delta_j y_j - \sum_{j=1}^{i} \delta_j x_j - (k+1+q)\sum_{j=1}^{i} \delta_j - \sum_{j=1}^{i} y_j]}{2\alpha + \beta[(k+1+2q)i - \sum_{j=1}^{i} x_j]}. \tag{2.2}$$

At present we suppose that x is non-stochastic. From (2.2), the marginal probability distributions of δ_j's can be obtained by the method of induction as

$$P(\delta_{i+1} = 1) = \tfrac{1}{2} - d_{i+1}, \tag{2.3}$$

where $d_1 = 0$ and for $i \geqslant 1$,

$$d_{i+1} = \frac{\beta}{2\alpha + \beta(i(k+1+q) - \sum_{j=1}^{i} x_j)} \left[\frac{1}{2} \sum_{j=1}^{i} (e^B_{x_j} - e^A_{x_j}) + \sum_{j=1}^{i} (e^A_{x_j} + e^B_{x_j})\delta_j - \sum_{j=1}^{i} (x_j + k + 1 + q) d_j \right], \tag{2.4}$$

with $e^A_x = \sum_{s=0}^{k+1} s p^A_{xs}$ and $e^B_x = \sum_{s=0}^{k+1} s p^B_{xs}$. But, under equivalence (i.e., under a_1), δ_j's are independently distributed Bernoulli ($\frac{1}{2}$) random variables and are distributed independently of y_j's.

3. Some asymptotic results

In this section we study the following asymptotic results: (i) Asymptotic distribution of $T_1 - T_2$ under equivalence, and (ii) PCS under a_2 or a_3 as n goes to infinity.

Solution (i): We first write, after the arrival of the nth patient, $n_x = \sum_{i=1}^{n} \eta_{xi}$, which represents the number of patients at the entering stage 'x'. Then, if $\pi_x = P(\eta_{xi} = 1)$, $x = 1, 2, \ldots, k$, $i = 1, 2, \ldots, n$, $(n_1, \ldots, n_{k-1})$ has multinomial $(n; \pi_1, \ldots, \pi_{k-1})$ distribution with $\sum_{x=1}^{k} \pi_x = 1$. Now, under equivalence, as y_i are distributed independently of δ_i, we have

$$E(T_1 - T_2) = 0.$$

From Rosenberger (1993), it is not difficult to find a normalizing sequence $\{v_n\}$ such that, as $n \to \infty$,

$$\frac{1}{\sqrt{v_n}}(T_1 - T_2) \xrightarrow{\mathrm{d}} \mathrm{N}(0, 1),$$

where $\{v_n\}$ is such that, as $n \to \infty$,

$$\frac{v_n}{n^2} \to 0.$$

Hence the proposed decision rule can be approximated by

Take action a_1 if $|T_1 - T_2| \leqslant \tau_{\gamma/2}\sqrt{v_n}$.

Take action a_2 or a_3 according as $T_1 - T_2 > \tau_{\gamma/2}\sqrt{v_n}$ or $< -\tau_{\gamma/2}\sqrt{v_n}$. (3.1)

Here '$\tau_{\gamma/2}$' is the upper $100\gamma/2\%$ point of an $\mathrm{N}(0, 1)$ distribution.

Solution (ii): Here we prove the following theorem:

Theorem 3.1. *PCS of the decision rule, under a_2 or a_3, goes to unity as $n \to \infty$.*

Proof. Here it is enough to prove the result for $B > A$. Then, for each x, we have P^A and P^B for which $\sum_{s=0}^{q} p_{xs}^A \geqslant \sum_{s=0}^{q} p_{xs}^B$ for all q with at least one strict inequality, implying $e_x^A < e_x^B$ for all x. From the result in the appendix we immediately have, as $n \to \infty$,

$$\frac{1}{n}(T_1 - T_2) \xrightarrow{\mathrm{p}} g, \tag{3.2}$$

where g is given by (A.3). Obviously, $g < 0$ or $g = 0$ according as $B > A$ or $B \equiv A$. Hence, using (3.1), the result follows.

4. An estimation problem

In this section we consider, under the equivalence of A and B, an estimation problem related to outgoing probability matrix under the simple model

$$p_{xs} = \binom{k+1}{s}\left(\frac{x\theta}{k+1}\right)^{s}\left(1 - \frac{x\theta}{k+1}\right)^{k+1-s}, \tag{4.1}$$

where $\theta \in (0,1)$ is the only unknown parameter. Defining n_x as in Section 3, if $n_x(s)$ represents the number of patients at outgoing stage 's', we have, given n_x,

$$(n_x(0),\ldots,n_x(k)) \sim \text{Multinomial}\ (n_x; p_{x0}, p_{x1}, \ldots, p_{xk}).$$

Taking the xth row of the outgoing probability matrix, the likelihood function is

$$L = \text{Constant} \times \left(\frac{x\theta}{k+1}\right)^{v_1(x)} \left(1 - \frac{x\theta}{k+1}\right)^{v_2(x)},$$

with $v_1(x) = \sum_{s=0}^{k+1} s n_x(s)$ and $v_2(x) = \sum_{s=0}^{k+1} s n_x(k+1-s)$. Here, for each x and given n_x, $(v_1(x), v_2(x))$ is sufficient for θ. Also it can be easily seen that $(1/n)\sum_{x=1}^{k} v_1(x)/x$ and $(1/n)\sum_{x=1}^{k} v_2(x)/(k+1-x)$ are both unbiased estimators of θ. A suitable weighted average of these two may be considered.

5. Numerical illustrations

Here we consider the following models for computing PCS and $\pi(A)$. Taking $k=3$ and $q=3$, the models in the form of P^A and P^B are given below:

Model 1:

$$P^A = \begin{array}{c} \\ 1 \\ 2 \\ 3 \end{array} \begin{array}{c} \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \end{array} \\ \begin{pmatrix} 0.90 & 0.05 & 0.05 & 0 & 0 \\ 0.75 & 0.15 & 0.05 & 0.05 & 0 \\ 0.60 & 0.20 & 0.10 & 0.05 & 0.05 \end{pmatrix} \end{array}$$

and

$$P^B = \begin{array}{c} \\ 1 \\ 2 \\ 3 \end{array} \begin{array}{c} \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \end{array} \\ \begin{pmatrix} 0.1 & 0.3 & 0.4 & 0.1 & 0.1 \\ 0 & 0.1 & 0.3 & 0.4 & 0.2 \\ 0 & 0 & 0.1 & 0.4 & 0.5 \end{pmatrix} \end{array}.$$

Model 2:

$$P^A = \begin{array}{c} \\ 1 \\ 2 \\ 3 \end{array} \begin{array}{c} \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \end{array} \\ \begin{pmatrix} 0.7 & 0.2 & 0.1 & 0 & 0 \\ 0.3 & 0.3 & 0.3 & 0.1 & 0 \\ 0.1 & 0.2 & 0.2 & 0.4 & 0.1 \end{pmatrix} \end{array}$$

and

$$P^B = \begin{array}{c} \\ 1 \\ 2 \\ 3 \end{array} \begin{array}{c} \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \end{array} \\ \begin{pmatrix} 0.2 & 0.2 & 0.3 & 0.2 & 0.1 \\ 0 & 0.1 & 0.5 & 0.3 & 0.1 \\ 0 & 0.1 & 0.2 & 0.5 & 0.2 \end{pmatrix} \end{array}.$$

Necessary computations are shown in Table 1 for some selected values of $\underset{\sim}{\pi} = (\pi_1, \pi_2, \pi_3)$ and c taking $n = 50$ and $\beta/\alpha = 1$.

Table 1

(π_1, π_2, π_3)	PCS						$\pi(A)$	
	$c=10$		$c=20$		$c=30$			
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
0.6, 0.2, 0.2	1	1	1	0.998	1	0.995	0.414	0.447
0.4, 0.1, 0.5	1	0.999	1	0.997	1	0.988	0.480	0.453
1/3, 1/3, 1/3	1	1	1	0.999	1	0.994	0.402	0.450
0.1, 0.3, 0.6	1	1	1	0.998	1	0.987	0.385	0.457

Table 2

θ	PCS			$\pi(A)$
	$c=5$	$c=10$	$c=20$	
0.2	0.283	0.559	0.926	0.500
0.4	0.993	0.969	0.777	0.480
0.6	1.000	1.000	0.996	0.459
0.8	1.000	1.000	1.000	0.436
0.95	1.000	1.000	1.000	0.418

Model 3: The probability model given by (4.1) is also used for numerical illustration. Here P^A is obtained at $\theta=0.2$ and P^B is obtained at any θ. The necessary computations are shown in Table 2 taking $\underset{\sim}{\pi}=(0.1, 0.3, 0.6)$ only.

The above computations show that, in each model, the PCS's are quite high and the proportion of allocation to the worse treatment are relatively small.

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Appendix A.

Result: As $n \to \infty$,

$$\frac{1}{n}E(T_1 - T_2) \to g \tag{A.1}$$

and

$$\frac{1}{n^2}\mathrm{Var}(T_1 - T_2) \to 0, \tag{A.2}$$

where

$$g=\frac{1}{2}\sum_{j=1}^{k}\pi_j(e_j^A-e_j^B)-d\sum_{j=1}^{k}(e_j^A+e_j^B)\pi_j-d\left(k-\sum_{j=1}^{k}j\pi_j\right), \tag{A.3}$$

with $d=\lim_{i\to\infty}d_i$.

Proof. Here it is enough to prove the result for the case when $B>A$. Then using (2.3) and (2.4) it can be easily shown that

$$\frac{1}{2}E(T_1-T_2)=\frac{n}{4}\left[\sum_{j=1}^{k}\pi_j e_j^A-\sum_{j=1}^{k}\pi_j e_j^B\right]$$
$$-\frac{1}{2}\sum_{i=1}^{n}d_i\left[\sum_{j=1}^{k}\pi_j e_j^A+\sum_{j=1}^{k}\pi_j e_j^B\right]-\frac{1}{2}\sum_{i=1}^{n}\left(k-\sum_{j=1}^{k}j\pi_j\right). \tag{A.4}$$

From Bandyopadhyay and Biswas (1996), we have, as $n\to\infty$

$$\frac{1}{n}\sum_{i=1}^{n}d_i\to d. \tag{A.5}$$

By (A.4) and (A.5), we get (A.1). Now to prove (A.2), we write

$$\mathrm{Var}(T_1-T_2)=4(V_n+C_n), \tag{A.6}$$

where

$$V_n=\sum_{i=1}^{n}V[(\delta_i-\tfrac{1}{2})(y_i-x_i+k)],$$

$$C_n=\sum_{i\neq i'}\mathrm{Cov}[(\delta_i-\tfrac{1}{2})(y_i-x_i+k),\ (\delta_{i'}-\tfrac{1}{2})(y_{i'}-x_{i'}+k)].$$

As $\{d_i,\ i\geqslant 1\}$ is a non-negative monotonic and bounded sequence we have

$$\lim_{i\to\infty}d_i=d\quad\text{and}\quad\lim_{i\to\infty}d_i^2=d^2\ \text{exists.}$$

Then, writing $w_j^A=\sum_{s=0}^{k+1}(s-j+k)^2p_{js}^A$ and $w_j^B=\sum_{s=0}^{k+1}(s-j+k)^2p_{js}^B$, we have, by Toeplitz's lemma, as $n\to\infty$,

$$\frac{1}{n^2}V_n=\frac{1}{4}\left(\sum_{j=1}^{k}\pi_j w_j^B\right)\frac{1}{n^2}\sum_{i=1}^{n}\left(\frac{1}{2}+d_i\right)+\frac{1}{4}\left(\sum_{j=1}^{k}\pi_j w_j^A\right)\frac{1}{n^2}\sum_{i=1}^{n}\left(\frac{1}{2}-d_i\right)$$
$$-\frac{1}{4}\left(\sum_{j=1}^{k}\pi_j e_j^B\right)^2\frac{1}{n^2}\sum_{i=1}^{n}\left(\frac{1}{2}+d_i\right)^2-\frac{1}{4}\left(\sum_{j=1}^{k}\pi_j e_j^A\right)^2\frac{1}{n^2}\sum_{i=1}^{n}\left(\frac{1}{2}-d_i\right)^2$$
$$+\frac{1}{2}\left(\sum_{j=1}^{k}\pi_j e_j^A\right)\left(\sum_{j=1}^{k}\pi_j e_j^B\right)\frac{1}{n^2}\sum_{i=1}^{n}\left(\frac{1}{4}-d_i^2\right)\to 0. \tag{A.7}$$

Also, it is easy to check that for $i < i'$, as in Bandyopadhyay and Biswas (1996),

$$P(\delta_{i'} = 1 | \delta_i = 1) = \tfrac{1}{2} - d_{i'}^{-(i)} \quad \text{(say)},$$

and, for each i, it can be easily shown that, as $l \to \infty$,

$$d_l^{-(i)} - d_l \to 0.$$

Similarly, it can be shown that, for some $d_{i'}^{=(i)}$ as above

$$P(\delta_{i'} = 1 | \delta_i = 0) = \tfrac{1}{2} - d_{i'}^{=(i)} \quad \text{(say)},$$

and, for each fixed i,

$$d_l^{=(i)} - d_l \to 0, \quad \text{as } l \to \infty.$$

Now, for $i < i'$, we get

$$\begin{aligned} &\mathrm{Cov}[(\delta_i - \tfrac{1}{2})(y_i - x_i + k), (\delta_{i'} - \tfrac{1}{2})(y_{i'} - x_{i'} + k)]. \\ &\quad = \tfrac{1}{4}(\tfrac{1}{2} + d_i)(d_{i'}^{=(i)} - d_{i'})(D_{BB} - D_{AB}) \\ &\qquad - \tfrac{1}{4}(\tfrac{1}{2} - d_i)(d_{i'}^{-(i)} - d_{i'})(D_{AB} - D_{AA}), \end{aligned}$$

where for $X, Y = A, B$, we have

$$D_{XY} = \sum_{j=1}^{k} \sum_{j'=1}^{k} \pi_j \pi_{j'} \left[\sum_{s=0}^{k+1} \sum_{s'=0}^{k+1} (s - j + k)(s' - j' + k) p_{js}^{X} p_{j's'}^{Y} \right].$$

Then, by Toeplitz's lemma, as $n \to \infty$,

$$\frac{1}{n^2} C_n \to 0. \tag{A.8}$$

Hence, combining (A.7) and (A.8), (A.2) follows from (A.6).

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