RECENT RESULTS ON USING THE PLAY THE WINNER SAMPLING RULE WITH BINOMIAL SELECTION PROBLEMS

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1. Introduction

The theory of clinical trials has been studied from many different points of view in recent years. Perhaps the feature of principal interest that distinguishes the clinical trial from analogous problems that arise in industrial statistics is the ethical factor. The doctor treating a patient in a clinical trial is not only obliged to derive information relevant for the treatment of a larger statistical population, but is also obliged to treat each patient in the best way that he is able. These two requirements are contradictory to a certain extent, and lend urgency to the design of clinical trials that goes at least part of the way towards incorporating both requirements in some rational fashion. Armitage's monograph [2] and a subsequent review by Anscombe [1] did much to frame the general problem and bring it to the attention of statisticians. Although Armitage's original thinking had envisaged a fairly straightforward application of sequential analysis to the choice of the better of two treatments, Colton, working at his suggestion [4] developed a different formulation that has attracted some interest.

In brief, Colton's model assumes that the total patient horizon N is known. Of these, a total of $2n$ patients are to be used to derive information about the relative worth of the two treatments, and the remaining $N - 2n$ patients are given the treatment designated as better in the testing phase. Under various assumptions about the underlying distributions, Colton has derived optimal fixed and sequential rules for calculating the optimal value of n. Zelen [16] considered a more specialized version of the Colton model, in which the response was assumed to be dichotomous rather than continuous. The new and interesting feature of Zelen's work was the suggestion that the sampling technique could be adapted to reduce the number of patients on the poorer treatment. Zelen applied

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the "Play the Winner" rule (to be abbreviated PW rule) to the clinical trial problem; it prescribes that a success with a given treatment generates a further trial on the same treatment while a failure generates a trial on the alternative treatment. This particular assignment procedure was first suggested by Robbins [10] in a discussion of the two-arm bandit problem and was subsequently elaborated by Isbell [7] and by Pyke and Smith [9]. Although the PW rule is not optimal in the context of either the two-arm bandit problem or the clinical trial problem, it is a simple and easily implemented sampling rule that does introduce a bias in favor of testing the better treatment. Zelen analyzed the PW rule both with respect to indefinitely extended trials and with respect to the finite patient horizon model of Colton. More recently, Cornfield, Halperin, and Greenhouse [5] have analyzed a Bayesian generalization of the Colton model. The model is generalized in three ways: the first being in the assumption of a prior distribution, the second being in the distribution of patients in the data gathering phase to the two treatments in the ratio $\theta:(1-\theta)$ rather than $1:2$, and the third being in the repeated application of the procedure for $k > 2$ stages. Their results still depend on some estimate of the patient horizon, but the dependence is much less sensitive to variations in N than the original Colton model. The possible improvement that might be afforded through application of the PW rule to this formulation has not been discussed to date.

In the present paper we will summarize some of our own recent research on the formulation of clinical trial problems. So far we have considered only the case of dichotomous response, where the effect of treatment is immediately available. These are considerable restrictions and leave open many interesting and useful problems for further investigation, but the general problem area even in its simplest formulation leads to difficult mathematical problems. Since we restrict ourselves to a version of the two-arm bandit problem, it is well to motivate later mathematical developments. A rigorous solution to the two-arm bandit problem would lead to an indefinitely extended series of trials in which the probability of choosing the better treatment at trial N trends to 1 as $N \to \infty$. Economic factors at the very least would imply a desire to terminate testing in some finite number of trials either with a decision that one or the other treatment is better or, in some applications, with a third decision that the two treatments are equally good. Furthermore, the Colton model seems somewhat artificial because some knowledge, Bayesian or otherwise, is implied about the patient horizon N, which is usually not available. If these premises are granted, it would seem desirable to develop a test method that allows one to reach a decision with a finite number of tests without any suppositions about the patient horizon.

We have recently discussed various aspects of the problem of choosing the best of $k \geqq 2$ binomial populations [13], [14], [15] using a formulation explored in some detail in a monograph by Bechhofer, Kiefer, and Sobel [3]. Let us consider two treatments A and B with success probabilities p and p' respectively, where $p > p'$. A correct selection corresponds to identifying A as the better

treatment after a series of tests. In the formulation of [13], one assumes that two constants P^* and Δ^* are given with $\frac{1}{2} < P^* < 1$ and $\Delta^* > 0$ and the termination rule is set up so that the probability of a correct selection, or $P\{\text{CS}\}$, $\geqq P^*$ whenever $p - p' \geqq \Delta^*$. Most of the work to be described below requires that one of the drugs be declared the better even though the condition $p - p' \geqq \Delta^*$ may not hold; some results have also been obtained for the three decision problem in which one is allowed to conclude that $p - p' < \Delta^*$.

In all of the models to be described, a decision is made after a finite number of tests, with probability one, and no assumptions are made about a patient horizon. The first question of interest relates to the effect of different sampling rules on the number of patients put on the poorer treatment. It is clear that in an infinitely extended series of trials, the PW rule is superior to the rule that prescribes alternate sampling $ABABA \ldots$ (this rule will be designated as the "Vector at a Time" rule or VT rule). For finite sets of trials, a comparison is of interest because it is not clear whether a decision can be reached more quickly by testing the same number of patients on both treatments, or whether the bias introduced by the PW rule does not extend the trial by so much that ultimately more patients are given the poorer drug than if the VT rule had been used.

The two sampling rules must, of course, be supplemented by stopping rules. Here again, a wide choice of rules can be considered, but we focus mainly on two stopping rules partly because of likelihood ratio considerations and partly because they lead to analytically tractable problems. The first rule depends on keeping track of the number of successes for both treatments at each stage and computing $|S_i - S_j| = \Delta S$ where S_i and S_j are the numbers of successes on the two treatments. The clinical trial is terminated when $\Delta S = r$, where r is a critical integer determined from P^* and Δ^*. The second stopping rule corresponds to inverse sampling in which the trial terminates when either S_i or S_j reaches a critical value r'. Although the first stopping rule is usually better since it incorporates more information, the inverse sampling procedure warrants analysis because it is easily generalized to choosing the best of $k > 2$ populations and because it can be used as a basis for comparisons.

In the next section we compare the performance of the VT rule with the PW rule when only two decisions are allowed, that is, that one or the other treatment is better, and the trials are potentially of unlimited duration. It should be noted, however, that with probability one the trials continue for only a finite number of tests and the expected number of trials to termination is finite for any fixed pair (p, p') with $0 < p' \leqq p < 1$. This will be followed by some results on selecting the best of $k > 2$ populations. Section 3 presents results obtained so far on truncated testing in which a maximum number of tests is prescribed. In Section 4 we describe some sequential procedures for $k \geqq 3$ and compare the PW and VT sampling rules by Monte Carlo Studies. In Section 5 some alternative and allied lines of current research are described. Finally, in the last section, we discuss some of the many open questions in this area of research.

2. Comparison of procedures R_{PW} and R_{VT}

Several results will be quoted here from different papers and some new tables will be appended to confirm that these results hold not only for $P^* \to 1$ and/or $\Delta^* \to 0$ but also for fixed smaller values of P^* and fixed larger values of Δ^*.

The basic termination rule is to stop sampling when $\Delta S = r$. For any pair $p = 1 - q$ and $p' = 1 - q'$ the integer $r = r_{PW}$ needed under PW sampling to satisfy the basic requirement

$$P\{\text{CS}\} \geqq P^* \quad \text{whenever} \quad p - p' \geqq \Delta^* \tag{2.1}$$

is found in [13] to be the smallest integer at least as large as the root in x of

$$\lambda^x = \frac{1}{2qP^*}\{\bar{q} - [\bar{q}^2 - 4qq'P^*(1 - P^*)]^{1/2}\}, \tag{2.2}$$

where $\lambda = p'/p < 1$ and $\bar{q} = \frac{1}{2}(q + q')$. In the least favorable (LF) configuration we set $p' = p - \Delta^*$ (or $q' = q + \Delta^*$) and minimize the $P\{\text{CS}\}$ or maximize the solution of (2.2) in x as a function of p for $\Delta^* \leqq p \leqq 1$. This minimum occurs at a p value close to 1 and has been obtained exactly for the calculation in Tables IIa through IId. Denote the resulting precedure by R_{PW}.

For the same termination rule we also consider the VT sampling rule and denote the resulting procedure by R_{VT}. Then, corresponding to (2.2), the integer $s = r_{VT}$ needed under VT sampling to satisfy (2.1) was found in [3] and in [12] to be the smallest integer at least as large as the root in x of

$$P^*(1 + \delta^x) = 1, \tag{2.3}$$

where $\delta = p'q/pq' < 1$. Under the LF configuration we set $p = \frac{1}{2}(1 + \Delta^*)$ and $p' = \frac{1}{2}(1 - \Delta^*)$ so that x is given explicitly by

$$x = \frac{\log\left[(1 - P^*)/P^*\right]}{2\log\left(\dfrac{1 - \Delta^*}{1 + \Delta^*}\right)}. \tag{2.4}$$

To compare the two sampling rules for the same pair (Δ^*, P^*) and the same termination rule we use two different criteria which are calculated exactly in [13] after the values of r_{PW} and r_{VT} are obtained. The first is the expected loss or risk $E\{L\}$ (which we write as $\bar{L}$ below) defined by

$$\text{E}\{L\} = (p - p')\text{E}\{N_B\} = \bar{L}, \tag{2.5}$$

say, where $E\{N_B\}$ denotes the number of patients put on the poorer drug. This has considerable interest in medical applications since it represents the difference in the expected number of successes between a conceptual set of trials in which the better treatment is always used and the actual set of trials; thus we have $E\{L|R_{PW}\}$ for PW sampling and $E\{L|R_{VT}\}$ for VT sampling.

The second criterion is the expected total number of trials needed for termination which can be written as

$$E\{N\} = E\{N_A\} + E\{N_B\}. \tag{2.6}$$

This is the standard criterion used in [3] for comparing procedures that satisfy the same (Δ^*, P^*) requirement (2.1); thus we have $E\{N|R_{PW}\}$ for PW sampling and $E\{N|R_{VT}\}$ for VT sampling.

It is found in [13] by an asymptotic ($P^* \to 1$) analysis that the ratio $E\{L|R_{PW}\}/E\{L|R_{VT}\} < 1$ when

$$p > \frac{3}{4} - \frac{\Delta^*}{8} + O(\Delta^{*3}). \tag{2.7}$$

Since Δ^* is usually small we can disregard the term of order (Δ^{*3}) and say that PW sampling is preferred (L) when $p > \frac{1}{8}(6 - \Delta^*)$ and that VT sampling is preferred when the reverse inequality holds.

Similarly, according to the $E\{N\}$ criterion it is found in [13] that the ratio $E\{N|R_{PW}\}/E\{N|R_{VT}\} < 1$ when

$$\bar{p} > \frac{3}{4} - \frac{\Delta^*}{8} + O(\Delta^{*3}) \tag{2.8}$$

where $\bar{p} = \frac{1}{2}(p + p')$ and $\bar{q} = 1 - \bar{p}$.

These results are corroborated in this paper by Tables IIa through IId and shown to hold for the four (Δ^*, P^*) pairs: (0.50, 0.75), (0.20, 0.75), (0.05, 0.95), and (0.20, 0.95). The exact integer values of r_{PW} and r_{VT} are obtained and exact values of

$$E\{L|R_{PW}\} = \frac{(p + 2qr)(1 - \lambda^r)(q' - q\lambda^r)}{2(q' - q\lambda^{2r})}, \tag{2.9}$$

$$E\{N|R_{PW}\} = \frac{(1 - \lambda^r)(q' - q\lambda^r)(\bar{p} + 2r\bar{q})}{(1 - \lambda)(q' - q\lambda^{2r})p},$$

$$E\{L|R_{VT}\} = \frac{s(1 - \delta^s)}{1 + \delta^s}, \qquad E\{N|R_{VT}\} = \frac{2s(1 - \delta^s)}{(p - p')(1 + \delta^s)} \tag{2.10}$$

are computed for the generalized least favorable (GLF) configuration in which $p' = p - \Delta^*$ and $\Delta^* \leqq p \leqq 1$. (A misprint in $E\{N|R_{PW}\}$ in (2.18) of [13] is corrected in (2.9) above.)

In addition, we have tabulated $E\{N_B\}$ for the equal parameter (EM) configuration (that is, for $p = p'$) as a function of p. Note that this function approaches infinity as $p \to 0$ or $p \to 1$ under VT sampling but this occurs only as $p \to 0$ under PW sampling.

These tables show a definite crossover pattern in which PW sampling is better for large p values and poorer for small p values. The results for VT sampling are more constant and tend to be symmetrical about $\frac{1}{2}$. The need for an adaptive procedure which switches from VT sampling to PW sampling when p (or when $\bar{p}$) appears to be larger than $\frac{1}{8}(6 - \Delta^*)$ is clearly demonstrated, but such a procedure has not yet been studied.

From (2.9) and (2.10) we can find exact expressions for $E\{N\}$ for $p = p'$ (or $\lambda = 1$) when Δ^* and P^* are fixed; our principal interest is in the case where the common p tends to 1 or 0. From (2.9) we have for $p = p'$

$$E\{N \mid R_{PW}\} = r + \frac{r^2 q}{p} \tag{2.11}$$

and from (2.10) we find that

$$E\{N \mid R_{VT}\} = \frac{2s(1 - \delta^s)}{(p - p')(1 + \delta^s)} \sim \frac{s^2}{pq}, \tag{2.12}$$

where the last expression is the limiting value as $p' \to p$.

If we now let $\Delta^* \to 0$ then we obtain from (2.2) and (2.4) for the respective LF configurations

$$r \sim \frac{\log\left((1 - P^*)/P^*\right)}{\log(1 - \Delta^*)}; \quad s \sim \frac{\log\left((1 - P^*)/P^*\right)}{2\log(1 - \Delta^*)}, \tag{2.13}$$

so that r is twice s for small Δ^*. For Δ^* sufficiently small we can disregard the r term in (2.11) and, using the fact that $r = 2s$, we note from (2.11) and (2.12) that for $p > \frac{1}{2}$ (and hence for $p \to 1$) $E\{N \mid R_{PW}\}$ is smaller than $E\{N \mid R_{VT}\}$. On the other hand for $p \leqq \frac{1}{2}$ (and hence for $p \to 0$) it is clear that $E\{N \mid R_{VT}\}$ is smaller. In fact, $E\{N \mid R_{VT}\}$ is smaller for $p < 0.70$ in most of our calculations. Hence there is no uniform result in this comparison.

In [14] and [15] the termination rule employed is the so-called inverse sampling where we stop when any one population has attained r' $(= r)$ successes; for convenience we drop the prime on r. New values r'_{PW} and r'_{VT} are obtained to satisfy the same basic requirement (2.1), let the resulting procedures be denoted by R'_{PW} and R'_{VT}, respectively. For this purpose we use the exact expression for any integer $r \geqq 1$

$$P\{CS \mid R'_{PW}\} = \tfrac{1}{2} E_r\{I_{q'}(X, r) + I_{q'}(X + 1, r)\}, \tag{2.14}$$

where $I_p(x, y)$ is the usual incomplete beta function $I_q(0, r) = 1 = 1 - I_p(r, 0)$ for $r \geqq 1$, and the E_r denotes expectation of the random variable X which has the discrete negative binomial probability law

$$f(x) = p^r \binom{x + r - 1}{x} q^x, \qquad x = 0, 1, \cdots. \tag{2.15}$$

For the Vector at a Time procedure R'_{VT} we obtain exactly the same result (2.14) so that the LF configurations must be identical for R'_{PW} and R'_{VT} and hence $r'_{PW} = r'_{VT}$ for any pair (Δ^*, P^*). (Similar results were found for $k > 2$, and E. Nebenzahl has noted the same result for a fixed sample size problem, see (2.26) and (5.2) below). This does not imply any equality in $E\{L\}$ or in $E\{N\}$ for R'_{PW} and R'_{VT} and we need these to compare these procedures. In [14] we obtain for $k = 2$ the exact expressions

$$(2.16)\quad E\{N|R'_{PW}\} = \left(\frac{1}{q}+\frac{1}{q'}\right)\left[\frac{rq}{p}+\frac{r}{p'}E_r\{I_{p'}(r+1,X)\}-\frac{r}{p}E_{r+1}\{I_{p'}(r,X)\}\right] + \frac{1}{2q'}-\frac{1}{2q'}E_r\{I_{p'}(r,X+1)\}+\frac{1}{2q}E_r\{I_{p'}(r,X)\},$$

$$(2.17)\quad E\{N|R'_{VT}\} = \frac{2r}{p}+\frac{2r}{p'}-\frac{r}{p}E_{r+1}\{I_{p'}(r,X)+I_{p'}(r,X+1)\} - \frac{r}{p'}E_r\{I_{q'}(X,r+1)+I_{q'}(X+1,r+1)\}.$$

In this form all the expectations in (2.16) and (2.17) tend to zero as $r \to \infty$. (This can occur because $\Delta^* \to 0$ or because $P^* \to 1$). Hence, it easily follows that for large r we have

$$(2.18)\quad E\{N|R'_{PW}\} < E\{N|R'_{VT}\}.$$

Again we note for the case of a common p that EN $\to \infty$ as $p \to 0$ or as $p \to 1$ under VT sampling but this happens only as $p \to 0$ under PW sampling. In another formulation David Hoel includes failures of the opponent and defines the score for A and B, respectively, as

$$(2.19)\quad \begin{aligned} R_A &= S_A + F_B, \\ R_B &= S_B + F_A, \end{aligned}$$

and then uses inverse sampling with these R values. The results are similar to those given here but one important difference is that $E\{N\}$ is bounded in his case.

For the $E\{L\}$ criterion we obtain from (2.19) in [14]

$$(2.20)\quad E\{L|R'_{PW}\} = \frac{\Delta}{q'}\left[\frac{rq}{p}+\frac{r}{p'}E_r\{I_{p'}(r+1,X)\}-\frac{r}{p}E_{r+1}\{r,X)\} + \frac{1}{2}-\frac{1}{2}E_r\{I_{p'}(r,X+1)\}\right],$$

and using the result in (2.17) above

$$(2.21)\quad E\{L|R'_{VT}\} = \frac{\Delta}{2}E\{N|R'_{VT}\}$$

Here again the expectations approach 0 as $r \to \infty$ and we obtain for large r

$$(2.22)\quad E\{L|R'_{PW}\} < E\{L|R'_{VT}\}.$$

In the common LF configuration, we found in [14] the interesting feature that the minimum of the $P\{CS\}$ (subject to $p - p' \geqq \Delta^*$) occurs when p and p' are centered at $\frac{2}{3}$ with difference Δ^*; this was obtained by disregarding terms of order $(\Delta^*)^2$. Then the appropriate r value for both R'_{PW} and R'_{VT} as a function of Δ^* and P^* is

$$(2.23)\quad r = \frac{8}{27}\left(\frac{\lambda}{\Delta^*}\right)^2$$

where $\lambda = \lambda(P^*)$ is the P^* percentage point of the standard normal distribution. This is obtained by assuming r is large and approximating the difference of two independent negative binomial chance variables by the appropriate normal approximation. It is estimated that (2.22) will hold when $r > p/2\Delta$ and the same estimate is obtained from (2.18) by dropping all the expectations in (2.16) and (2.17).

The question of whether waiting for a fixed number of failures is better than waiting for a fixed number of successes is also considered and it is found that for $p > \frac{1}{2}$ the latter is preferable but for $p < \frac{1}{2}$ the former is preferable.

In [15] we consider the inverse sampling procedure with $k \geqq 3$ populations and again compare the two procedures R'_{PW} and R'_{VT}. Here we order the populations (say, A, B, C for $k = 3$) and consider a cyclic variation PWC of the PW sampling rule. Observe A until it produces a failure. Switch to B until it produces a failure; then to C until it produces a failure. Then return to A and repeat the cycle. The results obtained are quite similar to those for $k = 2$: procedure R'_{PW} is uniformly better than R'_{VT} for large values of r whether the criterion $E\{N\}$ or

$$E\{L\} = \sum_{i=1}^{k} (p_1 - p_i)E\{N_i\}. \qquad p_1 = \max_i p_i, \tag{2.24}$$

is used. The exact formulas and the correction term to the normal approximation are of interest. For R'_{PWC} we obtain

$$P\{\mathrm{CS}\,|\,R'_{\mathrm{PWC}}\} = \frac{1}{k} E_r\left\{\prod_{j=2}^{k} I_{q_j}(X, r) + \sum_{\alpha=2}^{k}\left[\prod_{j=2}^{\alpha-1} I_{q_j}(X, r)\right]\left[\prod_{j=\alpha}^{k} I_{q_j}(X+1, r)\right]\right\}, \tag{2.25}$$

where X has the negative binomial probability law (2.15) with index $r \geqq 1$, success parameter p_1 and mean rq_1/p_1. For R'_{VT} we obtain, after the first step of minimization, exactly the same PCS in the form

$$P\{\mathrm{CS}\,|\,R'_{\mathrm{VT}}\} = \frac{1}{k} E_r\left\{\frac{I^k_{q_2}(X, r) - I^k_{q_2}(X+1, r)}{I_{q_2}(X, r) - I_{q_2}(X+1, r)}\right\} = P(\mathrm{CS}\,|\,R'_{\mathrm{PWC}}). \tag{2.26}$$

Hence, the LF configurations are the same and $r'_{\mathrm{PW}} = r'_{\mathrm{VT}}$. The value of r needed for both R'_{PW} and R'_{VT} and used in the formulas below is again approximately given by (2.23), except that $\lambda = \lambda(P^*, \rho, k)$ is the value of H that satisfies

$$\int_{-\infty}^{\infty} \Phi^{k-1}\left(\frac{x\sqrt{\rho} + H}{\sqrt{1-\rho}}\right) d\Phi(x) = P^* \tag{2.27}$$

where $\rho = \frac{1}{2} - \frac{3}{2}\Delta^* + O\{\Delta^{*2}\}$ (which we approximate by $\frac{1}{2}$), and $\Phi(x)$(resp., $\varphi(x)$) is the standard normal distribution (resp., density) function. Because $\rho \neq \frac{1}{2}$, it is desirable to introduce a correction term to the normal ranking integral (2.27). This is accomplished by proving a lemma about the left member of (2.27), which we call $A_{k-1}(\rho, H)$.

For $k \geqq 3$, any fixed H and positive $\rho < 1$

$$\frac{d}{d\rho} A_{k-1}(\rho, h) = \frac{(k-1)(k-2)\varphi(H)\varphi\left[H\left(\frac{1-\rho}{1+\rho}\right)^{1/2}\right]}{2(1+\rho)^{1/2}} \cdot A_{k-3}\left[\frac{\rho}{1+2\rho}, H\left(\frac{1-\rho}{(1+\rho)(1+2\rho)}\right)^{1/2}\right]. \tag{2.28}$$

Then the $P\{\mathrm{CS}|R'_{\mathrm{PWC}}\}$ in the LF configuration is approximated by

$$A_{k-1}\left(\frac{1}{2}, H\right) - \frac{3\Delta^*}{2}\frac{(k-1)(k-2)}{\sqrt{6}}\varphi(H)\varphi\left(\frac{H}{\sqrt{3}}\right)A_{k-3}\left(\frac{1}{4}, \frac{H}{\sqrt{6}}\right), \tag{2.29}$$

where $H = \Delta^*(27r/8)^{1/2}$. For example if $k = 3$, $P^* = 0.90$ and $\Delta^* = 0.10$, then the first term of (2.29) gives $H = 1.58$ and $r = 74$, but if we try $H = 1.59$ and 1.60 in (2.29) we find that the latter is closer and this leads to $r = 78$ and a minimum PCS $= 0.9008$.

For $E\{N\}$ and $E\{L\}$ the exact expressions are of less interest but the normal approximations to these are for large r with $p_1 = \max_i p_i$

$$E\{N|R'_{\mathrm{PWC}}\} \sim \frac{rq_1}{p_1}\left(\sum_{i=1}^{k}\frac{1}{q_i}\right), \tag{2.30}$$

$$E\{L|R'_{\mathrm{PWC}}\} \sim \frac{rq_1}{p_1}\sum_{i=1}^{k}\left(\frac{p_1 - p_i}{q_i}\right). \tag{2.31}$$

A Monte Carlo simulation by D. G. Hoel shows that these approximations are very close to those obtained in 1000 Monte Carlo experiments for $k = 3$, $\Delta^* = 0.2$ and $P^* = 0.95$. Some typical excerpts from his table are given in Table I.

TABLE I

$p_1 = \max p_i$	$E\{L\|R'_{\mathrm{PWC}}\}$ Observed (Monte Carlo)	$E\{L\|R'_{\mathrm{PWC}}\}$ Approximate (2.24)	$E\{N\|R'_{\mathrm{PWC}}\}$ Observed (Monte Carlo)	$E\{N\|R'_{\mathrm{PWC}}\}$ Approximate (2.23)
0.2	45.5	44.8	369	364
0.4	21.3	21.0	177	175
0.6	12.6	12.4	110	109
0.8	7.4	7.0	72	70
1.0	1.1	0.0	33	28

For the case of equal parameters (EM configuration) we obtain in [15] for $q < 1$

$$E\{N|R'_{\mathrm{PWC}}\} = \frac{1}{q}\sum_{\alpha=0}^{\infty} I_q(\alpha+1, r)\left[\frac{I_q^k(\alpha, r) - I_q^k(\alpha+1, r)}{I_q(\alpha, r) - I_q(\alpha+1, r)}\right], \tag{2.32}$$

which converges for $0 \leqq q < 1$; the case $q = 0$ is obtained by continuity. This is then approximated by

$$E\{N \mid R'_{\text{PWC}}\} \sim \frac{kr - \lambda_1(k-p)(r/q)^{1/2}}{p} - \left(\frac{k-p}{2q}\right), \tag{2.33}$$

where $\lambda_1 = \lambda_1(k)$ is the $(100k/k + 1)$st percentile of the standard normal distribution. The corresponding result in [15] for the VT rule is

$$E\{N \mid R'_{\text{VT}}\} = \frac{kr}{p} E_{r+1}\left\{\frac{I_q^k(X, r) - I_q^k(X+1, r)}{I_q(X, r) - I_q(X+1, r)}\right\}, \tag{2.34}$$

where E_{r+1} is defined as in (2.15) with r increased to $r + 1$. This is then approximated by

$$E\{N \mid R'_{\text{VT}}\} \sim \frac{k}{p}[r - \lambda_1(rq)^{1/2}] - \frac{k}{2}, \tag{2.35}$$

where λ_1 is defined after (2.33).

For $k = 3$, $\Delta^* = 0.2$ and $P^* = 0.95$ we need an r value equal to 29 for both procedures R'_{PW} and R'_{VT}. Using $r = 29$ the exact value of $E\{N \mid R_{\text{PW}}\}$ for $p_1 = p_2 = p_3 = 0.9$ from (2.32) is 59.8 and the approximate value from (2.33) is 59.4. For smaller values of the common p, the approximation is even more accurate.

For any common p, $0 < p < 1$, and any r we find that $E\{L\} = 0$ for both procedures.

In summary, the procedure R'_{PWC} is asymptotically $(r \to \infty)$ superior to R'_{VT} throughout the parameter space regardless of whether we use the criterion $E\{N\}$ or the criterion $E\{L\}$.

3. A truncated sequential procedure for k = 2 that uses vector-at-a-time

Another truncated version has been discussed by Kiefer and Weiss, [8], for the VT Rule. For this case a decision is made at or before test N (where each test is assumed to contain both treatments). The termination rule again requires $|S_A - S_B| = s$. Let us first calculate the probability of a correct selection for this procedure. If we let $U_k(n)$ be the probability of a correct selection on or before test pair n (for $p > p'$) given $S_A - S_B + s = k$ then the $U_k(n)$ satisfy

$$U_k(n+1) = \alpha U_{k+1}(n) + \beta U_k(n) + \gamma U_{k-1}(n), \tag{3.1}$$

where

$$\alpha = pq', \qquad \beta = pp' + qq', \qquad \gamma = p'q. \tag{3.2}$$

Equation (3.1) is to be solved subject to the boundary conditions $U_0(n) = 0$, $U_{2s}(n) = 1$, and the initial conditions $U_k(0) = 0$, $k \neq 2s$, $U_{2s}(0) = 1$. Equation (3.1) is more conveniently handled by defining a new set of variables

$$V_k(n) = U_k(\infty) - U_k(n) \tag{3.3}$$

TABLE IIa

COMPARISON OF EXACT RESULTS FOR VT AND PW SAMPLING RULES USING THE TERMINATION RULE BASED ON $|S_A - S_B| \geqq r$ IN THE BINOMIAL TWO ARM SELECTION PROBLEM

For $\Delta^* = 0.05$ and $P^* = 0.75$, we use $r_{PW} = 17$ and $r_{VT} = 6$, without randomization.

Note. Under the generalized least favorable (GLF) configuration, $p = p_A$ is the larger of the two probabilities of success and $p - \Delta^* = p_B$ is the smaller of the two. The GLF comparisons are made only for pairs $(p, p - \Delta^*)$ with $\Delta^* \leqq p \leqq 1$. Under the equal parameter (EM) configuration, p denotes the *common* probability of success on a single trial. $E\{N_B\}$ denotes the expected number of observations on the "poorer drug" and, for the EM configuration, L = 0 and $E\{N\} = 2E\{N_B\}$.

	GLF configuration				EM configuration	
$p = p_A$	$E\{L\|R_{PW}\}$	$E\{L\|R_{VT}\}$	$E\{N\|R_{PW}\}$	$E\{N\|R_{VT}\}$	$E\{N_B\|R_{PW}\}$	$E\{N_B\|R_{VT}\}$
0	—	—	—	—	∞	∞
0.05	16.2	6.0	663	240	2754	379
0.10	15.3	5.9	630	235	1309	200
0.20	13.5	4.7	556	187	587	113
0.30	11.0	3.8	457	153	346	86
0.40	8.5	3.4	354	136	225	75
0.50	6.3	3.2	266	129	153	72
0.60	4.6	3.3	194	131	105	75
0.70	3.2	3.6	137	143	70	86
0.75	2.6	3.8	112	153	57	96
0.80	2.0	4.2	90	167	45	113
0.85	1.5	4.7	71	187	34	141
0.90	1.1	5.3	53	212	25	200
0.95	0.7	5.9	36	235	16	378
1.00	0.3	6.0	21	240	9	∞

TABLE IIb

COMPARISON OF EXACT RESULTS FOR VT AND PW SAMPLING RULES USING THE TERMINATION RULE BASED ON $|S_A - S_B| \geqq r$ IN THE BINOMIAL TWO ARM SELECTION PROBLEM

For $\Delta^* = 0.20$ and $P^* = 0.75$, we use $r_{PW} = 4$ and $r_{VT} = 2$, without randomization.

	GLF configuration				EM configuration	
$p = p_A$	$E\{L\|R_{PW}\}$	$E\{L\|R_{VT}\}$	$E\{N\|R_{PW}\}$	$E\{N\|R_{VT}\}$	$E\{N_B\|R_{PW}\}$	$E\{N_B\|R_{VT}\}$
0	—	—	—	—	∞	∞
0.20	3.3	2.0	37	20	34	13
0.30	2.9	1.7	32	17	21	10
0.40	2.3	1.5	26	15	14	8
0.50	1.8	1.4	21	14	10	8
0.60	1.4	1.3	16	13	7	8
0.70	1.0	1.4	12	14	5	10
0.75	0.9	1.4	11	14	5	11
0.80	0.7	1.5	9	15	4	13
0.85	0.6	1.6	8	16	3	16
0.90	0.5	1.7	7	17	3	22
0.95	0.4	1.9	6	19	2	42
1.00	0.3	2.0	5	20	2	∞

TABLE IIc

COMPARISON OF EXACT RESULTS FOR VT AND PW SAMPLING RULES USING THE TERMINATION RULE BASED ON $|S_A - S_B| \geqq r$ IN THE BINOMIAL TWO ARM SELECTION PROBLEM

For $\Delta^* = 0.05$ and $P^* = 0.95$, we use $r_{PW} = 50$ and $r_{VT} = 15$, without randomization.

$p = p_A$	GLF configuration $E\{L\|R_{PW}\}$	$E\{L\|R_{VT}\}$	$E\{N\|R_{PW}\}$	$E\{N\|R_{VT}\}$	EM configuration $E\{N_B\|R_{PW}\}$	$E\{N_B\|R_{VT}\}$
0	—	—	—	—	∞	∞
0.05	47.5	15.0	1951	600	23.775	2368
0.10	45.1	15.0	1852	600	11.275	1250
0.20	40.1	14.8	1653	594	5.025	703
0.30	35.1	14.3	1455	573	2.941	536
0.40	30.1	13.8	1254	553	1.900	469
0.50	25.0	13.6	1049	544	1.275	450
0.60	19.8	13.7	841	547	858	469
0.70	14.7	14.1	634	562	561	536
0.75	12.1	14.3	533	573	442	600
0.80	9.7	14.6	433	584	338	703
0.85	7.3	14.8	337	594	246	882
0.90	5.0	15.0	243	599	164	1250
0.95	2.7	15.0	152	600	91	2368
1.00	0.5	15.0	64	600	25	∞

TABLE IId

COMPARISON OF EXACT RESULTS FOR VT AND PW SAMPLING RULES USING THE TERMINATION RULE BASED ON $|S_A - S_B| \geqq r$ IN THE BINOMIAL TWO ARM SELECTION PROBLEM

For $\Delta^* = 0.20$ and $P^* = 0.95$, we use $r_{PW} = 11$ and $r_{VT} = 4$, without randomization.

$p = p_A$	GLF configuration $E\{L\|R_{PW}\}$	$E\{L\|R_{VT}\}$	$E\{N\|R_{PW}\}$	$E\{N\|R_{VT}\}$	EM configuration $E\{N_B\|R_{PW}\}$	$E\{N_B\|R_{VT}\}$
0	—	—	—	—	∞	∞
0.20	8.9	4.0	100	40	248	50
0.30	7.8	4.0	89	40	147	38
0.40	6.8	3.8	78	38	96	33
0.50	5.7	3.7	68	37	66	32
0.60	4.6	3.7	56	37	46	33
0.70	3.5	3.7	45	37	31	38
0.75	3.0	3.8	40	38	26	43
0.80	2.4	3.8	34	38	21	50
0.85	1.9	3.9	29	39	16	63
0.90	1.4	4.0	24	40	12	89
0.95	0.9	4.0	19	40	9	168
1.00	0.5	4.0	14	40	6	∞

which satisfy equation (3.1), but have the boundary and initial conditions

$$V_0(n) = V_{2s}(n) = 0, \qquad V_k(0) = U_k(\infty), \qquad k \neq 2s, \qquad V_{2s}(0) = 0. \tag{3.4}$$

If we define

$$\mathbf{V}(n) = \begin{pmatrix} V_1(n) \\ V_2(n) \\ \vdots \\ V_{2s-1}(n) \end{pmatrix}, \qquad \mathbf{A} = \begin{bmatrix} \beta & \alpha & 0 & 0 & \cdots & 0 \\ \gamma & \beta & \alpha & 0 & \cdots & 0 \\ 0 & \gamma & \beta & \alpha & \cdots & 0 \\ & & \vdots & & & \\ 0 & 0 & 0 & \cdots & \gamma & \beta \end{bmatrix}, \tag{3.5}$$

then $\mathbf{V}(n+1) = \mathbf{A}\mathbf{V}(n)$ or

$$\mathbf{V}(n) = \mathbf{A}^n\mathbf{V}(0). \tag{3.6}$$

For tridiagonal matrices of the form of $\mathbf{A}$ one can calculate $\mathbf{A}^n$, and therefore $\mathbf{V}(n)$, by using a spectral decomposition. First we note that $\mathbf{A}$ is similar to a symmetric matrix $\mathbf{B}$ through the transformation $\mathbf{B} = \mathbf{T}^{-1}\mathbf{A}\mathbf{T}$, where $\mathbf{T}$ is a diagonal matrix with elements $T_{j,j} = (\gamma^{j-1}\alpha^{2s-1-j})^{1/2}$. The transformed matrix $\mathbf{B}$ is

$$\mathbf{B} = \begin{bmatrix} \beta & \zeta & 0 & 0 & 0 & \cdots & 0 \\ \zeta & \beta & \zeta & 0 & 0 & \cdots & 0 \\ 0 & \zeta & \beta & \zeta & 0 & \cdots & 0 \\ & & & & \vdots & & \\ 0 & 0 & 0 & 0 & \cdots & \zeta & \beta \end{bmatrix}, \tag{3.7}$$

where $\zeta = (\alpha\gamma)^{1/2} = (pp'qq')^{1/2}$. The spectral properties of $\mathbf{B}$ were studied by Rutherford [11]. Denoting the jth eigenvector of $\mathbf{B}$ by $\mathbf{u}_j$ and the corresponding eigenvalue by λ_j we have

$$\begin{aligned} (\mathbf{u}_j)_r &= \frac{1}{\sqrt{s}} \sin\left(\frac{\pi j r}{2s}\right), \qquad r = 1, 2, \cdots, 2s-1 \\ \lambda_j &= \beta + 2\zeta \cos\left(\frac{\pi j}{2s}\right). \end{aligned} \tag{3.8}$$

If $\mathbf{V}(n)$ and $\mathbf{V}(0)$ are expanded in terms of the eigenvectors $\mathbf{u}_j$ then a straightforward argument suffices to show that the elements of interest (the probability of a correct selection) are given by

$$V_s(n) = \frac{1}{s}\left(\frac{\alpha}{\gamma}\right)^{(s+1)/2} \sum_{r=1}^{2s-1} \frac{(-1)^{r+1}\lambda_r^n \sin\left(\frac{\pi r}{2}\right) \sin\left(\frac{\pi r}{2s}\right)}{1 + \frac{\alpha}{\gamma} - 2\left(\frac{\alpha}{\gamma}\right)^{1/2} \cos\left(\frac{\pi r}{2s}\right)}. \tag{3.9}$$

A similar set of calculations can be used to show that the probability that no decision will be made (that is, $|S_A - S_B| < s$ in all n trials) is

$$W(n) = \frac{1}{s}\left(\frac{\gamma}{\alpha}\right)^{(s-1)/2} \sum_{r=1}^{2s-1} \frac{\left[1 + (-1)^r\left(\frac{\alpha}{\gamma}\right)^s\right] \lambda_r^n \sin\left(\frac{\pi r}{2}\right) \sin\left(\frac{\pi r}{2s}\right)}{1 + \frac{\alpha}{\gamma} - 2\left(\frac{\alpha}{\gamma}\right)^{1/2} \cos\left(\frac{\pi r}{2s}\right)}. \tag{3.10}$$

TABLE III

VALUES OF s AND P_{max} FOR FIXED Δ^* AND N

N	$\Delta^* = 0.1$		$\Delta^* = 0.2$		$\Delta^* = 0.3$		$\Delta^* = 0.4$	
	s	P_{max}	s	P_{max}	s	P_{max}	s	P_{max}
25	2	0.678	3	0.837	3	0.949	3	0.989
50	3	0.751	4	0.934	5	0.991	5	0.9996
75	4	0.804	5	0.970	6	0.999		
100	5	0.844	6	0.986	8	0.9997		
150	7	0.895	6	0.992				
200	8	0.931						
300	10	0.968						
400	12	0.985						

TABLE IV

VALUES OF s AND N CORRESPONDING TO FIXED P^* AND Δ^*

Δ^*	$P^* = 0.75$		$P^* = 0.90$		$P^* = 0.95$		$P^* = 0.99$	
	s	N	s	N	s	N	s	N
0.1	3	50	7	155	9	241	14	453
0.2	2	13	3	39	4	61	7	112
0.3	1	5	2	16	3	26	5	50
0.4	1	3	2	10	2	14	3	26

We have not succeeded in deriving an exact expression for the expected number of trials to reach a decision or the expected number of patients on the poorer treatment, but good approximations are available that have been verified by Monte Carlo calculations.

Having obtained the general results of the last two paragraphs, we can now discuss the uses to which they can be put in designing a clinical trial. Two methods of using the exact information were discussed by Kiefer and Weiss [8]. The first assumed that Δ^* and N were fixed and that the probability of a correct selection was to be maximized, and the second that P^* and Δ^* were given and that the smallest N consistent with these requirements was to be chosen. Both of these problems were studied for the least favorable configuration which was shown to be $p = \frac{1}{2}(1 + \Delta^*)$ and $p' = \frac{1}{2}(1 - \Delta^*)$ as in the untruncated case. Table III gives values of s and P_{max}, where P_{max} is the maximum (over s) of the probability of a correct selection for fixed Δ^* and N. Table IV contains values of s and N for fixed P^* and Δ^*. The expected trial lengths have been calculated and are not appreciably shorter than those for unrestricted testing. Hence the most significant feature of the truncated tests is that an absolute upper bound can be placed on the number of tests, with the trial design retaining the same discriminatory ability as in the unrestricted design. A similar analysis can be made for PW sampling but no detailed calculations have been made so far to compare PW and VT sampling rules in their truncated versions.

4. Comparisons of PW and VT sampling rules using sequential likelihood rules

Several sequential procedures have been investigated but here we shall only report on one or two that do not include early elimination of noncontenders. The VT rule for k binomial populations based on likelihoods is the procedure described on pages 9, 270, and 324 of [3]; we refer to it as R_{BKS}. A remarkable feature of this procedure is that both $E\{N\}$ and $E\{L\}$ remain essentially constant for the GLF configurations with $p_{[1]} = p_{[2]} = \cdots = p_{[k-1]}, p_{[k]} = p_{[k-1]} + \Delta^*$ and Δ^* fixed, so that $p_{[k]}$ is the only variable. For example, for $k = 3$, $\Delta^* = 0.2$ and $P^* = 0.95$ a Monte Carlo study based on 1000 trials gave the results 78 ± 3.5 for $E\{N\}$ and 10.4 ± 0.5 for $E\{L\}$ for the GLF configurations $p = 0.2(0.05)1.0$ and $p_{[1]} = p_{[2]} = p - \Delta^*$.

Another procedure based on likelihoods and without elimination is R_{LPWC} (or likelihood exact) which considers the most likely of the three possible assignments of the observed data to the populations with ordered S values and then stops when the infimum over all configurations with $p_{[k]} - p_{[k-1]} \geqq \Delta^*$, of this maximum likelihood is at least P^*. To write down this stopping rule for $k = 3$ let $S_1 \leqq S_2 \leqq S_3$ denote the ordered S value (that is, the current numbers of successes) and let F_i denote the current number of failures associated with S_i, $i = 1, 2, 3$. After some simplification, the explicit rule is to stop when

$$\sup_{\Delta^* \leqq p \leqq 1} \left\{ \left(1 - \frac{\Delta^*}{p}\right)^{S_3 - S_2} \left(\frac{q}{q + \Delta^*}\right)^{F_2 - F_3} + \left(1 - \frac{\Delta^*}{p}\right)^{S_3 - S_1} \left(\frac{q}{q + \Delta^*}\right)^{F_1 - F_3} \right\} \leqq \frac{1 - P^*}{P^*}. \tag{4.1}$$

A modification of R_{LPWC} is R_{LCPWC} (or likelihood conservative) which replaces both factors $q/(q + \Delta^*)$ in (4.1) by their upper bound 1. For $P^* > \frac{1}{2}$ this procedure stops if $F_3 \leqq \min(F_1, F_2)$ and

$$(1 - \Delta^*)^{S_3 - S_2} + (1 - \Delta^*)^{S_3 - S_1} \leqq \frac{1 - P^*}{P^*}. \tag{4.2}$$

In both procedures we do not stop if $S_3 > \max(S_1, S_2)$ and $F_3 > \min(F_1, F_2)$. If $S_3 = S_2$ (or $S_3 = S_2 = S_1$) then we assign the subscript 3 to the population with fewer (fewest) failures. If $S_3 = S_2$ and $F_3 = F_2$ then the left side of (4.1) is larger than 1 and, for $P^* > \frac{1}{2}$, the inequality (4.1) will not hold. Under the PWC sampling rule, the differences $F_i - F_3$, $i = 1, 2$, can only take on the values 0 or 1.

Monte Carlo results for $k = 3$ show that R_{LPWC} and R_{LCPWC} procedures give similar results with R_{LPWC} showing a reduction of about 20 per cent in $E\{N\}$ over R_{LCPWC}. In comparing R_{LPWC} with the "constant" R_{BKS} we find, as for $k = 2$ in (2.7) and (2.8) above, that there is the same crossover pattern in which the PWC sampling rule is better for $p_{[3]} > 0.75$ and the VT sampling rule is better for $p_{[3]} < 0.75$ (approximately). These results have been confirmed by Hoel. Table V shows the Monte Carlo results obtained for $k = 3$, $\Delta^* = 0.2$ and $P^* = 0.95$.

TABLE V

SELECTING THE BEST ONE OF $k = 3$ BINOMIAL POPULATIONS (THREE ARMED BANDIT)

EXPECTED TOTAL NUMBER OF OBSERVATIONS $E\{N\}$ UNDER VARIOUS PROCEDURES FOR $k = 3$, $\Delta^* = 0.2$, $P^* = 0.95$ AND GLF CONFIGURATIONS $p_{[1]} = p_{[2]} = p - \Delta^*$

	Inverse Sampling Stopping Rules (asympt. ($\Delta^* \to 0$) normal approx.)		Sequential Stopping Rules Based on Likelihood (Monte Carlo results based on 1000 observations per entry)		
$p = \max p_i$ $i = 1, 2, 3$	R'_{VT}	R'_{PW}	R_{BKS}	Likelihood conservative R_{LCPWC}	Likelihood exact R_{LPWC}
0.20		364.0	74.6	223.3	184.8
0.25		288.8	77.1	210.3	171.2
0.30	$= E\{N \mid R'_{VT}\}$	238.5	77.2	196.6	164.1
0.35		202.4	77.6	188.2	155.5
0.40		175.0	76.9	178.8	145.9
0.45		153.5	77.9	162.5	134.5
0.50	$= \frac{3r}{p} > \frac{r}{p}\left(1 + \frac{2q}{q + \Delta^*}\right)$	136.0	78.0	153.5	126.1
0.55		121.4	76.5	141.8	115.1
0.60		108.9	76.7	126.8	103.0
0.65		97.9	77.4	116.3	94.5
0.70	$= E\{N \mid R'_{PW}\}$	88.0	78.3	102.9	83.0
0.75		78.8	81.3	90.3	74.7
0.80		70.0	80.2	75.9	61.4
0.85		61.2	81.6	62.4	51.0
0.90		51.9	80.9	49.6	39.3
0.95		41.3	80.4	36.5	30.2
1.00		28.0	80.1	23.7	20.2
	see (2.17) see [15]	based on (2.16)	see [3], pp. 259, 270, 324	see (4.2)	see (4.1)

5. Related problems under investigation

Some other variations of the PW, VT and allied sampling schemes are under investigation. E. Nebenzahl while at the University of Minnesota was studying the PW sampling rule for a fixed sample size procedure $R^{(N)}_{PW}$ with $k = 2$; that is, he wants to determine a total sample size N_{PW} (from both populations) such that

$$P\{CS \mid R^{(N)}_{PW}\} = P^* \quad \text{when} \quad p - p' = \Delta^*, \tag{5.1}$$

where $\Delta^* > 0$ and $P^* < 1$ are preassigned. He then compares N_{PW} with the N_{VT} required for the corresponding procedure $R^{(N)}_{VT}$ based on VT sampling. He has found that for any fixed even N

$$P\{\mathrm{CS} \mid R^{(N)}_{PW}\} = P\{\mathrm{CS} \mid R^{(N)}_{VT}\} \tag{5.2}$$

and hence $N_{PW} = N_{VT}$ for any pair (Δ^*, P^*).

In another three decision problem with $k = 2$ populations he allows the three decisions:

D_1: population 1 is better, that is, $p_1 > p_2$;
D_2: population 1 and 2 have approximately equal values of p;
D_3: population 2 is better, that is, $p_2 > p_1$.

Based on a total of N observations and the PW sampling rule, he uses the statistic

$$W = \frac{S_1 - S_2}{N}, \tag{5.3}$$

where S_i is the number of successes from population i, $i = 1, 2$. We make the decision

$$\begin{aligned} &D_1 \quad \text{if} \quad W > d, \\ &D_2 \quad \text{if} \quad -d \geqq W \geqq d, \\ &D_3 \quad \text{if} \quad W < -d, \end{aligned} \tag{5.4}$$

where $d > 0$ and N are to be determined. Let A and p_A correspond to the better population so that $p_A \geqq p_B$. If $p_1 = p_2$ and the common value is 0 or 1 then the power of the procedure based on PW sampling is clearly very poor. However, for specified P_1^*, P_2^*, Δ^* and γ^*, we can choose a pair (N, d) satisfying simultaneously the conditions

$$\begin{aligned} &\text{(a)} \quad P(\text{selecting } A) \geqq P_1^* \quad \text{when} \quad p_A - p_B \geqq \Delta^*, \\ &\text{(b)} \quad P(\text{deciding } D_2) \geqq P_2^* \quad \text{when} \quad p_A = p_B \leqq \gamma^*. \end{aligned} \tag{5.5}$$

where $P_i^* < 1$, $i = 1, 2$, $\Delta^* > 0$ and $0 < \gamma^* < 1$: for convenience it is also assumed that $\gamma^* \geqq \frac{1}{2}(1 + \Delta^*)$. The corresponding problem for the VT sampling rule is also considered (the condition $p_A = p_B \leqq \gamma^*$ in (b) is now replaced by $p_A = p_B$). A comparison of the results shows that the number of observations $N_{\text{PW}}(N_{\text{VT}})$ required by the PW sampling rule (VT sampling rule) asymptotically ($\Delta^* \to 0$) satisfies the inequality

$$N_{\text{PW}} \geqq N_{\text{VT}}. \tag{5.6}$$

In general for a fixed number of observations the VT sampling rule is preferable, but for a sequential problem neither sampling rule is uniformly preferable.

In another avenue of investigation, Nebenzahl showed that if we consider a class of inverse sampling procedures in which the ith procedure switches only after i successive failures, $i = 1, 2, \cdots$, then the best ranking and selection results are obtained by taking $i = 1$. More explicitly, he finds an r_i for procedure R_i' based on inverse sampling and switching after i successive failures such that (2.1) holds. He then computes $E\{N \mid R_i'\}$ and finds that: (1) for all i the supremum occurs when $p_A = p_B$, and (2) the smallest supremum is obtained by taking $i = 1$.

Y. S. Lin, at the University of Minnesota, is applying the PW sampling scheme to the problem of finding the "fairest" of two or more coins, that is, the one with p closest to 1/2. A trial consists of three tosses of a coin and if we observe 1 or 2 heads it is a success, otherwise it is a failure. The probability of success on a single trial, $3p^2q + 3pq^2 = 3pq$, is a maximum for $p = \frac{1}{2}$. Hence the coin with p closest to $\frac{1}{2}$ should give the most successes. In this way the problem is again brought into the framework of selecting the population with the highest probability of success on a single trial. The PW scheme is then applied to the trials and a comparison of the PW and the VT sampling scheme is made. It will also be compared with a straightforward (ranking and selection) approach to this problem of finding the fairest coin which was solved for $k = 2$ (the case $k > 2$ is still incomplete) by Sobel and Starr [12].

Along different lines D. Feldman with one of the authors has studied a modification of the PW sampling rule which is called the "Follow the Leader" (or FL) sampling rule. Here we again stick to any population as long as it provides successes. When it gives a failure and the current numbers of failures (F_1, F_2) are not equal then we switch as before. If $F_1 = F_2$ and $S_1 = S_2$ then we randomize, that is, perform an independent experiment with equal probability for each.

Exact formulas for the PCS, $E\{L\}$, and $E\{N\}$ were obtained for the procedure R_{FL} based on the FL sampling rule and termination rule $\Delta S = r$. Our first result was that for any fixed r

$$P\{\mathrm{CS}|R_{\mathrm{FL}}\} < P\{\mathrm{CS}|R_{\mathrm{PW}}\}. \tag{5.7}$$

It follows that the r value r_{PW} for R_{PW} is not greater than r_{FL} for R_{FL}. For any P^*, if Δ^* is *not* too small then $r_{\mathrm{FL}} = r_{\mathrm{PW}}$. When this happens the procedure R_{FL} becomes a serious competitor to R_{PW} and is superior (in the sense of a smaller $E\{L\}$ and $E\{N\}$) for most of the GLF configurations ($p = p' + \Delta^*$) with p varying from Δ^* to 1. On the other hand if $\Delta^* \to 0$ then R_{PW} is uniformly preferable to R_{FL}.

The corresponding comparisons for the fixed sample size problem and for the inverse sampling problem have not yet been investigated.

6. Open questions

Any enumeration of the practical difficulties associated with clinical trials is a good source of problems for future research. The principal shortcomings of the trial designs just described are the assumptions of dichotomous and instantaneous response to treatment. The first of these can be handled by some of the techniques given by Bechhofer, Kiefer, and Sobel [3] which principally use the VT rule and also more complicated termination rules than those described so far. No analogue of the PW rule has been proposed for the case in which the response is continuous—a very important consideration in the testing of anticancer treatments for which a natural measure of effectiveness is lifetime.

The example of testing anticancer treatments also suggests the second difficulty of a response at some random time after administration of the treatment. Zelen [16] has proposed an analogue to the PW rule for dichotomous response with random reporting intervals. His idea is to bias future assignments to the two treatments according to present trial results. Thus, every success with A would generate a future test with A and every failure with A generates a future test with B. Whenever a new patient arrives, the treatment assignment is made by randomly choosing one of the possibilities generated by past trials, or the choice is made with probability $\frac{1}{2}$ if all past results have been accounted for. The analysis of this sampling scheme in the context of our present formulation of terminating rules has not been made nor has it been compared to other alternatives.

Flehinger, Miller, and Louis [6] have discussed a fixed sample analogue of the PW rule for testing differences in mean survival time in two populations, each of which has an underlying negative exponential distribution of lifetimes. The method is a fairly complicated one in which the information at any stage is summarized in a six dimensional vector including the number of patients on each treatment who have died, those who are alive, and the total time lived by patients on the two treatments. Because of mathematical difficulties, results could only be obtained by Monte Carlo methods, and no comparison with other methods was made.

Much remains to be done on the problem of choosing the best of $k \geqq 2$ dichotomous populations. We have encountered great difficulties in trying to deal analytically with any termination rule other than the one prescribed by inverse sampling. Inverse sampling is probably inefficient for small Δ^*, as we have demonstrated in the case $k = 2$. It would certainly be of interest to consider the ranking problem for $k > 2$, keeping in mind the objective of doing so with as small a number of patients as possible on the poorer treatments. Another problem that has not been touched is that of multiple patient entries. It would seem of some interest to investigate multistage trials to alleviate the possibly overpessimistic designs generated by using the least favorable configuration.

Many further problems suggest themselves based both on practical difficulties in the expanding use of clinical trials and on the basic theory developed so far. There is clearly room for much further investigation in the area of clinical trials based on ethical and technical considerations.

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REFERENCES

[1] F. J. ANSCOMBE. "Sequential medical trials," *J. Amer. Statist. Assoc.*, Vol. 58 (1963), pp. 365–383.

[2] P. ARMITAGE. *Sequential Medical Trials*. Springfield, Thomas, 1960.

[3] R. E. BECHHOFER, J. KIEFER, and M. SOBEL. *Sequential Identification and Ranking Problems*. Chicago, University of Chicago Press, 1968.

[4] T. COLTON. "A model for selecting one of two medical treatments," *J. Amer. Statist. Assoc.*, Vol. 58 (1963), pp. 338–400.

[5] J. CORNFIELD, M. HALPERIN, and S. W. GREENHOUSE. "An adaptive procedure for sequential clinical trials," *J. Amer. Statist. Assoc.*, Vol. 64 (1969), pp. 759–770.

[6] B. J. FLEHINGER, J. M. MILLER, and T. A. LOUIS. "Clinical trials to test for difference in mean survival time: Data dependent assignment of patients," IBM Research Report RC 2737, 1969, pp. 1–46.

[7] J. R. ISBELL. "On a problem of Robbins," *Ann. Math. Statist.*, Vol. 30 (1959), pp. 606–610.

[8] J. KIEFER, and G. H. WEISS. "A truncated test for choosing the better of two binomial populations," *J. Amer. Statist. Assoc.*, to appear.

[9] R. PYKE, and C. V. SMITH. "The Robbins-Isbell two-armed bandit problem with finite memory," *Ann. Math. Statist.*, Vol. 36 (1965), pp. 1375–1386.

[10] H. ROBBINS. "A sequential procedure with a finite memory," *Proc. Nat. Acad. Sci., U.S.A.*, Vol. 42 (1956), pp. 920–923.

[11] D. E. RUTHERFORD. "Some continuant determinants arising in chemistry and physics," *Proc. Roy. Soc. Edinburgh Sect.*, Vol. 63A (1951), pp. 232–241.

[12] M. SOBEL, and N. STARR. "Selecting the t fairest coins," University of Minnesota, Department of Statistics, Technical Report, No. 99, 1968, pp. 1–8.

[13] M. SOBEL, and G. H. WEISS. "Play-the-winner sampling for selecting the better of two binomial populations," *Biometrika*, Vol. 57 (1970), pp. 357–365.

[14] ———. "Play-the-winner rule and inverse sampling in selecting the better of two binomial populations," *J. Amer. Statist. Assoc.*, to appear.

[15] ———. "Play-the-winner rule and inverse sampling for selecting the best of $k \geqq 3$ binomial populations," University of Minnesota, Department of Statistics, Technical Report, No. 126, 1969, pp. 1–25.

[16] M. ZELEN. "Play the winner rule and the controlled clinical trial," *J. Amer. Statist. Assoc.*, Vol. 64 (1969), pp. 131–146.