The Annals of Statistics
1986, Vol. 14, No. 3, 954–970

BAYES RULES FOR A CLINICAL-TRIALS MODEL WITH DICHOTOMOUS RESPONSES[1]

BY GORDON SIMONS

University of North Carolina

The risk in a trial to compare two medical treatments is borne by the patients who receive the inferior treatment during the experimental phase and by those remaining after the experiment who will all receive the inferior treatment if the results are misleading. The Bayes rule indicates, for the observed progression of successes and failures, when it is optimal to stop this experimental phase. This stopping rule can be described exactly, or nearly so, for symmetric two-point priors. Less precise descriptions are possible for other types of priors. An admissible stopping rule is described which is best possible, among symmetric Bayes rules, in that it minimizes the probability of choosing the inferior treatment no matter what the values are for the probabilities of success.

1. Introduction. Much of the literature on sequential clinical trials circumvents the difficulties of working with Bernoulli-type responses, "successes" and "failures," by assuming that the treatment responses are normally distributed. While such an assumption has certain advantages, it has significant disadvantages as well, including some technical disadvantages:

(i) The more delicate results for normally distributed treatment responses apparently are not directly obtainable [cf. Chernoff and Petkau (1981, 1985)]. One first studies a continuous-time free boundary problem associated with the heat equation and obtains suitable approximate solutions. Then suitable adjustments, additional approximations, are required to return to the discrete-time setting. This is a difficult agenda. The technical details can seem quite forbidding except, perhaps, to a few experts.

(ii) It is not easy to extrapolate from the normal results comparable results for the Bernoulli setting, particularly for small and moderate sample sizes.

The intent of the present paper is to derive a variety of results directly within the setting of Bernoulli-type responses. These, of course, have the advantage of direct applicability. Another advantage of working with Bernoulli-type responses is that the quality of approximations can easily be assessed by direct numerical calculations, without having to resort to more costly and less accurate simulation studies.

The model is as follows. Two contending treatments are to be assigned at random to pairs of patients. With the total number of patients, the "horizon," prespecified, this sampling by pairs is to continue until there is sufficient

Received August 1984; revised October 1985.

[1]This research was supported by National Science Foundation Grant DMS-8400602.

AMS 1980 *subject classifications*. Primary 60G40, 62C10, 62L05; secondary 62C15.

Key words and phrases. Clinical trials, Bayes rules, optimal stopping, Markovian states.

Institute of Mathematical Statistics is collaborating with JSTOR to digitize, preserve, and extend access to *The Annals of Statistics.* www.jstor.org

information about the relative quality of the two treatments that it is prudent to assign the more promising treatment to all of the remaining patients. This formulation was proposed by Anscombe (1963) for normally distributed treatment responses. The statistician's task is to find a suitable stopping rule which indicates when sampling by pairs, the "testing phase," should be stopped. The risk (function) used here is the "expected successes lost" (ESL) by the stopping rule because it is unknown which of the success probabilities p_1 and p_2 is larger. It is mathematically equal to the product of $|p_1 - p_2|$ and the expected number of patients assigned the inferior treatment.

For any prior distribution on (p_1, p_2), the posterior Bayes risk depends on the size of the horizon N and on the Markovian state (n, r, s), where n is the current number of sampled pairs, and where r and s are the current numbers of successes for the first and second treatments, respectively. If the prior distribution is supported by two symmetric points (a, b) and (b, a), then the optimal stopping rule depends on N and (n, r, s) only through the values of $t = N - 2n$, the number of patients remaining (the "time to go"), and $r - s$, the current "success difference."

There are several reasons for being interested in these two-point priors. It was demonstrated by Bather and Simons (1985) that the minimax stopping rule, for most of the first 200 values of N, is the Bayes stopping rule for a "least favorable" symmetric prior on two such points with $a + b = 1$ (a and b depending on N). Another reason is that for any symmetric stopping rule, the risk at $(p_1, p_2) = (a, b)$ is equal to the Bayes risk for a symmetric prior on the two points (a, b) and (b, a). (A symmetric stopping rule is one which is indifferent to the ordering of the treatments.) Thus the risk at a particular point $(p_1, p_2) = (a, b)$ can be minimized among all symmetric stopping rules by finding the Bayes stopping rule for the symmetric prior supported on (a, b) and (b, a). The value of this minimum risk is of some interest when one has little or no reason to think that one particular treatment is better than the other. It is a reasonable standard by which to evaluate the risk for any symmetric stopping rule. This kind of perspective has been pursued in another paper (Simons (1986)).

The Bayes stopping rules for two-point symmetric priors are discussed in Section 2. Inner and outer approximations to the stopping boundary are obtained (Theorems 2 and 4). These are good enough to provide an asymptotic description of the stopping boundary as $t \to \infty$. The inner approximation is exceptionally good for small as well as large values of t. In some cases, it quite reliably specifies the exact values of t at which the optimal boundary expands. Even when it is not this accurate, it suggests a barely suboptimal stopping rule. Approximations to the minimal Bayes risk are obtained (Theorem 3) which are good for most values of t.

It turns out that the optimal stopping boundaries for two-point symmetric priors have an outer envelope. This envelope is approached by letting (a, b) go to $(\frac{1}{2}, \frac{1}{2})$. There are several reasons for being interested in this envelope. Firstly, it is the optimal stopping boundary for an easily described random walk S_n when the stopping reward takes the form $t|S_n|$, where $t = N - 2n$ is the time to go. It is not difficult to find this optimal stopping boundary; the corresponding stopping

rule can be described as:

(1) Continue when $|S_n| = k$ if $t \geq T_k$, $\quad k \geq 0$,

where $T_0, T_1, T_2, \ldots$ is an increasing sequence of positive integers. The first twelve values are 2, 14, 41, 82, 136, 204, 285, 381, 490, 613, 749, 900.[2] Secondly, the outer envelope is an outer envelope in a much stronger sense: For any symmetric prior distribution G for (p_1, p_2) (i.e., any prior which is exchangeable in p_1 and p_2) and any horizon N, the Markovian state (n, r, s) is a point of optimal stopping if $t < T_k$, where $t = N - 2n$ and $k = |r - s|$. It might be difficult to give a complete description of the optimal stopping points (n, r, s) for G, but the sequence $T_0, T_1, \ldots$ can be used quite simply to establish large numbers of triplets (n, r, s) as points of optimal stopping. Thirdly, one is led to consider the simple symmetric "envelope" stopping rule:

(2) Continue when $|r - s| = k$ if $t = (N - 2n) \geq T_k$, $\quad k \geq 0$.

This rule is a Bayes rule (for a symmetric two-point prior depending on N), and it is admissible. Among Bayes symmetric stopping rules, it uniformly minimizes the error probability (the probability of choosing the inferior treatment) at all values of (p_1, p_2), providing the value $T_0 = 2$ is used instead of 3. (See footnote 2.) These ideas and assertions are discussed further in Section 3.

There are practical reasons why one might wish to work with other than symmetric prior distributions. A physician[3] may begin with a preference for one of the two treatments. In such a case he should choose a nonsymmetric prior. And even if he has no initial preference, he will probably develop a preference during the course of the clinical trial, i.e., his symmetric prior will probably become a nonsymmetric posterior eventually. One should be able to begin anew with this nonsymmetric posterior, viewing it as an updated prior. If one is to continue optimally from this point, one must be able to work with certain types of nonsymmetric priors.

On the other hand, there is no end to possible priors. Even the staunchest Bayesian must recognize the futility of asking a physician to specify a prior which accurately reflects his true beliefs in complete detail. With this in mind, the author suggests to those who are Bayesians (and perhaps to those who are not) that a simple compromise is possibly in order. It is suggested that the physician be asked to express his beliefs by specifying a single real, possibly integer-valued, parameter θ, one whose interpretation is easily communicated in a layman's language: It is positive when the first treatment is considered preferable, and negative when the second is preferred. Its magnitude is to denote the number of failures of the physician's preferred treatment, together with an equal number of successes of the other treatment, which jointly would cause the physician to come to view the two treatments as equally promising. For the Bayesian, the posterior effect on θ from assigning the two treatments at random

[2] The first of these is a matter of some indifference. The value $T_0 = 3$ is optimal as well.

[3] The word "physician" should be understood as referring to those whose medical judgments enter into the design of the clinical trial.

to a pair of patients is to increase θ by one if the first treatment is successful and the second is not, to decrease θ by one in the opposite circumstances, and to keep it the same if both treatments yield the same results. For this interpretation to make sense, one must begin with a "symmetrizable prior," a prior which permits (at least when θ is integer-valued) a symmetric posterior. If the physician, after due reflection, should choose a value of θ very far from zero, it seems likely that frequentists, like Bayesians, would be uncomfortable with a symmetric stopping rule. If one has a symmetric stopping rule which one is pleased with to handle situations of no initial treatment preference ($\theta = 0$), it easily can be modified to accommodate situations of an initial treatment preference ($\theta \neq 0$). The subject of symmetrizable priors is discussed in Section 4.

Our theory extends to encompass "ethical costs," which recently have been considered by Chernoff and Petkau (1985). An ethical cost occurs whenever it *appears* that a patient is being given the inferior treatment. This extension is discussed briefly in Section 5.

2. The Bayes stopping rule for two-point symmetric priors. Let G be any prior distribution for (p_1, p_2) and let E_n denote conditional expectation based on the results from assigning the two competing treatments at random to n pairs of patients. The conditional expected successes lost for these $2n$ patients is $nE_n|p_1 - p_2|$. Suppose N is the total number of patients. If all of the remaining $N - 2n$ patients are given the more promising treatment, their conditional expected successes lost is $(N - 2n)E_n(p_2 - p_1)^+$ or $(N - 2n)E_n(p_1 - p_2)^+$, whichever is smaller, depending on which treatment is the more promising. Thus the posterior Bayes risk at "time" n is

$$nE_n|p_1 - p_2| + (N - 2n)\min\left(E_n(p_2 - p_1)^+, E_n(p_1 - p_2)^+\right).$$

Conveniently, this can be rewritten as

$$\frac{N}{2}E_n|p_1 - p_2| - \left(\frac{N}{2} - n\right)|E_n(p_1 - p_2)|. \tag{3}$$

The first term is a martingale in n and, hence, has no bearing on the question of optimal stopping. Consequently, the problem of optimal stopping can be recast in terms of a *reward* sequence defined by

$$R_n = (N - 2n)|E_n(p_1 - p_2)|. \tag{4}$$

It can be easily checked that this problem is Markovian with a state parameter (n, r, s), where r and s are the numbers of successes produced by the first and second treatments, respectively, among the first n pairs of patients. For the prior G, one can identify certain states (n, r, s) as *optimal stopping states* (or *points*) and the remainder as *optimal continuation states* (or *points*). As a matter of convenience, states (n, r, s) for which stopping and continuation are *both* optimal will be assigned both appellations.

Now suppose that the prior G assigns the probability $\frac{1}{2}$ to each of two symmetric points (a, b) and (b, a) with $a > b$. Then (4) becomes

$$R_n = (a - b)(N - 2n)\tanh(|r - s|\alpha), \tag{5}$$

where

$$\alpha = \tfrac{1}{2}\log(a(1-b)/(1-a)b). \tag{6}$$

The Markovian state (n, r, s) can be replaced by the simpler Markovian state

$$(t, k) = (N - 2n, r - s). \tag{7}$$

Then $(a-b)^{-1}R_n$ becomes

$$R(t, k) = t\tanh(|k|\alpha). \tag{8}$$

The maximum expected reward using an optimal stopping time for the initial state (t, k) can be written as $(a-b)S(t, k)$, where $S(t, k)$ is defined recursively by

$$\begin{aligned} S(t, k) = \max\{&R(t, k), u_k S(t-2, k-1) \\ &+ vS(t-2, k) + w_k S(t-2, k+1)\}, \quad t \geq 2, \end{aligned} \tag{9}$$

with the initial values $S(t, k) = R(t, k)$ for $t = 0, 1$, where

$$\begin{aligned} v &= ab + (1-a)(1-b), \qquad u_k = \frac{\beta\cosh(k-1)\alpha}{\cosh k\alpha}, \\ w_k &= \frac{\beta\cosh(k+1)\alpha}{\cosh k\alpha}, \qquad \beta^2 = ab(1-a)(1-b). \end{aligned} \tag{10}$$

Observe that $\beta e^{\alpha} = a(1-b)$ and $\beta e^{-\alpha} = b(1-a)$, so that $2\beta\sinh\alpha = a - b$.

The point (t, k) is an optimal stopping point if $S(t, k) = R(t, k)$. It is an optimal continuation point if $S(t, k) > R(t, k)$ or if $u_k S(t-2, k-1) + vS(t-2, k) + w_k S(t-2, k+1) = R(t, k)$. In the latter case, (t, k) is both an optimal continuation point and an optimal stopping point (according to a previously announced convention).

THEOREM 1. *Given a, b with $0 < b < a < 1$, there is a strictly increasing sequence of positive integers $\tau_0, \tau_1, \tau_2, \ldots$ for which the state (t, k) is an optimal continuation point if $t \geq \tau_k$, and an optimal stopping point if $t < \tau_k$.*

PROOF. The difference $S(t, k) - R(t, k)$ satisfies recursive relationships akin to those in equations (22) and (23) of Bather and Simons (1985). The argument then proceeds as for their Theorem 5. □

Within the region of continuation, $S(t, k)$ satisfies the difference equation

$$Z(t, k) = u_k Z(t-2, k-1) + vZ(t-2, k) + w_k Z(t-2, k+1). \tag{11}$$

This equation has many solutions besides the one defined in (9), including some fairly simple solutions that can be used to obtain several useful approximations. The general form of the symmetric separable solutions is

$$Z(t, k) = (v + 2\beta\cosh x)^{t/2}\frac{\cosh kx}{\cosh k\alpha}, \tag{12}$$

where the variable x is arbitrary. When $x = \alpha$, this becomes $Z(t, k) \equiv 1$. A multiple of the partial derivative of the right side of (12) with respect to x, evaluated at $x = \alpha$, yields another solution, namely

$$Z(t, k) = t + \frac{2k}{a - b}\tanh k\alpha. \tag{13}$$

THEOREM 2. *The point* (t, k), $k \geq 0$ *is an optimal continuation point if*

$$t \geq 2 + \frac{2\sinh k\alpha \sinh(k + 1)\alpha}{(a - b)\sinh \alpha} + \frac{2k \tanh k\alpha}{a - b}. \tag{14}$$

PROOF. Consider a particular solution $Z(t, k)$ of (11). A point (t, k) will be called "good" if $Z(t, k) \geq R(t, k)$, and called "warm" if $Z(t, k) \leq S(t, k)$. If a point (t, k) is good and each of its immediate successors $(t - 2, k - 1)$, $(t - 2, k)$, $(t - 2, k + 1)$ is warm, then it is an optimal continuation point. For then

$$\begin{aligned} &u_k S(t - 2, k - 1) + vS(t - 2, k) + w_k S(t - 2, k + 1) \\ &\quad \geq u_k Z(t - 2, k - 1) + vZ(t - 2, k) + w_k Z(t - 2, k + 1) \\ &\quad = Z(t, k) \geq R(t, k). \end{aligned} \tag{15}$$

Clearly a point (t, k) is warm if $Z(t, k) \leq R(t, k)$ since $S(t, k) \geq R(t, k)$. But other warm points can be found. In particular, (t, k) is warm if each of its immediate successors is warm. For then

$$\begin{aligned} Z(t, k) &= u_k Z(t - 2, k - 1) + vZ(t - 2, k) + w_k Z(t - 2, k + 1) \\ &\leq u_k S(t - 2, k - 1) + vS(t - 2, k) + w_k S(t - 2, k + 1) \\ &\leq S(t, k). \end{aligned}$$

To prove the theorem, the particular solution $Z(t, k)$ must be chosen with some care. Consider a specific point (t_0, k_0), $k_0 \geq 0$. For $k_0 = 0$, the solution $Z(t, k) \equiv 0$ can be used to establish (14), namely that $(t_0, 0)$ is an optimal continuation point when $t_0 \geq 2$. For $k_0 > 0$, use

$$Z(t, k) = \tanh k_0\alpha\left[t + \frac{2k}{a - b}\tanh k\alpha\right] - \frac{2k_0}{a - b}\tanh^2 k_0\alpha, \tag{16}$$

which is a linear combination of (13) and $Z(t, k) \equiv 1$. The equation $Z(t, k) = R(t, k)$ divides the first quadrant into four regions as indicated in Figure 1.

The lattice points (t, k) in the cross-hatched regions II and IV satisfy the inequality $Z(t, k) \leq R(t, k)$ and, therefore are warm. It follows by straightforward induction, based on t, that all of the points in region I are warm as well. All of the points in regions I and III are good, but only some of them are optimal continuation points. To be optimal continuation points, it is enough that their immediate successors are warm. Thus every lattice point (t, k) in region I is an optimal continuation point except, possibly, those (upper) boundary points of the form (t, k_0) for which $(t - 2, k_0 + 1)$ is in region III. But if (t_0, k_0) satisfies (14), the point $(t_0 - 2, k_0 + 1)$ has to be in region II. So (t_0, k_0) is an optimal continuation point. □

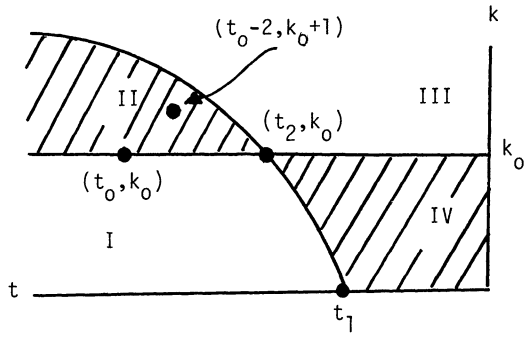

FIG. 1.

The values of t_1 and t_2, appearing in Figure 1, are

$$t_1 = \frac{2k_0}{b-a}\tanh k_0\alpha, \qquad t_2 = \frac{2k_0}{a-b}\tanh k_0\alpha + \frac{2}{\alpha(a-b)}\sinh^2 k_0\alpha.$$

Not only do Z and R agree at (t_2, k_0), but so do their first partial derivatives. Thus one should expect Z to closely approximate S in the vicinity of (t_2, k_0) [cf. Chernoff (1972), page 93, and Bather (1983)]. This is the case. For instance, when $a = 0.75$ and $b = 0.25$, the first several values of the right side of (14) are 2, 22.98, 189.56, and 1651.72, which exactly predict the integer-valued transition points referred to in Theorem 1: $\tau_0 = 2$, $\tau_1 = 23$, $\tau_2 = 190$, and $\tau_3 = 1652$. The same kind of accuracy has been observed for τ_0 through τ_7 when $a = 0.6$ and $b = 0.4$, except τ_3 is overestimated by one unit. The quality of the approximation is less when a and b are close together. For instance, when $a = 0.6$ and $b = 0.5$, the values of τ_0, τ_1, τ_9, τ_{10} and τ_{11} are exactly predicted But for τ_2 through τ_8 the predictions are too large by the amounts, 1, 2, 4, 5, 4, 2, and 1, respectively. This suggests that (14) is a good approximation for small and for large values of k.

The relevant question is: How well do the predicted transition points perform when used in place of the (harder to obtain) correct transition points? The answer is, they perform exceedingly well. For instance, for the case $a = 0.6$, $b = 0.5$ referred to above, the actual expected reward is within one-tenth of one percent of the optimal expected reward for every state (t, k), $t \le 2{,}500$. For $k = 0$ (which is relevant for computing the Bayes risk), it is always within two one-hundredths of one percent. (The worst values found for t are less than 200; it seems unlikely that t-values larger than 2,500 can cause problems.)

THEOREM 3. *The Bayes risk for the clinical trial is bounded above by*

$$\frac{a-b}{2}\left\{(1-\tanh k_0\alpha)N + \frac{2k_0}{a-b}\tanh^2 k_0\alpha\right\} \tag{17}$$

for each $k_0 = 0, 1, 2, \ldots$.

PROOF. The Bayes risk takes the form $((a-b)/2)(N - S(N,0))$. (See the discussion preceding Theorem 1.) Now, it is apparent from Figure 1 that the point $(N,0)$ is "warm" in the sense described in the proof of Theorem 2. That is, $Z(N,0) \leq S(N,0)$. The desired conclusion follows immediately from (16). □

The quality of the smallest obtainable upper bound is typically quite good. For instance, when $N = 100$, $a = 0.6$, and $b = 0.5$, the best choice for k_0 is 3, and the upper bound is 3.17. The actual value of the Bayes risk is 3.14. For $N = 2{,}500$, the best bound is 13.360 and the Bayes risk is 13.359.

There is an interesting analogue to Theorem 2.

THEOREM 4. *The point* (t, k) $(k \geq 0)$ *is an optimal stopping point if*

$$t \leq 2 + \frac{2\sinh k\alpha \sinh(k+1)\alpha}{(a-b)\sinh\alpha} \tag{18}$$

PROOF. Again let $Z(t, k)$ be a particular solution of (11). And again there is a need to refer to "good" and "warm" points, but with new meanings. *Here* a point (t, k) will be called "good" if $Z(t, k) \leq R(t, k)$, and called "warm" if $Z(t, k) \geq S(t, k)$. If a point (t, k) is good and each of its immediate successors $(t-2, k-1)$, $(t-2, k)$, $(t-2, k+1)$ is warm, then it is an optimal stopping point. This is proved by reversing the inequalities in (15).

Clearly, a point (t, k) is warm if $Z(t, k) \geq R(t, k)$ and $S(t, k) = R(t, k)$. But other warm points can be found. In particular, (t, k) is warm if $Z(t, k) \geq R(t, k)$ and each of its immediate successors is warm. For then

$$\begin{aligned} &u_k S(t-2, k-1) + vS(t-2, k) + w_k S(t-2, k+1) \\ &\quad \leq u_k Z(t-2, k-1) + vZ(t-2, k) + w_k Z(t-2, k+1) \\ &\quad = Z(t, k), \end{aligned}$$

so that

$$\begin{aligned} Z(t, k) &\geq \max(R(t, k), u_k S(t-2, k-1) + vS(t-2, k) + w_k S(t-2, k+1)) \\ &= S(t, k). \end{aligned}$$

If $Z \geq R$ at (t, k) and at all of the successors of (t, k), then (t, k) is warm. This is easily shown by induction.

To prove the theorem, the particular solution $Z(t, k)$ of (11) must be picked with care: Consider a specific point (t_0, k_0), $t_0 \geq 2$, $k_0 \geq 0$. The case $k_0 = 0$ is easily disposed of with $Z(t, k) \equiv 0$. For $k_0 > 0$, use

$$Z(t, k) = \frac{(a-b)t_0 \tanh k_0\alpha}{(a-b)t_0 + 2k_0 \tanh k_0\alpha}\left(t + \frac{2k}{a-b}\tanh k\alpha\right). \tag{19}$$

Since $R(t, k) = t \tanh |k|\alpha$, it follows that $Z(t_0, k_0) = R(t_0, k_0)$. Thus (t_0, k_0) is a good point. It must be shown that its immediate successors $(t_0 - 2, k_0 - 1)$, $(t_0 - 2, k_0)$, $(t_0 - 2, k_0 + 1)$ are warm. It is enough to show that $Z \geq R$ at *all* of the successors of (t_0, k_0).

Now the equation $Z(t, k) = R(t, k)$ divides the first quadrant into two regions as indicated in Figure 2. In region I, $Z \geq R$. In region II, $Z \leq R$, so that all of its

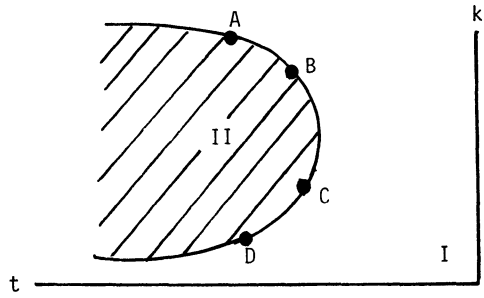

FIG. 2.

lattice points are good. The point (t_0, k_0) is located somewhere on the boundary of region II. If its position is like one of the points B and C, shown in Figure 2, all of its successors will be in region I, where $Z \geq R$, and the argument will be complete. However, if its position is like one of the points A and D, then some of its successors can be in the interior of region II, where $Z < R$. This situation must be avoided. It can be avoided by restricting the range of t_0. Because of Theorem 1, it is enough to complete the proof when

$$(20) \qquad \frac{2\sinh k_0\alpha \sinh(k_0+1)\alpha}{(a-b)\sinh\alpha} \leq t_0 \leq 2 + \frac{2\sinh k_0\alpha \sinh(k_0+1)\alpha}{(a-b)\sinh\alpha}.$$

For if (t_0, k_0) is an optimal stopping point whenever (20) holds, then it must also be an optimal stopping point whenever just the latter inequality in (20) holds.

When (20) holds, all of the successors of (t_0, k_0) are in region I. Since the proof of this is tedious but not difficult, it will be omitted. (Several elementary inequalities involving hyperbolic functions must be isolated and checked.) This completes the proof. □

Together, Theorems 2 and 4 provide for the proper classification of a large number of states (t, k). They show that the transition points τ_k, referred to in Theorem 1, grow asymptotically with k like $2\sinh k\alpha \sinh(k+1)\alpha/(a-b)\sinh\alpha$. Thus the boundary grows with t at the rate $(2\alpha)^{-1}\log t$. More precise statements are possible.

Certain pairs (t, k) are optimal stopping states for every a and b $(a > b)$. Some of these "universal optimal stopping states" can be found by using Theorem 4. It can be shown that the right side of (18) is (tightly) bounded below by $2 + 4k + 4k^2$. So (t, k) must be a universal optimal stopping state whenever $t \leq 2 + 4k + 4k^2$. Now the lower bound $2 + 4k + 4k^2$ is achieved only in the limit as a and b approach one-half. This suggests that the set of optimal stopping states approaches its minimal possible size as a and b approach one-half. Further encouragement for this suggestion is provided by the fact that the lower bound $(2 + 4k + 8k^2)$ of the right side of (14) is also achieved in the limit as a and b approach one-half. Since the suggestion is correct, it should not

be surprising that the key to characterizing the universal optimal stopping states is the examination of the limiting forms of $R(t, k)$ and $S(t, k)$ as a and b approach one-half.

For the first of these

$$\lim_{a,\, b \to 1/2} (a - b)^{-1} R(t, k) = \lim_{a,\, b \to 1/2} (a - b)^{-1} t \tanh|k|\alpha = 2t|k|. \tag{21}$$

It easily follows, by induction, from (9) and (21) that $(a - b)^{-1}S(t, k)$ converges to a limit $S^*(t, k)$ as $a, b \to \frac{1}{2}$ and that

$$\begin{aligned} S^*(t, k) = \max\{&2t|k|, \tfrac{1}{4}S^*(t - 2, k - 1) \\ &+ \tfrac{1}{2}S^*(t - 2, k) + \tfrac{1}{4}S^*(t - 2, k + 1)\}, \qquad t \geq 2, \end{aligned} \tag{22}$$

with initial values $S^*(t, k) = 2t|k|$ for $t = 0, 1$.

THEOREM 5. *The pair (t, k) is an optimal stopping state for every a and b $(a > b)$ if and only if $S^*(t, k) = 2t|k|$. Moreover, there is an increasing sequence of positive integers $T_0, T_1, T_2, \ldots$ for which $S^*(t, k) = 2t|k|$ if and only if $t < T_k$. The first five values of the sequence are* 3, 14, 41, 82, 136.

PROOF. The second assertion is proved in the same way Theorem 1 is proved, and the values of the sequence are found by direct numerical calculations using (22). If (t, k) is an optimal stopping state for every a and b, then

$$S^*(t, k) = \lim_{a,\, b \to 1/2} (a - b)^{-1} S(t, k) = \lim_{a,\, b \to 1/2} (a - b)^{-1} t \tanh|k|\alpha = 2t|k|.$$

Now consider a specific pair a and b, $a > b$. To establish the converse, it will be shown that

$$\frac{4\beta \cosh k\alpha}{(a - b)} [S(t, k) - t \tanh|k|\alpha] \leq S^*(t, k) - 2t|k| \tag{23}$$

for all pairs (t, k). It will follow whenever $S^*(t, k) = 2t|k|$ that $S(t, k) = t \tanh|k|\alpha$, so that (t, k) is an optimal stopping state for a and b. Denote the left and right sides of (23) by $Q(t, k)$ and $Q^*(t, k)$, respectively. It follows from (9) and (22) that for $t \geq 2$,

$$Q(t, k) = \begin{cases} vQ(t - 2, 0) + 2\beta Q(t - 2, 1) + 4\beta(t - 2), & k = 0, \\ \max(0, \overline{Q}(t, k)), & k \neq 0, \end{cases} \tag{24}$$

and

$$Q^*(t, k) = \begin{cases} \tfrac{1}{2}Q^*(t - 2, 0) + \tfrac{1}{2}Q^*(t - 2, 1) + t - 2, & k = 0, \\ \max(0, \overline{Q}^*(t, k)), & k \neq 0, \end{cases} \tag{25}$$

where

$$\begin{aligned} \overline{Q}(t, k) = {} & \beta Q(t - 2, k - 1) + vQ(t - 2, k) \\ & + \beta Q(t - 2, k + 1) - \frac{8\beta}{a - b} \sinh|k|\alpha \end{aligned} \tag{26}$$

and

$$\overline{Q}^*(t,k) = \tfrac{1}{4}Q^*(t-2,k-1) + \tfrac{1}{2}Q^*(t-2,k) + \tfrac{1}{4}Q^*(t-2,k+1) - 4|k|. \tag{27}$$

The task is to show that $Q^*(t,k) \geq Q(t,k)$ for all (t,k). This is obvious from (23) for $t = 0, 1$; both sides of (23) are zero for all k. The proof proceeds by induction. Assume that $Q^*(t-2,k) \geq Q(t-2,k)$ for all k. Then

$$Q^*(t,0) - Q(t,0) = \left(\tfrac{1}{4} - \beta\right)\left(Q^*(t-2,1) + 4(t-2)\right) + \left(\tfrac{1}{2} - v\right)Q^*(t-2,0) + \left(\tfrac{1}{4} - \beta\right)Q^*(t-2,1) \tag{28}$$

and since $Q(t-2,k) \geq 0$ for all k and

$$\frac{8\beta}{a-b}\sinh|k|\alpha \geq \frac{8\beta|k|}{a-b}\sinh\alpha = 4|k|,$$

one obtains for $k \neq 0$,

$$\overline{Q}^*(t,k) - \overline{Q}(t,k) \geq \left(\tfrac{1}{4} - \beta\right)Q^*(t-2,k-1) + \left(\tfrac{1}{2} - v\right)Q^*(t-2,k) + \left(\tfrac{1}{4} - \beta\right)Q^*(t-2,k+1). \tag{29}$$

It will be shown that the right sides of (28) and (29) are nonnegative, so that $Q^*(t,0) \geq Q(t,0)$, and $\overline{Q}^*(t,k) \geq \overline{Q}(t,k)$ for $k \neq 0$. From (24) and (25), it follows that $Q^*(t,k) \geq Q(t,k)$ for all (t,k).

The right sides of (28) and (29) have the form $a_1x_1 + a_2x_2 + a_1x_3$ with $(a_1, a_2) = (\frac{1}{4} - \beta, \frac{1}{2} - v)$. Since, in general, $a_1x_1 + a_2x_2 + a_1x_3 = a_1(x_1 + x_3 - 2x_2) + (2a_1 + a_2)x_2$, this expression is nonnegative if

$$a_1 \geq 0, \qquad 2a_1 + a_2 \geq 0, \qquad x_2 \geq 0, x_1 + x_3 - 2x_2 \geq 0.$$

But $a_1 \geq 0$ since $\beta^2 = a(1-a)b(1-b) \leq \frac{1}{16}$, and $2a_1 + a_2 \geq 0$ since $4\beta^2 = 4a(1-a)b(1-b) \leq (a(1-b) + b(1-a))^2 = (1-v)^2$. Clearly, the values of x_2, arising from the right sides of (28) and (29), are nonnegative. Finally, it follows from Proposition 1 below that the values of $x_1 + x_3 - 2x_2$, arising from the right sides of (28) and (29), are nonnegative. [It is enough to consider $k > 0$ since (19) is symmetric in k.] □

PROPOSITION 1. *For each $t \geq 0$, the sequence $Q^*(t,1) + 4t, Q^*(t,0), Q^*(t,1), Q^*(t,2), \ldots$ is convex in the sense that all of its second differences are nonnegative.*

PROOF. This is obvious for $t = 0$ and 1 since, for such $t, Q^*(t,k) = 0$ for all k. Suppose the sequence is convex when t is replaced by $t-2$, $t \geq 2$. The task is to show the convexity for t. It is enough [see (25)] to show that the sequence $\overline{Q}^*(t,1) + 4t, Q^*(t,0), \overline{Q}^*(t,1), \overline{Q}^*(t,2), \ldots$ is convex. For convenience,

$Q^*(t-2, k)$ will be abbreviated to $Q(k)$. Then

$$\begin{aligned}(\overline{Q}^*(t,1) + 4t) + \overline{Q}^*(t,1) - 2Q^*(t,0) \\ = -\tfrac{1}{2}Q(0) + \tfrac{1}{2}Q(2) + 2(t-2) \\ = \tfrac{1}{2}([Q(1) + 4(t-2)] + Q(1) - 2Q(0)) + \tfrac{1}{2}(Q(0) + Q(2) - 2Q(1)) \geq 0.\end{aligned}$$

Likewise,

$$\begin{aligned}Q^*(t,0) + \overline{Q}^*(t,2) - 2\overline{Q}^*(t,1) \\ = -\tfrac{1}{4}Q(1) + \tfrac{1}{4}Q(3) + (t-2) \\ = \tfrac{1}{4}([Q(1) + 4(t-2)] + Q(1) - 2Q(0)) + \tfrac{1}{2}(Q(0) + Q(2) - 2Q(1)) \\ + \tfrac{1}{4}(Q(1) + Q(3) - 2Q(2)) \geq 0.\end{aligned}$$

Finally, for $k \geq 2$,

$$\begin{aligned}\overline{Q}^*(t, k-1) + \overline{Q}^*(t, k+1) - 2\overline{Q}^*(t, k) \\ = \tfrac{1}{4}Q(k-2) + \tfrac{1}{4}Q(k+2) - \tfrac{1}{2}Q(k) \geq 0.\end{aligned}$$

□

3. The Bayes stopping rule for symmetric priors. Let G be a symmetric prior distribution for (p_1, p_2) and let N denote the horizon. As noted earlier, the Bayes stopping rule can be described in terms of Markovian states (n, r, s), where n represents the (current) number of sampled pairs, and where r and s are the (current) numbers of successes for the first and second treatments, respectively.

It seems unlikely that there is anything comparable to Theorem 1 which could provide a simple description of the optimal continuation region for this more general setting. For instance, $(n, r+1, s+1)$ need not be an optimal continuation state when (n, r, s) is. This cannot happen with two-point symmetric priors because, for such priors, the relevant Markovian state is $(t, k) = (N-2n, r-s)$. Moreover, (n, r, s) can be an optimal continuation state even though $(n-1, r, s)$ is not for a larger horizon. Again, this cannot happen with two-point symmetric priors. The full range of possibilities is unknown.

Nevertheless, there is one simple result which can be used to identify certain triplets (n, r, s) as optimal stopping states.

THEOREM 6. *The triplet (n, r, s) is an optimal stopping state for a symmetric prior G if for each (a, b), $a > b$ in the support of G, $(t, k) = (N-2n, r-s)$ is an optimal stopping state for the symmetric prior on the two points (a, b) and (b, a). In particular, (n, r, s) must be an optimal stopping state if*

$$S^*(N-2n, r-s) = 2(N-2n)|r-s|, \tag{30}$$

where S^* is defined in (22).

PROOF. Let $U(n, r, s)$ and $V(n, r, s)$ denote the reward for stopping [implicitly defined in (4)] and the optimal stopping reward, respectively, for the state (n, r, s). Further, denote the functions $R(t, k)$ and $S(t, k)$ (described in Section

2) by $R_{a,b}(t,k)$ and $S_{a,b}(t,k)$, $a > b$, in order to reflect their dependence on a and b. For $b > a$, let $R_{a,b}(t,k) = R_{b,a}(t,k)$ and $S_{a,b}(t,k) = S_{b,a}(t,k)$. It is easily checked that

$$U(n,r,s) = \int_0^1 \int_0^1 |a-b| R_{a,b}(N-2n, r-s) G(da, db|n,r,s), \tag{31}$$

where $G(\cdot|n,r,s)$ denotes the posterior distribution for (p_1, p_2) in the state (n,r,s). Finally, by a routine backward induction argument based on the size of n, it can be shown that

$$V(n,r,s) \le W(n,r,s), \tag{32}$$

for all possible states (n,r,s), where

$$W(n,r,s) = \int_0^1 \int_0^1 |a-b| S_{a,b}(N-2n, r-s) G(da, db|n,r,s).$$

Now consider the first statement of the theorem. By assumption, $S_{a,b}(t,k) = R_{a,b}(t,k)$ for every pair (a,b) in the support of G. Thus $W(n,r,s) = U(n,r,s)$, and it follows from (32) that $V(n,r,s) = U(n,r,s)$. Consequently, (n,r,s) is an optimal stopping state. When (30) holds, it follows from Theorem 5, that $S_{a,b}(t,k) = R_{a,b}(t,k)$ for *every* pair (a,b). □

Let us briefly consider the stopping rule suggested by Theorem 6, namely stop as soon as one reaches a state (n,r,s) for which (30) holds. Stated more explicitly: *stop in state* (n,r,s) *if* $2n > N - T_k$ *where* $k = |r-s|$. The beginning of the sequence $T_0, T_1, \ldots$ is given in Theorem 5, and the terms of the sequence can be computed using (22). Additional values are given in the introduction. Since $(a-b)^{-1}S(t,k) \to S^*(t,k)$ as $a, b \to \frac{1}{2}$ (see Section 2), it can be shown that the rule is Bayes for appropriately chosen symmetric prior distributions, depending on N, and that it is admissible.[4] It can be expected to perform well, from a Bayesian perspective, whenever the prior distribution is symmetric and concentrated near $(p_1, p_2) = (\frac{1}{2}, \frac{1}{2})$.

One pleasant feature of this stopping rule, when $T_0 = 2$, is that it minimizes for every pair (p_1, p_2) the probability of rejecting the better treatment among all Bayes symmetric stopping rules. While the probability of rejecting the better treatment is not of direct concern under Anscombe's (1963) model, Bather (1985) has made a reasonable case for its consideration in the context of sequential clinical trials. The proof that this probability is minimized depends upon two facts. Firstly, among Bayes symmetric stopping rules, this "envelope" rule with $T_0 = 2$ is the largest possible, i.e., the slowest to stop. This is a consequence of Theorem 6. Secondly, for any symmetric prior distribution, the sequence of posterior probabilities of rejecting the better treatment, for $n = 0, 1, 2, \ldots$, $2n \le N$, is a supermartingale. Consequently, the obvious is true: the longer one samples by pairs the smaller is the probability of rejecting the better treatment.

[4] These assertions are still true if the value $T_0 = 2$ is used instead of the value $T_0 = 3$ given in Theorem 5. The risk function is unaffected by the change.

It seems highly plausible that this "envelope rule" is, in fact, the largest *admissible* symmetric stopping rule.[5] If so, then the obvious rule based on $N/2$ pairs is excluded because of the loss structure; it could not be admissible.

Finally, some insight into the nature of this stopping rule can be obtained by considering the random walk $S_0 = 0$, $S_1, S_2, \ldots$ whose step sizes $-1, 0, 1$ are taken with probabilities $\frac{1}{4}, \frac{1}{2}, \frac{1}{4}$, respectively. The same stopping rule with $|r - s|$ replaced by $|S_n|$ is optimal for the reward sequence $(N - 2n)|S_n|$, i.e., it is optimal to stop as soon as $2n > N - T_k$, where $k = |S_n|$. The connection is apparent from the form of (22). One can use $T_0 = 2$ or $T_0 = 3$. (See footnote 4.) The values of all of the other T_k's may be unique; no other exceptions have been found between $k = 1$ and $k = 23$. ($T_{23} = 3{,}773$.)

4. Symmetrizable distributions. The rationale for this topic has already been indicated in the introduction. It is not always appropriate to use a symmetric prior. And yet it seems too much to expect to find a theory of much depth which includes all possible priors. Both of these issues are addressed by the consideration of symmetrizable distributions. The class of symmetrizable priors is probably sufficiently large to meet the needs of practitioners. And yet they are convenient to work with theoretically. Roughly speaking, whatever is true for symmetric priors is also true, in a suitably modified sense, for symmetrizable priors. Currently, the theory for symmetric two-point priors is quite a bit more satisfactory than is the theory for general symmetric priors. This distinction carries over to symmetrizable priors.

The emphasis in this section is expository. While the concepts and results are stated precisely, no proofs are given. Most of the proofs are fairly straightforward and can easily be supplied by the reader.

A distribution G on the open unit square is said to be *symmetrizable* with *associated parameter* θ, and one writes $G \in \Phi(\theta)$, if $G(p_1 \neq p_2) > 0$ and the measure G' defined by

$$G'(dp_1, dp_2) = \begin{cases} (p_1 q_2)^{-\theta} G(dp_1, dp_2), & \theta \geq 0, \\ (p_2 q_1)^{\theta} G(dp_1, dp_2), & \theta < 0, \end{cases} \tag{33}$$

is symmetric in p_1 and p_2, where $q_1 = 1 - p_1$ and $q_2 = 1 - p_2$. The restriction to the *open* unit square is for convenience and seems harmless. Likewise, a prior G for which $G(p_1 \neq p_2) = 0$ is of no interest here. The parameter θ can assume any real value. When θ is integer-valued (and the horizon N is sufficiently large), G can have a symmetric posterior.

In the sequel, it is convenient to think of the measure G' as a prior. It may not be a finite measure, in which case it is better thought of as an improper prior—it cannot be normalized to make it a probability measure.

---

[5] The envelope rule *is* the largest *admissible* symmetric stopping rule. As Larry Brown has pointed out to the author, this easily follows from a remarkable lemma appearing in Gutmann (1982): Any admissible symmetric stopping rule must be Bayes and, hence, no larger than the envelope (stopping) rule.

The associated parameter θ is unique. Moreover,

$$\text{sign}\left(\int_0^1\int_0^1 (p_1 - p_2)G(dp_1, dp_2)\right) = \text{sign}(\theta). \tag{34}$$

So when G is the prior distribution, the sign of θ indicates which treatment is preferred. The first treatment is preferred when $\theta > 0$, and the second when $\theta < 0$. When $\theta = 0$, neither treatment is preferred because G is symmetric.

Suppose $G \in \Phi(\theta)$ is a prior distribution. Then the posterior distribution G_n, after the two treatments have been assigned to n pairs of patients, is symmetrizable with the associated parameter

$$\theta_n = \theta + r - s, \tag{35}$$

where r and s are the numbers of successes with the first and second treatments, respectively. Without having to compute any posterior expectations, one can decide which treatment is currently preferred by simply examining the sign of θ_n.

Now suppose G is a prior on two symmetric points (a, b) and (b, a). Then $G \in \Phi(\theta)$, where

$$\theta = \frac{1}{2\alpha}\log(G((a, b))/G((b, a))), \tag{36}$$

and where α is defined in (6). Under this prior, the problem of optimal stopping, described in Section 2, depends upon the Markovian state (t, k) defined in (7). There are analogues of Theorems 2, 3, and 4. The analogue of Theorem 2 states that (t, k) is an optimal continuation state if

$$t \geq 2 + \frac{2\sinh(k + \theta)\alpha \sinh(k + \theta + 1)\alpha}{(a - b)\sinh\alpha} + \frac{2(k + \theta)\tanh(k + \theta)\alpha}{a - b}, \tag{37}$$

$$k + \theta \geq 0.$$

It seems likely that the stopping rule which continues as long as (37) holds will perform very nearly as well as the optimal stopping rule.

The picture is less complete for a general symmetrizable prior G. When $\theta \neq 0$, G is not symmetric and it is convenient to work, instead, with the symmetric "prior" G' defined in (33). For the sake of definiteness, assume $\theta > 0$. The horizon N and the Markovian state (n, r, s) need to be replaced by $N' = N + 2\theta$ and $(n', r', s') = (n + \theta, r + \theta, s)$, respectively. These are easiest to interpret when θ is an integer. In any event, the new "number of patients remaining," $N' - 2n'$, in state (n', r', s') is an integer, and it is equal to the old number of patients remaining, $N - 2n$, in the state (n, r, s). So even if θ is not an integer, there is no inherent problem in carrying out the required backward induction to decide which points (n', r', s') are optimal continuation points under G', and which are optimal stopping points. Notice that

$$p_1^{r'}p_2^{s'}q_1^{n'-r'}q_2^{n'-s'}G'(dp_1, dp_2) = p_1^r p_2^s q_1^{n-r}q_2^{n-s}G(dp_1, dp_2). \tag{38}$$

So even if G' is viewed as an improper prior, there is a proper posterior in state (n', r', s'). And as (38) shows, this posterior agrees with that for G in the state (n, r, s). It follows that (n, r, s) is an optimal continuation point under G

whenever (n', r', s') is an optimal continuation point under G'. And the same relationship applies to optimal stopping points.

It is presently impossible to obtain many of the benefits promised by the "machinery" just described because the current theory for general symmetric priors is far from adequate. Nevertheless, Theorem 6 can be exploited when θ is an integer: The point (n, r, s) is an optimal stopping state for the symmetrizable prior $G \in \Phi(\theta)$ if $2n > N - T_k$, where $k = |r + \theta - s|$. (The meaning of T_k has been discussed in previous sections.)

A second benefit suggests itself for those who already have a stopping rule which they prefer to use whenever there is little or no reason to believe that one treatment is better than the other. [Several candidates for this kind of rule have been suggested by Vogel (1960a, b), by Anscombe (1963), by Lai, Levin, Robbins and Siegmund (1980), and by Bather and Simons (1985). Such rules can be modified to handle situations for which there is an initial preference; *stop in state* (n, r, s) *if the preferred rule says to stop in state* (n', r', s').

5. Ethical costs. Chernoff and Petkau (1985) have recently shown how "ethical costs" can be incorporated into Anscombe's (1963) model when the treatment responses are normally distributed. The same thing can be done when the treatment responses are "successes" and "failures." The idea is quite simple: For any prior G, after n pairs of patients have been treated, with the results observed, one expects the two treatments to yield successes in the future with probabilities $E_n p_1$ and $E_n p_2$, where "E_n" denotes conditional expection given the results from the n pairs of patients. Thus $|E_n(p_1 - p_2)|$ represents a reasonable estimate of the "expected successes lost" (a fraction of one) should a future patient be assigned to the *apparently* inferior treatment. According to Chernoff and Petkau's reckoning, the physician incurs an ethical cost $\gamma|E_n(p_1 - p_2)|$ if the inferior appearing treatment is actually assigned to a future patient, where the proportionality constant $\gamma \geq 0$ is a known parameter.

The mathematical effect of this innovation is fairly slight. Instead of the reward sequence described in (4), one must use

$$R_n = (N - 2n)|E_n(p_1 - p_2)| - 2\gamma \sum_{m=0}^{n-1} |E_m(p_1 - p_2)|. \tag{39}$$

In general, this reward is no longer a function of a Markovian state (n, r, s), where r and s are the numbers of successes registered by the first and second treatments. Nevertheless, the optimal stopping problem is still Markovian, i.e., dependent on (n, r, s). Intuitively, this is because the ethical cost $\gamma\sum_{m=0}^{n-1} |E_m(p_1 - p_2)|$, entering into (39), is the result of *past* decisions; it is nonrecoverable. Consequently, the difference between the optimal stopping reward and the reward for stopping is a function of the state (n, r, s). When this is strictly positive, it is optimal to continue; when this is zero, it is optimal to stop.

The previous results in this paper can be extended to this setting without much difficulty. For instance, for Theorem 2, the simpler Markovian state (t, k) is still appropriate, and it turns out that (t, k), $k \geq 0$ is an optimal continuation

point whenever

$$t \geq 2 + \frac{2(1+\gamma)\sinh k\alpha \sinh(k+1)\alpha}{(a-b)\sinh\alpha} + \frac{2k\tanh k\alpha}{a-b}.$$

The asymptotic growth rate of the transition points τ_k, referred to in Theorem 1, is increased by the factor $1+\gamma$. The boundary still grows with t at the rate $(2\alpha)^{-1}\log t$, independent of γ (as a first-order approximation).

Acknowledgments. The author is grateful to John Bather for numerous conversations, during the author's sabbatical at the University of Sussex, which have contributed to the development of the ideas in this paper. Readers who are familiar with his techniques for approximating stopping boundaries, from within and from without, will recognize the influence his ideas have had on Theorems 2, 3 and 4. See Bather (1983). In addition, the author is indebted to John Bather and an unknown referee for very helpful comments on the original version of this paper.

REFERENCES

ANSCOMBE, F. J. (1963). Sequential medical trials. *J. Amer. Statist. Assoc.* **58** 365–383.

BATHER, J. A. (1983). Optimal stopping of Brownian motion: A comparison technique. In *Recent Advances in Statistics* (M. H. Rizvi, J. S. Rustagi, and D. Siegmund, eds.) 19–49. Academic, New York.

BATHER, J. A. (1985). On the allocation of treatments in sequential medical trials. *Internat. Statist. Rev.* **53** 1–14.

BATHER, J. A. and SIMONS, G. D. (1985). The minimax risk for two-stage procedures in clinical trials. *J. Roy. Statist. Soc. Ser. B* **47** 466–475.

CHERNOFF, H. (1972). *Sequential Analysis and Optimal Design*. SIAM, Philadelphia.

CHERNOFF, H. and PETKAU, A. J. (1981). Sequential medical trials involving paired data. *Biometrika* **68** 119–132.

CHERNOFF, H. and PETKAU, A. J. (1985). Sequential medical trials with ethical costs. *Proc. Berkeley Conf. in Honor of Jerzy Neyman and Jack Kiefer* (L. Le Cam and R. Olshen, eds.) **1**. Wadsworth, Monterey, Calif.

GUTMANN, S. (1982). Stein's paradox is impossible in problems with finite sample space. *Ann. Statist.* **10** 1017–1020.

LAI, T. L., LEVIN, B., ROBBINS, H. and SIEGMUND, D. (1980). Sequential medical trials. *Proc. Nat. Acad. Sci. U.S.A.* **77** 3135–3138.

SIMONS, G. (1986). A comparison of seven allocation rules for a clinical trial model. *Sequential Anal.* To appear.

VOGEL, W. (1960a). A sequential design for the two-armed bandit. *Ann. Math. Statist.* **31** 430–443.

VOGEL, W. (1960b). An asymptotic minimax theorem for the two-armed bandit problem. *Ann. Math. Statist.* **31** 444–451.

DEPARTMENT OF STATISTICS
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NORTH CAROLINA 27514