LEVEL

A SEQUENTIAL CLINICAL TRIAL FOR TESTING $p_1 = p_2$

BY

D. SIEGMUND and P. GREGORY

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ABSTRACT

Sequential designs are proposed for clinical trials to compare two binomial success probabilities, \( p_1 \) and \( p_2 \). Approximations to the operating characteristics and expected sample size are obtained and compared with simulations. Special reference is made to the problem of comparing vasopressin and placebo for stopping upper gastrointestinal hemorrhage.

AMS 1970 Subject Classification. Primary 62L10.

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A SEQUENTIAL CLINICAL TRIAL FOR TESTING $p_1 = p_2$

1. Introduction

This paper presents a class of sequential tests for comparing two binomial success probabilities $p_1$ and $p_2$. Although the method is a general one, it was motivated by a clinical trial for testing the efficacy of vasopressin (a hormone which constricts blood vessels) in stopping upper gastrointestinal hemorrhage; and although this report is primarily theoretical, reference will be made to the trial of vasopressin because it seems to illustrate clearly certain advantages and disadvantages of a sequential design in clinical trials.

Two conditions indicating a sequential design are (i) a serious disease, so that ethical considerations mandate the early termination of a trial in which one treatment appears especially effective, and (ii) a response time which is short compared to the time between patient arrivals, so that it is feasible to evaluate the current state of affairs before admitting new patients to the study. Massive upper gastrointestinal hemorrhage satisfies these requirements, since failure to control it within hours may lead to death or to surgical intervention.

One other circumstance which seems to indicate a sequential trial in this particular case is the existence of earlier, favorable reports on the use of vasopressin for stopping upper gastrointestinal hemorrhage. (See especially Conn et al., 1975.)
Although certain reservations concerning these earlier trials and the desire to investigate a much simpler mode of administration of the drug suggest a new trial, a sequential design provides protection against the lengthy continuation of this trial, should the previous, favorable results be repeated.

For purposes of sequential analysis this trial is one of comparing the probability $p_1$ of success using vasopressin to the probability $p_2$ of success with placebo. Success is defined as a cessation of bleeding within five hours and no recurrence within six. Other endpoints of interest are the time until bleeding initially ceases, recurrence of bleeding, severity of bleeding measured by transfusion requirements, the need for surgical intervention, and death. Choice of a sequential design for testing $p_1 = p_2$ makes the implicit assumption that if $p_1$ appears to be considerably larger than $p_2$, that by itself is sufficient to terminate the trial and indicate the use of vasopressin. In practice one would probably be reluctant to terminate early unless the other factors also consistently favor vasopressin, although it would defeat the purpose of a sequential trial to insist that these factors show "statistically significant" differences between treatment and control. Conversely, in the absence of a strong indication for vasopressin based on success rate alone, it may be desirable to analyze other factors rather carefully. The extent to which a sequential design introduces a bias which makes these other analyses difficult is perhaps its most serious disadvantage. (This point will be discussed again in Section 2.)
In addition to studying the specific problem of testing $p_1 = p_2$, a primary goal of this paper is to indicate how arguments developed by Siegmund (1977, 1978) to deal with normally distributed data can be adapted and supplemented by simulations to obtain a reasonably clear understanding of a similar but more difficult problem.

Section 2 reviews pertinent material for an analogous problem with normal data. A modification of the repeated significance tests advocated by Armitage (1975) is suggested and their properties studied. Section 3 returns to the problem of testing $p_1 = p_2$. Mathematical results are collected in three appendices.
2. Normal Data With Known Variance

The normal distribution with known variance is relatively simple both conceptually and technically and suggests useful approximations for more complex situations. In this section known results for the repeated significance tests advocated by Armitage (e.g., Armitage, 1975) are reviewed and a modification of these tests suggested and studied.

The simplest situation occurs in a paired comparison design, in which for each \( n = 1, 2, \ldots \) the observation \( x_n \) represents the difference in response of the \( n \)th pair of subjects, one of whom receives treatment A and the other treatment B. It is assumed that the \( x_n \) are independent and normally distributed with expectation \( \mu \) and known variance \( \sigma^2 \). Let \( s_n = x_1 + \ldots + x_n \), and given \( b_1 > 0 \) and \( m_0 = 1, 2, \ldots \), define

\[
T_1 = \text{first } n \geq m_0 \text{ such that } |s_n| > b_1 \sigma \sqrt{n}.
\]

Let \( m_1 \geq m_0 \) be a positive integer. The sequential test of \( H_0 : \mu = 0 \) against \( H_1 : \mu \neq 0 \) which terminates sampling at \( \min(T_1, m_1) \) and rejects \( H_0 \) if and only if \( T_1 \leq m_1 \) is the repeated significance test of Armitage (1975).

Let \( \theta = \mu / \sigma \). The distribution of \( T_1 \) and hence the power function of this test depend on \( \mu \) and \( \sigma \) only through the value of \( \theta \). By repeated numerical integration McPherson and Armitage (1971)—see also Armitage (1975)—have provided tables which allow one to choose the design parameters \( m_1 \) and \( b_1 \) to attain a specified significance level.
See text.
Figure 1.
Table 1 gives numerical examples illustrating various relations among fixed sample size, repeated significance tests, and the modified tests suggested here. The approximations given in Appendices A and B were used to perform the required calculations, except for those entries which could be obtained from Armitage (1975), p. 104. (Simulations indicate that these approximations are quite accurate.) For all tests the over-all significance level is .05 and $m_0 = 1$. The maximum sample sizes were taken to be equal and large enough to include the apparent range of possibilities for the proposed vasopressin study. The entry $m_f$ denotes that fixed sample size which would yield the same power at the indicated $\theta$ as the given sequential test. One measure of the savings in sample size for the sequential tests compared to fixed sample size tests is $R = (m_f - \text{expected sample size})/m_f$. For the modified tests $b$ was chosen fairly large, so that $P_{\theta\{T \leq m\}}$ is slightly less than .02. The entry $1 - \beta^*$ denotes the probability at $\theta$ of early termination, $P_\theta\{T \leq m\}$.

A reasonable over-all conclusion seems to be that for about a 10% increase in the maximum sample size of a fixed sample test, a modified sequential test can yield about the same power and a 40% reduction in the expected sample size for $|\theta|$ large enough that the power approaches one. Comparatively, a repeated significance test obtains a greater reduction in expected sample size for large $|\theta|$ at the cost of a considerable increase in the maximum sample size and some loss of power. The relative advantages and disadvantages of the repeated significance tests compared to the modified tests become more pronounced with larger patient horizons.
<table>
<thead>
<tr>
<th></th>
<th>Fixed Sample Size</th>
<th>Repeated Significance Test</th>
<th>Modified Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>m = 49</td>
<td>m₁ = 49, b₁ = 2.8</td>
<td>m = 49, b = 3.15, c = 2.13</td>
</tr>
<tr>
<td>θ</td>
<td>1 - β</td>
<td>1 - β E₀(T₁ ^ m₁) m₁</td>
<td>1 - β E₀(T ^ m) m₁</td>
</tr>
<tr>
<td>.6</td>
<td>.99</td>
<td>.95 21 37</td>
<td>.98 25 45 .90</td>
</tr>
<tr>
<td>.4</td>
<td>.80</td>
<td>.61 35 32</td>
<td>.75 39 44 .47</td>
</tr>
<tr>
<td></td>
<td>m = 111</td>
<td>m₁ = 111, b₁ = 2.89</td>
<td>m = 111, b = 3.25, c = 2.13</td>
</tr>
<tr>
<td>θ</td>
<td>1 - β</td>
<td>1 - β E₀(T₁ ^ m₁) m₁</td>
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<tr>
<td>.4</td>
<td>.99</td>
<td>.95 47 82</td>
<td>.98 59 101 .88</td>
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<tr>
<td>.3</td>
<td>.88</td>
<td>.71 72 71</td>
<td>.85 87 100 .57</td>
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The most obvious appeal of these modified repeated significance tests is that they provide insurance against a long trial should one treatment seem considerably superior without as large a maximum sample size or as great a loss of power to detect smaller differences as the usual repeated significance tests.

Although difficult to quantify, the following additional arguments in favor of the modified tests seem to warrant some discussion.

(1) One disadvantage of the possible early termination of a sequential test is that it may prevent the accumulation of sufficient evidence against $H_0$ to be thoroughly convincing. For a repeated significance test, if $T_1 = n < m$, the observed significance level or P-value of the test may be defined as $P_0(T_1 \leq n)$. This is a simple index of how convincing the data against $H_0$ are; but since $P_0(T_1 \leq n)$ is approximately proportional to $\log n$ (Siegmund, 1977, or Appendix A), even for $n$ much smaller than $m$ it may not be appreciably smaller than the over-all significance level, $P_0(T_1 \leq m)$. For example, for the first repeated significance test in Table 1, which has $m = 49$ and $\alpha = .05$, if $T_1 = 16$, the observed significance level is

$$P_0(T_1 \leq 16) \approx .032.$$  

By way of contrast, for a modified test the over-all significance level is

$$\alpha = P_0(T \leq m) + P_0(T > m, \frac{b}{m} < |s_m| < \frac{b}{m}) .$$

If $T = n \leq m$, the observed significance $P_0(T \leq n)$ is no greater than $P_0(T \leq m)$, which may be made small by taking $b$ large. For the first
modified test in Table 1, \( P_0(T \leq 49) \approx .018 \) and \( P_0(T \leq 16) \approx .011 \). A similar argument applies to other indices of "convincingness," e.g., a lower confidence bound on \( |\theta| \) (cf. Siegmund, 1978).

(ii) In many cases the parameter \( \theta \) represents one direction in a multidimensional space. Implicit in the use of a sequential test is the assumption that if \( |\theta| \) appears to be large, that by itself will play a dominant role in the choice of treatment (although one would presumably look at other factors to see that they are reasonably consistent with this conclusion). However, if \( |\theta| \) is small, a more detailed analysis of these other factors may be important. For example, if vasopressin reduces bleeding sufficiently that surgery need not be performed on an emergency basis, it would be a useful treatment, even though its "success" rate may be no higher than for placebo.

Use of a data dependent stopping rule introduces a bias which tends to make \( |\theta| \) seem larger than it actually is. (See Siegmund, 1978, for a discussion of the magnitude of this bias.) By using a modified test with \( b \) large enough that \( P_\theta(T \leq m) \) is relatively small for small \( |\theta| \), one reduces the biasing effect of the stopping rule, particularly for small \( |\theta| \) when analysis of other variables may play an important role.
3. Comparing Two Binomials

The clinical trial of vasopressin may be regarded as one of comparing two binomial success probabilities \( p_1 \) and \( p_2 \), where \( p_1 \) is the probability of success with vasopressin and \( p_2 \) the probability of success with placebo. There are possibilities for stratifying the population, e.g., according to the cause of bleeding, but initially it is easier to suppose that all data are pooled.

To simplify the discussion it is assumed that observations are taken in pairs with one member of each pair assigned to treatment and the other to control. The biased coin design of Efron (1971) provides a reasonable scheme for approximating this situation while maintaining a high level of unpredictability as to exactly which treatment will be assigned to the next patient. For the first two tests discussed below patients may easily be assigned to treatment or control in a 2 to 1 or other ratio. The matched pairs test described later relies heavily on approximately balanced allocation to treatment and control.

For theoretical discussions of clinical trials it is customary to consider testing \( p_1 = p_2 \) against the two-sided alternative \( p_1 \neq p_2 \), and that custom is followed here. For a comparison of treatment and placebo it is sometimes appropriate to consider only the one-sided alternative \( p_1 > p_2 \). The appropriate modifications are obvious, and for the numerical examples presented later give tests having a significance level about one-half that of the two-sided tests.
Assume then that the data consists of pairs \((x_1, y_1), (x_2, y_2), \ldots\), where the \(x\)'s and \(y\)'s are independent random variables assuming the values 1 and 0. Let \(P(x_n = 1) = p_1, P(y_n = 1) = p_2\),
\(q_1 = 1 - p_1\) and \(q_2 = 1 - p_2\). It is desired to obtain a sequential test of \(H_0 : p_1 = p_2\) against \(H_1 : p_1 \neq p_2\) which on the average requires a small number of observations to reach a decision whenever \(p_1\) and \(p_2\) differ substantially.

Two obvious candidates are sequential versions of the generalized likelihood ratio test and of the \(\chi^2\) test for independence in 2x2 tables. As one might expect, these tests perform similarly; but there are slight differences which may be important in some applications.

Let \(H(x) = x \log x + (1 - x) \log (1 - x)\) and \(I(x, y) = H(x) + H(y) - 2H\left(\frac{1}{2}(x + y)\right)\). The log generalized likelihood ratio for testing \(H_0 : p_1 = p_2\) against \(H_1 : p_1 \neq p_2\) based on \(n\) pairs of observations is \(\ell_n = n I(\overline{x}_n, \overline{y}_n)\), where \(\overline{x}_n = n^{-1} \sum_1^n x_k\) and \(\overline{y}_n = n^{-1} \sum_1^n y_k\). In analogy with (1), given integers \(m_0 \leq m\) and real numbers \(0 < c \leq b\), define

\[
T = \text{first } n \geq m_0 \text{ such that } (2 \ell_n)^{1/2} > b.
\]

Stop at \(\min(T, m)\) and reject \(H_0\) if either \(T \leq m\) or \(T > m\) and \((2 \ell_m)^{1/2} > c\).

A Taylor series expansion about \((p_1, p_2)\) shows that \((2 \ell_n)^{1/2}\) behaves approximately like the absolute value of a sum of \(n\) independent identically distributed random variables with mean

\[
\mu = [2I(p_1, p_2)]^{1/2}
\]
and variance

\[ \sigma^2 = \left( p_1 q_1 \log^2(p_1 - q_1 p) + p_2 q_2 \log^2(p_2 - q_2 p) \right) / 2 I(p_1, p_2) \]

where \( \bar{p} = (p_1 + p_2) / 2 \) and \( \bar{q} = 1 - \bar{p} \). This suggests that under

\( H_1 : p_1 \neq p_2 \), one may approximate the behavior of \( (2n \ell_n^{1/2}) \) by Brownian motion with drift \( \mu \) and variance \( \sigma^2 \) for the purpose of computing the power and expected sample size of the test. The relevant formulas are summarized in Appendices A and B. Table 2 below indicates that these approximations are reasonably accurate.

Approximating the significance level of this test poses a more difficult problem. Let \( P_{(p_1, p_2)} \) denote the probability measure on sequences \((x_1, y_1), (x_2, y_2), \ldots\), determined by \( p_1 \) and \( p_2 \). The significance level of the modified repeated significance test defined above is

\[ \alpha(p) = P_{(p, p)}(T < m) + P_{(p, p)}(T > m, (2\ell_m^{1/2}) > c) \]

The difficulties arise with the first term on the right hand side of (7). The second term may be approximated by the upper bound

\[ P_{(p, p)}(c < (2\ell_m^{1/2}) \leq b) \]

which may in turn be approximated by

\[ 2[\Phi(b) - \Phi(c)] \]

since \( 2\ell_m \) is asymptotically \( \chi^2 \) with one degree of freedom under \( H_0 \). In principle the methods of Lai and Siegmund (1977) may be adapted to give an asymptotic approximation to \( P_{(p, p)}(T \leq m) \) as \( b \to \infty, m \to \infty \), and \( m_0 \to \infty \) in such a way that \( bm^{-1/2} \to \theta_1 \) and \( bm_0^{-1/2} \to \theta_0 \). A heuristic sketch of the rather elaborate computations is given in Appendix C. The resulting formula involves a numerical integration,
which was easy in the case of normal random variables, but in this case remains a difficult unsolved problem. A further "no overshoot" approximation to this integral yields a crude but simple approximate upper bound: for $p \leq \frac{1}{2}$,

$$P_{(p,p)}\{T \leq m\} < (\pi^{-1}pqa)^{\frac{1}{2}} e^{-a} \int_{(0,2p)\cap\{\xi: \theta_0 < \{2I(\xi,2p-\xi)\}^{\frac{1}{2}} < \theta_1\}} [I(\xi,2p-\xi)\xi(1-\xi)(2p-\xi)(2q-1+\xi)]^{-\frac{1}{2}} \, d\xi.$$  

Table 2 gives two numerical examples, which are roughly comparable to the normal examples in Table 1. The first entry in each cell is a Monte Carlo estimate; the parenthetical entries are analytic approximations. The ± figures are one estimated standard error. Where no ± figure is given, the Monte Carlo estimate is a relative frequency, the standard error of which may be estimated by the usual $\frac{r(1-r)}{N}$, where $N$ is the number of repetitions of the experiment. Except for the probabilities $P_{(p,p)}\{T \leq m\}$ and $\alpha(p)$, $N = 900$. For these probabilities $N = 5000$ and the method of importance sampling mentioned in Appendix C was used. Generally speaking, the analytic approximations are reasonably good except for the null hypothesis probabilities $P_{(p,p)}\{T \leq m\}$ and $\alpha(p)$, for which they are too large as expected. The author has performed other simulations and found the approximations to hold up over a wider range of parameter values than those reported here.

Because of the discreteness of the underlying data, the choice of $m_0$ can have a substantial effect on $P_{(p,p)}\{T \leq m\}$. Taking $m_0$ about equal to $m^{\frac{1}{2}}$ seems reasonable and has the additional desirable property
TABLE 2
SEQUENTIAL GENERALIZED LIKELIHOOD RATIO TEST

\[
\begin{array}{cccc}
(p_1, p_2)^* & P(T < m) & P(\text{Reject } H_0) & E(TA_m) \\
\hline
\text{Case I: } m_0 = 7, \; m = 49, \; b = 3.15, \; c = 2.15 \\
.5, .5 & .017 \pm .001 (.023) & .045 \pm .003 (.053) & 48.5 \pm .1 \\
.7, .5 & .238 (.231) & .474 (.451) & 44.1 \pm .4 \\
.8, .5 & .629 (.623) & .851 (.849) & 35.7 \pm .5 (34.7) \\
.4, .4 & .019 \pm .001 (.024) & .041 \pm .002 (.054) & 48.3 \pm .1 \\
.6, .4 & .208 (.225) & .448 (.435) & 44.3 \pm .4 \\
.7, .4 & .578 (.571) & .827 (.816) & 36.5 \pm .5 (37.0) \\
.8, .4 & .902 (.900) & .983 (.981) & 25.8 \pm .4 (24.9) \\
.3, .3 & .018 \pm .001 (.024) & .046 \pm .003 (.054) & 48.3 \pm .1 \\
.7, .3 & .885 (.880) & .979 (.976) & 25.9 \pm .4 (25.8) \\
.2, .2 & .016 \pm .001 (.017) & .046 \pm .003 (.047) & 48.4 \pm .1 \\
\hline
\text{Case II: } m_0 = 10, \; m = 100, \; b = 3.2, \; c = 2.15 \\
.5, .5 & .018 \pm .001 (.021) & .045 \pm .004 (.051) & 98.5 \pm .3 \\
.7, .5 & .506 (.510) & .802 (.775) & 79.0 \pm .9 (82.7) \\
.8, .5 & .948 (.945) & .995 (.992) & 45.7 \pm .8 (45.4) \\
.4, .4 & .017 \pm .001 (.021) & .044 \pm .004 (.051) & 98.5 \pm .3 \\
.6, .4 & .479 (.496) & .761 (.757) & 79.1 \pm .9 (85.7) \\
.7, .4 & .917 (.918) & .988 (.986) & 51.4 \pm .9 (48.4) \\
.8, .4 & .998 (.998) & 1.00 (1.00) & 28.8 \pm .5 (27.0) \\
.3, .3 & .019 \pm .001 (.024) & .046 \pm .004 (.054) & 99.1 \pm .3 \\
.7, .3 & .998 (.998) & 1.00 (1.00) & 30.2 \pm .6 (28.3) \\
.2, .2 & .017 \pm .001 (.021) & .035 \pm .004 (.051) & 98.9 \pm .3 \\
\end{array}
\]

*The cases \((p_1, p_2) = (.5, .3), (.6, .3), (.5, .2),\) and \((.6, .2)\) are by symmetry the same as \((.7, .5), (.7, .4), (.8, .5),\) and \((.8, .4)\) respectively.
of making \( P_{(p,p)}(T \leq m) \) fairly constant as a function of \( p \), at least for \( p \) not too near 0 or 1. For this choice of \( m_0 \), \( P_{(p,p)}(T \leq m) \) also seems to be quite well approximated by the analogous probability for normal random variables with \( m_0 = 1 \). Although there is no apparent reason why this should be so, it seems to provide reasonable guidelines for tentatively selecting \( b \) and \( m \) subject to verification by a Monte Carlo experiment.

The customary \( \chi^2 \) statistic for testing \( p_1 = p_2 \) is

\[
\chi^2_n = n(\bar{x}_n - \bar{y}_n)^2/2p_n q_n, \quad \text{where} \quad p_n = \frac{1}{2}(\bar{x}_n + \bar{y}_n) \quad \text{and} \quad q_n = 1 - p_n.
\]

A sequential test analogous to that discussed above may be defined by the stopping rule (4) with \( \chi_n^2 \) in place of \( (2\bar{x}_n)^{1/2} \). Again sampling terminates at \( \min(T, m) \) and \( H_0 \) is rejected if either \( T \leq m \) or \( T > m \) and \( \chi^2_m > c \).

For given \( b, c, m_0, \) and \( m \), simulations show that \( P_{(p_1,p_2)}(T \leq m) \) is generally smaller for this test and the expected sample size larger than for the likelihood ratio tests. If \( b \) and \( c \) are decreased to make \( P_{(p,p)}(T \leq m) \) and the significance levels comparable, there seems to be essentially no difference in the power and expected sample size of the two tests, at least over the range studied in Table 2. Brownian motion approximations similar to those of Table 2 seem adequate when \( p_1 \neq p_2 \), although in this case the approximating random walk has the slightly different expectation

\[
\mu_1 = (p_1 - p_2)/(2p q)^{1/2}
\]
and variance

\[ \sigma^2 = p_1q_1f_+(p_1,p_2) + p_2q_2f_-(p_1,p_2), \]

where

\[ f_\pm(p_1,p_2) = \frac{[\pm \bar{p} \bar{q} - (p_1 - p_2)(q_1 - p_2)/4]^2}{2(\bar{p} \bar{q})^3}. \]

One slight advantage that the likelihood ratio test seems to have over the \( \chi^2 \) test is that its value of \( P(T \leq m) \) may be more nearly constant as \( p \) gets close to 0 or 1. Previous experience suggests that extreme values of \( p \) are not likely in the case of upper gastrointestinal hemorrhage, and hence they were not systematically investigated. Of course, the \( \chi^2 \) statistic is easier to compute. Otherwise, the authors' slight preference for the likelihood ratio test is based on the existence of the primitive but interesting null hypothesis theory which may be developed for it and which makes selection of the design parameters \( m_0, m, b, \) and \( c \) slightly easier.

Yet a third test of \( p_1 = p_2 \) (one which differs from the other two in several important respects) is obtained by discarding those pairs for which \( x_i = y_i \) and basing a test on the number of times \( x_i = 1 \) among those pairs for which \( x_i \neq y_i \). This device was suggested by Wald (1947, p. 107) and has been advocated by Armitage (1975) for general use in making sequential binomial comparisons. It reduces the problem of testing the equality of two binomial parameters \( p_1 \) and \( p_2 \) to that of testing whether a single binomial parameter \( \lambda \) equals \( \frac{1}{2} \), where

\[ \lambda = \frac{p_1q_2}{p_1q_2 + p_2q_1} = P(p_1,p_2)_{x_i=1|x_i \neq y_i}. \]
Let $n^\#$ be the number of pairs $i \leq n$ with $x_i \neq y_i$ and let $z^\# = \frac{\sum_{i=1}^{n^\#} x_i}{n^\#}$ be the proportion of pairs with $x_i = 1$ among those with $i \leq n$ and $x_i \neq y_i$.

The log generalized likelihood ratio for testing $H_0 : \lambda = \frac{1}{2}$ against $H_1 : \lambda \neq \frac{1}{2}$ is

$$\lambda^\# = \frac{n^\# [H(z^\#) - H(\frac{1}{2})]}{n} .$$

In analogy with (4), given $b$, $c$, $m_0$, and $m$ let

$$T^\# = \text{first } n^\# \geq m_0 \text{ such that } \left(\frac{2\lambda^\#}{n}\right)^\frac{1}{2} > b .$$

Stop sampling at $T^\#$ if $T^\# < m$ and otherwise when $n^\# = m$. Reject $H_0$ if $T^\# < m$ or $T^\# > m$ and $\left(\frac{2\lambda^\#}{n}\right)^\frac{1}{2} > c .

Although a direct numerical approach is easy, for present purposes it is simpler to adapt the methods introduced already to compute approximately various properties of these tests. For Brownian motion approximations to the distribution of $T^\#$ under $H_1$, the appropriate mean and variance are

$$\mu_2 = \{2 [H(\lambda) - H(\frac{1}{2})]\}^{\frac{1}{2}}$$

and

$$\sigma^2_2 = \lambda(1 - \lambda) \log^2 \left[\frac{\lambda}{(1 - \lambda)}\right]/2 [H(\lambda) - H(\frac{1}{2})] ,$$

where $\lambda = p_1 q_2 / (p_1 q_2 + p_2 q_1)$. A "no overshoot" approximation analogous to (8) is

$$P_{T^\# \leq m} \leq \frac{2a}{\pi} \int_{(0,2)} \{(1 - \xi) [H(\xi) - H(\frac{1}{2})]\}^{-\frac{1}{2}} d\xi .$$

$$(0,2) \cap \{\xi : \theta_0 < \{2 [H(\xi) - H(\frac{1}{2})]\}^{\frac{1}{2}} < \theta_1\}$$
For \( b = 3.15, c = 2.15, m = 49, \) and \( m_0 = 8 \) (it is impossible to stop before \( n^* = 8 \) for this value of \( b \)), (12) gives \( P_{(p, p)}(T^* \leq m) < .020 \). Monte Carlo estimates based on 5000 repetitions for this probability and the over-all significance level are respectively .018 ± .000 and .056 ± .002. For \( p_1 = p_2 \) about equal to .5, it takes on average about two pairs \((x_n, y_n)\) to obtain one pair with \( x_n \neq y_n \). Thus, a maximum value \( m = 49 \) corresponds roughly to a maximum value of \( n = 98 \). Hence, for \( p_1 = p_2 \approx .5 \) this test is comparable to the second test in Table 2, although its over-all significance level is somewhat larger. Table 3 gives 900 repetition Monte Carlo and analytic approximations for some additional comparisons with the second test in Table 2. The analytic approximations to \( P_{(p_1, p_2)}(\text{Reject } H_0) \) are obtained by a normal approximation with continuity correction; the other analytic results use Brownian motion with mean and variance given by (10) and (11). These figures suggest that in terms of operating characteristic and expected sample size there is no strong reason for preferring one test to the other. If the values of \( c \) were altered slightly to make the over-all significance levels of the matched pairs test and the two population test more nearly equal, the power functions would tend to converge, and the two tests would appear to be even more similar.

There are several important differences between the matched pairs test and the likelihood ratio test defined by (4). As was noted earlier, the matched pairs test cannot be used unless approximately equal numbers of patients are allocated to treatment and control, whereas the likelihood ratio test has no such restriction. Even in the
### Table 3

**Matched Pairs Test: m₀ = 8, m = 49, b = 3.15, c = 2.15**

<table>
<thead>
<tr>
<th>(p₁, p₂)</th>
<th>λ</th>
<th>P(p₁, p₂){T̂ ≤ m}</th>
<th>P(p₁, p₂){Reject H₀}</th>
<th>E(p₁, p₂) ((T̂ ≤ m)/(p₁q₂ + p₂q₁))</th>
</tr>
</thead>
<tbody>
<tr>
<td>.7, .5</td>
<td>.7</td>
<td>.506 (.501)</td>
<td>.822 (.809)</td>
<td>76.8 (73.6)</td>
</tr>
<tr>
<td>.8, .5</td>
<td>.8</td>
<td>.933 (.942)</td>
<td>.996 (.997)</td>
<td>48.6 (40.4)</td>
</tr>
<tr>
<td>.6, .4</td>
<td>.69</td>
<td>.462 (.442)</td>
<td>.767 (.762)</td>
<td>75.2 (70.8)</td>
</tr>
<tr>
<td>.7, .4</td>
<td>.78</td>
<td>.860 (.885)</td>
<td>.979 (.990)</td>
<td>51.5 (48.9)</td>
</tr>
<tr>
<td>.8, .4</td>
<td>.86</td>
<td>1.00 (.995)</td>
<td>1.00 (1.00)</td>
<td>30.2 (28.6)</td>
</tr>
</tbody>
</table>
case of equal allocations to treatment and control the matched pairs test has the disadvantage that its maximum sample size is a random variable. If \( N \) denotes the number of pairs \((x_n, y_n)\) which must be observed until \( n = m \), then \( N \) is the waiting time until \( m \) "successes" in Bernoulli trials with success probability \( \delta = p_1 q_2 + p_2 q_1 \). Hence, 
\[
\begin{align*}
E(N) &= m/\delta \quad \text{and} \quad \var(N) = m(1-\delta)/\delta^2.
\end{align*}
\] 
If in the preceding example \( p_1 = p_2 = .5 \), then \( E(N) = \var(N) = 98 \). However, if \( p_1 = p_2 = .3 \), then \( E(N) = 116.7 \) and \( \var(N) = (12.7)^2 \), so one may with reasonably large probability attain 49 pairs having \( x_n \neq y_n \) in fewer than 116.7 - 12.7 = 104 or more than 116.7 + 12.7 \( \approx 130 \) total pairs. The situation is worse for larger departures from \( \delta = 1/2 \).

Without some compensating feature it seems doubtful that one would prefer this test to that determined by (4), except perhaps in those cases when \( p_1 \) and \( p_2 \) are expected to be near 0 or 1.

There are, however, compensating features, the most important of which is the use of the matched pairs test to deal with stratified populations. By pairing observations within strata it is often possible in effect to increase the value of \( \lambda \) and hence the sensitivity of the test. (See Armitage, 1975, especially p. 86.)

Upper gastrointestinal hemorrhage has several common causes. Very tentative figures from previous studies suggest that both the spontaneous remission rate and the success rate with vasopressin vary with cause. With some grouping of causes according to these apparent remission rates, perhaps 90-95\% of all patients can be put into three strata: (a) esophagitis, gastritis, Mallory-Weiss tear; (b) various
ulcers; and (c) esophageal varices. Highly speculative success rates with and without vasopressin may be approximately .7 and .5 for (a), .5 and .3 for (b), and .7 and .3 for (c). It is also difficult to guess the size of the various strata. (For example, the percentage of variceal patients is larger in populations with a large proportion of alcoholics--hence, typically larger at V. A. hospitals than at others.) But the ratio 25:25:50 may be a reasonable approximation. If these figures are correct, then in the entire population $p_1 = .65$ and $p_2 = .35$, so random pairing gives $\lambda = .775$. Matching pairs within strata gives $\lambda = .778$. Modest variations in these assumed figures consistently yield differences in $\lambda$ of less than .01. In general, stratification increases slightly the average number of pairs required to obtain a pair with $x_n \neq y_n$, which cancels to some extent the small advantage gained by increasing $\lambda$.

The failure of stratification to produce a more dramatic effect is presumably due to the fact that with the maximum sample sizes envisaged here, a treatment effect with an appreciable probability of being detected must be as large or larger than differences among strata. For larger experiments designed to detect smaller treatment effects, the value of stratification should be re-examined.

The preceding analysis ignores the possibility of a time trend, against which pairing of patients according to their arrival time provides protection. The history of the treatment of upper gastrointestinal bleeding and the simple mode of administration of vasopressin in this trial suggest that time trends do not pose serious problems.
In summary, the modest increase in sensitivity of the matched pairs test in the range of parameters and sample sizes considered for the vasopressin study does not seem sufficient compensation for the random variation in its maximum sample size and its failure to deal adequately with unbalanced allocations to treatment and control.
APPENDIX A

PROBABILITY APPROXIMATIONS FOR NORMAL DATA

Let \( x_1, x_2, \ldots \), be independent normally distributed random variables with mean \( \theta \) and variance 1. Let \( s_n = x_1 + \ldots + x_n \) and

\[
(A.1) \quad T = \text{first } n > m_0 \text{ such that } |s_n| > bn^{1/2}
\]

Let \( m > m_0 \) and \( 0 < c \leq b \). The over-all significance level of the modified repeated significance test studied in Section 2 is

\[
(A.2) \quad \alpha = P_0\{T < m\} + P_0\{T > m, |s_m| > cm^2\}.
\]

An upper bound for the second term which is fairly accurate when \( c \) is small compared to \( b \) is

\[
(A.3) \quad P_0\{cm^{1/2} < |s_m| \leq bm^{1/2}\}.
\]

The first term may be approximated using results of Siegmund (1977). If \( b + \infty \) and \( m + \infty \) in such a way that \( b = m^{1/2}\theta_1 \), then

\[
(A.5) \quad P_0\{T < m\} \sim (2/\pi)^{1/2} b e^{-b^2/2} \int_{\theta_1}^{\infty} \frac{v(x)}{x} dx,
\]

where

\[
(A.6) \quad v(x) = 2 \exp\left[-2 \sum_{n=1}^{\infty} \phi(-\frac{1}{2} x n^{1/2}) / x^2\right].
\]

The approximation (A.5) is very accurate when \( m_0 = 1 \). For larger values of \( m_0 \) one seems to obtain a better approximation by assuming in addition that \( m_0 + \infty \) and \( b = m_0^{1/2}\theta_0 \). Then
Although the first term on the right hand side of (A.7) is of smaller order of magnitude than the second, and hence there is no good mathematical reason for including it, its inclusion seems to give more accurate numerical results when compared with simulations (cf. equation (50) of Siegmund, 1977).

It is easy to compute the function $\nu(x)$ defined in (A.6) numerically. Woodroofe (1978b) has tabled an integral equivalent to that in (A.5). Siegmund (1979) has shown that for $x$ less than about 2, $\nu(x)$ is well approximated by $\exp(-.583x)$, and hence for many values of $\theta_0$ and $\theta_1$ the integrals in (A.5) and (A.7) may be obtained from tables of the exponential integral and the value

$$
\int_0^\infty [\nu(x)/x]dx \approx .224 .
$$

Let $T_+$ be defined by (A.1) with $s_n$ in place of $|s_n|$. According to Siegmund (1978), if $b=\infty$, $m=\infty$, and $b=\frac{b}{m^{\frac{1}{2}}}$, for each fixed $\theta > 0$, $x > 0$

(A.8) \hspace{1cm} P_\theta[T_+ < m, s_m < bm^{\frac{1}{2}} - x] \approx \nu(\theta_1) \phi[\frac{m^{\frac{1}{2}}(\theta_1 - \theta)}{m^{\frac{1}{2}}}] e^{-\theta x/m^{\frac{1}{2}}\theta} .

For Brownian motion the corresponding approximation has 1 in place of $\nu(\theta_1)$. Together with the obvious decomposition

$$
P_\theta[T_+ < m] = P_\theta[s_m > bm^{\frac{1}{2}}] + P_\theta[T_+ < m, s_m < bm^{\frac{1}{2}}] ,
$$

(A.8) allows one to approximate $P_\theta[T_+ < m]$ for $\theta \neq 0$. 

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APPENDIX B

APPROXIMATE EXPECTED SAMPLE SIZE FOR NORMAL DATA

Let \( \{X(t), 0 \leq t < \infty\} \) be a Brownian motion process with drift \( \theta \) and variance 1 per unit time. Let \( T = \inf\{t : t > m_0, |X(t)| = bt^{\frac{1}{2}}\} \). It may be shown (e.g., Siegmund, 1977) that for each \( \theta \neq 0 \), as \( b \to \infty \)

\[
E_{\theta} T = \frac{(b^2 - 1)}{\theta^2} + o(1)
\]

For discrete normal random walk the corresponding expansion contains a term to account for excess over the stopping boundary, which can be computed numerically and for small \( \theta \) is about

\[
(\text{B.2}) \quad 1.166/\theta
\]


For sequential tests of the kind discussed in this paper the expected sample size is

\[
E_{\theta} \text{min}(T, m) = E_{\theta} T - \int_{\{T > m\}} E_{\theta}(T - m | X(m)) dP_{\theta}
\]

Suppose that \( b \to \infty \) and \( m \to \infty \) in such a way that \( b = \theta_1 m^{\frac{1}{2}} \). For \( \theta \) in a neighborhood of \( \theta_1 \), say \( \theta = \theta_1 + \xi m^{\frac{1}{2}} \), it is possible to estimate the second term on the right hand side of (B.3) to provide reasonable approximations to \( E_{\theta} \text{min}(T, m) \).

Theorem. Suppose \( b \to \infty \) and \( m \to \infty \) so that for some \( \theta_1 \neq 0 \), \( b = \theta_1 m^{\frac{1}{2}} \). For \( \theta = \theta_1 + \xi m^{-\frac{1}{2}} \)
\[(B.4) \quad E_0 \min(T, m) = (b^2 - 1)/\theta^2 - \{m^2[\theta - 1/(2\theta)]^{-1}[\phi(\xi) - \xi \phi(-\xi)]\}
\]
\[
+ \theta^{-2}_1[\phi(-\xi)(1+\xi^2) - \xi \phi(\xi)] + o(1)
\]

A sketch of a proof goes as follows. By (B.1) it suffices to consider the second term on the right hand side of (B.3), which may be rewritten as

\[(B.5) \quad \int_0^\infty P_0\{X(m) \in \Theta_1 m - dx\}(1 - P_0\{T < m|X(m) = \Theta_1 m - x\}) E_0 \tau_m(x),
\]

where

\[\tau_m(x) = \inf\{t: t > 0, X(t) = \Theta_1 m^2[(m+t)^{1/2} - m^{1/2}] + x\}.
\]

Since \(\Theta_1 m^2[(m+t)^{1/2} - m^{1/2}] \leq \frac{1}{2} \Theta_1 t\), a standard argument using Wald's identity yields

\[(B.6) \quad E_0 \tau_m(x) \leq x/(\Theta_1 - \frac{1}{2} \Theta_1).
\]

Writing the integral in (B.5) as the sum of integrals over \((0, m^{1/8})\), \((m^{1/8}, m^{1/2} \log m)\) and \((m^{1/2} \log m, \infty)\), one sees from (B.6) that the first and third integrals converge to 0 as \(m \to \infty\). It may also be shown as in Siegmund (1977) that uniformly in \(x \geq m^{1/8}\),

\[P_0\{T < m|X(m) = \Theta_1 m - x\} = o(m^{-1}),\]

and hence by (B.5) and (B.6) it suffices to find an approximation for

\[(B.7) \quad \int_{m^{1/8}}^{m^{1/2} \log m} \phi(m^{1/2}(\Theta_1 - \Theta) - x m^{-1/2}) E_0 \tau_m(x) dx.
\]
A Taylor series expansion and some calculation with Wald's identity shows that uniformly for \( x < \frac{1}{2} \log m \)

\[
E_0 \tau_m(x) = \frac{x}{(\theta - \frac{1}{2} \theta_1)} - \frac{x^2}{m \theta_1^2} + o(x^2/m),
\]

which when substituted into (B.7) yields the theorem.

For the entries in Table 1, the quantity (B.2) was added to (B.4) to obtain a slightly better approximation to \( E_0 T \). It seems doubtful that estimating the excess over the boundary in the correction term \( \int_{(T>m)} E_0 (T - m|x) dP_0 \) is worth the effort, since this term is already relatively small in those cases where the over-all approximation can be expected to be accurate. The entries in Table 2 were obtained from the Brownian motion approximation with mean and variance given by (5) and (6).
APPENDIX C

APPROXIMATE SIGNIFICANCE LEVEL FOR BERNOULLI DATA

Let \( \bar{x}_n, \bar{y}_n, H, I, \text{ and } L_n \) be as in Section 3. The stopping rule \( T \) defined by (4) may be rewritten

\[
T = \text{first } n \geq m_0 \text{ such that } L_n > a,
\]

where \( a = b^2/2 \). The significance level of the sequential test studied in Section 3 is given by (7). In this appendix an asymptotic expression similar to (A.5) is obtained for \( P(T \leq m) \) as \( m \to \infty, m_0 \to \infty, \)

\[
b \to \infty \text{ in such a way that } b = m_0^{1/2} \theta_1 = m_0^{1/2} \theta_0.
\]

The method utilizes the non-linear renewal theorem and an interesting adaptation of the methods of Lai and Siegmund (1977). Since the computations are rather elaborate, they are only given heuristically. The following likelihood ratio identity is also very helpful in simulating \( \alpha \).

Let \( F_1 \subset F_2 \subset \ldots \) be an increasing sequence of sub-\( \sigma \)-algebras of a basic \( \sigma \)-algebra \( F \). Let \( P \) and \( Q \) be two probabilities on \( F \) such that the restriction \( P^{(n)} \) of \( P \) to \( F_n \) is absolutely continuous relative to the corresponding restriction \( Q^{(n)} \) of \( Q \). Let \( L_n = dP^{(n)}/dQ^{(n)} \) be the likelihood ratio of these restrictions. One version of the fundamental identity of sequential analysis says that for any stopping time \( \sigma \) and any event \( A \) such that \( A \cap \{ \sigma = n \} \in F_n \) for all \( n \),

\[
P(A \cap \{ \sigma < \infty \}) = \int_{A \cap \{ \sigma < \infty \}} L_\sigma \, dQ.
\]

(The proof follows at once by writing \( \{ \sigma < \infty \} = \bigcup_{n=1}^{\infty} \{ \sigma = n \} \) and using the additivity of the integral.)
In what follows $P_{(p_1, p_2)}$ will be as in Section 3 and

$$Q = \int_{0}^{1} \int_{0}^{1} p_{(p_1, p_2)} \, dp_1 \, dp_2.$$ 

Taking $P = P_{(p, p)}$ gives

$$(C.3) \quad L_n = dP_{(p, p)}^{(n)} / dQ^{(n)} = \left( \begin{array}{c} n \\ s_n \end{array} \right) \left( \begin{array}{c} n \\ s_n^* \end{array} \right) p^n q^{n-s_n^*} (n+1)^2,$$

where $s_n = \sum_{1}^{n} x_k$ and $s_n^* = \sum_{1}^{n} y_k$. The identity (C.2) gives representations for $P_{(p, p)} \{T \leq m\}$ and $P_{(p, p)} \{T > m, (2 \xi_m)^{1/2} > c\}$ which are useful in estimating these probabilities by Monte Carlo methods. One samples

$(x_1, y_1), (x_2, y_2), \ldots$ according to $Q$ and estimates $P_{(p, p)} \{T \leq m\}$, for example, by averages of $I_{\{T \leq m\}} L_T$. (See Siegmund, 1975, for a general discussion of such importance sampling in sequential analysis and Lai and Siegmund, 1977, for an application in a context similar to the present one.) This estimator has three advantages over direct simulation: (i) its variance is smaller; (ii) the expectation under $Q$ of $\min(T, m)$ is smaller than under $P_{(p, p)}$ where it essentially equals the maximum sample size $m$; and (iii) $P_{(p, p)} \{T \leq m\}$ may be estimated simultaneously for several values of $p$ using the same random numbers. For estimating $\alpha(p)$ for a test with $c$ small compared to $b$ this technique is not variance reducing, but advantages (ii) and (iii) hold in this case as well.

In contrast to the case of normal variables, where a direct representation of the probability that $T \leq m$ by means of (C.2) provided the starting point of a fruitful asymptotic analysis, in this case an
indirect approach seems advisable. Let \( u > 0, v > 0 \), and let

\[
P = \int_0^1 P(\xi) \xi^u(1-\xi)^v \, d\xi / B(u+1, v+1)
\]

so

\[
P = \int_0^1 P(\xi) \xi^u(1-\xi)^v \, d\xi / B(u+1, v+1)
\]

Of course, \( P \) defined by (C.4) depends on \( u \) and \( v \). If \( u \to \infty \) and \( v \to \infty \) in such a way that \( u/(u+v) \to p \), then the distribution with density

\[
\xi^u(1-\xi)^v / B(u+1, v+1)
\]

converges weakly to a point mass at \( p \), so for each fixed \( m \)

\[
(P \{ T \leq m \} \to (p, p) \{ T \leq m \})
\]

Hence for large \( u \) and \( v \) with \( u/(u+v) \to p \) an approximation for \( P \{ T \leq m \} \)

"should be" an approximation for \( P \{ T \leq m \} \).

Fix \( 0 < p_1, p_2 < 1 \). Stirling's formula and the strong law of large numbers applied to (C.3) show that with \( P_{(p_1, p_2)} \) probability one, as \( n \to \infty \)

\[
\log L_n = - \frac{n}{2} \log n + \frac{1}{2} \log \frac{1}{n} + \frac{1}{2} \log \frac{1}{p_1 q_1 p_2 q_2} + u \log p + v \log q
\]

\[
- \log 2 \pi / 2 - \log B(u+1, v+1) + o(1)
\]

where \( \tilde{p} = \frac{1}{2} (p_1 + p_2) \) and \( \tilde{q} = 1 - \tilde{p} \). Suppose now that \( a = b^2/2 \to \infty \),

\( m_0 \to \infty \), and \( m \to \infty \) in such a way that \( b = \theta_1 m^k = \theta_0 m_0^k \). Substitution of

(C.7) into (C.2) and an argument similar to that of Lai and Siegmund

(1977) yields
(C.8) \( P(T \leq m) \)

\[
- \frac{1}{2} [B(u+1, v+1)]^{-1} (\pi^{-1} a)^{\frac{1}{2}} e^{-a} \\
\times \int_0^1 \int_0^{1} e^{-(t/T-a)} (T/a)^{\frac{1}{2}} \frac{p}{q} (p/q_1 q_2)^{\frac{1}{2}} dp_1 dp_2 \\
- \frac{1}{2} [B(u+1, v+1)]^{-1} (\pi^{-1} a)^{\frac{1}{2}} e^{-a} \\
\times \int_0^1 \int_0^{1} \tilde{\nu}(p_1, p_2) [I(p_1, p_2)]^{-\frac{1}{2}} \frac{p}{q} (p/q_1 q_2)^{\frac{1}{2}} \frac{u-v}{p} dp_1 dp_2, \\
\{0 < \theta_1 < [2I(p_1, p_2)]^{\frac{1}{2}} < \theta_0\}
\]

where

\[
\tilde{\nu}(p_1, p_2) = \lim_{a \to \infty} E_{(p_1, p_2)} \exp\left[-(t/T-a)\right]
\]

exists by an application of Theorem 1 of Lai and Siegmund (1977).

(Actually, in order that this theorem be applicable it is necessary
that a certain random walk associated with the process \( \kappa_n \) be non-
 arithmetic, which is the case for all \( p_1, p_2 \) with at most a denumerable
number of exceptions. This suffices in view of the subsequent integra-
tion over \( p_1 \) and \( p_2 \).)

Now suppose that \( u \to \infty \) and \( v \to \infty \) with \( u/(u+v) = p < \frac{1}{2} \). Some
calculation shows that the measure \( K_{u,v} (dp_1, dp_2) = [B(u+1, v+1)]^{-1} p^{u-v} dp_1 dp_2 \) has total mass converging to \( 4p \) and
converges weakly to a measure uniform on \( \frac{1}{2}(p_1 + p_2) = p \). Hence, \( a^{\frac{1}{2}} e^{a} \)
times the right hand side of (C.8) converges to
Together with (C.6) this suggests that

\[
(C.10) \quad P(p,p)\{T \leq m\} \sim C(p;\theta_0,\theta_1) a^{1/2} e^{-a} \quad (0 < p \leq \frac{1}{2}) ,
\]

where \( C(p;\theta_0,\theta_1) \) denotes the expression in (C.9). For \( \frac{1}{2} \leq p < 1 \), a similar result holds with \( C(q;\theta_0,\theta_1) \) in place of \( C(p;\theta_0,\theta_1) \).

It should be emphasized that the preceding argument is only heuristic, although it seems to be possible to make it rigorous by taking \( u \) and \( v \) as functions of \( m \) which tend to \( \infty \) slowly with \( m \). The final result appears to agree formally with a similar very general result of Woodroofe (1978a), which however, does not apply in this case because certain smoothness conditions important to Woodroofe's method are not satisfied.
REFERENCES


Sequential designs are proposed for clinical trials to compare two binomial success probabilities, \( p_1 \) and \( p_2 \). Approximations to the operating characteristics and expected sample size are obtained and compared with simulations. Special reference is made to the problem of comparing vasopressin and placebo for stopping upper gastrointestinal hemorrhage.