The Minimax Risk for Clinical Trials

by

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Summary

The risk involved in a trial to compare two medical treatments is shared by patients who receive the inferior treatment during the experimental phase and those remaining after the experiment who might all receive the inferior treatment if the results are misleading. We consider the maximum of this risk with respect to the unknown probabilities of success and seek allocation rules that minimise this quantity, for a given total of patients. It needs extensive computations to find such minimax procedures, but there are simple and almost equally effective allocation rules based on a truncated sequential probability ratio test.

Key words: CLINICAL TRIALS; BAYES PROCEDURES; SEQUENTIAL PROBABILITY RATIO TEST; MINIMAX ALLOCATION RULES.

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1. Introduction

Consider the task of allocating a total of t patients who suffer from the same illness to two available treatments which successfully treat the illness with unknown probabilities p_1 and p_2, respectively. Initially, $2N$ patients are assigned sequentially in pairs to the two treatments and then the remaining $t - 2N$ patients are assigned to the apparently superior treatment. The task is to choose N so as to maximise the expectation $E(r)$, where r is the number of successfully treated patients.

The expected successes lost (ESL), due to ignorance of the values of p_1 and p_2, is given by the difference $t \max(p_1,p_2) - E(r)$. It is mathematically equal to the expected number of patients assigned to the inferior treatment multiplied by the factor $|p_1-p_2|$. Thus, we can imagine a fixed loss $\delta = |p_1-p_2|$ for each assignment to the inferior treatment. If Δ denotes a sequential rule for choosing N, upon which the evaluation of $E(r)$ is based, then the ESL becomes the risk function, denoted $R_\Delta(p_1,p_2,t)$, associated with the allocation rule Δ. The problems of maximising $E(r)$ and minimising the risk with respect to Δ are equivalent.

We are not concerned with all possible allocation rules, but only with the class $\mathcal{D}$ of two-stage procedures, where each rule Δ has a stopping time N which determines the length of the sequence of paired observations in the first stage. The aim here is to find, for each t, a rule which is minimax within the class $\mathcal{D}$. It is not obvious *a priori* but, for many values of t, the minimax allocation rules belong to a certain subclass of $\mathcal{D}$ and our search can be reduced by considering only stopping times of the corresponding special form.

For the first n pairs of patients assigned to the two treatments, let S_n denote the number of successes produced by the first treatment minus the number produced by the second. The stochastic sequence $S_1,S_2,\ldots,S_{[t/2]}$ is a random walk having steps which equal -1, 0, 1 with probabilities $(1-p_1)p_2$, $p_1p_2 + (1-p_1)(1-p_2)$, $p_1(1-p_2)$, respectively. In order to reduce our search,

we shall restrict attention to allocation rules corresponding to stopping rules of the form:

$$N = \min \{n,\ 1 \le n \le t/2 : S_n \in A_n\} , \tag{1}$$

where $A_1, A_2, \ldots, A_{[t/2]}$ are subsets of the real line. It will be argued in Section 4 that this restriction on N does not seriously affect matters. An allocation rule Δ will be called *symmetric* if the subsets defining N are symmetrical about zero. The use of a symmetric allocation rule seems appropriate when one has little or no reason to believe that one particular treatment is better than the other. For symmetric rules, there is a very useful computational formula for the risk function:

$$R_\Delta(p_1,p_2,t) = \delta\left[\frac{t}{2} - E\left\{\left(\frac{t}{2} - N\right)\frac{\gamma^{|S_N|}-1}{\gamma^{|S_N|}+1}\right\}\right] , \tag{2}$$

where

$$\gamma = \max\{p_1(1-p_2)/p_2(1-p_1)\ ,\ p_2(1-p_1)/p_1(1-p_2)\} . \tag{3}$$

Suppose, for the moment, that t is an even integer. Then $\delta t/2$ is the risk associated with the allocation rule Δ_0 which assigns half of the t patients to each of the treatments and the quantity

$$\delta\ E\left\{\left(\frac{t}{2} - N\right)\frac{\gamma^{|S_N|}-1}{\gamma^{|S_N|}+1}\right\} \tag{4}$$

can be interpreted as the expected successes saved (ESS) by using the symmetric rule Δ instead of Δ_0. The ESS is always non-negative, and it is strictly positive whenever

$$p_1 \neq p_2 \quad \text{and} \quad P\left(N < \frac{t}{2}\ ,\ S_N \neq 0\right) > 0 .$$

By using (2), the risk function can be evaluated easily, rapidly and accurately on a mainframe computer, even for fairly large values of t. Costly and less accurate simulation studies can be avoided.

A simple and, we believe, a revealing indicator of the overall effectiveness of an allocation rule is given by the maximum risk

$$M_\Delta(t) = \max_{p_1,p_2} R_\Delta(p_1,p_2,t) . \tag{5}$$

Any rule $\tilde{\Delta}$ which minimises this indicator within the class $\mathcal{D}$ is, of course, minimax. Of some significance is the actual size of the *minimax value*:

$$M(t) = \min_{\Delta\in\mathcal{D}} M_\Delta(t) . \tag{6}$$

For given t and any allocation rule Δ, there must be a pair of values p_1,p_2 for which the risk $R_\Delta(p_1,p_2,t)$ is at least as large as $M(t)$. In this sense, $M(t)$ indicates how well one can do. This investigation will be mainly concerned with $M(t)$ and the minimax rules $\tilde{\Delta} = \tilde{\Delta}(t)$ such that $M_{\tilde{\Delta}}(t) = M(t)$. Our results also include simpler allocation rules with risk functions which come very close to attaining the minimax value.

It is easily seen that $M(t) \to \infty$ as $t \to \infty$. Computer calculations, using formula (2), indicate that, for large t,

$$M(t) \simeq 0.3714t^{\frac{1}{2}} .$$

For comparison, we observe that $M_\Delta(t) = 0.5t$ for the simplest allocation rule $\Delta = \Delta_0$.

We have been able, for many values of t, to determine a (symmetric) minimax rule $\tilde{\Delta}$ and thereby to evaluate the ratio $M(t)/t^{\frac{1}{2}}$. These rules are Bayes procedures for a two-point prior distribution which assigns equal probabilities to the points $(p_1,p_2) = \left(\frac{1}{2}(1\pm\delta), \frac{1}{2}(1\mp\delta)\right)$. For fixed δ, the minimal Bayes risk can be rapidly computed using backwards induction: see Section 4 for the details. Our approach is to choose the least favourable value of δ so as to maximise the minimal Bayes risk and it turns out that this produces the minimax allocation rule for most of the values of $t \le 201$. This

assertion is based on extensive calculations we have made, using formula (2), to verify that the maximum of the risk function coincides with the minimal Bayes risk, for an appropriate choice of δ. The computations are described in Section 5, including some exceptional cases, and the results are summarised in Section 6.

In fact, there are quite simple symmetric allocation rules Δ for which the ratio $M_\Delta(t)/t^{\frac{1}{2}}$ is very nearly as small as $M(t)/t^{\frac{1}{2}}$. One of these uses a sequential probability ratio test (SPRT), truncated after $[t/2]$ pairs. This type of rule was first investigated by Vogel (1960) who established an inequality for the risk function and deduced an asymptotic upper bound on the ratio $M(t)/t^{\frac{1}{2}}$, as $t \to \infty$. As we shall see in Section 3, his inequality can be extended to provide a close upper bound for all values of t. It follows that a truncated SPRT can be specified so that it behaves, for all practical purposes, like the corresponding minimax rule.

Another allocation procedure is a simple adaptation of a rule suggested by Anscombe (1963) for a related setting with normal data. Such procedures also behave like minimax rules; they have comparable risk functions which are quite flat in the variables p_1, p_2. Anscombe's rule has been recommended by others: see Lai *et al.* (1980) and Chernoff and Petkau (1981). However, the truncated SPRT seems preferable because of its simplicity and also because of its lack of sensitivity to changes in t : see Section 6.

The comparison in Table 1 also includes an allocation rule adapted from one suggested by Lai *et al.* This does fairly well, with $M_\Delta(t)/t^{\frac{1}{2}}$ approximately equal to 0.41 for large values of t. It suffers from the fact that no more than about a third of the patients can be assigned in pairs, which causes difficulties when p_1 and p_2 are close together.

The basic loss structure assumed here was developed for normal data in the papers by Anscombe (1963) and Colton (1963). Since then, several other two-stage procedures have been suggested in the literature. For example, Begg and Mehta (1979) considered approximate Bayes procedures, using normal prior distributions on the mean difference between two treatments. Bayes allocation rules and the corresponding minimal Bayes risks have been accurately computed, for a similar model in continuous time, in the paper by Chernoff and Petkau. In particular, they found that Anscombe's rule is remarkably efficient from a Bayesian point of view, for a wide range of normal prior distributions.

There are strong practical reasons for restricting attention to two-stage procedures in medical trials: the allocation of treatments can be randomised for each pair of patients during the experimental phase, giving protection against the possibility of bias in the results. The truncated SPRT also has the practical advantage of simplicity. Table 2 gives an illustration of what can be achieved by comparing its risk function, for the case $t = 100$, with that of the corresponding minimax rule. However, our results and those mentioned above for normal models suggest that similar risk functions can be produced by other allocation rules. In this paper, we focus attention on the risk function and its maximum, but it must be recognised that other criteria, such as final error probabilities, are also relevant to the design of clinical trials.

Our investigation is concerned with a restricted version of the two-armed bandit problem and it is worth considering what reductions in risk might be achieved by extending the class $\mathcal{D}$ of two-stage procedures to permit arbitrary switching from one treatment to the other. The more general problem has been widely studied. For example, it is known that the two-point prior distributions used here lead to reasonably simple Bayes procedures for the two-armed bandit problem but, unfortunately, such allocation rules perform badly at other points (p_1,p_2), where the risk is of order t : see Bather (1981), Section 3.1.

The paper by Berry (1978) includes computations of the minimal Bayes risk when p_1 and p_2 are assumed to have independent beta densities, but these average risks give very little indication of the corresponding maxima and the underlying procedures are complicated. For our purposes, a more useful result is an asymptotic lower bound established in Bather (1982). The minimax risk $M^*(t)$ for the extended class of allocation rules has the property that

$$\liminf_{t \to \infty} \; M^*(t)/t^{\frac{1}{2}} \geq 0.306 \; .$$

This gives some idea of the possible reductions in risk, but no indication of the allocation rules involved.

2. Risk and error formulae for symmetric allocation rules

Let Δ be an allocation rule and let N be the stopping time, defined as in (1), which represents the number of pairs of patients assigned by Δ during its testing phase. The remaining $t - 2N$ patients are assigned to the first treatment if $S_N > 0$; to the second if $S_N < 0$ and, by tossing a fair coin, to either of the two treatments if $S_N = 0$.

Theorem 1. If Δ is a symmetric allocation rule, then the risk function $R_\Delta(p_1,p_2,t)$ can be computed by means of formula (2).

Proof. For definiteness, let $p_1 > p_2$ so that the second is the inferior treatment, $\delta = p_1-p_2$ and $\gamma = p_1(1-p_2)/p_2(1-p_1) > 1$. The expected number of patients assigned to the inferior treatment can be expressed, for any Δ , in terms of indicator random variables such as $1(S_N < 0)$ and then re-written as follows:

$$E\{N + (t-2N)\left(1(S_N < 0) + \tfrac{1}{2}\, 1(S_N = 0)\right)\} =$$

$$\frac{t}{2} - E\{(\frac{t}{2} - N)\left(1(S_N > 0) - 1(S_N < 0)\right)\} . \qquad (7)$$

If Δ is symmetric, then, given $N = n$ and $|S_n| = i > 0$, the ratio of the probabilities for a path leading to $S_n = i$ and for its reflection leading to $S_n = -i$ is γ^i . Consequently, the corresponding conditional expectation of the difference $1(S_n > 0) - 1(S_n < 0)$ assumes the form $(\gamma^i-1)/(\gamma^i+1)$; so the desired conclusion follows from (7). □

When (p_1,p_2) is a boundary point of the unit square, the steps of the random walk $S_1,S_2,\ldots,S_{[t/2]}$ all have the same sign, non-negative if $p_1 > p_2$, and $\gamma = \infty$. Formula (2) remains valid if the ratio $(\gamma^{|S_N|}-1)/(\gamma^{|S_N|}+1)$ is interpreted as $1(S_N \neq 0)$. It follows from the expression on the left of (7) that, at such boundary points, if $P(S_N = 0, N < t/2) = 0$, then

$$R_\Delta(p_1,p_2,t) = \delta\, E(N) = E|S_N| .$$

The latter equality is a consequence of Wald's equation: $E(S_N) = E(S_1)E(N)$, since $|E(S_N)| = E|S_N|$ here. More generally, for points on the boundary of the unit square, formula (2) must be replaced by

$$R_\Delta(p_1,p_2,t) = E|S_N| + \delta(\frac{t}{2} - m)(1-\delta)^m , \tag{8}$$

where m is the least index n for which $S_n = 0$ is a stopping point for N. The random walk is monotone in such cases, so we must have either $S_1 = S_2 = \ldots = S_m = 0$ or $S_N \neq 0$.

The *error probability* α for an allocation rule Δ is defined as the probability that the $t - 2N$ patients assigned according to S_N at the end of the testing phase are actually assigned to the inferior treatment. Clearly, this probability depends on p_1 and p_2; and, by convention, we set $\alpha = \frac{1}{2}$ when $p_1 = p_2$. The proof of the following result is similar to that for Theorem 1.

Theorem 2. If Δ is a symmetric allocation rule, then

$$\alpha = E\{1/(\gamma^{|S_N|}+1)\} . \tag{9}$$

When (p_1,p_2) is a boundary point of the unit square,

$$\alpha = \tfrac{1}{2} P(S_N = 0) = \tfrac{1}{2}(1-\delta)^m ,$$

where m is defined as in formula (8).

3. Vogel's inequality for the truncated SPRT

Let $\Delta = D$ denote the symmetric allocation rule defined by stopping as soon as the process reaches the level $\pm D$, or when $n = [t/2]$. The stopping time is

$$N = \min\{n \geq 1 : |S_n| = D , [t/2]\} .$$

Let $R_D(p_1,p_2,t)$ denote the corresponding risk function, $D = 1,2,\ldots$. It is convenient to refer to these allocation rules as truncated SPRT's, since the unbounded version $(t = \infty)$ is a sequential probability ratio test for the two simple hypotheses represented by the points (p_1,p_2) and (p_2,p_1). As we shall see, the truncated SPRT with an appropriate choice of D, depending on t, is very nearly minimax. Its maximum risk $M_D(t)$ coincides with $M(t)$ for small values of t and, in general, it is only slightly larger.

Vogel (1960) discovered an upper bound for R_D which can be derived easily from formula (2):

Theorem 3. For the truncated SPRT described above and even values of $t \geq 2$,

$$R_D(p_1,p_2,t) \leq \delta\, t\, \varepsilon + D(1-2\varepsilon)^2 , \tag{10}$$

where

$$\varepsilon = 1/(\gamma^D + 1) . \tag{11}$$

Observe that ε is the error probability of the unbounded SPRT that stops at time $N' = \min\{n \geq 1 : |S_n| = D\}$. In general, the true error probability α exceeds ε.

Proof of Theorem 3. The ratio $(\gamma^{|S_N|}-1)/(\gamma^{|S_N|}+1) = (\gamma^D-1)/(\gamma^D+1)$ in (2), whenever $t/2 - N > 0$, and one obtains

$$R_D(p_1,p_2,t) = \delta\, t\, \varepsilon + (1-2\varepsilon)\, \delta\, E(N) .$$

Since $N' \geq N$ always holds and since $E(S_1)E(N') = E(S_{N'})$, by Wald's equation, we have

$$\delta\, E(N) \leq |E(S_1)|\, E(N') = |E(S_{N'})| = D(1-\varepsilon) - D\,\varepsilon = D(1-2\varepsilon) ,$$

which establishes the required inequality (10). □

Vogel's inequality provides an upper bound for the maximum risk $M_D(t)$, given by

$$U_D(t) = \max_{p_1,p_2} \{\delta\, t\, \varepsilon + D(1-2\varepsilon)^2\} . \tag{12}$$

This must be evaluated numerically, but a two-dimensional search for the maximum can be avoided by using (13) below. Notice that, when (p_1,p_2) is on the boundary of the unit square, $\varepsilon = 0$ and the expression on the right of (12) reduces to D. Thus, $U_D(t) \geq D$.

Theorem 4. The expression $\delta\, t\, \varepsilon + D(1-2\varepsilon)^2$, appearing in (12), always attains its maximum at a point (p_1,p_2) on the diagonal line $p_1 + p_2 = 1$. Hence,

$$U_D(t) = \max_{0<\delta\leq 1} \{\delta\, t\, \varepsilon_0 + D(1-2\varepsilon_0)^2\} , \tag{13}$$

where

$$\varepsilon_0 = \frac{(1-\delta)^{2D}}{(1+\delta)^{2D} + (1-\delta)^{2D}} .$$

Proof. If the expression $\delta\, t\, \varepsilon + D(1-2\varepsilon)^2$ attains its maximum on the boundary of the unit square, then, as noted in the previous paragraph, the same maximal value D is attained at all boundary points and, in particular, at the point $(p_1,p_2) = (1,0)$ where $p_1 + p_2 = 1$. Thus it is sufficient to show, for each fixed δ, that the expression $\delta\, t\, \varepsilon + D(1-2\varepsilon)^2$ is maximised at a point (p_1,p_2) which is either on the diagonal line $p_1 + p_2 = 1$ or on the boundary of the unit square.

For definiteness, let $p_1 > p_2$ and write $p_1 = \frac{1}{2}(1+\delta+\mu)$, $p_2 = \frac{1}{2}(1-\delta+\mu)$, where $0 < \delta \leq 1$ and $|\mu| \leq 1-\delta$. Then $\delta = p_1 - p_2 > 0$ and

$$\gamma = p_1(1-p_2)/p_2(1-p_1) = \left((1+\delta)^2-\mu^2\right)/\left((1-\delta)^2-\mu^2\right) > 1 .$$

The diagonal line $p_1 + p_2 = 1$ corresponds to $\mu = 0$; the boundary of the unit square corresponds to $|\mu| = 1-\delta$. For fixed $\delta > 0$, as $|\mu|$ increases from 0 to $1-\delta$, γ increases from $(1+\delta)^2/(1-\delta)^2$ to infinity and hence, ε , given by (11), decreases from ε_0 to zero. Since the expression $\delta\, t\, \varepsilon + D(1-2\varepsilon)^2$ is convex in ε , for fixed δ , it must attain its maximum at one of the end points $\varepsilon = 0$ or $\varepsilon = \varepsilon_0$. In the first case, $|\mu| = 1-\delta$ and (p_1,p_2) is a boundary point, while in the second, $\mu = 0$ and (p_1,p_2) is on the diagonal $p_1 + p_2 = 1$. □

The value

$$V(t) = \min_{D=1,2,\ldots} U_D(t)$$

is an upper bound on the minimax risk $M(t)$. The minimising choice of D here suggests a value of D for the truncated SPRT and this was the approach used in our preliminary investigations, for even values of t . Subsequently, we developed techniques for evaluating $M_D(t)$ itself and we were able to minimise this directly and accurately with respect to D , for odd as well as even t . However, it is worth noting that $V(t)$ is a good approximation to $\min M_D(t)$: our computations indicated that the excess involved in using $V(t)$ is less than 1% for $t = 2,4,\ldots,200$.

Vogel (1960) used the inequality (10) to obtain the asymptotic result

$$V(t) \sim 0.375\, t^{\frac{1}{2}} .$$

His argument is not very clear, but the same result can be justified simply by treating D as a continuous variable in the definition of $V(t)$, which also shows that $D \sim 0.292\, t^{\frac{1}{2}}$. The coefficient in the first result is recorded as

.376 and also as .367 in Vogel's paper: in fact, the value .375 given here is correct to six decimal places, but it is not exactly 3/8 .

4. Bayes procedures

Consider the symmetric prior distribution defined by assigning probability $\frac{1}{2}$ to each of the hypotheses

$$H_1 : p_1 = \tfrac{1}{2}(1+\delta),\ p_2 = \tfrac{1}{2}(1-\delta)\ ; \qquad H_2 : p_1 = \tfrac{1}{2}(1-\delta),\ p_2 = \tfrac{1}{2}(1+\delta)\ .$$

Given the number of patients t and any fixed δ, $0 < \delta \leq 1$, let $B(\delta,t)$ denote the minimal Bayes risk within $\mathcal{D}$. The aim, in this section, is to obtain an algorithm (20) from which $B(\delta,t)$ can be computed. Theorem 5 establishes the general form of the corresponding Bayes procedure $\Delta = \Delta(\delta,t)$ within the class $\mathcal{D}$.

Later, we shall be concerned with

$$\mu(t) = \max_{0<\delta\leq 1} B(\delta,t) \tag{14}$$

and the least favourable choice $\delta = \delta_\mu$ which attains this maximum. We know that, for every allocation rule $\Delta \in \mathcal{D}$, the maximum risk $M_\Delta(t)$ must exceed the Bayes risk with respect to any prior distribution. This statement is not restricted to stopping times of the form (1): any well-defined allocation rule Δ for paired observations would lead, if $M_\Delta(t) < B(\delta,t)$, to a contradiction of the fact that $B(\delta,t)$ is the smallest possible average risk with respect to the given prior distribution. It follows that

$$\mu(t) = B(\delta_\mu,t) \leq M(t) \leq M_{\Delta_\mu}(t)\ , \tag{15}$$

where $\Delta_\mu = \Delta(\delta_\mu,t)$ is the Bayes procedure associated with δ_μ. The computations described in the next section will be used to verify, for most values of t, that $\mu(t) = M_{\Delta_\mu}(t)$, which is enough to confirm that Δ_μ is the minimax allocation rule.

Suppose that, after n pairs of patients have been assigned to the two treatments, we have obtained r_i successes with p_i, $i = 1,2$. The above prior distribution leads to posterior probabilities Π_1 and Π_2 for the two hypotheses with

$$\frac{\Pi_1}{\Pi_2} = \gamma^{r_1-r_2}, \qquad \gamma = \left(\frac{1+\delta}{1-\delta}\right)^2 > 1. \tag{16}$$

Let $j = r_1-r_2$, so that $\Pi_1 = \gamma^j/(\gamma^j+1)$, $\Pi_2 = 1/(\gamma^j+1)$. The posterior error probability, if we stop and decide optimally in favour of H_1 or H_2, is

$$\alpha_j = \min(\Pi_1,\Pi_2) = 1/(\gamma^{|j|}+1). \tag{17}$$

It is convenient to work by backwards induction using the variable $s = t-2n$, which represents the number of patients left after sampling n pairs. The stopping cost at the point (j,s), excluding previous sampling, is

$$K_j(s) = s\,\alpha_j. \tag{18}$$

For example, if $j > 0$ so that $\alpha_j = \Pi_2 < \Pi_1$, a decision to stop would allocate all the remaining patients to the first treatment. On the other hand, if we observe another pair of patients, this produces a transition from (j,s) to $(j+1, s-2)$, $(j, s-2)$ or $(j-1, s-2)$ with posterior probabilities u_j, v_j and w_j, respectively. It is easily verified that

$$\begin{aligned} u_j &= \tfrac{1}{4}(1+\delta^2) + \tfrac{1}{2}\delta\frac{(\gamma^j-1)}{(\gamma^j+1)}, \qquad v_j = \tfrac{1}{2}(1-\delta^2), \\ w_j &= \tfrac{1}{4}(1+\delta^2) - \tfrac{1}{2}\delta\frac{(\gamma^j-1)}{(\gamma^j+1)}, \qquad u_j + v_j + w_j = 1. \end{aligned} \tag{19}$$

Let us define $Q_j(s)$ as the minimum expected number of allocations of the inferior treatment among the s remaining patients, starting in state j.

Of course, we are mainly interested in the minimal Bayes risk $B(\delta,t) = \delta\, Q_0(t)$, which corresponds to the initial point $(0,t)$. This can be computed from the relations: $Q_j(0) = 0$, $Q_j(1) = \alpha_j$ and, for $s \geq 2$,

$$Q_j(s) = \min\{K_j(s),\ 1 + u_j Q_{j+1}(s-2) + v_j Q_j(s-2) + w_j Q_{j-1}(s-2)\}\ . \tag{20}$$

For example, if t is odd, we must determine $Q_j(3), Q_j(5), \ldots$ in succession, each for an appropriate set of states j, until we can evaluate $Q_0(t)$. The relevant states are those accessible from the optimal continuation region which consists of all points (j,s) at which $Q_j(s) < K_j(s)$.

In order to see the form of this continuation region, let

$$R_j(s) = K_j(s) - Q_j(s) \geq 0\ . \tag{21}$$

Thus, $R_j(s)$ is the advantage of continuation over stopping. A Bayes procedure is determined by applying, at each point (j,s) encountered during the sampling process, the rule: take another pair of observations if and only if $R_j(s) > 0$. It is not difficult to obtain the relations satisfied by $R_j(s)$ from (20). Clearly $R_j(0) = R_j(1) = 0$ and, for $s \geq 2$, $j \neq 0$, we have

$$R_j(s) = \max\{0,\ 2\alpha_j - 1 + u_j R_{j+1}(s-2) + v_j R_j(s-2) + w_j R_{j-1}(s-2)\}\ . \tag{22}$$

However, for $j = 0$, this is replaced by

$$R_0(s) = \max\{0,\ \tfrac{1}{2}\delta(s-2) + u_0 R_1(s-2) + v_0 R_0(s-2) + w_0 R_{-1}(s-2)\}\ . \tag{23}$$

We remark that $K_j(s) = K_{-j}(s)$ and according to (19), $u_j = w_{-j}$, $u_{-j} = w_j$. It follows that $Q_j(s)$ and $R_j(s)$ are symmetric in j and, in particular, $R_1(s-2) = R_{-1}(s-2)$ in relation (23). Notice also that $2\alpha_j - 1 < 0$ in (22), but $R_0(s) \geq \tfrac{1}{2}\delta(s-2)$ in (23), which guarantees continuation whenever $s > 2$.

Theorem 5. The optimal continuation region is determined by the rule: continue if and only if $|j| < d_s$, where $d_0 = d_1 = d_2 = 0$, $d_3 = d_4 = 1$, and, in general, d_s is non-decreasing in s with either $d_s = d_{s-2}$ or $d_s = d_{s-2} + 1$.

Proof. For a given point (j,s), consider using the Bayes procedure as if starting in state j with $s-1$ patients left and then allocating the final patient according to whether j is positive or negative. This policy is sub-optimal at (j,s) and hence, $Q_j(s) \leq Q_j(s-1) + \alpha_j$. Since $K_j(s) = K_j(s-1) + \alpha_j$, it follows from (21) that, in general,

$$R_j(s) \geq R_j(s-1) . \tag{24}$$

By direct calculation, $R_j(2) = 0$ for all j, so $d_0 = d_1 = d_2 = 0$. For $s \geq 3$ and any $j \neq 0$, $2\alpha_j - 1 < 0$ and equation (22) shows that $R_j(s) = 0$ whenever $R_{j+1}(s-2) = R_j(s-2) = R_{j-1}(s-2) = 0$. Hence, $R_j(3) = R_j(4) = 0$ when $j \neq 0$, but $R_0(4) \geq R_0(3) > 0$, so $d_3 = d_4 = 1$. The same argument based on (22) shows that, in general, $d_s \leq d_{s-2} + 1$. Finally, it follows from (24) that $d_s \geq d_{s-1}$ and the proof is complete. □

Before describing the computations, it will be helpful to modify the notation. Allocation rules of the type described in Theorem 5 can be converted to the standard form (1) by defining $A_n = \{j : |j| \geq c_n\}$, $c_n = d_{t-2n}$, $n = 1,2,\ldots,[t/2]$. Notice that this specification depends on the given value of t: c_n is the critical value of $|S_n|$ after observing n pairs of patients. We shall be mainly concerned with the behaviour of $B(\delta,t)$ and changes in the corresponding Bayes procedure $\Delta(\delta,t)$ as δ varies, for fixed t, so the notation will be simplified by writing $B(\delta) = B(\delta,t)$ and $\Delta(\delta) = \Delta(\delta,t)$.

5. Computations

Two computer programmes were essential for our work. One evaluates the minimal Bayes risk $B(\delta)$ and determines the corresponding allocation rule $\Delta(\delta)$ for the symmetric prior distribution on the two points $(p_1,p_2) = \left(\tfrac{1}{2}(1\pm\delta), \tfrac{1}{2}(1\mp\delta)\right)$, $0 < \delta \leq 1$. The other evaluates the risk $R_\Delta(p_1,p_2,t)$ for any pair (p_1,p_2) and any symmetric allocation rule Δ arising from a stopping time of the form:

$$N = \min\{n \geq 1 : |S_n| \geq c_n, [t/2]\} . \tag{25}$$

The first programme is based on the algorithm (20) described in the previous section. It can be accelerated by making use of Theorem 5 and by performing only those calculations needed in the algorithm to obtain $B(\delta) = \delta\, Q_0(t)$ and $\Delta(\delta)$. This requires some care. Serious problems with "overflow", the occurrence of numbers too large for the machine, are also avoided by the elimination of inessential calculations. We found it possible to evaluate $B(\delta)$ and $\Delta(\delta)$ accurately for values of t as large as 1200. Contrary to a widely held belief, there are non-trivial settings for which backwards induction algorithms are quite practical for large "horizons".

The programme used to evaluate the risk $R_\Delta(p_1,p_2,t)$ is based on formula (2). The relevant algorithm is best described for a general expectation of the form $E\, f(N,S_N)$ with the stopping time appearing in (1).

$$E\{f(N,S_N)\} = \sum_{n=1}^{[t/2]} \sum_{i\in A_n} p_{ni}\, f(n,i) ,$$

where $p_{ni} = P(N \geq n, S_n = i)$. The probabilities p_{ni} can be evaluated recursively in terms of $q_i = P(S_1=i)$: $q_1 = p_1(1-p_2)$, $q_0 = p_1p_2 + (1-p_1)(1-p_2)$, $q_{-1} = (1-p_1)p_2$ and all other $q_i = 0$. We have $p_{1i} = q_i$ and

$$p_{n+1,j} = \sum_{i \notin A_n} p_{ni}\, q_{j-i} , \qquad n = 1,2,\ldots,[t/2]-1 .$$

We are concerned with subsets of the form $A_n = \{j : |j| \geq c_n\}$ with critical values c_n specified in various ways.

For most values of t, the minimax allocation rule is given by the Bayes procedure $\Delta_\mu = \Delta(\delta_\mu)$, where δ_μ is the least favourable δ, i.e., the value of δ which maximises $B(\delta)$. The programme which evaluates $B(\delta)$ and determines $\Delta(\delta)$ can be used to find this "candidate" Δ_μ. The risk function can then be computed, using the other programme, to discover whether the candidate is minimax. According to the inequalities (15), it is enough to show that

$$R_{\Delta_\mu}(p_1,p_2,t) \leq B(\delta_\mu) \tag{26}$$

for all (p_1,p_2) in the unit square. Although we were not able to establish this analytically, as a result of extensive calculations we are convinced that Δ_μ is minimax for all but 23 of the first 201 values of t.

There are three different cases revealed by the computations and the most common of these will be described first.

Case A. (i) As δ increases from 0 to 1, the allocation rules $\Delta(\delta)$ make a number of transitions.

For example, when $t = 20$, the sequence $c_1,c_2,\ldots,c_{10}$ which gives the critical values of $|S_n|$ and specifies $\Delta(\delta)$ begins as 2 2 2 1 1 1 1 1 0 0. It switches to 2 2 1 1 1 1 1 1 0 0 at about $\delta = .06$, to 2 1 1 1 1 1 1 1 0 0 at about $\delta = .29$, and to 1 1 1 1 1 1 1 1 0 0 at about $\delta = .38$.

(ii) The function $B(\delta)$ is continuous and unimodal. It is differentiable except at transition points, where it has "corners".

(iii) The mode δ_μ does not occur at a transition point, so that $B(\delta)$ has zero slope at $\delta = \delta_\mu$.

For example, when $t = 20$, δ_μ is about .39 and, to four significant figures, $B(\delta) = 1.717$ from $\delta = .385$ to $\delta = .395$.

(iv) For each fixed $\delta > 0$, and for $(p_1,p_2) = \left(\tfrac{1}{2}(1+\delta+\mu), \tfrac{1}{2}(1-\delta+\mu)\right)$, $|\mu| \le 1-\delta$, the risk $R_{\Delta_\mu}(p_1,p_2,t)$ is symmetric and unimodal in μ with its maximum at $\mu = 0$. Thus the maximum of $R_{\Delta_\mu}(p_1,p_2,t)$ over the unit square must occur somewhere on the diagonal line $p_1 + p_2 = 1$.

(v) The risk $R_{\Delta_\mu}(p_1,p_2,t)$ along the diagonal, where $(p_1,p_2) = \left(\tfrac{1}{2}(1+\delta), \tfrac{1}{2}(1-\delta)\right)$, has a local maximum at $\delta = \delta_\mu$. This follows from (ii) and (iii), because the risk agrees with $B(\delta)$ wherever $\Delta(\delta) = \Delta_\mu$.

(vi) The risk $R_{\Delta_\mu}(p_1,p_2,t)$, where $(p_1,p_2) = \left(\tfrac{1}{2}(1+\delta), \tfrac{1}{2}(1-\delta)\right)$, is symmetric in δ and non-decreasing for $0 \le \delta \le \delta_\mu$. It is either non-increasing for $\delta_\mu \le \delta \le 1$ or it decreases to some minimal value and increases thereafter.

(vii) The risk $R_{\Delta_\mu}(p_1,p_2,t)$ at $(p_1,p_2) = (1,0)$ does not exceed $B(\delta_\mu)$.

In case A, it is clear from these conditions that Δ_μ is the minimax allocation rule.

There are two ways in which the search for a minimax rule can fail, by a violation of (iii) or by a violation of (vii). In practice, the latter is more important, so it is convenient to classify the exceptional situations as follows.

Case B. Condition (vii) does not hold and, perhaps, (iii) also fails.

Case C. Condition (iii) does not hold, but all the other conditions are satisfied.

In case B, the risk function referred to in (vi) does begin to increase for large values of δ and the inequality (26) is violated at $\delta = 1$. This case occurs for the first time when $t = 21$.

When condition (iii) does not hold, the notation $\Delta_\mu = \Delta(\delta_\mu)$ is misleading since there are two allocation rules which attain the minimal Bayes risk $B(\delta_\mu)$. The first, Δ_ℓ, is Bayes for δ in some interval $[a,\delta_\mu]$ to the left of δ_μ and the second, Δ_r, is Bayes for δ in an interval $[\delta_\mu,b]$ on the right, $a < \delta_\mu < b$. The function $B(\delta)$ has a corner at its maximal point δ_μ, a positive slope on the left and a negative slope on the right. Consider $R_{\Delta_\ell}(p_1,p_2,t)$, with $(p_1,p_2) = \left(\tfrac{1}{2}(1+\delta), \tfrac{1}{2}(1-\delta)\right)$, as δ varies. It agrees with $B(\delta)$ on $[a,\delta_\mu]$ and, therefore, has a strictly positive slope at $\delta = \delta_\mu$. It must increase further to the right of δ_μ, so (26) cannot hold. Thus, we are unable to deduce that Δ_ℓ is minimax and, likewise, Δ_r is effectively eliminated as a candidate. There are several examples of this type to be mentioned and, to avoid confusion, the allocation rules Δ_ℓ and Δ_r will be treated separately, as examples of case B or case C.

Conditions (iii) and (vii) are violated when $t = 23$ and both rules Δ_ℓ and Δ_r are examples of case B. The first occurrence of case C is when $t = 57$, for Δ_r. The sequence $c_1,c_2,\ldots,c_{28}$ which describes Δ_ℓ begins with 3 3 2 2 ... and condition (vii) does not hold. However, the corresponding sequence for Δ_r begins with 2 2 2 2 ... and (vii) is valid for this rule. For all other values of t, $1 \le t \le 201$, only one of the cases A, B, or C occurs. In particular, the next examples of case C are when $t = 65$, for both Δ_ℓ and Δ_r.

We conjecture that, when there are two candidates Δ_ℓ and Δ_r and both satisfy condition (vii), there is a randomised mixture of Δ_ℓ and Δ_r which is minimax.

We shall say that an allocation rule Δ is *essentially minimax* if

$$R_\Delta(p_1,p_2,t) \le B(\delta_\mu) + 10^{-5}t^{\frac{1}{2}} \qquad (27)$$

for all (p_1,p_2) in the unit square. An examination of the computations shows, in every instance of case C, $1 \le t \le 201$, that the allocation rule concerned is essentially minimax. In other words, the distinction between cases A and C has no practical significance: if $R_{\Delta_\mu}(1,0,t) \le B(\delta_\mu)$, then Δ_μ is, for all practical purposes, a minimax allocation rule.

The programme for computing $R_\Delta(p_1,p_2,t)$ can be used to analyse other allocation rules. We have investigated the truncated SPRT, an adaptation of a rule recommended by Anscombe (1963) and one adapted from a rule suggested by Lai, Levin, Robbins and Siegmund (1982). The results of these investigations are included in the next section. The stopping time for Anscombe's allocation rule takes the form:

$$N = \min\{n \ge 1 : 1 - \Phi\big((2/n)^{\frac{1}{2}}\,|S_n|\big) \le n/t,\ [t/2]\}\ ,$$

where $\Phi(x) = \int_{-\infty}^{x} \phi(u)\,du$, $\phi(u) = (2\pi)^{-\frac{1}{2}} e^{-\frac{1}{2}u^2}$. For the Lai-Levin-Robbins-Siegmund (LLRS) rule, the stopping time is given by

$$N = \min\{n \ge 1 : g\big((2/n)^{\frac{1}{2}}\,|S_n|\big) \ge t/2n\}\ ,$$

where

$$g(x) = \frac{2\Phi(x)-1}{x\phi(x)} + 1\ , \qquad x > 0\ , \qquad g(0) = 3\ .$$

Observe that g is increasing and, hence, $N < 1 + t/6$, so $N \leq t/6$ when the latter is an integer. Thus, the LLRS rule samples no more than about a third of the patients before a decision is reached in favour of one or other of the treatments.

6. Numerical results

Table 1 lists the normalised maximum risks $M_\Delta(t)/t^{\frac{1}{2}}$ for the four allocation rules described in the previous section: the minimax rule; the truncated SPRT with D chosen optimally; the adaptation of Anscombe's rule, and the LLRS rule. For convenience, only even values of t are included. The table includes one example of case B, described earlier. The figure in the first column for $t = 60$ is $B(\delta_\mu)/(60)^{\frac{1}{2}} = .3742$, but $M_{\Delta_\mu}(60)/(60)^{\frac{1}{2}} = .3873$ so $\Delta_\mu = \Delta(\delta_\mu)$ is obviously not minimax, by comparison with the SPRT. However, the figures also make clear that the SPRT is very close to being minimax, since the minimax risk is at least $B(\delta_\mu)$.

Observe that some entries occur in more than one column, not always for the same reason. When t is small, there are only a few reasonable symmetric rules from which to choose and, sometimes, the same rule is selected by more than one method. In other cases, a repeated entry only reflects a near equality, within four decimal places, such as in the first two columns when $t = 20$. In still further cases, two rules have rather different risk functions, but the same maxima $M_\Delta(t)$, occurring at the exceptional point $(p_1,p_2) = (1,0)$. When $p_1 = 1$, $p_2 = 0$, the process $S_1,S_2,\ldots$ is deterministic and two different rules can easily have the same stopping time and, hence, the same risk: see formula (8). This situation arises in the last two columns when $t = 20$.

A "discreteness effect" is clearly visible in the first two columns of Table 1. The effectiveness of the best available rule varies with t . For example, for the SPRT, the optimal D value is 1 when $t = 2,4,\ldots,24$ and then it switches to $D = 2$ for $t = 26,28,\ldots,72$. Near the middle of the first range, at $t = 12$, $D = 1$ gives a good "fit" and the ratio $.3579$ is relatively small. At $t = 20$, the fit of $D = 1$ is not so good, but better than $D = 2$, and the ratio $.3841$ is larger. Similarly, the middle of the

range for $D = 2$ is near $t = 50$, where the ratio .3702 is again relatively small. The discreteness effect is also apparent in the first column, but the pattern is harder to analyse because there are many more allocation rules available.

The ratios $M_\Delta(t)/t^{\frac{1}{2}}$ are all fairly stable for $t \geq 30$ and it can be seen that there is little difference between the minimax, SPRT and Anscombe rules. The LLRS procedure does less well. This seems to be because paired sampling must stop with about a third or less of the total number of patients sampled, which causes difficulties when p_1-p_2 reaches its critical levels, at values proportional to $t^{-\frac{1}{2}}$.

Table 2 provides a detailed comparison of the risk functions for the minimax rule and the truncated SPRT when $t = 100$. In this case, the least favourable prior distribution corresponds to $\delta_\mu = .188$. The sequence $c_1,c_2,\ldots,c_{50}$ which describes the stopping time N for the minimax rule, according to (25), consists of 26 threes, 16 twos, 6 ones and 2 zeros, in that order. The optimal choice of critical level for the truncated SPRT is $D = 3$. For every pair of entries in the table, the minimax rule has a smaller, or the same, risk. This suggests that the truncated SPRT is inadmissible, but the differences are small except where p_1 and p_2 are both near 0 or both near 1. The risk functions are quite flat, apart from the steep descent to zero near the line $p_1 = p_2$. It would be interesting to compare these with the risk functions of fully adaptive Bayes procedures, such as those considered by Berry (1978). However, the allocation rules involved are much more complicated and difficult to evaluate without extensive simulations.

It appears that the minimax risk $M(t)$ has a growth rate close to $.3714\ t^{\frac{1}{2}}$. The evidence for this is provided by our numerical evaluations of $M_\Delta(t)$ for large values of t when $\Delta = \Delta_\mu$ is the minimax rule: the ratio $M_\Delta(t)/t^{\frac{1}{2}}$ is .3705 for $t = 100$, .3722 for $t = 200$, .3714 for $t = 800$ and .3714 for $t = 1200$. A limiting ratio between .371 and .372 seems very likely.

Consider the sequence $c_1,c_2,\ldots,c_{[t/2]}$ which characterises the allocation rule Δ_μ. For $t = 1,2,\ldots,20$, the sequence takes the form 1 1 ... 1 0 or 1 1 ... 1 0 0, according as t is odd or even. Each of these

is an example of case A, in the terminology of Section 5, and Δ_μ is minimax. The critical value 2 first appears in the sequence when $t = 21$ and this leads to complications for $t = 21,22,\ldots,26$: when c_1 shifts from 1 to 2 , the normalised risk $R_{\Delta_\mu}(p_1,p_2,t)/t^{\frac{1}{2}}$ at $(p_1,p_2) = (1,0)$ changes from $1/t^{\frac{1}{2}}$ to $2/t^{\frac{1}{2}}$, which causes the location of its maximum to move from an interior point of the unit square to the point $(1,0)$ in the corner. These values of t are covered by case B described in the previous section and we cannot claim that Δ_μ is minimax. Since the ratio $2/t^{\frac{1}{2}}$ is decreasing in t , one might expect the problem to disappear, and it does when $t = 27$. However, the same phenomenon reappears when the critical value 3 first has an effect, at $t = 57$, and it persists for $t = 58, 59, \ldots, 63$. The introduction of 4's at the start of the sequence $c_1,c_2,\ldots$ causes the same problem when $t = 113, 114$ and 115 . We have not tried to locate the first occurrence of 5's in the sequence, but it seems doubtful whether this phenomenon can recur indefinitely.

The reader is reminded that, when $t = 57$, the allocation rules Δ_ℓ and Δ_r illustrate case B and case C, respectively. The rule Δ_r is essentially minimax, as in all the other examples of case C . These occur for seven other values of t in the range $1 \le t \le 201$: $t = 65, 87, 123, 125, 132,$ 189 and 198. We can confidently assert that Δ_μ is a minimax rule for at least 178 of the first 201 values of t .

It is worth commenting on the choice of the parameter D in the truncated SPRT. As we have shown, this type of allocation rule can reduce the maximum risk to a level very close to the minimax value $M(t)$. The exact specification of D to attain $\min M_D(t)$ involves extensive computations, but almost the same results can be obtained by using simpler approximations. Table 3 demonstrates this by comparing three methods. Column (a) shows the even values of $t \le 300$ for which $D = 1, 2, 3, 4$ or 5 is optimal. The other two columns give similar ranges obtained in the following way. Method (b) is based on the upper bound :

$M_D(t) \leq U_D(t)$, established in Theorem 4 and, for each t , the corresponding D is determined by minimising $U_D(t)$. This is a straightforward computation using formula (13). Method (c) is a direct application of Vogel's asymptotic result, quoted at the end of Section 3. For column (c), D is defined simply as the nearest positive integer to $0.292\, t^{\frac{1}{2}}$. The table shows few differences between the three methods and these occur only when t is near a value at which there is a change in the optimal value of D . In such cases, because of the minimisation, there is very little difference between the two competing values of $M_D(t)$. For practical purposes, the simplest method (c) is quite effective and it can also be used for $t > 300$. Another obvious feature of the table is that D changes slowly with t . It may not be easy to decide what is a realistic value of t , in designing a medical trial: see the discussion in Anscombe's paper (1963). Hence, the lack of sensitivity of the truncated SPRT with respect to t may be another practical advantage.

The discrete process $S_1, S_2, \ldots, S_{[t/2]}$ can be replaced by a Wiener process with an unknown drift parameter and one obtains a model for which it can be shown analytically, rather than numerically, that the minimax allocation rule is Bayes for an appropriate symmetric two-point prior distribution. The Bayes rule can be obtained, in principle, as the solution of a free boundary problem involving the heat equation. In recent work, so far unpublished, Simons has obtained close inner and outer approximations to the entire stopping boundary, using techniques developed earlier by Bather: a description of these techniques and other applications is given in the recent paper by Bather (1983). The same continuous time model has been studied in some detail by Chernoff and Petkau (1981), but for a normal prior distribution on the unknown drift. They conclude that the sub-optimal rule suggested by Anscombe (1963) performs very well. Since Anscombe's rule, in the present setting, is nearly minimax, as is the truncated SPRT, we are further encouraged to recommend the latter.

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TABLE 1

Normalised maximum risk $M_{\Delta}(t)/t^{\frac{1}{2}}$ for four allocation rules

t	Minimax	SPRT	Anscombe	LLRS
2	.7071	.7071	.7071	.7071
4	.5000	.5000	.5000	.5000
6	.4103	.4103	.4103	.4593
8	.3726	.3726	.3726	.3854
10	.3598	.3598	.3598	.3870
12	.3579	.3579	.3579	.5774
14	.3613	.3613	.5345	.5345
16	.3676	.3676	.5000	.5000
18	.3754	.3754	.4714	.4714
20	.3841	.3841	.4472	.4472
30	.3811	.3886	.3842	.4222
40	.3697	.3714	.3701	.4721
50	.3697	.3702	.3759	.4246
60	.3742*	.3760	.3865	.4196
70	.3757	.3852	.3829	.4106
80	.3730	.3786	.3801	.4026
90	.3710	.3738	.3716	.4130
100	.3705	.3721	.3707	.4129
120	.3730	.3741	.3779	.4124
140	.3727	.3803	.3780	.4043
160	.3713	.3747	.3767	.4095
180	.3712	.3729	.3754	.4110
200	.3722	.3736	.3792	.4063

* Δ_{μ} is not minimax in this case: see text.

TABLE 2

Risk function $R_{\Delta}(p_1,p_2,t)$ for $t = 100$; minimax rule

(lower values) and SPRT (upper values)

p_2 \ p_1	.1	.2	.3	.4	.5	.6	.7	.8	.9	1
0	2.849 2.447	2.999 2.927	3.000 2.995	3.000 3.000	3.000 3.000	3.000 3.000	3.000 3.000	3.000 3.000	3.000 3.000	3.000 3.000
.1		2.761 2.653	3.125 3.065	3.083 3.070	3.038 3.037	3.015 3.015	3.005 3.005	3.001 3.001	3.000 3.000	3.000 3.000
.2			2.942 2.906	3.418 3.386	3.279 3.268	3.129 3.128	3.047 3.047	3.012 3.012	3.001 3.001	3.000 3.000
.3				3.083 3.067	3.638 3.619	3.416 3.407	3.173 3.171	3.047 3.047	3.005 3.005	3.000 3.000
.4					3.152 3.142	3.715 3.699	3.416 3.407	3.129 3.128	3.015 3.015	3.000 3.000
.5						3.152 3.142	3.638 3.619	3.279 3.268	3.038 3.037	3.000 3.000
.6							3.083 3.067	3.418 3.386	3.083 3.070	3.000 3.000
.7								2.942 2.906	3.125 3.065	3.000 2.995
.8									2.761 2.653	2.999 2.927
.9										2.849 2.447

TABLE 3

Range of even $t \leq 300$ with parameter D in SPRT; methods (a), (b), (c)

D	(a)	(b)	(c)
1	2 - 24	2 - 24	2 - 26
2	26 - 72	26 - 72	28 - 72
3	74 - 138	74 - 142	74 - 142
4	140 - 230	144 - 236	144 - 236
5	232 ...	238 ...	238 - 354