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Approximate confidence intervals after a sequential clinical trial comparing two exponential survival curves with censoring

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Abstract

A sequential test is considered for comparing two exponential survival curves with unknown failure rates $\theta_1, \theta_2 > 0$. The survival times are censored by both real time and an independent censoring variable. It is shown how very weak expansions for the bivariate version of the signed root transformation may be used to construct an approximate confidence interval for $\delta = \log(\theta_1/\theta_2)$ following the test. The accuracy of the method is illustrated by simulation results for several sequential tests and data-dependent allocation rules. © 1997 Elsevier Science B.V.

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1. Introduction

Suppose we wish to use a sequential test to compare two exponential survival curves with censoring. This problem has been studied by, among others, Flehinger and Louis (1971), Louis (1977) and Hayre and Turnbull (1981). The parameter of interest is the ratio of expected survival times. The above authors derive sequential probability ratio tests for which the error probability is insensitive to the allocation rule. This property led to the consideration of data-dependent allocation rules which assign more patients to the better treatment, relative to pairwise allocation. However, the question of estimation following the tests was not considered.

The main purpose of this paper is to show how an approximate confidence interval for the ratio of expected survival times may be constructed following a sequential test. The tests considered here are based on the large-sample test statistic studied by

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Hayre and Turnbull (1981) and Coad (1994). These authors restricted attention to tests with parallel stopping boundaries. Here a more general sequential procedure is developed which includes as special cases tests with converging or diverging straightline boundaries and tests with curved boundaries. For some related work, see also Hayre (1979).

The work provides a two-sample extension to the one-sample problem studied by Coad and Woodroofe (1996). The confidence interval method described here uses the bivariate version of the signed root transformation studied by Bickel and Ghosh (1990) to construct an approximate pivot. This transformation is applied to a reparameterised version of the problem. Very weak expansions as in Woodroofe (1986, 1992a) are then derived for this transformation from which an approximate pivot is easily identified. Our results go beyond earlier work by allowing for a nuisance parameter and including sequential allocation.

The two-sample survival analysis model is described in Section 2 and the general form of the sequential tests under consideration is given. Very weak expansions are reviewed in Section 3, and then the bivariate version of the signed root transformation is described. In Sections 4 and 5, Stein's identity is used to obtain expansions for the posterior expectation of functions of the transformed parameter, and an approximately pivotal quantity is constructed for the ratio of expected survival times. A number of different data-dependent allocation rules are described in Section 6, and the results of a simulation study of these rules and of two sequential tests are reported in Section 7. Possible extensions to the work are indicated in Section 8. Theoretical justification of the method is provided in an appendix.

2. The model

Consider a clinical trial in which patients can be assigned to one of two treatments. Patients enter the trial at unit times, $1,2,\ldots$, and are assigned to one of the two treatments. Let t_{ij} denote the time at which the jth patient assigned to treatment i enters the trial for $i=1,2$ and $j=1,2,\ldots$. The survival and censoring times for this patient are denoted by L_{ij} and C_{ij}, respectively. We assume that the L_{ij}, $j=1,2,\ldots$, are independent exponential random variables with unknown failure rate $\theta_i>0$, $i=1,2$. It is further assumed that the C_{ij} are independent positive random variables with unknown distribution function G, and that the C_{ij} and L_{ij} are independent.

Let n_i denote the number of patients assigned to treatment i at time n, and let

$$X_{nij}=\min(L_{ij},C_{ij},n-t_{ij}+1),$$

$$\delta_{nij}=1\{L_{ij}\leqslant\min(C_{ij},n-t_{ij}+1)\} \tag{1}$$

for $n=1,2,\ldots$, $i=1,2$ and $j=1,\ldots,n_i$. At time n, X_{nij} denotes the time on test for the jth patient assigned to treatment i and δ_{nij} is an indicator variable with value one if this patient has died while under test, and zero otherwise. Thus, the survival times for each treatment are censored by both real time and an independent censoring variable.

As indicated in Section 1, the parameter of interest is $\delta = \log(\theta_1/\theta_2)$, and it is convenient to reparameterise the problem in terms of δ and $\omega = \theta_2$. The log-likelihood function at time n can then be written as

$$\ell_n(\delta,\omega) = K_{n1}\delta + (K_{n1} + K_{n2})\log\omega - \omega(e^{\delta}S_{n1} + S_{n2}), \tag{2}$$

where $K_{ni} = \sum \delta_{nij}$ and $S_{ni} = \sum X_{nij}$, $i = 1,2$, and all summations are over $j = 1,\ldots,n_i$. The maximum likelihood estimators of δ and ω are

$$\hat{\delta}_n = \log\left(\frac{K_{n1}S_{n2}}{S_{n1}K_{n2}}\right) \quad \text{and} \quad \hat{\omega}_n = \frac{K_{n2}}{S_{n2}}$$

for $K_{ni} \geqslant 1$, $i = 1,2$.

The sequential tests we shall consider depend on three design parameters, $a > 0$ and $0 < m < N$. The quantity $i_n^2 = K_{n1}K_{n2}/(K_{n1} + K_{n2})$ can be regarded as a measure of information at time n. The tests require this information to be at least m and are truncated when the information first reaches N. Specifically, let g be a convex function for which $g(x) > 0$ for all $x \neq 0$, and let

$$(K_{t1}, K_{t2}) = \text{first}\{(K_{n1}, K_{n2}) : i_n^2 g(\hat{\delta}_n) > a\}. \tag{3}$$

Then the tests terminate at time $\tau = \tau_1 + \tau_2$, where

$$i_\tau^2 = \min\{N, \max(i_t^2, m)\}. \tag{4}$$

The test studied by Hayre and Turnbull (1981) and Coad (1994) for testing H_0: $\delta < 0$ against H_1: $\delta > 0$ is of the form (3) with $g(\hat{\delta}_n) = |\hat{\delta}_n|$. With this choice of g, (3) and (4) resemble a truncated sequential probability ratio test, but with nuisance parameters estimated. If we let $b = a/N$ and $g(\hat{\delta}_n) = b + |\hat{\delta}_n|$, then (3) and (4) give a triangular test for testing H_0 against H_1. Now consider testing H_0: $\delta = 0$ against H_1: $\delta \neq 0$, using a repeated significance test. Then this test can be written in the form (3) with $g(\hat{\delta}_n) = |\hat{\delta}_n|^2$.

Sequential tests of the form (3) are appealing for several reasons. A general result of Hayre and Turnbull (1981) suggests that, for a given g, the error probability is insensitive to the allocation rule. Our simulations confirm their findings for a wider class of functions g. The tests are simple and natural extensions of the one-sample tests for normal data considered by Woodroofe (1992b), and can also be used as a basis for a simple sequential procedure for comparing more than two exponential survival curves; see Section 8.

3. The pivotal quantity

The goal is to find confidence intervals for δ which are asymptotically accurate to a high order. To accomplish this, an approximately pivotal quantity $z_{\tau 1}^* = z_{\tau 1}^*(\delta; \text{data})$

is constructed which is asymptotically standard normal to third order in the very weak sense of Woodroofe (1986). That is, letting a be as in (3),

$$\int_{\Omega} E_{\delta,\omega}\{h(z_{\tau 1}^{*})\}\xi(\delta,\omega)\,\mathrm{d}\delta\,\mathrm{d}\omega = \Phi h + \mathrm{o}(1/a) \tag{5}$$

as $a \to \infty$, for large classes of functions h and twice continuously differentiable densities ξ with compact support in Ω, where

$$\Phi h = \int_{-\infty}^{\infty} h(z)\phi(z)\,\mathrm{d}z \tag{6}$$

and ϕ denotes the standard normal density function. For example, letting h be the indicator of $[-c, c]$, where $c > 0$, (5) becomes

$$\int_{\Omega} \mathrm{pr}_{\delta,\omega}(|z_{\tau 1}^{*}| \leqslant c)\xi(\delta,\omega)\,\mathrm{d}\delta\,\mathrm{d}\omega = \Phi(c) - \Phi(-c) + \mathrm{o}(1/a)$$

as $a \to \infty$, for twice continuously differentiable compactly supported ξ, where Φ denotes the standard normal distribution function. This is the theoretical basis for the confidence intervals. Woodroofe (1986, 1989) calls relations of the form (5) "very weak expansions" and writes $E_{\delta,\omega}\{h(z_{\tau 1}^{*})\} = \Phi h + \mathrm{o}(1/a)$ very weakly. He argues that very weak expansions are strong enough to support a frequentist interpretation of confidence intervals, essentially because parameter values will vary in repeated applications.

To describe the approximately pivotal quantity, recall that $\hat{\delta}_n$ and $\hat{\omega}_n$ denote the maximum likelihood estimates of δ and ω at time n, and let $\hat{\omega}_n(\delta)$ denote the restricted maximum likelihood estimate of ω at time n, given δ. It is easily verified using (2) that

$$\hat{\omega}_n(\delta) = \frac{K_{n1} + K_{n2}}{\mathrm{e}^{\delta} S_{n1} + S_{n2}}.$$

Following Bickel and Ghosh (1990), consider the bivariate version of the signed root transformation given by

$$\begin{aligned} z_{n1}(\delta,\omega) &= \surd[2\{\ell_n(\hat{\delta}_n, \hat{\omega}_n) - \ell_n(\delta, \hat{\omega}_n(\delta))\}]\mathrm{sign}(\delta - \hat{\delta}_n), \\ z_{n2}(\delta,\omega) &= \surd[2\{\ell_n(\delta, \hat{\omega}_n(\delta)) - \ell_n(\delta,\omega)\}]\mathrm{sign}(\omega - \hat{\omega}_n(\delta)) \end{aligned} \tag{7}$$

for $-\infty < \delta < \infty$, $\omega > 0$, when $K_{ni} \geqslant 1$, $i = 1,2$, where $\ell_n(.,.)$ is given by (2). It can be shown that

$$\ell_n(\hat{\delta}_n, \hat{\omega}_n) - \ell_n(\delta, \hat{\omega}_n(\delta)) = (K_{n1} + K_{n2}) I\left(\frac{K_{n1}}{K_{n1} + K_{n2}}, \mathrm{e}^{\delta - \hat{\delta}_n}\right), \tag{8}$$

where $I(y,z) = \log(yz + 1 - y) - y\log z$ for $0 < y < 1$, $z > 0$, that

$$\ell_n(\delta, \hat{\omega}_n(\delta)) - \ell_n(\delta,\omega) = (K_{n1} + K_{n2}) H\left\{\frac{\omega}{\hat{\omega}_n(\delta)}\right\},$$

where $H(x) = x - 1 - \log x$ for $x > 0$, and that (7) is a one-to-one transformation of δ and ω. Observe that $\ell_n(\delta,\omega) = \ell_n(\hat{\delta}_n, \hat{\omega}_n) - \frac{1}{2}\|z_n\|^2$ for all $-\infty < \delta < \infty$, $\omega > 0$ and

$K_{ni} \geqslant 1$, $i = 1,2$, where $\|.\|$ denotes the Euclidean norm of a vector. The transformed parameter vector (z_{n1}, z_{n2}) is approximately standard bivariate normal for n large, under mild conditions on the allocation rule.

Now observe from (7) and (8) that z_{n1} is a function of δ only. Thus, z_{n1} may be regarded as a first approximation to a pivotal quantity. The main results in this paper include very weak asymptotic expansions for the mean of $z_{\tau 1}$ and a related variance for stopping times τ of the form (4). We may use these expansions to construct an approximately pivotal quantity $z^*_{\tau 1}$, by standardisation, whose distribution can be approximated by a standard normal.

4. Expansions

Observe that the left-hand side of (5) may be written as the expectation of $h(z^*_{\tau 1})$ in a Bayesian model in which δ and ω have prior density ξ on Ω. So, the left-hand side of (5) may be studied by approximating posterior distributions. To derive asymptotic expansions, consider a Bayesian model in which δ and ω have a prior density ξ on $(-\infty, \infty) \times (0, \infty)$. Expectation in the Bayesian model is denoted by E_ξ, while conditional expectation given $\{X_{kij}, \delta_{kij}, k = 1, \ldots, n,\ i = 1,2,\ j = 1, \ldots, k_i\}$ is denoted by E^n_ξ. If $K_{ni} \geqslant 1$, $i = 1,2$, then the conditional joint density of (δ, ω) given $\{X_{kij}, \delta_{kij},\ k = 1, \ldots, n,\ i = 1,2,\ j = 1, \ldots, k_i\}$ is

$$\xi_n(\delta, \omega) \propto e^{\ell_n(\delta,\omega)} \xi(\delta, \omega),$$

and, hence, the conditional joint density of (z_{n1}, z_{n2}) given $\{X_{kij}, \delta_{kij}, k = 1, \ldots, n,\ i = 1,2,\ j = 1, \ldots, k_i\}$ is

$$\zeta_n(z) \propto \xi(\delta, \omega) J_1\left(\frac{\omega}{\hat{\omega}_n(\delta)}\right) J_2\left(\frac{K_{n1}}{K_{n1} + K_{n2}}, e^{\delta - \hat{\delta}_n}\right) e^{-(1/2)\|z\|^2},$$

where $J_1(x) = \sqrt{\{2H(x)\}}/|H'(x)|$ for $x > 0$ and $J_2(y,z) = \sqrt{\{2I(y,z)\}}/|z - 1|$ for $0 < y < 1$, $z > 0$, represent Jacobian terms. Thus, the conditional joint density of (z_{n1}, z_{n2}) given $\{X_{kij}, \delta_{kij},\ k = 1, \ldots, n,\ i = 1,2,\ j = 1, \ldots, k_i\}$ may be written in the form

$$\zeta_n(z) = f_n(z)\phi_2(z),$$

where

$$f_n(z) = \frac{1}{c_n} J_1\left(\frac{\omega}{\hat{\omega}_n(\delta)}\right) J_2\left(\frac{K_{n1}}{K_{n1} + K_{n2}}, e^{\delta - \hat{\delta}_n}\right) \xi(\delta, \omega), \tag{9}$$

$z = (z_1, z_2)$ is related to (δ, ω) by (7), ϕ_2 denotes the standard normal bivariate density function, and c_n is a normalising constant.

If ξ is twice continuously differentiable with compact support, then a version of Stein's identity (Stein, 1986) may be applied to the posterior distributions of (z_{n1}, z_{n2})

in order to obtain asymptotic expansions. Let h be a function of polynomial growth, and define Φh by (6). The Stein transformation is defined as

$$Uh(z) = \mathrm{e}^{(1/2)z^2} \int_z^\infty \{h(y) - \Phi h\} \mathrm{e}^{-(1/2)y^2}\, \mathrm{d}y.$$

Observe that U is a linear transformation. For example, if $h_i(z) = z^i$ for $i = 1,2$, then $Uh_1(z) = 1$ and $Uh_2(z) = z$ for all $-\infty < z < \infty$. To state the result, it is convenient to denote selected partial derivatives by $'$. Specifically, let $f' = \partial f/\partial z_1$, $f'' = \partial^2 f/\partial z_1^2$ and $J_2'(y,z) = \partial J_2(y,z)/\partial z$. Then

$$\begin{aligned} E_\xi^\tau\{h(z_{\tau 1})\} &= \Phi h + E_\xi^\tau \left\{ Uh(z_{\tau 1}) \frac{f_\tau'(z_\tau)}{f_\tau(z_\tau)} \right\} \\ &= \Phi h + \Phi Uh E_\xi^\tau \left\{ \frac{f_\tau'(z_\tau)}{f_\tau(z_\tau)} \right\} + E_\xi^\tau \left\{ U^2 h(z_{\tau 1}) \frac{f_\tau''(z_\tau)}{f_\tau(z_\tau)} \right\}, \end{aligned} \tag{10}$$

where

$$\Phi Uh = \int_{-\infty}^\infty Uh(z)\phi(z)\, \mathrm{d}z = \int_{-\infty}^\infty zh(z)\phi(z)\, \mathrm{d}z$$

and U^2 denotes the composition of U with itself. See Corollary 1 of Woodroofe and Coad (1997) for a derivation. Using (9), the derivatives may be computed explicitly, and it is easily seen that $f_\tau'(z_\tau)/f_\tau(z_\tau)$ and $f_\tau''(z_\tau)/f_\tau(z_\tau)$ are of order $1/\sqrt{a}$ and $1/a$, respectively, where a is as in (3). Letting $\Gamma_{a,1} = \sqrt{a} f_\tau'(z_\tau)/f_\tau(z_\tau)$, $\Gamma_{a,2} = a f_\tau''(z_\tau)/f_\tau(z_\tau)$, $K_\tau = K_{\tau 1} + K_{\tau 2}$ and $\alpha_\tau = K_{\tau 1}/K_\tau$, the conditional expectation in (10) may be rewritten as

$$E_\xi^\tau\{h(z_{\tau 1})\} = \Phi h + \frac{\Phi Uh}{\sqrt{a}} E_\xi^\tau(\Gamma_{a,1}) + \frac{1}{a} E_\xi^\tau\{U^2 h(z_{\tau 1}) \Gamma_{a,2}\}, \tag{11}$$

where

$$\begin{aligned} \Gamma_{a,1} = \sqrt{\left(\frac{a}{K_\tau}\right)} \Bigg[& \frac{\omega}{\hat{\omega}_\tau(\delta)} \frac{1}{1-\alpha_\tau} \mathrm{e}^{\delta - \hat{\delta}_\tau} \frac{J_1'}{J_1} \left(\frac{\omega}{\hat{\omega}_\tau(\delta)} \right) J_2(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) \\ & + \frac{\hat{\omega}_\tau}{\hat{\omega}_\tau(\delta)} \frac{K_{\tau 1} K_{\tau 2}}{i_\tau^4} \left\{ J_2(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) \frac{\partial \xi/\partial \delta}{\xi} + \mathrm{e}^{\delta - \hat{\delta}_\tau} J_2'(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) \right\} \Bigg] \end{aligned}$$

and

$$\begin{aligned} \Gamma_{a,2} = \frac{a}{K_\tau} \Bigg\{ & \frac{\hat{\omega}_\tau}{\hat{\omega}_\tau(\delta)} \frac{K_\tau^2}{i_\tau^4} \Bigg(\left\{ \frac{\hat{\omega}_\tau}{\hat{\omega}_\tau(\delta)} J_2'(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) + \alpha_\tau \mathrm{e}^{\delta - \hat{\delta}_\tau} J_2(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) \right\} \\ & \times \left[\mathrm{e}^{\delta - \hat{\delta}_\tau} J_2'(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) + \left\{ \frac{\omega}{\hat{\omega}_\tau} \alpha_\tau \mathrm{e}^{\delta - \hat{\delta}_\tau} \frac{J_1'}{J_1} \left(\frac{\omega}{\hat{\omega}_\tau(\delta)} \right) + \frac{\partial \xi/\partial \delta}{\xi} \right\} J_2(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) \right] \\ & + \frac{\hat{\omega}_\tau}{\hat{\omega}_\tau(\delta)} J_2(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) \Bigg[J_2(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) \frac{\partial^2 \xi/\partial \delta^2}{\xi} + \left(\mathrm{e}^{\delta - \hat{\delta}_\tau} + 2 \frac{\partial \xi/\partial \delta}{\xi} \right) \\ & \times J_2'(\alpha_\tau, \mathrm{e}^{\delta - \hat{\delta}_\tau}) + \frac{\omega}{\hat{\omega}_\tau} \alpha_\tau \mathrm{e}^{\delta - \hat{\delta}_\tau} \frac{J_1'}{J_1} \left(\frac{\omega}{\hat{\omega}_\tau(\delta)} \right) \end{aligned}$$

$$\times\left\{\left(2\frac{\partial\xi/\partial\delta}{\xi}+1\right)J_2(\alpha_\tau,e^{\delta-\hat{\delta}_\tau})+2J_2'(\alpha_\tau,e^{\delta-\hat{\delta}_\tau})\right\}$$

$$\left.\left.\left.+J_2''(\alpha_\tau,e^{\delta-\hat{\delta}_\tau})+\left(\frac{\omega}{\hat{\omega}_\tau}\alpha_\tau e^{\delta-\hat{\delta}_\tau}\right)^2\frac{J_1''}{J_1}\left(\frac{\omega}{\hat{\omega}_\tau(\delta)}\right)J_2(\alpha_\tau,e^{\delta-\hat{\delta}_\tau})\right]\right)\right\}.$$

5. Approximate confidence interval for δ

To proceed further, some conditions are needed on the design. Suppose that

$$\rho_i(\delta,\omega):=\operatorname*{plim}_{a\to\infty}\frac{a}{K_{\tau i}} \tag{12}$$

exists for all $-\infty<\delta<\infty$ and $\omega>0$, $i=1,2$. It is required that ρ_i be continuous functions which are absolutely continuous in δ for fixed ω, that $\partial\rho_i/\partial\delta$ be continuous almost everywhere under Lebesgue measure, and that $\partial\rho_i/\partial\delta$ be locally square integrable. These conditions do not require $\partial\rho_i/\partial\delta$ to be continuous everywhere. Our examples illustrate how discontinuities may arise.

Further, suppose that $K_{\tau i}\geqslant 1$ and that condition (A.1) of the Appendix holds. Then, specializing (11) to $h(w)=w$ leads to $E_\xi^\tau(z_{\tau 1})=(1/\sqrt{a})E_\xi^\tau(\Gamma_{a,1})$, since then $Uh=1$. From the consistency of the maximum likelihood estimators and relation (12), it is easily seen that

$$\Gamma_{a,1}\to\Gamma_1(\delta,\omega):=\sqrt{\left(\frac{\rho_1+\rho_2}{\rho_1\rho_2}\right)}\left[\rho_2\frac{J_1'}{J_1}(1)J_2\left(\frac{\rho_2}{\rho_1+\rho_2},1\right)\right.$$
$$\left.+(\rho_1+\rho_2)\left\{J_2\left(\frac{\rho_2}{\rho_1+\rho_2},1\right)\frac{\partial\xi/\partial\delta}{\xi}+J_2'\left(\frac{\rho_2}{\rho_1+\rho_2},1\right)\right\}\right]$$

in probability for all $-\infty<\delta<\infty$ and $\omega>0$. This suggests the approximation $E_\xi(z_{\tau 1})\simeq(1/\sqrt{a})E_\xi\{\Gamma_1(\delta,\omega)\}=(1/\sqrt{a})\int_\Omega\Gamma_1\xi\,d\delta\,d\omega$. Then integrating the term involving $\partial\xi/\partial\delta$ by parts and using the relations $J_1(1)=1$, $J_1'(1)=\frac{2}{3}$,

$$J_2\left(\frac{\rho_2}{\rho_1+\rho_2},1\right)=\frac{\sqrt{(\rho_1\rho_2)}}{\rho_1+\rho_2}$$

and

$$J_2'\left(\frac{\rho_2}{\rho_1+\rho_2},1\right)=-\frac{1}{3}\sqrt{\left(\frac{\rho_2}{\rho_1}\right)}\left\{1-\left(\frac{\rho_2}{\rho_1+\rho_2}\right)^2\right\}$$

leads to

$$E_\xi(z_{\tau 1})\simeq\frac{1}{\sqrt{a}}\int_\Omega\Gamma_1\xi\,d\delta\,d\omega=\frac{1}{\sqrt{a}}\int_\Omega\gamma_1\xi\,d\delta\,d\omega, \tag{13}$$

where

$$\gamma_1(\delta,\omega)=-\sqrt{(\rho_1+\rho_2)}\left(\frac{1}{2}\frac{(\partial\rho_1/\partial\delta)+(\partial\rho_2/\partial\delta)}{\rho_1+\rho_2}+\frac{1}{3}\frac{\rho_1}{\rho_1+\rho_2}\right), \tag{14}$$

which does not involve ξ. Since (14) does not involve ξ, and (13) holds for all twice continuously differentiable densities ξ with compact support, (13), in turn, may be written in the form of the very weak approximation,

$$\mu_a(\delta,\omega) := E_{\delta,\omega}(z_{\tau 1}) \simeq \frac{\gamma_1(\delta,\omega)}{\sqrt{a}}.$$

The latter expression may be estimated. Let $\hat{\mu}_a = \max[-1, \min\{1, \mu_a(\hat{\delta}_\tau, \hat{\omega}_\tau)\}]$ and

$$\sigma_a^2(\delta,\omega) = E_{\delta,\omega}\{(z_{\tau 1} - \hat{\mu}_a)^2\}.$$

Then, as above,

$$\int_\Omega \sigma_a^2(\delta,\omega)\xi(\delta,\omega)\,\mathrm{d}\delta\,\mathrm{d}\omega = E_\xi\{(z_{\tau 1} - \hat{\mu}_a)^2\} = E_\xi[E_\xi^\tau\{(z_{\tau 1} - \hat{\mu}_a)^2\}]$$

and

$$\begin{aligned} E_\xi^\tau\{(z_{\tau 1} - \hat{\mu}_a)^2\} &= E_\xi^\tau(z_{\tau 1}^2) - 2\hat{\mu}_a E_\xi^\tau(z_{\tau 1}) + \hat{\mu}_a^2 \\ &= 1 + \frac{1}{a}\{E_\xi^\tau(\Gamma_{a,2}) - 2\hat{\gamma}_{a,1}E_\xi^\tau(\Gamma_{a,1}) + \hat{\gamma}_{a,1}^2\}, \end{aligned}$$

where $\hat{\gamma}_{a,1} = \sqrt{a}\hat{\mu}_a$. Further, $\Gamma_{a,2}$ converges in probability to a limit $\Gamma_2(\delta,\omega)$ for fixed δ and ω. So, the term inside the brackets converges to $\tilde{\gamma}_2(\delta,\omega) := \Gamma_2(\delta,\omega) - 2\gamma_1(\delta,\omega)\Gamma_1(\delta,\omega) + \gamma_1^2(\delta,\omega)$ in probability as $a \to \infty$ for fixed δ and ω. Assuming that limiting operations and expectations may be interchanged, using the additional relations $J_1''(1) = -\frac{5}{18}$ and

$$\begin{aligned} J_2''\left(\frac{\rho_2}{\rho_1+\rho_2}\right) &= \frac{1}{2}\sqrt{\left(\frac{\rho_2}{\rho_1}\right)}\left\{1 - \left(\frac{\rho_2}{\rho_1+\rho_2}\right)^3\right\} \\ &\quad - \frac{1}{9}\sqrt{\left(\frac{\rho_2}{\rho_1}\right)}\frac{\rho_1+\rho_2}{\rho_1}\left\{1 - \left(\frac{\rho_2}{\rho_1+\rho_2}\right)^2\right\}^2, \end{aligned}$$

and integrating by parts, now leads to the approximation

$$\int_\Omega \sigma_a^2 \xi\,\mathrm{d}\delta\,\mathrm{d}\omega = 1 + \frac{1}{a}\int_\Omega \tilde{\gamma}_2\xi\,\mathrm{d}\delta\,\mathrm{d}\omega + \mathrm{o}\left(\frac{1}{a}\right) = 1 + \frac{1}{a}\int_\Omega \gamma_2\xi\,\mathrm{d}\delta\,\mathrm{d}\omega + \mathrm{o}\left(\frac{1}{a}\right), \tag{15}$$

where

$$\begin{aligned} \gamma_2(\delta,\omega) &= (\rho_1+\rho_2)\left\{\frac{1}{4}\left(\frac{(\partial\rho_1/\partial\delta) + (\partial\rho_2/\partial\delta)}{\rho_1+\rho_2}\right)^2 + \frac{1}{3}\left(\frac{(\partial\rho_1/\partial\delta) - (\partial\rho_2/\partial\delta)}{\rho_1+\rho_2}\right)\right. \\ &\quad \left. + \frac{1}{18}\frac{\rho_1^2 + 3\rho_1\rho_2 - 2\rho_2^2}{(\rho_1+\rho_2)^2}\right\}. \end{aligned}$$

Again, γ_2 does not depend on ξ, and (15) is valid for all twice continuously differentiable ξ with compact support, so that (15) may be written as a very weak approximation

$$\sigma_a^2(\delta,\omega) \simeq 1 + \frac{1}{a}\gamma_2(\delta,\omega),$$

which may be estimated by $\hat{\sigma}_a^2 = \max[\frac{1}{2}, \min\{2, \sigma_a^2(\hat{\delta}_\tau, \hat{\omega}_\tau)\}]$. Let

$$z_{\tau 1}^* = \frac{z_{\tau 1} - \hat{\mu}_a}{\hat{\sigma}_a}.$$

Then it may be shown that (5) holds for all symmetric h and all twice continuously differentiable compactly supported ξ. This is the basis for our confidence procedure. Given a desired confidence level $0 < \gamma < 1$, let

$$\mathscr{I}_a = (z_{\tau 1} - \hat{\mu}_a) \pm \hat{\sigma}_a \Phi^{-1}\left(\frac{1+\gamma}{2}\right).$$

Then

$$\mathrm{pr}_{\delta,\omega}(\delta \in \mathscr{I}_a) = \mathrm{pr}_{\delta,\omega}\left\{|z_{\tau 1}^*| \leqslant \Phi^{-1}\left(\frac{1+\gamma}{2}\right)\right\} = \gamma + \mathrm{o}\left(\frac{1}{a}\right)$$

as $a \to \infty$, in the very weak sense.

6. Allocation rules

In order to apply the confidence interval method, we need to specify the $\rho_i(\delta,\omega)$, $i = 1,2$, as defined by (12). These depend on both the stopping boundary and the allocation rule. At the end of Section 2, we described some sequential tests. We now describe three allocation rules. For details of some of their properties, see Hayre and Turnbull (1981) and Louis (1977).

Let $\varepsilon_0 = a/N$ and $\varepsilon_1 = m/a$ with $0 < \varepsilon_1 < 1/\varepsilon_0$. Then, it may be shown, by using (3) and (4), that

$$\operatorname*{plim}_{a\to\infty} \frac{a}{i_\tau^2} = \max\left[\varepsilon_0, \min\left\{g(\delta), \frac{1}{\varepsilon_1}\right\}\right] \tag{16}$$

for all $-\infty < \delta < \infty$ and $\omega > 0$. Also let

$$\Lambda(\theta_i) = \lim_{n_i\to\infty} \frac{K_{ni}}{n_i} = \mathrm{pr}_{\theta_i}(L_i \leqslant C_i) = \int_0^\infty (1 - \mathrm{e}^{-\theta_i x}) G\{\mathrm{d}x\} \tag{17}$$

for $i = 1,2$, the long-run proportion of patients who have died on treatment i.

The Hayre and Turnbull rule (HT). This rule initially allocates one patient to each treatment; it subsequently allocates the next patient to treatment 1 if $K_{n1} \leqslant K_{n2}$, and to treatment 2 otherwise. Thus, we have that $K_{\tau 1} \simeq K_{\tau 2}$. It follows from (16) that

$$\rho_i(\delta,\omega) = \frac{1}{2}\max\left[\varepsilon_0, \min\left\{g(\delta), \frac{1}{\varepsilon_1}\right\}\right] \quad \text{for } i = 1,2.$$

Equal randomisation rule (ER). For this rule, initially allocate one patient to each treatment; subsequently allocate the next patient to treatment 1 if $n_1 \leqslant n_2$, and to treatment 2 otherwise. Thus, we have that $\tau_1 \simeq \tau_2$. Further, from (17), we see that $K_{\tau i} \simeq \tau_i \Delta(\theta_i)$ for $i=1,2$. It follows from (16) that

$$\rho_1(\delta,\omega)=\frac{\Delta(\omega)}{\Delta(e^{\delta}\omega)+\Delta(\omega)}\max\left[\varepsilon_0,\ \min\left\{g(\delta),\frac{1}{\varepsilon_1}\right\}\right], \tag{18}$$

and similarly for $\rho_2(\delta,\omega)$.

The Louis rule (LS). This rule initially allocates one patient to each treatment; it subsequently allocates the next patient to treatment 1 if $K_{n1}/K_{n2} \leqslant Q(e^{\hat{\delta}_n})$, and to treatment 2 otherwise, where

$$Q(x)=\frac{x^2-1-\log(x^2)}{x^2\log(x^2)-x^2+1}$$

for $x>0$. Thus, we have that $K_{\tau 1}/K_{\tau 2} \simeq Q(e^{\hat{\delta}_\tau})$. It follows from (16) that

$$\rho_1(\delta,\omega)=\frac{1}{Q(e^{\delta})+1}\max\left[\varepsilon_0,\ \min\left\{g(\delta),\frac{1}{\varepsilon_1}\right\}\right],$$

and similarly for $\rho_2(\delta,\omega)$.

7. Simulation results

7.1. General

In order to assess the accuracy of the approximations presented in Section 5, a simulation study based on 10 000 replications was conducted, for selected values of the design parameters. The results are presented separately for two of the sequential tests described in Section 2.

Since the distribution function of the censoring times, G, is unknown, we require estimates of $\Delta(\theta_i)$ and $\Delta'(\theta_i)$, $i=1,2$, for use in (18) and in the corresponding expressions for $\partial\rho_i/\partial\delta$, $i=1,2$. Consistent sequences of estimates for these quantities are given by

$$\tilde{\Delta}_{ni}=\frac{K_{ni}}{n_i}=\frac{1}{n_i}\sum_{j=1}^{n_i}\delta_{nij}$$

and

$$\tilde{\Delta}'_{ni}=\frac{1}{n_i}\sum_{j=1}^{n_i}(1-\delta_{nij})X_{nij} \quad \text{for } i=1,2.$$

In the simulation study, the censoring times were independent exponential random variables with failure rate $\lambda=1.0$. In this case, it is easily seen that $\Delta(\theta_i)=\theta_i/(\theta_i+1)$ for $i=1,2$.

Table 1
Monte Carlo estimates of error probabilities and expected sample sizes for a truncated sequential probability ratio test: the order of the figures is HT, ER and LS

θ_1	$\mathrm{pr}_{\delta,\omega}(\text{error})$	$E_{\delta,\omega}(\tau)$	$E_{\delta,\omega}(\tau_1)$	$E_{\delta,\omega}(K_\tau)$
1.0	0.490	124.34	62.13	62.03
	0.494	129.06	64.53	64.39
	0.493	121.21	60.53	60.45
1.3	0.122	101.09	47.68	53.46
	0.119	104.32	52.16	55.36
	0.139	98.79	42.99	52.00
1.6	0.021	73.53	33.28	40.42
	0.021	76.00	38.01	42.20
	0.026	73.82	28.43	39.98
1.9	0.004	55.37	24.27	31.32
	0.004	57.44	28.71	33.02
	0.009	57.50	20.21	31.72
2.2	0.001	45.17	19.35	26.06
	0.001	46.53	23.26	27.47
	0.004	48.28	15.71	26.93
2.5	0.001	38.45	16.14	22.53
	0.001	39.71	19.85	23.95
	0.002	41.87	12.65	23.50

7.2. *Truncated sequential probability ratio test*

We first consider testing H_0: $\delta<0$ against H_1: $\delta>0$, using a test of the form (3) with $g(\hat{\delta}_n)=|\hat{\delta}_n|$. Monte Carlo results are reported in detail when $\theta_2=1.0$, $m=1$, $a=5.0$ and $N=20$. These parameter values produce a test with an error probability of approximately 0.04 and total expected sample size of about 80 when $\delta=\pm 0.4$.

Monte Carlo estimates of the error probabilities and expected sample sizes are reported in Table 1. It is clear that the error probabilities are insensitive to the allocation rule used. By comparing the three allocation rules, we see that the Hayre and Turnbull rule and the Louis rule generally assign significantly fewer patients to the inferior treatment. Notice that a reduction in the number of patients on the inferior treatment does not necessarily lead to an increase in the total expected sample size. This is an important point from a practical point of view.

Table 2 gives Monte Carlo estimates of the first two moments of $z_{\tau 1}$ and $z^*_{\tau 1}$ for the three allocation rules described in Section 6. The second and third columns clearly show that the standard normal distribution provides a poor approximation to the distribution of $z_{\tau 1}$. From column 4, we see that the approximation $\hat{\mu}_a$ consistently overestimates the Monte Carlo values, but $|E_{\delta,\omega}(z^*_{\tau 1})|$ is much less than $|E_{\delta,\omega}(z_{\tau 1})|$, except for $\delta=1.0$, when both are small. It appears from column 5 that substituting $\hat{\delta}_\tau$ and $\hat{\omega}_\tau$ into the expression for σ_a^2, tends to underestimate σ_a^2 when δ is small. Also, the estimates of the second moment of $z^*_{\tau 1}$ in column 5 for the Louis rule are not in such close agreement with the nominal value of 1 as the estimates for the other

Table 2
Monte Carlo estimates of moments of $z_{\tau 1}$ and $z^*_{\tau 1}$ for a truncated sequential probability ratio test for three allocation rules: the order of the figures is HT, ER and LS

θ_1	$E_{\delta,\omega}(z_{\tau 1})$	$\surd E_{\delta,\omega}(z^2_{\tau 1})$	$E_{\delta,\omega}(z^*_{\tau 1})$	$\surd E_{\delta,\omega}(z^{*2}_{\tau 1})$
1.0	−0.030	1.29	0.021	1.06
	−0.010	1.25	0.036	1.03
	−0.026	1.36	0.029	1.11
1.3	−0.218	1.19	0.028	1.02
	−0.207	1.16	0.034	1.01
	−0.228	1.28	0.028	1.07
1.6	−0.277	1.09	0.032	1.00
	−0.251	1.06	0.044	1.00
	−0.325	1.16	0.005	1.03
1.9	−0.291	1.05	0.020	1.00
	−0.246	1.02	0.047	1.00
	−0.316	1.11	0.019	1.01
2.2	−0.259	1.03	0.041	0.99
	−0.240	1.01	0.041	1.00
	−0.293	1.10	0.039	1.01
2.5	−0.252	1.04	0.041	1.00
	−0.231	1.02	0.038	1.02
	−0.300	1.10	0.028	1.01

two rules. This may be due to the highly adaptive nature of the Louis rule, as can be seen from Table 1. However, in general, the Monte Carlo estimates of $E_{\delta,\omega}(z^*_{\tau 1})$ and $\{E_{\delta,\omega}(z^{*2}_{\tau 1})\}^{1/2}$ are in reasonably close agreement with the nominal values of 0 and 1.

Monte Carlo estimates of $\mathrm{pr}_{\delta,\omega}(z^*_{\tau 1} \leqslant z)$ for $z = -1.960$, -1.645, 1.645 and 1.960 are given in Table 3. Although, in general, these are in good agreement with the normal values, there is poor agreement for small values of θ_1 in the right tail of the distribution for the Louis rule. Values are also included for $\mathrm{pr}_{\delta,\omega}(|z^*_{\tau 1}| \leqslant z)$ for $z = 1.960$ and 1.645. These suggest that the use of a standard normal distribution for the distribution of $z^*_{\tau 1}$ should provide reasonably accurate confidence intervals for δ.

Simulation results were also obtained for the two combinations of design parameters, $m = 1$, $a = 4.0$ and $N = 15$, and $m = 1$, $a = 5.0$ and $N = 30$, corresponding to tests with error probabilities of approximately 0.04 when $\delta = \pm 0.5$ and 0.05 when $\delta = \pm 0.3$, respectively. The approximations in Section 5 were slightly less accurate for the first combination than when $N = 20$, especially in the right tail of the distribution of $z^*_{\tau 1}$ for θ_1 near 1.3. The accuracy of the approximations for the second combination was comparable with that when $N = 20$.

7.3. Triangular test

We now consider testing H_0: $\delta < 0$ against H_1: $\delta > 0$ using a test of the form (3) with $g(\hat{\delta}_n) = b + |\hat{\delta}_n|$. Monte Carlo results are reported in detail when $\theta_2 = 1.0$, $m = 1$, $a = 10.0$

Table 3
Monte Carlo estimates of $\mathrm{pr}_{\delta,\omega}(z^*_{\tau 1} \leqslant z)$ for a truncated sequential probability ratio test for three allocation rules: the order of the figures is HT, ER and LS

θ_1	$\mathrm{pr}_{\delta,\omega}(z^*_{\tau 1} \leqslant z)$				$\mathrm{pr}_{\delta,\omega}(\lvert z^*_{\tau 1}\rvert \leqslant z)$	
	$z=-1.960$	$z=-1.645$	$z=1.645$	$z=1.960$	$z=1.960$	$z=1.645$
1.0	0.027	0.052	0.940	0.967	0.940	0.888
	0.023	0.043	0.943	0.969	0.946	0.900
	0.034	0.061	0.925	0.958	0.924	0.864
1.3	0.024	0.044	0.928	0.963	0.939	0.884
	0.023	0.045	0.934	0.966	0.943	0.889
	0.029	0.057	0.912	0.950	0.921	0.855
1.6	0.025	0.045	0.950	0.972	0.947	0.905
	0.023	0.049	0.950	0.971	0.948	0.901
	0.027	0.055	0.949	0.968	0.941	0.894
1.9	0.024	0.052	0.954	0.982	0.958	0.902
	0.020	0.046	0.948	0.977	0.957	0.902
	0.021	0.051	0.946	0.974	0.953	0.895
2.2	0.022	0.042	0.948	0.977	0.955	0.906
	0.024	0.049	0.948	0.976	0.952	0.899
	0.021	0.049	0.945	0.971	0.950	0.896
2.5	0.024	0.051	0.949	0.974	0.950	0.898
	0.030	0.046	0.946	0.972	0.942	0.900
	0.017	0.048	0.945	0.973	0.956	0.897

and $N=20$. For this choice of design parameters, the test has an error probability of approximately 0.05 and total expected sample size of about 80 when $\delta = \pm 0.4$.

Monte Carlo estimates of the error probabilities and expected sample sizes are presented in Table 4. As in Table 1, the error probabilities are insensitive to the allocation rule. Note also that there is a reasonable matching of the error probabilities for the two sequential tests. The estimates of the expected sample sizes generally confirm the conclusions for the truncated sequential probability ratio test.

Table 5 gives Monte Carlo estimates of the first two moments of $z_{\tau 1}$ and $z^*_{\tau 1}$. As for the truncated sequential probability ratio test, columns 2 and 3 clearly indicate the poor approximation that the standard normal distribution provides to the distribution of $z_{\tau 1}$. The Monte Carlo estimates in column 5 are in closer agreement with the nominal value of 1 than the corresponding estimates in Table 2.

Monte Carlo estimates of the distribution function of $z^*_{\tau 1}$ are given in Table 6. There is remarkably close agreement with the normal values for all three allocation rules. Indeed, the accuracy of the results seems to be comparable with the accuracy of those in Table 4 of Coad and Woodroofe (1996).

Simulation results were also obtained for the two combinations of design parameters, $m=1$, $a=8.0$ and $N=15$, and $m=1$, $a=10.0$ and $N=30$, corresponding to tests with error probabilities of approximately 0.04 when $\delta = \pm 0.5$ and 0.05 when $\delta = \pm 0.3$, respectively. The accuracy of the approximations was similar to that when $N=20$.

Table 4
Monte Carlo estimates of error probabilities and expected sample sizes for a triangular test: the order of the figures is HT, ER and LS

θ_1	$\mathrm{pr}_{\delta,\omega}(\text{error})$	$E_{\delta,\omega}(\tau)$	$E_{\delta,\omega}(\tau_1)$	$E_{\delta,\omega}(K_\tau)$
1.0	0.486	109.57	54.69	54.57
	0.491	111.42	55.71	55.48
	0.505	108.81	54.56	54.19
1.3	0.134	92.95	43.91	49.11
	0.134	94.79	47.42	50.28
	0.141	93.80	40.85	49.36
1.6	0.023	75.24	34.07	41.40
	0.025	76.45	38.24	42.47
	0.026	77.88	30.11	42.24
1.9	0.004	62.84	27.50	35.55
	0.004	64.24	32.13	36.96
	0.004	66.44	23.00	36.61
2.2	0.001	54.73	23.33	31.62
	0.001	55.89	27.95	33.04
	0.002	59.70	18.95	33.27
2.5	0.000	49.27	20.58	28.93
	0.000	50.15	25.07	30.31
	0.000	55.13	16.22	30.91

Table 5
Monte Carlo estimates of moments of $z_{\tau 1}$ and $z^*_{\tau 1}$ for a triangular test for three allocation rules: the order of the figures is HT, ER and LS

θ_1	$E_{\delta,\omega}(z_{\tau 1})$	$\sqrt{E_{\delta,\omega}(z^2_{\tau 1})}$	$E_{\delta,\omega}(z^*_{\tau 1})$	$\sqrt{E_{\delta,\omega}(z^{*2}_{\tau 1})}$
1.0	−0.025	1.17	0.027	1.02
	−0.018	1.15	0.032	1.01
	0.029	1.20	0.073	1.04
1.3	−0.142	1.10	0.025	1.00
	−0.115	1.08	0.047	1.00
	−0.134	1.15	0.040	1.04
1.6	−0.158	1.02	0.041	0.99
	−0.151	1.03	0.038	1.00
	−0.166	1.06	0.046	1.01
1.9	−0.161	1.00	0.039	0.98
	−0.144	1.01	0.044	1.00
	−0.210	1.06	0.009	1.01
2.2	−0.161	1.02	0.035	1.00
	−0.147	1.01	0.036	1.01
	−0.190	1.05	0.028	1.00
2.5	−0.139	1.01	0.055	1.00
	−0.140	1.01	0.038	1.01
	−0.183	1.05	0.035	1.01

Table 6
Monte Carlo estimates of $\mathrm{pr}_{\delta,\omega}(z^*_{\tau 1} \leqslant z)$ for a triangular test for three allocation rules: the order of the figures is HT, ER and LS

θ_1	$\mathrm{pr}_{\delta,\omega}(z^*_{\tau 1} \leqslant z)$				$\mathrm{pr}_{\delta,\omega}(\lvert z^*_{\tau 1}\rvert \leqslant z)$	
	$z = -1.960$	$z = -1.645$	$z = 1.645$	$z = 1.960$	$z = 1.960$	$z = 1.645$
1.0	0.024	0.048	0.941	0.969	0.945	0.893
	0.026	0.049	0.946	0.974	0.948	0.897
	0.024	0.045	0.933	0.962	0.938	0.888
1.3	0.026	0.050	0.947	0.975	0.949	0.897
	0.022	0.046	0.944	0.971	0.949	0.898
	0.027	0.052	0.941	0.970	0.943	0.889
1.6	0.022	0.046	0.947	0.971	0.949	0.901
	0.024	0.047	0.946	0.970	0.946	0.899
	0.025	0.050	0.947	0.969	0.944	0.897
1.9	0.020	0.042	0.951	0.975	0.955	0.909
	0.023	0.044	0.945	0.971	0.948	0.901
	0.027	0.052	0.950	0.975	0.948	0.898
2.2	0.026	0.049	0.946	0.972	0.946	0.897
	0.025	0.049	0.946	0.974	0.949	0.897
	0.028	0.051	0.948	0.974	0.946	0.897
2.5	0.021	0.043	0.944	0.974	0.953	0.901
	0.025	0.051	0.946	0.971	0.946	0.895
	0.024	0.046	0.947	0.972	0.948	0.901

8. Discussion

A natural extension is to consider a clinical trial in which patients can be assigned to one of $k > 2$ treatments. The response variable for the jth patient assigned to treatment i is assumed to be exponential with unknown failure rate $\theta_i > 0$ for $i = 1, \ldots, k$ and $j = 1, 2, \ldots$. The censoring mechanism is assumed to be the obvious extension of that described in Section 2, so that the data are of the form (1) but with $i = 1, \ldots, k$.

During the trial, a treatment can be eliminated if it does not look promising. At the end of the trial, we wish to choose the treatment with the highest mean survival time. The sequential procedure we suggest is a natural generalisation of the one studied by Coad (1995) for normal data. Suppose that we are at stage $(K_{n1}, \ldots, K_{nk})$ in the trial, that is, K_{ni} of the n_i patients assigned to treatment i, $i = 1, \ldots, k$, have died. Let

$$z_{ij}(n_i, n_j) = i^2_{nij}\, g(\hat{\delta}_{nij}), \tag{19}$$

where

$$i^2_{nij} = \frac{K_{ni}K_{nj}}{K_{ni} + K_{nj}}, \qquad \hat{\delta}_{nij} = \log\left(\frac{\hat{\theta}_{nj}}{\hat{\theta}_{ni}}\right)$$

and $\hat{\theta}_{ni}$ denotes the maximum likelihood estimator of θ_i. At each stage in the trial, we compute (19) for all pairs of treatments that have not been eliminated before that stage. We eliminate any treatment j for which $z_{ij}(n_i, n_j) > a$ for some $i \neq j$, where $a > 0$. Defining the error probability to be the probability of eliminating the best treatment, simulation results of Coad (1995) suggest that, for a given g, the error probabilities for the above procedure will be insensitive to the allocation rule.

A useful development to the present work is to attempt to construct an approximate confidence interval for the ratio of expected survival times for the best two treatments. The methods of Woodroofe and Coad (1997) might be useful for this problem. However, we have not attempted such an extension in this paper.

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Appendix: Theoretical justification of the method

Theoretical justification of the confidence procedure is supplied by the following result: *let* $\tau = \tau_a$ *be as in* (4); *if* (12) *holds, and for every compact* $C \subset (-\infty, \infty) \times (0, \infty)$ *there is an* $\eta = \eta_C > 0$ *for which*

$$\int_C \mathrm{pr}_{\delta,\omega}(K_{\tau i} < a\eta)\,\mathrm{d}\delta\,\mathrm{d}\omega = \mathrm{o}\left(\frac{1}{a}\right), \tag{A.1}$$

$i = 1, 2$ *as* $a \to \infty$, *then*

$$\int_\Omega E_{\delta,\omega}\{h(z^*_{\tau 1})\}\xi(\delta,\omega)\,\mathrm{d}\delta\,\mathrm{d}\omega = \Phi h + \mathrm{o}\left(\frac{1}{a}\right) \tag{A.2}$$

for every bounded, symmetric measurable $h : \mathbb{R} \to \mathbb{R}$ *and all twice continuously differentiable densities* ξ *with compact support.*

The proof of relation (A.2) is outlined in this appendix. It suffices to verify the relation for fixed h and ξ.

For fixed h and ξ, the left-hand side of (A.2) is just $E_\xi\{h(z^*_{\tau 1})\}$. Let C be the compact support of ξ and B_a be the event $\{K_{\tau i} \geqslant a\eta,\ i = 1, 2\}$, where $\eta = \eta_C$. Then

$$|E_\xi\{h(z^*_{\tau 1})\} - \Phi h| = \left|\int_{B_a} [E^\tau_\xi\{h(z^*_{\tau 1})\} - \Phi h]\,\mathrm{dpr}_\xi\right| + \mathrm{o}\left(\frac{1}{a}\right).$$

Clearly, $h(z^*_{\tau 1}) = h^*_a(z_{\tau 1})$, where $h^*_a(w) = h\{(w - \hat{\mu}_a)/\hat{\sigma}_a\}$. So, by (11),

$$E^\tau_\xi\{h(z^*_{\tau 1})\} - \Phi h = \Phi h^*_a - \Phi h + \frac{1}{\sqrt{a}}\Phi U h^*_a E^\tau_\xi(\Gamma_{a,1}) + \frac{1}{a}E^\tau_\xi\{U^2 h^*_a(z_{\tau 1})\Gamma_{a,2}\}. \tag{A.3}$$

Using simple Taylor series expansions, it is easily seen that

$$\Phi h_a^* - \Phi h = \frac{1}{a}\,\Phi U^2 h(\hat{\gamma}_{a,1}^2 - \hat{\gamma}_{a,2}) + \frac{R_{a,0}}{a^{3/2}},$$

$$\Phi U h_a^* - \Phi U h = -\frac{2}{\sqrt{a}}\Phi U^2 h \hat{\gamma}_{a,1} + \frac{R_{a,1}}{a},$$

$$\Phi U^2 h_a^* - \Phi U^2 h = \frac{R_{a,2}}{\sqrt{a}} \tag{A.4}$$

and

$$|E_\xi^\tau\{\Phi U^2 h(z_{\tau 1}^*) - \Phi U^2 h\}| \leqslant \frac{R_{a,3}}{\sqrt{a}} \tag{A.5}$$

on B_a, where $R_{a,i}$, $i = 0, 1, 2, 3$, are uniformly bounded, $\hat{\gamma}_{a,2} = a(\hat{\sigma}_a^2 - 1)$, and

$$\Phi U^2 h = \int_{-\infty}^{\infty} U^2 h(z)\phi(z)\,\mathrm{d}z = \frac{1}{2}\int_{-\infty}^{\infty}(z^2 - 1)h(z)\phi(z)\,\mathrm{d}z.$$

So, using (A.4) and (A.5), the right-hand side of (A.3) may be written

$$\frac{\Phi U^2 h}{a}\{\hat{\gamma}_{a,1}^2 - \hat{\gamma}_{a,2} - 2\hat{\gamma}_{a,1}E_\xi^\tau(\Gamma_{a,1}) + E_\xi^\tau(\Gamma_{a,2})\} + \mathrm{o}_p\left(\frac{1}{a}\right).$$

Finally, it may be shown that the limiting operations, $a \to \infty$ and integration, may be interchanged. It follows that

$$\limsup_{a\to\infty} a|E_\xi\{h(z_{\tau 1}^*)\} - \Phi h| \leqslant \left|\int_\Omega (\gamma_1^2 - \gamma_2 - 2\gamma_1\Gamma_1 + \Gamma_2)\xi\,\mathrm{d}\delta\,\mathrm{d}\omega\right|, \tag{A.6}$$

and the latter integral is zero by an integration by parts.

Justifying the interchange of limiting operations is, perhaps, the most challenging of the calculations omitted above. It follows the general outline of Woodroofe (1992a) and uses the special structure of the exponential distribution. Due to the complicated notation, showing that the integral on the right-hand side of (A.6) is zero is tedious.

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