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SEQUENTIAL LINEAR RANK TESTS FOR TWO-SAMPLE CENSORED SURVIVAL DATA[1]

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Under extremely general patterns of patient-arrival, allocation to treatment and loss to follow-up in (randomized) clinical trial settings, the sequentially computed logrank statistic (Mantel, 1966) is shown (under the null hypothesis of identically distributed lifetimes) to have exactly uncorrelated increments, and is shown via Rebolledo's (1980) martingale invariance principle to satisfy a functional central limit theorem, justifying sequential logrank tests of Jones and Whitehead (1979). Generalizations are made to other two-sample rank tests for censored survival data, and practical applicability to real randomized clinical trials is discussed.

1. Introduction. Human survival testing and randomized clinical trials have come in recent years to be regarded as a class of biostatistical applications where the standard arguments in favor of sequential analysis have special force (cf. Armitage, 1975, Pocock, 1977). Because of the large ethical and financial costs entailed in protracting a clinical trial beyond the earliest point when one of two treatments seems definitely superior, many trials can and should be stopped early. (In survival testing with laboratory animals there are convincing purely economic or decision-theoretic justifications for sequential procedures.) However, the theoretical basis for sequential or repeated significance tests is only now advancing to the point of allowing realistically general patterns of patient arrival, allocation to treatment, and withdrawal.

The important paper of Breslow (1969) was the first to use weak-convergence theory to provide a rigorous basis for parametric sequential analysis of two-sample exponential survivorship data when patients enter study at random times but are never lost to follow-up. Then, for the case where two large groups of patients with identically distributed lifetimes enter treatment simultaneously and are progressively censored (but never lost to follow-up), Chatterjee and Sen (1973) proved martingale and weak-convergence results for a large class of linear rank statistics, one of which (the modified Savage statistic = the negative of the Mantel-Haenszel or logrank statistic of Mantel, 1966) was adopted for sequential testing by Koziol and Petkau (1978). Following heuristic but imprecise martingale formulations due to Mantel (1966) and Cox (1975) of rank statistics for censored data, Aalen (1978) and Gill (1980) introduced counting-process methods and square-integrable martingale theory into censored survival analysis. Aalen (1978)

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gave a stochastic-integral representation for the linear rank statistics on censored data, and he proposed to apply general martingale invariance principles like those of McLeish (1974) to their asymptotic distribution theory. Gill (1980) proved under fixed and random censorship models for two groups of simultaneously entering patients with identical lifetime distributions that a broad class of linear rank statistics if evaluated continuously in time would in the large-sample limit converge weakly (in $D[0, \infty)$) to time-changed Brownian motion. Sen (1981) in a similar setting gave the large-sample theory for sequential (progressive-censoring) hypothesis testing in Cox's (1972) proportional-hazards regression model.

Sequential statistical procedures based on general arrival patterns and censored data have developed along a different line. In a series of *Biometrika* papers, Whitehead (1978), Jones and Whitehead (1979) and Whitehead and Jones (1979) introduced the continuous-time sequential logrank test for the analysis of large clinical trials. Because of the generality of the stopping boundaries discussed in the last of these papers, it emerges that Whitehead and Jones interpret the logrank statistic (defined in Mantel, 1966, Peto and Peto, 1972) computed at successive death times as forming asymptotically a Brownian motion under the null hypothesis of identical lifetime distributions. Whitehead and Jones (1979) place no specific restrictions on the mechanisms of patient entry and allocation to treatment group, but rely for the validity of their procedures on a heuristic argument of Whitehead (1978) analogizing a "partial likelihood" (Cox, 1975) for ranks of two-sample censored survival data with the likelihood of partial sums of independent normal variables. This same argument of Whitehead (1978) is used to imply in Jones and Whitehead (1979) also that the sequentially computed modified-Wilcoxon statistic (originated by Gilbert, 1962, and Gehan, 1965) forms asymptotically for large trials an independent increment process, but a correction by Jones and Whitehead (1981) acknowledges that this is wrong under staggered patient entry. Slud and Wei (1982) have shown that modified-Wilcoxon increments for censored survival data are generally correlated except in the case of simultaneous patient entry with progressive censoring (the one case simulated by Jones and Whitehead, 1979). Therefore the application of Whitehead's (1978) sequential W_u test to sequential logrank testing requires new justification. In the meantime, Tsiatis (1981, 1982) has provided a rigorous asymptotic distribution theory for the logrank statistic (and other linear rank statistics) evaluated at a finite number of chronological times in a fixed interval $[0, T]$, in the setting where patient entry is staggered, random and independent of the (independent) survival and censoring times. In the same setting as Tsiatis (1981), Slud and Wei (1982) have proved weak convergence in $D[0, T]$ (under null and alternative hypotheses) for the sequentially computed modified-Wilcoxon statistic in the large-sample limit, using a U-statistic representation. Their results can, as they show, be implemented in a practical repeated significance test, and Tsiatis (1982) remarks that such tests can similarly be constructed for all the linear rank statistics he studies. Most recently, Sellke and Siegmund (1983) have proved theorems on weak convergence of normalized time-changed partial-likelihood

score statistics in general proportional-hazards settings. However, as we describe further in our discussion at the end of Section 4, the sequential hypothesis tests provided by Sellke and Siegmund are applicable only to large clinical trials of indefinite duration and of size much smaller than the ultimate "horizon" of patients with iid data and random group-allocation.

The present paper provides an extremely general theoretical framework for two-group clinical trials, allowing random or fixed patient arrival times, random or fixed allocation to treatment group, and random censoring time which may depend both on treatment group and on survival time (but must be "uninformative"). Definitions, assumptions, and an appropriate null-hypothetical model for a finite-sample clinical trial are formulated in Section 2. Discussion of the martingales associated with the linear rank statistics then leads (Proposition 2.5) to martingales approximating an important subclass of statistics containing the logrank. A striking corollary is that these statistics have exactly uncorrelated increments in chronological time. Square-integrable martingale methods and stochastic integrals with respect to counting processes are used throughout, and our general reference for these is Liptser and Shiryaev (1977, chapters 5, 18). For the small amount of "random measure theory" we introduce, see the survey of Shiryaev (1981, Section 4) and references cited there. Section 3 contains examples showing that the sequentially computed logrank statistic in settings other than simultaneous entry need not form a martingale. Section 4 gives general asymptotic conditions under which Rebolledo's (1980) martingale invariance principle applies to prove weak convergence in the large-sample limit for the logrank (and other linear rank) statistics as continuous-time processes. In Section 5 we apply our results to justify and generalize the sequential logrank tests of Jones and Whitehead (1979). The discussion concluding the paper in Section 6 points out some extensions and limitations of our proof techniques and addresses some practical questions in the implementation of sequential nonparametric survival tests in medical trials.

Readers interested primarily in applicable results rather than techniques of proof should proceed from the notational discussion of Section 2 preceding Lemma 2.1 directly to the statement of Corollary 2.4 and then to Theorem 4.2, the discussion following it, and Sections 5 and 6.

2. Notations and martingale results. Throughout this section, $\{(E_i, Z_i, X_i, Y_i)\}_{i=1}^{\infty}$ denotes a fixed sequence of independent quadruples of data for patients in a clinical trial: E_i denotes the time of entry for the patient labeled i (who is not necessarily the ith to enter); Z_i is the indicator equal to 1 if patient i is allocated to treatment group A and 0 if to group B; X_i denotes the latent random time for patient i until the endpoint (death, tumor recurrence, etc.) under investigation; and Y_i denotes the time from entry until patient i is lost to followup (whether because of administrative censoring, withdrawal from study, or death from competing risks). The sequence $\{(E_i, Z_i)\}$ of pairs may be fixed or random, but we assume that the joint conditional distribution function of (X_i, Y_i) given (E_i, Z_i) is $F_{1i}(\cdot, \cdot)$ if $Z_i = 1$ and $F_{0i}(\cdot, \cdot)$ if $Z_i = 0$, not depending on E_i. For all

bivariate distribution functions F defined in this paper, we use the notation $\bar{F}$ for the complementary function $\bar{F}(s, t) \equiv 1 - F(s-, \infty) - F(\infty, t-) + F(s-, t-)$, e.g. $\bar{F}_{1i}(s, t) = P(X_i \geq s, Y_i \geq t \mid Z_i = 1)$.

Although we do not assume that X_i and Y_i are conditionally independent or that (X_i, Y_i) are identically distributed, we are interested in a two-sample hypothesis test of equality of death hazards, so to ensure that censoring be "uninformative", we assume throughout the paper the null hypothesis

$$(\mathscr{H}_0) \quad H(t) \equiv \int_0^t \int_{x-}^{\infty} [\bar{F}_{\varepsilon i}(x, x)]^{-1} F_{\varepsilon i}(dx, dy) \quad \text{for} \quad \varepsilon = 0, 1; \quad i = 1, 2, \cdots$$

or informally, $H(dt) = P(X_i \in [t, t + dt) \mid Z_i = \varepsilon, \min(X_i, Y_i) \geq t)$ does not depend on Z_i or i. If X_i and Y_i are independent given Z_i, $H(\cdot)$ is the ordinary cumulative hazard function for X_i. Note that the definite integrals $\int_a^b$ denote $\int I_{(a,b]}$, so that $\int_{a-}^{b}$ means $\int I_{[a,b]}$. The function $H(\cdot)$ is non-decreasing right-continuous.

At chronological time $t > 0$, the only data observable is $\{X_i(t), Z_i, \Delta_i(t), E_i: E_i \leq t\}$, where $X_i(t) \equiv \min(X_i, Y_i, t - E_i)$ and $\Delta_i(t) \equiv I[X_i \leq \min(Y_i, t - E_i)]$. Let $N_E(t) \equiv \sum_{j=1}^{\infty} I[E_j \leq t]$ be the counting process for entering patients, which we assume to satisfy $E(N_E(t)) < \infty$ for all t. For each $i \geq 1$ and $u, t \geq 0$, we define

$$N_i(u, t) \equiv \Delta_i(t) I[X_i(t) \leq u], \quad r_i(u, t) \equiv I[X_i(t) \geq u].$$

Throughout the paper, t indexes chronological time while u indexes time-on-test. Thus $r_i(u, t)$ indicates whether patient i is observed by clock time t to have been "at risk" after time u on test. For patient i with $X_i \leq Y_i$ who enters at E_i, the *random measure* $N_i(du, dt)$ on $[0, \infty)^2$ (cf. Shiryaev, 1981, Section 4) is simply the point-mass $\delta_{(X_i, X_i + E_i)}$. Next we define the numbers-at-risk and counts of observed deaths from which the linear rank statistics are constructed. For $0 \leq u$, t let

$$r(u, t) = \sum_i r_i(u, t) = \sum_i I[X_i(t) \geq u], \quad \rho(u, t) = \sum_i Z_i r_i(u, t)$$

$$N(u, t) = \sum_i N_i(u, t), \quad N_A(u, t) = \sum_i Z_i N_i(u, t)$$

$$\Gamma(u, t) = \rho(u, t)/r(u, t) \quad (\text{with} \quad 0/0 = 0).$$

For each $j \geq 1$, on the completed probability space $(\Omega, \mathscr{F}, P)$ where $\{(E_i, Z_i, X_i, Y_i)\}$ is defined (with $\mathscr{N}$ denoting the P-null sets), we define $U_j \equiv \min(X_j, Y_j)$ and

$$\mathscr{F}^j_t = \sigma(\mathscr{N}, I[E_j \leq t], Z_j I[E_j \leq t], \Delta_j(t), I[U_j \leq t - E_j], U_j I[U_j \leq t - E_j])$$

$$\mathscr{G}^j_u = \sigma(\mathscr{N}, E_j, Z_j, I[X_j \leq \min(u, Y_j)], I[U_j \leq u], U_j I[U_j \leq u]).$$

In addition, the increasing right-continuous families of σ-fields

$$\mathscr{F}_t = \sigma(\mathscr{F}^j_t, j \geq 1), \quad \mathscr{G}_u = \sigma(\mathscr{G}^j_u, j \geq 1)$$

respectively describe the information available by chronological time t and time-on-test u.

Let $\varphi(u, t)$ denote a random $\mathscr{F}_t \cap \mathscr{G}_u$ measurable scoring function, which as

a function of (ω, u, t) on $\Omega \times \mathbb{R} \times \mathbb{R}$ is $\mathscr{P}(\{\mathscr{G}_u\}) \times \mathscr{B}(\mathbb{R})$ measurable, where $\mathscr{P}(\{\mathscr{G}_u\})$ is the predictable σ-field generated by left-continuous $\mathscr{G}_u$-adapted processes on Ω. Typically φ is of the form $\varphi(u, t) = \Phi(u, \rho(u, t), r(u, t), \hat{S}_{\mathrm{KM}}(u, t))$, where $\hat{S}_{\mathrm{KM}}(\cdot, t)$ denotes the left-continuous Kaplan-Meier (1958) survival curve estimator for $\{X_i\}$ based on the data from the combined treatment groups observable up to time t, and Φ is continuous on $[0, \infty)^3 \times [0, 1]$. The general linear rank statistic with score φ adapted to $\mathscr{F}_t$ is defined as in Tsiatis (1982) by

$$S_\varphi(t) \equiv \sum_i \Delta_i(t)\varphi(X_i(t), t)(Z_i - \rho(X_i, t)/r(X_i, t)).$$

We assume that for all $t > 0$, $E(\int \varphi^2(u, t)r(u, t)H(du)) < \infty$ so that $S_\varphi(\cdot)$ will be locally square-integrable. The modified partial-likelihood score statistics of Peto and Peto (1972) correspond to S_φ with φ depending only on $\hat{S}_{\mathrm{KM}}(u, t)$; when φ depends only on $\rho(u, t)$ and $r(u, t)$, S_φ is a censored data analogue of the regression rank statistics of Sen and Ghosh (1972); and the class of statistics of Tarone and Ware (1977) is the class of S_φ with φ depending only on $r(u, t)$. The common member of all these classes, with $\varphi \equiv 1$, is the Mantel-Haenszel numerator or logrank statistic (due to Mantel, 1966)

$$\mathrm{MH}(t) = \sum_i \Delta_i(t)(Z_i - \rho(X_i, t)/r(X_i, t)).$$

We now construct counting-process related martingales and stochastic integral formulas for S_φ. The following Lemma follows immediately from a standard result for point-processes (Liptser and Shiryaev, vol. II, Theorem 18.2, 1977; Shiryaev, 1981, page 204) and is closely related to Proposition 3.1 of Jacod (1975).

LEMMA 2.1.

$$N_j(u, t) - \int_0^{\min(u, t-E_j)} r_j(v, v + E_j)H(dv)$$

$$= \int_0^u \int_0^t r_j(v, s)[\delta_{(X_j, X_j+E_j)}(dv, ds) - \delta_{E_j+v}(ds)H(dv)]$$

is a $\{\mathscr{F}_t^j\}$ *martingale for fixed* $u \le \infty$ *and a* $\{\mathscr{G}_u^j\}$ *martingale for fixed* $t \le \infty$, *where* δ_u *and* $\delta_{(u,t)}$ *denote delta measures on* $[0, \infty)$ *and* $[0, \infty)^2$ *respectively.*

At this point it is convenient to introduce the notion of *martingale random measure* (Shiryaev, 1981, Section 4; Jacod, 1975): we say $m(du, dt) = m(\omega; du, dt)$ is a $\{\mathscr{G}_u\}$ (respectively $\{\mathscr{F}_t\}$) martingale random measure on $[0, \infty) \times [0, \infty)$, if $m(\omega; \cdot, \cdot)$ is a Borel signed measure on $[0, \infty)^2$ such that for each u, $t \ge 0$

$$(*) \qquad \bar{m}(u, t) = \bar{m}(\omega, u, t) \equiv \int_0^u \int_0^t m(\omega; dv, ds)$$

is $\mathscr{G}_u \times \mathscr{B}(\mathbb{R}) \times \mathscr{B}(\mathbb{R})$ (respectively $\mathscr{F}_t \times \mathscr{B}(\mathbb{R}) \times \mathscr{B}(\mathbb{R})$) measurable and is a $\mathscr{G}_\cdot$ (resp. $\mathscr{F}_\cdot$) martingale for fixed $t \le \infty$ (resp., fixed $u \le \infty$). We say that m is

(locally) square-integrable if $\bar{m}(\cdot, u, t)$ is square-integrable (for finite u, t). For two such locally square-integrable random measures m and m' (with respect to both $\{\mathscr{F}_t\}$, $\{\mathscr{G}_u\}$, and with $\bar{m}$ and $\bar{m}'$ defined as in (*)), the *covariance process* $\langle m, m'\rangle(u, t)$ is uniquely determined (Shiryaev, 1981, Section 4; Liptser and Shiryaev, vol. I, Theorem 5.2) as the difference between two increasing (in both u and t) $\mathscr{G}_u \cap \mathscr{F}_t$-predictable processes such that for $v < u$, $s < t$, almost surely

$$E\{\bar{m}(u, t)\bar{m}'(u, t) \mid \mathscr{G}_v \cap \mathscr{F}_s\}$$

$$= \bar{m}(v, s)\bar{m}'(v, s) + E\left\{ \int_v^u \int_s^t \langle m, m'\rangle\,(dx, dy) \mid \mathscr{G}_v \cap \mathscr{F}_s \right\}.$$

Moreover, if $J(u, t)$ and $K(u, t)$ are jointly measurable and $\mathscr{G}_u$-predictable as random functions of u, then

$$\tilde{m}(u) = \int_0^u \int_0^\infty J(v, s)m(dv, ds) \quad \text{and} \quad \tilde{m}'(u) = \int_0^u \int_0^\infty K(v, s)m'(dv, ds)$$

are $\mathscr{G}_u$ martingales such that almost surely

$$\langle \tilde{m}, \tilde{m}'\rangle(u) = \int_0^u \int_0^\infty J(v, s)K(v, s)\langle m, m'\rangle(dv, ds)$$

(Shiryaev, 1981; for covariance process of stochastic integrals with respect to square-integrable martingales, see Liptser and Shiryaev, vol. I, chapter 5).

From Lemma 2.1 we observe that

$$m_j(du, dt) = r_j(u, t)(\delta_{(X_j, X_j+E_j)}(du, dt) - \delta_{E_j+u}(dt)H(du))$$

is a martingale random measure with respect to both $\{\mathscr{F}_t\}$ and $\{\mathscr{G}_u\}$; and from Shiryaev (1981, page 204), using mutual independence for different j of the families $\{\mathscr{F}_t^j \cap \mathscr{G}_u^j\}_{u,t}$ we have almost surely

$$\langle m_i, m_j\rangle(du, dt) = \delta_{ij}r_j(u, t)(1 - \Delta H(u))\delta_{E_j+u}(dt)H(du)$$

where $\Delta H(u) \equiv H(u) - H(u-)$. Summing the martingale random measures m_i, with and without the multiples Z_i, now yields martingale random measures

$$M(du, dt) = \textstyle\sum_j [N_j(du, dt) - r_j(u, t)\delta_{E_j+u}(dt)H(du)]$$

$$M_A(du, dt) = \textstyle\sum_j Z_j[N_j(du, dt) - r_j(u, t)\delta_{E_j+u}(dt)H(du)]$$

with $\bar{M}(u, t) \equiv \int_0^u \int_0^t M(du, dt) = N(u, t) - \sum_j \int_0^u r_j(v, v + E_j)I[v + E_j \le t]H(dv)$ $= N(u, t) - \int_0^t r(v, t)H(dv)$ (here we make use of the identity $r_j(v, v + E_j)I[v + E_j \le t] = r_j(v, t)$). Similarly $\bar{M}_A(u, t) = N_A(u, t) - \int_0^u \rho(v, t)H(dv)$. Defining also $M_B = M - M_A$, we have

PROPOSITION 2.2. *$M_A(du, dt)$ and $M_B(du, dt)$ are $\{\mathscr{G}_u\}$, $\{F_t\}$ martingale*

random measures on $[0, \infty)^2$ *such that* $\langle M_A, M_B \rangle \equiv 0$ *and*

$$\langle M_A, M_A \rangle(u, t) = \int_0^u \rho(v, t)(1 - \Delta H(v))H(dv)$$

$$\langle M_B, M_B \rangle(u, t) = \int_0^u (r(v, t) - \rho(v, t))(1 - \Delta H(v))H(dv).$$

Since $\varphi(u, t)$ is assumed to be $\mathcal{G}_u$-predictable for fixed t and $\Gamma(\cdot, t)$ is left-continuous, the discussion above implies

$$S_\varphi(u, t) \equiv \int_0^u \int_0^t \varphi(v, t)[(1 - \Gamma(v, t))M_A(dv, ds) - \Gamma(v, t)M_B(dv, ds)]$$

is a $\mathcal{G}_u$-martingale, which $= \int_0^u \varphi(v, t)[\bar{M}_A(dv, t) - \Gamma(v, t)\bar{M}(dv, t)] = \int_0^u \varphi(v, t)[N_A(dv, t) - \rho(v, t)H(dv) - \Gamma(v, t)N(dv, t) + \Gamma(v, t)r(v, t)H(dv)] = \sum_j \Delta_j(t)I[X_j \le u]\varphi(X_j, t)(Z_j - \Gamma(X_j, t))$. Thus we have proved

COROLLARY 2.3. *$S_\varphi(u, t)$ is a $\mathcal{G}_u$-martingale which for $u = +\infty$ equals $S_\varphi(t)$. If all $E_i = 0$, then $M_A(du, dt)$ and $M_B(du, dt)$ are random measures* a.s. *supported on the diagonal $\{u = t\}$, and $S_\varphi(u, \infty) = S_\varphi(u)$ is a $\{\mathcal{G}_u\}(= \{\mathcal{F}_u\})$ martingale.*

COROLLARY 2.4. *If $\varphi(u, t) = q(u)$ is* a.s. *constant in t, then $S_\varphi(t)$ has uncorrelated increments.*

PROOF. For $s < t$, $S_\varphi(t) - S_\varphi(s) = \int_0^\infty \int_0^t q(u)(\Gamma(u, s) - \Gamma(u, t))M(du, dx) + \int_0^\infty \int_s^t q(u)[(1 - \Gamma(u, s))M_A(du, dx) - \Gamma(u, s)M_B(du, dx)]$ by the calculations preceding Corollary 2.3 and a little algebra, while

$$S_\varphi(s) = \int_0^\infty \int_0^s q(u)[(1 - \Gamma(u, s))M_A(du, dx) - \Gamma(u, s)M_B(du, dx)].$$

Since all integrands are $\mathcal{G}_u$-predictable, our discussion of covariances for stochastic integrals with respect to martingale random measures implies

$$E\{(S_\varphi(t) - S_\varphi(s))S_\varphi(s)\} = E\{\int_0^\infty \int_0^s q^2(u)(\Gamma(u, s) - \Gamma(u, t)) \cdot [(1 - \Gamma(u, s)) \cdot \langle M, M_A \rangle(du, dx) - \Gamma(u, s)\langle M, M_B \rangle(du, dx)]\} = 0$$

by Proposition 2.2. □

The following Proposition is motivated by a setting, to be made precise in Section 4, where $\varphi(u, t)$ is closely approximated by a $\mathcal{G}_u$-predictable random function $q(u)$ of u alone, as is $\Gamma(u, t)$ by $L(u)$. We provide an $\mathcal{F}_t$ martingale $M_{q,L}(t)$ which is to approximate $S_\varphi(t)$.

PROPOSITION 2.5. *Suppose $q(u)$ and $L(u)$ are $\mathcal{G}_u$-predictable measurable random functions satisfying $0 \le L(u) \le 1$ and for each t, $E\{\int_0^\infty q^2(u)r(u, t)H(du)\}$*

$< \infty$; *and suppose that* $H(\cdot)$ *is continuous. Then*

$$M_q(t) = M_{q,L}(t) \equiv \int_0^\infty \int_0^t q(u)[(1 - L(u))M_A(du, ds) - L(u)M_B(du, ds)]$$

is a locally square-integrable $\mathscr{F}_t$ *martingale with*

$$\langle M_q, M_q \rangle(t) = \int_0^\infty q^2(u)\{(1 - L(u))^2\rho(u, t) + L^2(u)(r(u, t) - \rho(u, t))\}H(du).$$

Moreover, $R_\varphi(t) = S_\varphi(t) - M_{q,L}(t)$ *satisfies*

$$ER_\varphi^2(t) = E\left\{\int_0^\infty (\varphi(u, t) - q(u))^2 \cdot[(1 - L(u))^2\rho(u, t) + L^2(u)(r(u, t) - \rho(u, t))]H(du)\right\} + E\left\{\int_0^\infty \varphi^2(u, t)(L(u) - \Gamma(u, t))^2 r(u, t)H(du)\right\}.$$

PROOF. Follows immediately from the $\mathscr{G}_u$-predictability of integrands, the general discussion of martingale random measures, and Proposition 2.2. □

3. Special examples for the logrank. We have seen (Corollary 2.3, following Chatterjee and Sen, 1973, Gill, 1980, and Sen, 1981) that if all $E_i = 0$—the so-called progressive censoring case—then $\mathrm{MH}(\cdot)$ $(= S_\varphi(\cdot)$ with $\varphi \equiv 1)$ is an $\mathscr{F}_t$ martingale. If there is no censoring, i.e., $Y_i \equiv \infty$, and patient entry is purely sequential, with $E_{i+1} \geq E_i + X_i \equiv t_i$ a.s., then Sen and Ghosh (1972) show that $\mathrm{MH}(t_k)$ is an $\mathscr{F}_{t_k}$ martingale. We give three examples to show that in other situations $\mathrm{MH}(\cdot)$ may not be a martingale. In Example 3.3, $t_1 \leq t_2 \leq \cdots$ denote the ordered death times, i.e., the ordered elements of $\{E_i + X_i\colon X_i \leq Y_i\}_{i \geq 1}$.

EXAMPLE 3.1. $\mathrm{MH}(t)$ need not be a martingale when E_i and Y_i are fixed. Suppose $X_k = 1$ or 25, each with probability ½, and $Y_k = 2$ with probability 1, for $k = 1, 2, 3, 4$. Put $Z_1 = Z_3 = Z_4 = 1$, $Z_2 = 0$; $E_1 = 0$, $E_2 = 5$, $E_3 = 10$, $E_4 = 15$; and $E_i \equiv \infty$ for $i > 4$. We compute $\mathrm{MH}(t)$ at $t = 13, 20$. Denoting $\Delta_k \equiv I_{[X_k \leq Y_k]}$, we note that $\mathrm{MH}(13)$ is computed from the 2×2 table

$\Delta_1 + \Delta_3$	$2 - \Delta_1 - \Delta_3$
Δ_2	$1 - \Delta_2$

as $\mathrm{MH}(13) = \Delta_1 + \Delta_3 - 2(\Delta_1 + \Delta_2 + \Delta_3)/3 = (\Delta_1 + \Delta_3 - 2\Delta_2)/3$. Similarly $\mathrm{MH}(20) = (\Delta_1 + \Delta_3 + \Delta_4 - 3\Delta_2)/4$. Now given $\mathrm{MH}(13) = ⅓$, we know $\Delta_2 = 0$, $\Delta_1 + \Delta_3 = 1$, and therefore $E(\mathrm{MH}(20) \mid \mathrm{MH}(13) = ⅓) = (¼)(1 + E(\Delta_4)) = ⅜ \neq ⅓$. Hence $E(\mathrm{MH}(20) \mid \mathrm{MH}(13)) \not\equiv \mathrm{MH}(13)$. However, it is easy to check that $E((\mathrm{MH}(20) - \mathrm{MH}(13))\mathrm{MH}(13)) = 0$ as in Corollary 2.4.

EXAMPLE 3.2. Logrank statistics are usually computed after fixed intervals of real time (rather than after a fixed number of deaths). Already in the case of purely sequential entry, however, it may happen under some (random) arrival patterns that $E(\mathrm{MH}(t)) \neq 0$, even when there is no censoring.

Consider two individuals with $Z_1 = 0$, $Z_2 = 0$, $E_1 = 0$, $E_2 = X_1$, X_1 and X_2 i.i.d. with continuous d.f. F such that $F(0) = 0$, $F(1) = 1$, and $Y_1 = Y_2 = \infty$. Then for $1 \leq t < 2$,

$$E(\mathrm{MH}(t)) = \tfrac{1}{2}\,(P\{X_1 \leq \min(X_2,\, t - X_1)\} - P\{X_2 \leq \min(X_1,\, t - X_1)\})$$

$$= \tfrac{1}{2}\,E[F(\min(X_2,\, t/2)) - F(\min(X_1,\, t - X_1))] > 0$$

as long as F is not constant on $(t/2,\, 1]$ or on $[0,\, t/2]$, since $\min(X_1,\, t - X_1) < \min(X_1,\, t/2)$ almost surely.

Such phenomena are well known in the context of size-biased sampling of renewal processes, but do not seem to have been mentioned as a danger in applying Mantel-Haenszel tests. Of course, the possibility of uncentered logrank statistics is ruled out as soon as the two groups under study are entered and allocated precisely symmetrically.

EXAMPLE 3.3. An anonymous referee gives an example with fixed entry times and no censoring where $\{\mathrm{MH}(t_k)\}$ is not a martingale. Let $(E_1,\, Z_1) = (0,\, 1)$, $(E_2,\, Z_2) = (1,\, 0)$, $E_i = \infty$ for $i \geq 3$, $Y_1 = Y_2 = \infty$, X_1 and X_2 independent exponential variables with mean 1. Then $\mathrm{MH}(t_1) = 0$ iff $X_1 < 1 + X_2$ (in which case $X_1 = t_1$), and given $\mathrm{MH}(t_1) = 0$,

$$MH(t_2) = \tfrac{1}{2}\,(I[X_1 < X_2] - I[X_2 < X_1 < X_2 + 1]).$$

Hence

$$E(\mathrm{MH}(t_2) \mid \mathrm{MH}(t_1) = 0)$$

$$= \frac{1}{2}\left(\frac{P(X_1 < X_2) - P(X_2 < X_1 < X_2 + 1)}{P(X_1 < X_2 + 1)}\right) = \frac{1}{2}\,(2e - 1)^{-1} \neq 0.$$

4. Weak convergence for large samples. We continue to assume the null-hypothetical model $(\mathscr{H}_0)$ of Section 2, but we introduce an index ν to parameterize the size of the clinical trial. All the notations of Section 2 (except H, which is assumed the same for all ν) should now be written with superscripts $^{(\nu)}$ (e.g. $E_i^{(\nu)}$, $X_i^{(\nu)}$, $r^{(\nu)}(u,\, t)$, $\varphi^{(\nu)}$, $N_E^{(\nu)}$, $\mathscr{F}_t^{(\nu)}$), but when there is no danger of ambiguity we suppress superscripts. Our interest in this section lies in proving functional central limit theorems for statistics $(N_E^{(\nu)}(t))^{-1/2} S_\varphi^{(\nu)}(t)$ as $\nu \to \infty$. To this end, we list some assumptions governing passage to the limit.

(A.0) For $\nu \geq 1$, $\{(E_i^{(\nu)},\, Z_i^{(\nu)},\, X_i^{(\nu)},\, Y_i^{(\nu)})\}_{i \geq 1}$ is a sequence of independent quadruples with $P(X_i^{(\nu)} \leq x,\, Y_i^{(\nu)} \leq y \mid E_i^{(\nu)},\, Z_i^{(\nu)} = \varepsilon) = F_{\varepsilon i}^{(\nu)}(x,\, y)$ for $\varepsilon = 0,\, 1$, $i \geq 1$. In addition, for all ν, ε, i

$$H(t) \equiv \int_0^t \int_{x-}^{\infty} (\bar{F}_{\varepsilon i}^{(\nu)}(x,\, x))^{-1} F_{\varepsilon i}^{(\nu)}(dx,\, dy) \quad \text{is continuous in } t.$$

(A.1) For each $\nu \geq 1$, $\{\tau^{(\nu)}(s)\colon 0 \leq s \leq 1\}$ is a family of strictly increasing continuous (in s) $\sigma(\{E_i^{(\nu)}\colon E_i^{(\nu)} \leq \cdot\})$ stopping times such that $\tau^{(\nu)}(0) \equiv 0$. We denote $N_E^{(\nu)}(\tau^{(\nu)}(1))$ by $n(\nu)$ and assume $E(n(\nu)) < \infty$ for each ν. In addition, as $\nu \to \infty$, $n(\nu)^{-1}N_E^{(\nu)}(\tau^{(\nu)}(s) - u) \to_P J(u, s)$ for all $u, s \geq 0$, where J is a nonrandom function, continuous in s, such that $J(0, s) > 0$ for $s > 0$.

(A.2) There exists a constant $K > 0$ and distribution functions $G_0^*(\cdot)$, $G_1^*(\cdot)$ not depending on ν such that uniformly in ε (= 0, 1), i and $u > 0$,

$$\bar{F}_{\varepsilon i}^{(\nu)}(u, u) \leq K \cdot \bar{G}_\varepsilon^*(u)$$

where $\bar{G}_\varepsilon^*(u) = 1 - G_\varepsilon^*(u-)$ and $\int_0^\infty (\bar{G}_0^*(u) + \bar{G}_1^*(u))H(du) < \infty$.

(A.3) For each ν, $i \geq 1$, and $u \geq 0$, $\bar{F}_{0i}^{(\nu)}(u, u) = \bar{F}_{1i}^{(\nu)}(u, u)$ with

$$N_E(\tau(t) - u)^{-1} \textstyle\sum_{i: E_i \leq \tau(t)-u} \bar{F}_{1i}^{(\nu)}(u, u) \to_P \bar{G}_1(u) \equiv \bar{G}_0(u)$$

as $\nu \to \infty$ whenever $J(u, t) > 0$. The sequence $\{Z_i^{(\nu)}\}_{i \geq 1}$ is i.i.d. with $P(Z_1^{(\nu)} = 1) = \gamma$, where $0 < \gamma < 1$, and is independent of $\{E_i^{(\nu)}\}_{i \geq 1}$.

(A.3′) For each ν, $i \geq 1$, $\varepsilon = 0$ or 1, and $u \geq 0$, $\bar{F}_{\varepsilon i}^{(\nu)}(u, u) \equiv \bar{G}_\varepsilon(u)$. In addition, for a fixed γ, $0 < \gamma < 1$, as $\nu \to \infty$, whenever $J(u, s) > 0$

$$\textstyle\sum_j Z_j I[E_j \leq \tau^{(\nu)}(s) - u]/N_E^{(\nu)}(\tau^{(\nu)}(s) - u) \to_P \gamma$$

and

$$\int_0^\infty N_E^{(\nu)}(\tau^{(\nu)}(s) - u)(\gamma - \textstyle\sum_j Z_j I[E_j \leq \tau^{(\nu)}(s) - u]/N_E^{(\nu)}(\tau^{(\nu)}(s) - u))^2 \cdot (\gamma \bar{G}_1(u) + (1 - \gamma)\bar{G}_0(u))H(du) = \mathcal{O}_P(\log^2 n(\nu))$$

where the integrand is understood to be 0 when $N_E(\tau(s) - u) = 0$ and $A_\nu = \mathcal{O}_P(B_\nu)$ means for all $\delta > 0$ there exists $M(\delta)$ so large that $P\{|A_\nu| \leq M(\delta)|B_\nu|\} \geq 1 - \delta$ for all ν.

(A.4) There exist $\{\mathcal{F}_t^{(\nu)}\}$ stopping times $\{s_j^{(\nu)}\}_{j=0}^{m(\nu)}$, $0 = s_0 < s_1 < \cdots < s_{m(\nu)} = \tau^{(\nu)}(1)$, with $m(\nu) = o(n(\nu)/\log^2 n(\nu))$ as $\nu \to \infty$, such that as $\nu \to \infty$,

$$(1) \qquad n(\nu)^{-1/2} \max_{0 \leq j < m(\nu)} \textstyle\sum_i \Delta_i(s_j) \dfrac{r(X_i, s_{j+1}) - r(X_i, s_j)}{r(X_i, s_{j+1})} \to_P 0.$$

$$(2) \qquad n(\nu)^{-1/2} \max_{0 \leq j < m(\nu)} (N^{(\nu)}(s_{j+1}) - N^{(\nu)}(s_j)) \to_P 0.$$

In (A.4) and in what follows we make use of the abbreviated notations

$$N^{(\nu)}(t) \equiv N^{(\nu)}(+\infty, t), \quad N_A^{(\nu)}(t) \equiv N_A^{(\nu)}(+\infty, t).$$

Of these assumptions, (A.0) simply repeats the setting of Section 2, and (A.1)–(A.3′) are large-sample regularity properties for fixed sequences $\{E_i^{(\nu)}\}$, $\{(Z_i^{(\nu)}, Y_i^{(\nu)})\}$ which can serve in place of the laws of large numbers which hold when these sequences are i.i.d. On the other hand, (A.4) is a purely technical and artificial assumption required for the weak-convergence proof of Theorem 4.1(2) below. The author had succeeded in proving (A.4) only for very special arrival processes before the independent work of Sellke and Siegmund (1983)

appeared. In fact, the powerful technical Lemma 4 of Sellke and Siegmund (in the case $\beta = 0$) with only minor notational changes proves in the general setting of (A.0) that (A.4) holds with sequence $\{s_j^{(\nu)}\}_{j=1}^{m(\nu)}$ given by $s_j^{(\nu)} = j$th smallest time $E_i^{(\nu)} + \min(X_i^{(\nu)}, Y_i^{(\nu)})$ for $1 \le j \le n(\nu)^{\epsilon} \equiv j_0$, and

$$s_j^{(\nu)} \equiv \min[\tau^{(\nu)}(1), \inf\{s: s \ge s_{j_0}^{(\nu)}, E(N^{(\nu)}(s)) \ge (j - j_0)^{1+\epsilon}\}]$$
$$\text{for} \quad j_0 \le j \le n(\nu)^{1/(1+\epsilon)}$$

where $0 < \epsilon < 1/5$ and $m(\nu) =$ greatest integer $\le n(\nu)^{1/(1+\epsilon)}$. For this reason, we will not specifically list (A.4) as an assumption in our Theorem 4.1 although we will use it in the proof.

REMARKS. (a) For fixed ν, $\tau^{(\nu)}(\cdot)$ is the "operational clock" for the clinical trial, whose speed may vary with the patient accrual rate. Assumption (A.2) is a uniformity condition on $\{F_{\epsilon i}^{(\nu)}\}$ which is satisfied, with $K = 1$, if $X_i^{(\nu)} = \min(X_i^0, C_i^{(\nu)})$, $Y_i^{(\nu)} = \min(Y_i^0, D_i^{(\nu)})$ where (X_i^0, Y_i^0) are conditionally i.i.d. given $Z_i^{(\nu)} = \epsilon$ with $P(\min(X_i^0, Y_i^0) \le u \mid Z_i^{(\nu)} = \epsilon) \equiv G_\epsilon(u)$. In other words, (A.2) holds if all $\min(X_i^{(\nu)}, Y_i^{(\nu)})$ are stochastically less than or equal to variables $\min(X_i^0, Y_i^0)$ which are conditionally i.i.d. given $Z_i = \epsilon$ with law not depending on ν. In particular, (A.2) follows from (A.3′).

(b) In the special case of Tsiatis (1981, 1982) and Slud and Wei (1982), $\tau^{(\nu)}(s) \equiv sT$ for fixed $T > 0$, for all $\nu \ge 1$; $(X_i^{(\nu)}, Y_i^{(\nu)})$ are conditionally i.i.d. given $Z_i = \epsilon$; $n(\nu) = N_E^{(\nu)}(T)$ is a fixed increasing sequence and $\{(E_i^{(\nu)}, Z_i^{(\nu)}): E_i^{(\nu)} \le T\}$ is i.i.d. with $P(E_i \le sT \mid E_i \le T) = \Lambda(sT)/\Lambda(T)$, $P(E_i \le sT, Z_i = 1 \mid E_i \le T) = \Lambda_A(sT)/\Lambda(T)$. In this case, if $\Lambda_A(sT)/\Lambda(sT) \equiv \gamma$ for all s, then (A.1) and (A.3′) are easy to check, with $J(u, s) = \Lambda(sT - u)/\Lambda(T)$. The point is that $\{Z_i\}_{i=1}^n$ are then i.i.d. with $P(Z_1 = 1) = \gamma$ and are independent of $\{E_i\}_{i=1}^n$, so that the expected value of the integral in (A.3′) is

$$\gamma(1 - \gamma) \int_0^\infty (\gamma \bar{F}_{11}(u, u) + (1 - \gamma)\bar{F}_{01}(u, u))H(du).$$

(c) In the special case of simultaneous patient entry, where all $E_i^{(\nu)} = 0$, $1 \le i \le n(\nu)$, whenever $t_1 \ge t_0$ and $\Delta_i(t_0) = 1$, it follows that $r(X_i, t_1) = r(X_i, t_0)$. Hence (A.4) (1) is trivially satisfied for any choice of $\{s_j^{(\nu)}\}_{j=1}^{m(\nu)}$ for which $m(\nu) = o(n(\nu)/\log^2 n(\nu))$, and (A.4) (2) is obvious if $s_j^{(\nu)} \equiv \inf\{\tau^{(\nu)}(1)\} \cup \{t: N^{(\nu)}(t) \ge jn(\nu)/m(\nu)\}$.

LEMMA 4.1. *Under assumptions* (A.0) *and* (A.1) *along with either* (A.3) *or* (A.3′), *for each* u, s *with* $J(u, s) > 0$, *as* $\nu \to \infty$

$$\Gamma^{(\nu)}(u, \tau^{(\nu)}(s)) \to_P L(u)$$

where $L(u) = \gamma$ *if* (A.3) *holds, and* $L(u) = \gamma\bar{G}_1(u)/(\gamma\bar{G}_1(u) + (1 - \gamma)\bar{G}_0(u))$ *if* (A.3′) *holds.*

PROOF. For $u \ge 0$, $0 < s \le 1$, let $\mathscr{R}^{(\nu)}(u, s) \equiv \{i \ge 1: E_i^{(\nu)} \le \tau^{(\nu)}(s) - u\}$. Given $N_E^{(\nu)}(\tau^{(\nu)}(s) - u)$, $\mathscr{R}^{(\nu)}(u, s)$, and $\{Z_i: i \in \mathscr{R}^{(\nu)}(u, s)\}$, $\rho^{(\nu)}(u, \tau^{(\nu)}(s))$ is a sum over

$\mathscr{R}^{(\nu)}(u, s)$ of indicators $Z_i I[\min(X_i, Y_i) \geq u]$, and $r^{(\nu)}(u, \tau^{(\nu)}(s))$ is a sum of $I[\min(X_i, Y_i) \geq u]$. Whenever $J(u, s) > 0$, we have $N_E^{(\nu)}(\tau^{(\nu)}(s) - u) \to_P \infty$ by (A.1). Then the simplest non-i.i.d. variant of the law of large numbers (Loève, 1955, page 277) implies as $\nu \to \infty$ almost surely

$$n(\nu)^{-1}[r^{(\nu)}(u, \tau^{(\nu)}(s)) - \textstyle\sum_{i \in \mathscr{R}(u,s)} (Z_i \bar{F}_{1i}^{(\nu)}(u, u) + (1 - Z_i)\bar{F}_{0i}^{(\nu)}(u, u))] \to_P 0$$

$$n(\nu)^{-1}[\rho^{(\nu)}(u, \tau^{(\nu)}(s)) - \textstyle\sum_{i \in \mathscr{R}(u,s)} Z_i \bar{F}_{1i}^{(\nu)}(u, u)] \to_P 0$$

and under either (A.3) or (A.3′), $n(\nu) = \mathscr{O}_p(r^{(\nu)}(u, \tau^{(\nu)}(s)))$ and

$$n(\nu)^{-1} [\textstyle\sum_{i \in \mathscr{R}(u,s)} Z_i \bar{F}_{1i}^{(\nu)}(u, u) - L(u)$$

$$\cdot \textstyle\sum_{i \in \mathscr{R}(u,s)} (Z_i \bar{F}_{1i}^{(\nu)}(u, u) + (1 - Z_i)\bar{F}_{0i}^{(\nu)}(u, u))] \to_P 0.$$

From the three preceding statements, the Lemma follows immediately. □

We are now in a position to combine our assumptions and Rebolledo's (1980) martingale functional central limit theorem to prove weak convergence in $D[0, 1]$ of $n(\nu)^{-1} S_\varphi^{(\nu)}(\tau^{(\nu)}(\cdot))$. For the rest of the paper, we denote conditional expectations given $\{E_i^{(\nu)}\}_{i \geq 1}$ by $\mathscr{E}$.

THEOREM 4.1. *Assume* (A.0) – (A.2) *and either* (A.3) *or* (A.3′). *In addition, assume* $\varphi^{(\nu)}(u, t) \equiv q^{(\nu)}(u)$ *is a* $\mathscr{G}_u^{(\nu)}$*-predictable process with* $|q^{(\nu)}(u)| \leq C < \infty$ *for all* ν, u, *and such that* $q^{(\nu)}(u) \to_P q(u)$ *as* $\nu \to \infty$, *where* $q(u)$ *is nonrandom. Let* $M_q^{(\nu)}(\cdot)$ *denote the* $\{\mathscr{F}_t^{(\nu)}\}$ *martingale defined in Proposition* 2.5 *in terms of* $q^{(\nu)}(\cdot)$ *and* $L(\cdot)$, *where* $L(\cdot)$ *is as in Lemma* 4.1, *and define* $R_\varphi^{(\nu)}(\cdot) \equiv S_\varphi^{(\nu)} - M_q^{(\nu)}$ *and* $\bar{J}(u, t) \equiv J(u, t)(\gamma \bar{G}_1(u) + (1 - \gamma)\bar{G}_0(u))$. *Then*

(1) *if* $V(t) \equiv \int_0^\infty L(u)(1 - L(u))q^2(u)\bar{J}(u, t)H(du)$ *and* $\beta(x) \equiv \inf\{t: V(t) > x\}$, *then as* $\nu \to \infty$, $n(\nu)^{-1/2} M_q^{(\nu)}(\tau^{(\nu)}(\beta(\cdot))) \to_{\mathscr{D}} W(\cdot)$ *in* $D[0, V(1)]$ *where* $W(\cdot)$ *is a Wiener process, and for* $0 \leq t \leq 1$, $R_\varphi^{(\nu)}(\tau^{(\nu)}(t)) = \mathscr{O}_P(\log n(\nu))$ *as* $\nu \to \infty$;

(2) $n(\nu)^{-1/2} S_\varphi^{(\nu)}(\tau^{(\nu)}(\beta(\cdot))) \to_{\mathscr{D}} W(\cdot)$ *in* $D[0, V(1)]$ *and* $n(\nu)^{-1/2} R_\varphi^{(\nu)}(\tau^{(\nu)}(\cdot)) \to_{\mathscr{D}} 0$. *In this case, if* $\beta^{(\nu)}(x) \equiv \inf\{s: n(\nu)^{-1} < M_q^{(\nu)}, M_q^{(\nu)} > (\tau^{(\nu)}(s)) > x\}$, *then* $n(\nu)^{-1/2} S_\varphi^{(\nu)}(\tau^{(\nu)}(\beta^{(\nu)}(\cdot))) \to_{\mathscr{D}} W(\cdot)$ *in* $D[0, V(1)]$.

PROOF. By the integral expression for $M_q^{(\nu)}$ in Proposition 2.5 and the definition of M_A and M_B, we have

$$M_q^{(\nu)}(t) = \int_0^\infty q^{(\nu)}(u)[N_A(du, t) - L(u)N(du, t)]$$

$$- \textstyle\sum_i \int_0^{t - E_i} q^{(\nu)}(u) r_i(u, u + E_i)[Z_i - L(u)]H(du)$$

and $\Delta M_q^{(\nu)}(t) \equiv M_q^{(\nu)}(t) - M_q^{(\nu)}(t-) = \sum_i q^{(\nu)}(X_i) I[X_i + E_i = t, X_i \leq Y_i]$ $\cdot (Z_i - L(X_i))$ by continuity of $H(\cdot)$. Thus $\sup_t |\Delta M_q^{(\nu)}(t)| \leq C$ by continuity of $H(\cdot)$, implying Rebolledo's (1980) "asymptotic rarefaction of jumps" condition for $n(\nu)^{-1/2} M_q^{(\nu)}(\cdot)$.

Now by Proposition 2.5,

$$n(\nu)^{-1}\,\langle M_q^{(\nu)}, M_q^{(\nu)}\rangle\,(\tau^{(\nu)}(t))$$
$$= n(\nu)^{-1}\int_0^\infty (q^{(\nu)}(u))^2\{(1-L(u))^2\Gamma(u,\tau^{(\nu)}(t)) + L^2(u)(1-\Gamma(u,\tau^{(\nu)}(t)))\}r(u,\tau^{(\nu)}(t))H(du)$$

which we will show converges in probability as $\nu\to\infty$. Fix arbitrarily small $\delta>0$, and find B large enough that $\int_B^\infty (\bar G_0^*(u)+\bar G_1^*(u))H(du)<\delta$ (cf. (A.2)) but also $H(B)<\infty$. Then using $|L(u)|\le 1$ and $|q^{(\nu)}(u)|\le C$, we find

$$\mathscr{P}\left|\, n(\nu)^{-1}\langle M_q^{(\nu)}, M_q^{(\nu)}\rangle(\tau^{(\nu)}(t)) - \int q^{(\nu)}(u)^2L(u)(1-L(u))\bar J(u,t)H(du)\,\right|$$
$$\le \mathscr{E}\int_B^\infty C^2 r(u,\tau^{(\nu)}(t))n(\nu)^{-1}H(du) + \int_B^\infty C^2\bar J(u,t)H(du)$$
$$+ \mathscr{E}\int_0^B C^2\,|\,r(u,\tau^{(\nu)}(t))n(\nu)^{-1}-\bar J(u,t)\,|\,H(du)$$
$$+ \mathscr{E}\int_0^B I[J(u,t)>0]C^2\,|\,L(u)-\Gamma(u,\tau^{(\nu)}(t))\,|\,H(du)$$
$$+ \mathscr{E}\int_0^B I[J(u,t)=0]C^2 r(u,\tau^{(\nu)}(t))n(\nu)^{-1}H(du)$$
$$\le 2C^2K\delta + C^2\int_0^B I[J(u,t)>0]\,\mathscr{E}\,|\,L(u)-\Gamma(u,\tau^{(\nu)}(t))\,|\,H(du)$$
$$+ C^2\int_0^B \mathscr{E}\,|\,r(u,\tau^{(\nu)}(t))n(\nu)^{-1}-\bar J(u,t)\,|\,H(du)$$
$$+ C^2\int_0^B I[J(u,t)=0]N_E^{(\nu)}(\tau^{(\nu)}(t)-u)n(\nu)^{-1}H(du)$$

for all ν, where K is as in (A.2). As $\nu\to\infty$, dominated convergence, Lemma 4.1 and (A.1) imply that the final three integrals converge in probability (with respect to the law of $\{E_i^{(\nu)}\}_{i\ge1}$) to 0. Since $\delta>0$ was arbitrary, we conclude as $\nu\to\infty$ (using $q^{(\nu)}\to q$ and dominated convergence once more)

$$n(\nu)^{-1}\langle M_q^{(\nu)}, M_q^{(\nu)}\rangle(\tau^{(\nu)}(t))$$
$$\to_P \int q^2(u)L(u)(1-L(u))\bar J(u,t)H(du)\equiv V(t)$$

which is continuous nondecreasing in t by (A.1) because $J(u,t)$ is. Letting $\beta(x)\equiv\inf\{t\colon V(t)\ge x\}$ we have $V(\beta(x))=x$ for $x\in[0,V(1)]$. Rebolledo's (1980)

Theorem 2.2 and Propositions 1.5 and 2.1 now applied to the $\mathscr{F}_t^{(\nu)}$ martingale $n^{-1/2}(\nu)M_\varphi^{(\nu)}(\tau^{(\nu)}(\beta(\cdot)))$ give weak convergence in $D[0, V(1)]$ to Brownian motion $W(\cdot)$.

To get the last statement of (1), we appeal to Proposition 2.5 (with expectations replaced by conditional expectations given $\{E_i\}_{i\geq 1}$), uniform boundedness of $q^{(\nu)}(\cdot)$, and the following Lemma.

LEMMA 4.2. *Under either assumption* (A.3) *or* (A.3′),

$$\mathscr{E}\left(\int (L(u) - \Gamma^{(\nu)}(u, \tau^{(\nu)}(s)))^2 r(u, \tau^{(\nu)}(s)))H(du)\right) = \mathscr{O}(\log^2 n(\nu)).$$

PROOF. First, if (A.3) holds, then $L(u) = \gamma$ and given $r(u, t)$ and $N_E(t - u)$, with $t \equiv \tau^{(\nu)}(s)$, $\rho(u, t)$ has Binomial $(r(u, t), \gamma)$ distribution. Hence

$$\mathscr{E}\{(L(u) - \Gamma(u, t))^2 \mid r(u, t)\} = \gamma(1 - \gamma)/r(u, t),$$

and

$$\begin{aligned}\mathscr{E}\int (L(u) - \Gamma^{(\nu)}(u, t))^2 r^{(\nu)}(u, t)H(du) &\\ = \mathscr{E}\int \gamma(1 - \gamma)I[r(u, t) \geq 1]H(du) &\\ \leq \gamma(1 - \gamma)\,\mathscr{E}[(\max\{H(X_i): E_i \leq t\})] = \mathscr{O}(\log n(\nu)) &\end{aligned}$$

since $H(X_i)$ are independent random variables each stochastically smaller than an exponentially distributed variable with mean 1.

Second, if (A.3′) holds, then we introduce notations for fixed ν, $t = \tau^{(\nu)}(s)$ and u: $n_1 = \sum_i Z_i I[E_i \leq t - u]$, $n_2 = N_E(t - u) - n_1$, $p_1 = \bar{G}_1(u)$, $p_2 = \bar{G}_0(u)$, $\bar{n} = n_1 p_1 + n_2 p_2$. Our assumption implies that given n_1 and n_2, $\xi \equiv \rho(u, t)$ and $\eta \equiv r(u, t) - \rho(u, t)$ are independent with Binomial (n_1, p_1) and Binomial (n_2, p_2) distributions. Then

$$\begin{aligned}\mathscr{E}[(L(u) - \Gamma(u, t))^2 r(u, t)] &\\ = \mathscr{E}[(L(u) - \xi/(\xi + \eta))^2(\xi + \eta)] &\\ = (L(u) - n_1 p_1/\bar{n})^2 \bar{n} - \mathscr{E}[\xi\eta(\xi + \eta)^{-1} - n_1 p_1 n_2 p_2 \bar{n}^{-1}] &\end{aligned}$$

and using the binomial distributions of ξ and η it is easy to check that

$$\mathscr{E}(\xi\eta(\xi + \eta)^{-1}) = n_1 p_1 n_2 p_2 \int_0^1 x(1 - p_1 + p_1 x)^{n_1 - 1}(1 - p_2 + p_2 x)^{n_2 - 1}\, dx.$$

Now, breaking the integral into integrals over intervals $[0, 1 - \delta]$ and $[1 - \delta, 1]$, where $\delta = 2\bar{n}^{-1}\log n(\nu)$, bounding the terms $\log(1 - p_i(1 - x))$ by $-p_i(1 - x)$ for

$0 \le x \le 1 - \delta$ and Taylor-expanding them for $1 - \delta \le x \le 1$, one finds as $\nu \to \infty$

$$(n_1p_1n_2p_2)^{-1}\mathscr{E}(\xi\eta(\xi+\eta)^{-1})$$
$$= \mathscr{O}(n(\nu)^{-2}) + (1 + \mathscr{O}(\delta + \delta^2\bar{n}))\int_{1-\delta}^{1} \exp[-\bar{n}(1-x)]\,dx$$
$$= \bar{n}^{-1}[1 + \mathscr{O}(\bar{n}^{-1}\log n(\nu))]$$

where $\mathscr{O}$ is uniform with respect to u, s. Reassembling terms and making use of the estimate $|L(u) - n_1p_1/\bar{n}| \le |\gamma - n_1(n_1+n_2)^{-1}|/\min(\gamma, 1-\gamma)$, we have

$$\mathscr{E}\int (L(u) - \Gamma(u,t))^2 r(u,t)H(du)$$
$$= \mathscr{O}\left(\int [\gamma - n_1/(n_1+n_2)]^2 N_E(t-u)(\bar{G}_0(u) + \bar{G}_1(u))H(du)\right)$$
$$+ \mathscr{O}\left(\int I[\max(n_1p_1, n_2p_2) > \log n(\nu)]\log n(\nu)H(du)\right.$$
$$\left. + \mathscr{E}\int I[\max(n_1p_1, n_2p_2) \le \log n(\nu)]r(u,t)H(du)\right)$$
$$= \mathscr{O}(\log^2 n(\nu)),$$

where we have used (A.3′) and the fact that $H(x) \le -\log \bar{G}_i(x)$ for $i = 0, 1$. □

The first statement of (2) in Theorem 4.1 will follow from (1) if we show $n^{-1/2}(\nu)R_\varphi^{(\nu)}(\tau^{(\nu)}(\cdot)) \to_{\mathscr{D}} 0$ in $D[0,1]$. Let $\{s_j^{(\nu)}\}_{j=1}^{m(\nu)}$ be the sequences guaranteed to exist by (A.5), and without loss of generality we assume $\max_{1\le j\le m(\nu)} |\tau^{-1}(s_j) - \tau^{-1}(s_{j-1})| \to 0$ as $\nu \to \infty$, where $\tau^{-1}(\cdot)$ exists for each ν by (A.1). Then as $\nu \to \infty$,

$$n(\nu)^{-1}\mathscr{E}[\max_{1\le j\le m(\nu)} |M_q^{(\nu)}(s_j) - S_\varphi^{(\nu)}(s_j)|^2]$$
$$\le n(\nu)^{-1}\textstyle\sum_{j=1}^{m(\nu)} \mathscr{E}[R_\varphi^{(\nu)}(s_j)]^2 = \mathscr{O}_P(m(\nu)n(\nu)^{-1}\log^2 n(\nu)) \to_P 0.$$

Also, for $s_j \le s < s_{j+1}$,

$$|S_\varphi^{(\nu)}(s) - S_\varphi^{(\nu)}(s_j)|$$
$$\le \int |q^{(\nu)}(u)|(N(du,s) - N(du,s_j))$$
$$+ \int |q^{(\nu)}(u)\|\Gamma(u,s) - \Gamma(u,s_j)|N(du,s_j)$$
$$\le C\left(N^{(\nu)}(s_{j+1}) - N^{(\nu)}(s_j) + \textstyle\sum_i \Delta_i(s_j)\dfrac{r(X_i,s_{j+1}) - r(X_i,s_j)}{r(X_i,s_{j+1})}\right),$$

so that by (A.4)

$$\max_{0\le j<m(\nu)} \sup_{s_j\le s<s_{j+1}} n(\nu)^{-1/2}|S_\varphi^{(\nu)}(s) - S_\varphi^{(\nu)}(s_j)| \to_P 0 \quad \text{as} \quad \nu \to \infty.$$

By the weak convergence already proved in (1),

$$\max_{1\le j\le m(\nu)}\sup_{s_j\le s<s_{j+1}} n^{-1/2}(\nu)\,|\,M_\varphi^{(\nu)}(s) - M_\varphi^{(\nu)}(s_j)\,| \to_P 0 \quad \text{as} \quad \nu\to\infty.$$

Finally, since

$$\begin{aligned} n(\nu)^{-1/2}&\sup_{0\le s\le\tau(1)}|\,R_\varphi^{(\nu)}(s)\,| \\ &\le n(\nu)^{-1/2}\max_{1\le j\le n(\nu)}|\,R_\varphi^{(\nu)}(s_j)\,| \\ &\quad + n(\nu)^{-1/2}\max_{0\le j<m(\nu)}\sup_{s_j\le s<s_{j+1}}|\,R_\varphi^{(\nu)}(s) - R_\varphi^{(\nu)}(s_j)\,| \to_P 0 \end{aligned}$$

as $\nu\to\infty$, we conclude $n(\nu)^{-1/2}R_\varphi^{(\nu)}(\tau^{(\nu)}(\cdot)) \to_{\mathcal{D}} 0$ in $D[0, 1]$.

Finally if $\beta^{(\nu)}(x)$ is as defined in (2), then it is a nondecreasing (in x) $\mathcal{F}_t^{(\nu)}$ stopping-time sequence. The Rebolledo (1980) theorem applied to the martingale $n^{-1/2}(\nu)M_\varphi^{(\nu)}(\beta^{(\nu)}(\cdot))$ gives weak convergence to Brownian motion W in $D[0, V(1)]$ as $\nu\to\infty$, while again $n^{-1/2}(\nu)R_\varphi^{(\nu)}(\beta^{(\nu)}(\cdot)) \to_{\mathcal{D}} 0$ in $D[0, V(1)]$. Hence $n^{-1/2}(\nu)S_\varphi^{(\nu)}(\beta^{(\nu)}(\cdot)) \to_{\mathcal{D}} W$ in $D[0, V(1)]$ as $\nu\to\infty$. □

REMARK (d). It is a corollary of the foregoing proof that the assertions of Theorem 4.1 remain valid if $\beta^{(\nu)}(\cdot)$ is everywhere replaced by

$$\begin{aligned}\hat\beta^{(\nu)}(x) \equiv \min[1, \inf\{s:\ &\textstyle\sum_i \Delta_i(\tau(s))q^2(X_i)\Gamma(X_i, \tau(s)) \\ &\cdot (1 - \Gamma(X_i, \tau(s))) \ge xn(\nu)\}].\end{aligned}$$

We summarize the most easily applicable staggered-entry case of our theorem, together with the technical comments on assumptions contained in Remarks (a), (b) and (d), in the following theorem.

THEOREM 4.2. *Assume for* $\nu \ge 1$ *that* $n(\nu)$ *is nonrandom and* $\{(E_i^{(\nu)}, Z_i^{(\nu)}, X_i^{(\nu)}, Y_i^{(\nu)})\}_{i=1}^{n(\nu)}$ *is a sequence of* i.i.d. *quadruples satisfying* (A.0) *such that* $P(Z_i^{(\nu)} = 1) = 1 - P(Z_i^{(\nu)} = 0) = \gamma \ne 0, 1$; $P(E_i^{(\nu)} \le s) = \Lambda(s)$ *for* $0 \le s \le T$, *where* T *is fixed,* $\Lambda(T) = 1$, *and* $\Lambda(\cdot)$ *is continuous; and for* $\varepsilon = 0, 1$, $F_{\varepsilon i}^{(\nu)}(x, y) = F_\varepsilon(x, y)$ *does not depend on* ν *or* i. *Let* $\bar G_\varepsilon(x) \equiv \bar F_\varepsilon(x, x)$, *and let* $\varphi(u, t) \equiv q(u)$ *be nonrandom and uniformly bounded. Then as* $\nu\to\infty$,

$$n(\nu)^{-1/2}S_\varphi^{(\nu)}(\tilde\beta^{(\nu)}(\cdot)) \to_{\mathcal{D}} W(\cdot) \quad \text{in} \quad D[0, V_{\max}]$$

where $W(\cdot)$ *is standard Brownian motion, and*

$$\begin{aligned}\tilde\beta^{(\nu)}(x) \equiv \min[T, \inf\{s\in[0, T]:\ &\textstyle\sum_i \Delta_i(s)q^2(X_i)\Gamma(X_i, s) \\ &\cdot (1 - \Gamma(X_i, s)) \ge xn(\nu)\}]\end{aligned}$$

$$V_{\max} = \bar V(T) \text{ where } \bar V(t) \equiv \gamma(1-\gamma)\int_0^t \frac{\Lambda(x-u)\bar G_1(u)\bar G_0(u)q^2(u)}{\gamma\bar G_1(u) + (1-\gamma)\bar G_0(u)}\,H(du).$$

and for $0 \le x \le V_{\max}$, *whenever* $\bar V^{-1}(x)$ *is a point of right increase for* $\bar V$,

$$\tilde\beta^{(\nu)}(x) \to_P \min\{t\in[0, T],\ \bar V(t) \ge x\}.$$

This Theorem, which follows immediately from Theorem 4.1 and Remarks (a), (b), and (d), is the direct generalization to continuous time of the finite-

dimensional distribution convergence theorems of Tsiatis (1981, 1982). As observed by Tsiatis (1981) and Slud and Wei (1982), the setting of i.i.d. quadruples (E_i, Z_i, X_i, Y_i) essentially covers the case of arrivals from a nonhomogeneous Poisson process.

The results of Sellke and Siegmund (1983) in our setting are on the one hand more special than our Theorem 4.1 in considering only i.i.d. sequences $\{(Z_i, X_i, Y_i)\}$ and not triangular arrays, but on the other hand more general in allowing unrestricted arrival mechanisms and proportional-hazards alternatives to the null hypothesis ($\mathscr{H}_0$); however their weak-convergence theorems are expressed (according to our notations) in terms either of the intrinsic time-scale $\langle M_q, M_q \rangle$ or of a time-change

$$\overline{\beta}^{(\nu)}(x) \equiv \inf\{t: \textstyle\sum_i \Delta_i(t) q^2(X_i) \Gamma(X_i, t)(1 - \Gamma(X_i, t)) \geq \ell(\nu) x\}$$

where $\ell(\nu)$ is an artificial parameter which is $o(n(\nu))$ as $\nu \to \infty$. In other words, by not imposing regularity conditions like our (A.1), (A.3′), Sellke and Siegmund cannot make use of a natural time-scale $\hat{\beta}^{(\nu)}(\cdot)$ scaled by sample-size $n(\nu)$ but must instead use $\overline{\beta}^{(\nu)}(\cdot)$ which asymptotically increases at a much slower rate. This means that a sequential test based on their results can make use only of an asymptotically small fraction of the $n(\nu)$ patients.

5. Application to sequential survival testing. Consider a clinical trial with two treatment groups, A and B, in which patients enter according to a nonhomogeneous Poisson process—with large continuous cumulative arrival intensity $\Lambda(\cdot)$ as long as patient-accrual continues—and are independently allocated with probability γ to treatment A, and with probability $1 - \gamma$ to treatment B. Assume that latent patient survival and censoring times are independent identically distributed pairs within each treatment group and do not depend in any way on time of arrival. We want to test (sequentially in real time) the null hypothesis of no difference in death hazards between groups A and B, where the trial is to continue at most until time T_0 or T time units after a maximum of n patients are accrued, whichever comes first. This description is a reasonably accurate idealization of a great many large two-group clinical trials (except for the common use of block-randomization—which falls well within assumption (A.3′)—and for the occurrence of trends in patient populations, which we discuss in Section 6). If a nonparametric test is desired, as is more and more often the case, a natural choice of test statistic is one of the partial-likelihood score statistics of Peto and Peto (1972), which for particular parameterized families of alternatives (and before modification by Kaplan-Meier estimates) are precisely of the form $S_\varphi(t)$ with $\varphi(u, s) \equiv q(u)$ nonrandom, not depending on s, and usually bounded. The logrank statistic corresponding to $\varphi \equiv 1$ is the most frequent choice.

Our objective in this section is to show how the theory of Section 4 justifies in the situation of the previous paragraph a sequential S_φ test generalizing the sequential logrank test of Jones and Whitehead (1979). First of all, to formalize the description above, $n(\nu)$ is Poisson with parameter $\Lambda(T_0)$, and given $n(\nu)$, we assume $\{(E_i, Z_i, X_i, Y_i)\}_{i \geq 1}$ independent with $E_i > T_0$ for $i > n(\nu)$, and E_i i.i.d. for

$1 \le i \le n(\nu)$ with continuous d.f. $\Lambda(\cdot)/\Lambda(T_0)$ on $[0, T_0]$. The sequence $\{Z_i\}$ is Bernoulli (γ) independent of $\{E_i\}$, and we assume $(\mathscr{H}_0)$ of Section 2 with continuous $H(\cdot)$ and $\{X_i, Y_i\}$ i.i.d. We define times $\tau(s)$ for $0 \le s \le 1$ as follows: $\tau(s) = sT_0$ for $s \le s_* \equiv \min\{s\colon N_E(s\ T_0) \ge n\}$, and for $s \ge s_*$, $\tau(s) = \min\{sT_0, s_*T_0 + ((s - s_*)/(1 - s_*))T\}$. The numbers $n \le \Lambda(T_0)$ are assumed large (e.g. one hundred or more). As n approaches ∞, Theorem 4.1(2) applies (cf. Theorem 4.2), and we define $V(s)$ as in Theorem 4.1 and estimate $nV(s)$ consistently by

$$\hat{V}_\varphi(s) \equiv \sum_i \Delta_i(\tau(s))q^2(X_i)\Gamma(X_i, \tau(s))(1 - \Gamma(X_i, \tau(s))).$$

If $b_-(\cdot) \le b_+(\cdot)$ are continuous functions with $b_-(0) < 0 < b_+(0)$ (determining a "stopping boundary") then for large n

$$P\left\{b_-\left(\frac{\hat{V}_\varphi(s)}{n}\right) \le \frac{S_\varphi(\tau(s))}{(\hat{V}_\varphi(s))^{1/2}} \le b_+\left(\frac{\hat{V}_\varphi(s)}{n}\right) \quad \text{for} \quad 0 \le s \le 1\right\}$$

$$\simeq P\{b_-(u) \le u^{-1/2}W(u) \le b_+(u) \quad \text{for} \quad 0 < u \le V(1)\}$$

where $W(\cdot)$ is a Wiener process. Therefore if $V_{\max} \le V(1)$ and n are known parameters, the sequential test of $(\mathscr{H}_0)$ which rejects at the first time $\tau(s)$ for which

$$\hat{V}_\varphi(s)/n \le V_{\max} \quad \text{and} \quad \frac{S_\varphi(\tau(s))}{(\hat{V}_\varphi(s))^{1/2}} \notin \left[b_-\left(\frac{\hat{V}_\varphi(s)}{n}\right), b_+\left(\frac{\hat{V}_\varphi(s)}{n}\right)\right]$$

and accepts if there is no such s, has approximate size (for large n) =

$$1 - P\{u^{1/2}b_-(u) \le W(u) \le u^{1/2}b_+(u) \quad \text{for} \quad 0 \le u \le V_{\max}\}.$$

This test procedure generalizes Jones and Whitehead's (1979) sequential logrank test (in which $\hat{V}_\varphi(s) = \gamma(1 - \gamma)N(\tau(s))$). See Whitehead and Jones (1980) for discussion of the choice of boundaries $b_\pm$ and for some approximate size, power and sample-number calculations, and see Jones and Whitehead (1979) for numerical worked examples. These authors implicitly restrict attention to trials terminated after fixed numbers of deaths.

If n and $V_{\max}$ or $V(1)$ cannot be treated as known parameters, the unorthodox notion of stopping-boundary in the paper of Slud and Wei (1981) can be used to construct a repeated S_φ-based significance test. The extension of that idea to give continuous-time sequential tests is a topic of current research.

6. Extensions and discussion. The techniques of the present paper can be used to prove many other results, of which we mention one in particular. In the case of alternatives $(\mathscr{H}_\delta)$ to $(\mathscr{H}_0)$ of the special form $H_1(dt) = \exp(\delta \cdot C(t))H_0(dt)$, where $H_e(t) \equiv \int_0^t \int_{x-}^\infty (\bar{F}_{ei}(x, x))^{-1}F_{ei}(dx, dy)$, it is not hard to show that $\int_0^\cdot (N_A(du, t) - \tilde{\Gamma}(u, t)N(du, t))$ is a $\mathscr{G}(\cdot, t)$ martingale, where

$$\tilde{\Gamma}(u, t) = \frac{\rho(u, t)\exp(\delta C(t))I[r(u, t) \ge 1]}{r(u, t) + \rho(u, t)(\exp(\delta C(t)) - 1)}$$

and that the other theorems of Sections 2 and 4 have analogues for $\tilde{S}_\varphi(t) \equiv \int q(u)(N_A(du, t) - \tilde{\Gamma}(u, t)N(du, t))$. In this way, the asymptotic efficiency

calculations of Schoenfeld (1981) for contiguous alternatives can be reproduced rigorously. Within the framework of Section 5, it turns out that if $\delta \sim Dn^{-1/2}$ as $n \to \infty$, under $(\mathscr{K}_\delta)$

$$n^{-1/2}S_\varphi(\beta(\cdot)) \to_{\mathscr{D}} W(\cdot) + D\int q(u)C(u)L(u)(1 - L(u))J(u, \beta(\cdot))H(du)$$

in $D[0, V(1)]$ if the integral is absolutely convergent. This gives an explicit drift term for calculating the power of sequential S_φ tests against contiguous alternatives.

The main technical improvements needed in Section 4 concern the weak convergence of $n(\nu)^{-1/2}S_\varphi^{(\nu)}(\tau^{(\nu)}(\cdot))$ in cases where $\varphi^{(\nu)}(u, t)$ has nontrivial dependence on t. When $\varphi^{(\nu)}(u, t)$ has the Peto-Peto (1972) form $\Phi(u, \hat{S}_{\mathrm{KM}}^{(\nu)}(u, t))$, where $\hat{S}_{\mathrm{KM}}^{(\nu)}(\cdot, t)$ denotes the left-continuous Kaplan-Meier (1958) survival curve estimator based on data $\{X_i^{(\nu)}(t), \Delta_i^{(\nu)}(t)\colon i \geq 1\}$, the author has been unable, even under stringent conditions on Φ and $\{(X_i^{(\nu)}, Y_i^{(\nu)}, E_i^{(\nu)}, Z_i^{(\nu)})\}$, to prove the uniform in-probability bounds as $\nu \to \infty$ on expressions like

$$(\log n(\nu))^{-2}\int (\varphi^{(\nu)}(u, \tau^{(\nu)}(s)) - q(u))^2 r(u, \tau^{(\nu)}(s))H(du),$$

$$(n(\nu))^{-1/2}\int (\varphi^{(\nu)}(u, \tau^{(\nu)}(s)) - q(u)) \cdot (N_A(du, \tau^{(\nu)}(s)) - \Gamma(u, \tau^{(\nu)}(s))N(du, \tau^{(\nu)}(s)))$$

which would be needed to extend Theorem 4.1 (here $q(u) \equiv \Phi(u, \exp[-H(u)])$.) Such bounds seem to require extension of the recent powerful results of Gill (1983) to the two-parameter stochastic process $\hat{S}_{\mathrm{KM}}^{(\nu)}(u, t)$. Another, more fundamental, type of dependence of $\varphi^{(\nu)}$ on t occurs in statistics such as the modified-Wilcoxon, with $\varphi^{(\nu)}(u, s)$ a function of $r^{(\nu)}(u, s)$, for which our approach via approximating martingales $M_q^{(\nu)}$ fails utterly and a new idea is needed.

In spite of the appeal of sequential designs for medical trials, three commonly cited obstacles suggest directions for further research. The first and most obvious difficulty is the administrative impossibility of instantaneous and simultaneous reporting of events in multicenter clinical trials. For this reason Pocock (1977) has proposed group-sequential methods of analysis (by batches of entrants, batches of deaths, or fixed intervals of time). The second difficulty is that followup data and further deaths will often be observed after the batch of data on which an early-stopping decision is based (i.e., before the decision to stop the trial is implemented). There seems to be no statistical theory on how to handle such delayed data, although Anderson (1964) has recognized the problem and treated a simple model. A group-sequential approach will to some extent diminish the practical importance of this technical objection. The third and most serious obstacle to sequential analysis of randomized clinical trials is that the characteristics of arriving patients typically change with time. Even for fixed-sample analysis, patient-trends raise problems in specifying the family of alternatives to test against. If the patient population does not change too rapidly or unpredictably, nothing prevents the form of the stopping boundary from taking the change into account. In fact, estimation of the population trend could be an important

function of followup data, including the delayed followup data mentioned above. However, the theoretical work on these problems remains to be done.

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