

Group Sequential Procedures for Poisson Process Data with Frailty

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SUMMARY

Exit boundaries and sample size ratios are tabulated to control the overall type-I and type-II error rates, for design and analysis of local Poisson process data with frailty, in which case the increments of the test statistics are not independent. Applications in a rodent trial with recurrent tumors are discussed, using the procedures such as the group sequential tests and the repeated confidence intervals. Minimal cost analysis is considered for determining the optimal combination of study duration and sample size.

1. Introduction

This paper investigates group sequential procedures for recurrent events data, allowing frailty (see Oakes, 1992), or the random heterogeneity of event frequencies among different subjects (see Lawless, 1987; Turnbull, Jiang, and Clark, 1997). Recurrent events data consist of individuals each being able to develop a number of events over time. Examples include data from medical studies of epileptic seizures, asthmatic attacks, infections, etc. In this context, “frailty” means that different individuals in the data set can have different “baseline” event rates (on entry of study)

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which may be regarded as sampled from an imaginary distribution. As we show in Section 2, when frailty is present, the increments of the sequentially calculated partial-likelihood score statistics no longer have the convenient independent properties (e.g., Tsiatis, Boucher, and Kim, 1995; Lan and DeMets, 1983), implying that the usual stopping rules or exit boundaries are no longer valid in general.

Sequential analyses with fixed number of subjects but with variable follow-up times have been discussed in a different context of repeated measured data by Armitage, Stratton and Worthington (1985); Geary (1988); Lee and DeMets (1991); Lee and DeMets (1992). Cook (1995) discussed the fixed design of clinical trials for recurrent events data in the same context of the present paper. Few works exist on sequential analysis of recurrent events data. In a recent paper, Cook and Lawless (1996) used robust pseudo-score test statistics which do not necessarily have independent increment structures and considered the evaluation of stopping boundaries of various types. The important idea of using the robust score-type tests, stemming from Lawless and Nadeau (1995), Cook, Lawless and Nadeau (1996) and applied to sequential analyses in Cook and Lawless (1996), has the virtue of (i) no distributional assumption is needed for the event process except for the assumption of the mean process; (ii) the score statistic does not require obtaining the parameter estimate to start with; (iii) The temporal trend of the mean process is modeled non-parametrically.

The current paper is intended to focus more on the design issue, and to directly model and investigate the effects of frailty, by focusing on the specific situation when the recurrent events data set can be modeled by local Poisson processes with frailty. Here, “local” means that the event rate of a same individual is allowed to change over time. When transformed to the process of the cumulative count of events, this model is essentially a generalization of the Andersen-Gill Model (Andersen et al., 1993) incorporating frailty. A “frailty parameter” α is introduced in Section 2, which is proportional to the between-subject variance of the baseline event rate.

In particular, we address the following aspects different from Cook and Lawless (1996), in an

attempt to provide some guidelines for study design.

(i) We consider the Wald statistics which are often used in biomedical studies.

(ii) We consider the asymptotic joint distribution of the sequential test statistics under local alternatives (Section 2) to derive the formulas for obtaining stopping boundaries and sample size planning (Section 3), and repeated confidence intervals (Section 4) that allow extra flexibility for interim analyses (Jennison and Turnbull, 1984; Lai, 1984). For uniform follow-up plans (Section 3) we transform the test statistics and derive an iterative algorithm in the form of Armitage, McPherson and Rowe (1969) for calculating stopping boundaries and planning sample size. For 2 to 5-stage interim analyses procedures with equal increments of expected number of observed events (Section 3), we present concise tables (Tables 3,4,5) for the stopping boundaries and sample size planning, labeled by one parameter related to frailty.

(iii) We illustrate the calculation of a correlation parameter defined in (12), to see how the dependence of the increments of the test statistic is induced by frailty. Two properties of the test statistics caused by frailty are discussed (P1 and P2 in Section 2), with their implication on study planning discussed in Section 3.

(iv) For studies with recurrent events data, designers often have their own choice on increasing the sample size or the length of study period to achieve certain error rates. We present a minimal cost analysis (Section 5) for determining the optimal combination of sample size and study duration.

(v) Cook and Lawless (1996) considers the error spending function approach, and estimates the covariance matrix of the sequential statistics to obtain the stopping boundaries stage by stage from data. This approach has the virtue of robustness under model misspecifications. We consider the original Pocock (Pocock, 1977) and OF (O'Brien and Fleming, 1979) designs and summarize the covariance matrix in terms of the frailty parameter, under the local Poisson process model with frailty. This approach is more model-specific, but is especially suitable for designing problems, due to the ease of summarizing the procedures in terms of pre-planned stopping boundaries and sample

sizes using the frailty parameter.

(vi) All the stopping criteria and sample size calculations are based on the *joint* asymptotic normality of the sequentially calculated score-type statistics. However, since the independent increment properties fail, the *joint* normality is not automatic even if under mild regularity conditions the sequential score statistics are *marginally* asymptotically normal. We outline a proof of the *joint* asymptotic normality in Lemma 1 in the Appendix.

In Section 2 the robust test statistics are introduced to account for frailty. Joint distributions of the test statistics evaluated at different interim analysis dates are derived and expressed in terms of certain correlation coefficients, which can be calculated for different models. From the joint distributions, we calculate the adjusted exit boundaries of the Pocock and the OF types, and tabulate them (Tables 1,2) in terms of the correlation coefficient, when there is only one interim analysis (Section 3). Recipes are also introduced for calculating sample sizes (Section 3) and constructing (Section 4) repeated confidence intervals. Optimal choice between increasing sample size and study duration is discussed in Section 5. We then retrospectively use a rats experiment data to illustrate the methods of this paper (Section 6), followed by a brief discussion (Section 7).

2. Model and notation

First, let us consider a trial with a fixed design, with n independent subjects labeled as $i = 1, \dots, n$. Each subject is randomly assigned to a certain treatment ($Z = 1$) or a placebo ($Z = 0$) with equal probabilities. The study duration is parameterized as Day 0 ($t = 0$) to Day $K - 1$ ($t = K - 1$). During the study period, subject i enters at $t = t_e$ and exits either at the end of study K or at a censoring time c due to a loss to follow-up. The purpose of the trial is to detect the treatment effect in reducing the frequency of certain outcome events. For subject i at time t , the response variable \tilde{Y}_{it} is the number of events, observed or not. Let $Y_{it} = H_{it}\tilde{Y}_{it}$ be the number of observed events, where we introduce an indicator H_{it} which takes value 1 if subject i is observed at

t , and 0 otherwise. We assume that the follow-up process $\{H_{it}\}$ is independent of the event process $\{\tilde{Y}_{it}\}$. A semi-parametric model of the multiplicative form is specified as

$$E^c(Y_{it}) = H_{it}\psi_i\Lambda_t e^{Z_i\beta}, \quad (1)$$

where β is the coefficient for treatment effect (log risk ratio), Λ_t is a discrete baseline intensity function which represents the natural trend of disease progression, E^c represents the expectation conditional on the follow-up process, treatment assignment and a “frailty” factor ϕ_i . Note that in this model even if treatment assignments are the same for two patients, the event frequencies can differ due to different frailty ψ_i ’s, which can come from all the different personal attributes (age, gender, genetic factors, family history, etc). We simplistically assume that ψ_i ’s are independent and identically distributed (i.i.d.) random variables, and have mean 1 and variance α (the frailty parameter). In the following we will assume a local Poisson regression model, where Y_{it} ’s conditional on the Z_i ’s, H_{it} ’s and the frailty ψ_i ’s are independent Poisson random variables with mean expressed in (1). We use this model as an example to formulate our method, which itself allows other models as well.

For the model described above, it is known (Lawless and Nadeau, 1995; Jiang, 1996; Jiang and Turnbull, 1997) that the usual partial likelihood estimate $\hat{\beta}$ is consistent for the treatment effect β , and is asymptotically normal with variance well estimated by a robust sandwich-type estimator, despite the existence of frailty. The partial likelihood score test is also valid, after using a robust estimate of the variance, for testing the null hypothesis $H_0 : \beta = \beta_0$. The results can be summarized as follows. Let the partial likelihood estimate be

$$\hat{\beta} = \arg \max_{b \in R} \mathcal{L}(b) \text{ where } \mathcal{L}(b) = \log \prod_{i=1}^n \prod_{t=0}^{K-1} \left(\frac{e^{Z'_i b}}{\sum_{j=1}^n H_{jt} e^{Z'_j b}} \right)^{Y_{it}}. \quad (2)$$

Denoting $U(b) := \nabla_b \mathcal{L}(\cdot)$, the partial likelihood score statistic is $U(\hat{\beta})$. We have, under mild

regularity conditions as $n \rightarrow \infty$, that

$$n^{1/2}(\hat{\beta} - \beta_0) \rightarrow \text{Normal} \{0, n \text{var}(\hat{\beta})\} \text{ in distribution,} \quad (3)$$

and

$$n^{-1/2}U(\beta_0) \rightarrow \text{Normal} \{0, n^{-1}\text{var}\{U(\beta_0)\}\} \text{ in distribution,} \quad (4)$$

under the null hypothesis $H_0 : \beta = \beta_0$.

Robust estimates of the asymptotic variances $\text{var}(\hat{\beta})$ and $\text{var}\{U(\beta_0)\}$ are discussed in Lawless and Nadeau (1995), and Jiang (1996) (Equation (6.25)), for example. In the present notation, they are

$$\hat{\text{var}}(\hat{\beta}) = (n\hat{\mathcal{I}}^{-1})(n^{-1}\hat{\mathcal{V}})(n\hat{\mathcal{I}}^{-1}) \text{ and } \hat{\text{var}}\{U(\beta_0)\} = (n^{-1}\hat{\mathcal{V}}),$$

where

$$\hat{\mathcal{I}} = -\nabla_b^2 \mathcal{L}(\cdot)|_{b=\hat{\beta}} \quad (5)$$

and

$$\hat{\mathcal{V}} = \sum_{i=1}^n \left[\sum_{t=0}^{K-1} H_{it} \left\{ Y_{it} - \left(\frac{\sum_{j=1}^n Y_{jt}}{\sum_{j=1}^n H_{jt} e^{Z_j \hat{\beta}}} \right) e^{Z_i \hat{\beta}} \right\} \left\{ Z_{ik} - \left(\frac{\sum_{j=1}^n H_{jt} Z_j e^{Z_j \hat{\beta}}}{\sum_{j=1}^n H_{jt} e^{Z_j \hat{\beta}}} \right) \right\} \right]^2.$$

Denote $I(b) := -\nabla_b^2 \ell(b)$ where $\ell(b) := \sum_{t=0}^{K-1} E[Y_{it}\{Z_i b - \log E(H_{it} e^{Z_i b})\}]$ is the uniform strong asymptotic limit of the $n^{-1}\mathcal{L}$ upto a constant independent of b . The (strong) asymptotic limit of $\hat{\mathcal{I}}$ is just $I(\beta)$, when the true parameter is β , which will be used in the discussion below.

We now come to a sequential design, where we divide the whole study period into $[0, K) = [K_0, K_1) \cup [K_1, K_2) \cup \dots \cup [K_{Q-1}, K_Q)$, where $K_0 = 0$ and $K_Q = K$. Q analyses are scheduled at $t = K_1, \dots, K_Q$, to perform the Wald test or the score test by examining $\hat{\beta}_q$ or $U_q(\beta_0)$ based on data in $t \in [0, K_q)$, $q = 1, \dots, Q$, allowing early termination of the trial. From now on, a subscript q represents the quantity evaluated from data in $t \in [0, K_q)$, $q = 1, \dots, Q$. To establish the stopping rules to control the overall type-I error rate, we need to know the *joint* distributions of $(\hat{\beta}_q - \beta_0)$, $q = 1, \dots, Q$, and of $U_q(\beta_0)$, $q = 1, \dots, Q$. Under a sequence of local alternatives, where

the true parameter is $\beta = \beta_0 + n^{-1/2}\delta$, the joint distribution of the $U_q(\beta_0)$'s turns out to be asymptotically normal under mild regularity conditions. See Lemma 1 in the Appendix.

The joint asymptotic distribution of the $n^{1/2}(\hat{\beta}_q - \beta_0)$'s can be obtained by noticing that $n^{1/2}(\hat{\beta}_q - \beta_0)$ is $n^{1/2}\{I_q(\beta_0)\}^{-1}\{n^{-1}U_q(\beta_0)\} + o_p(1)$ as $n \rightarrow \infty$. When the test statistics $U_q(\beta_0)$'s and $(\hat{\beta}_q - \beta_0)$'s are normalized by being divided by their asymptotic standard errors, they both have the same asymptotic distribution. Denote the normalized statistic as $s_q(\beta_0) = U_q(\beta_0)[\text{var}\{U_q(\beta_0)\}]^{-1/2}$, and $w_q(\beta_0) = (\hat{\beta}_q - \beta_0)\{\text{var}(\hat{\beta}_q)\}^{-1/2}$, $q = 1, \dots, Q$. Then we have the following theorem.

THEOREM 1. *If the true parameter is $\beta = \beta_0 + n^{-1/2}\delta$ (local alternative), then under mild regularity conditions,*

$$\begin{bmatrix} w_1(\beta_0) \\ \dots \\ w_Q(\beta_0) \end{bmatrix} \text{ and } \begin{bmatrix} s_1(\beta_0) \\ \dots \\ s_Q(\beta_0) \end{bmatrix} \rightarrow \text{Normal} \left\{ \begin{bmatrix} \Delta_1 \\ \dots \\ \Delta_Q \end{bmatrix}, \begin{bmatrix} \gamma_{11} & \dots & \gamma_{1Q} \\ \dots & \dots & \dots \\ \gamma_{Q1} & \dots & \gamma_{QQ} \end{bmatrix} \right\} \quad (6)$$

in distribution, as $n \rightarrow \infty$. Here for $q, q' \in \{1, \dots, Q\}$, $\Delta_q = I_q(\beta)[n^{-1}\text{var}\{U_q(\beta)\}]^{-1/2}\delta + o(1)$, and $\gamma_{qq'} = \text{corr}\{U_q(\beta), U_{q'}(\beta)\} + o(1)$, as $n \rightarrow \infty$.

For the rest of this section, we derive expressions for Δ_q and $\gamma_{qq'}$'s. We introduce the notation

$$\phi = \phi(\beta) = e^\beta(1 + e^\beta)^{-1} \quad (7)$$

$$\text{and } \Lambda(T_{i,qq'}) = \sum_{t=K_q}^{K_{q'}-1} H_{it}\Lambda_t \text{ for } q, q' \in \{1, \dots, Q\} \text{ and } q < q'. \quad (8)$$

We will also often omit the subscript i for a generic subject.

In the present randomization set-up, the treatment variable $Z = 0, 1$ with equal probability and is assumed independent of the follow-up process. Straightforward calculation leads to $I_q(\beta) = 2^{-1}\phi(\beta)E\{\Lambda(T_{i,0q})\}$.

In order to evaluate $\text{var}\{U_q(\beta)\}$'s and the correlation $\gamma_{qq'}$, we need to evaluate the covariance of the following form: $\text{cov}\{U_q(\beta), U_{q'}(\beta)\}$, $q, q' \in \{1, \dots, Q\}$. Noticing that the score $U_q(\beta)$ is linear in the outcome variable Y_{it} . Under the local Poisson regression model with frailty parametrized by variance α , The covariance of Y_{it} 's conditional on the Z_i 's and the H_{it} 's is

$$\text{cov}\{Y_{it}, Y_{it'} | Z_i \text{'s} \ \& \ H_{it} \text{'s}\} = \delta_{it'} \{ \delta_{tt'} H_{it} \Lambda_t e^{Z_i \beta} + \alpha (H_{it} \Lambda_t e^{Z_i \beta}) (H_{it'} \Lambda_{t'} e^{Z_i \beta}) \}, \quad (9)$$

by first conditioning on the frailty ψ_i 's. Here $\delta_{ab} = 1$ if $a=b$, and 0 otherwise.

Next, note that expectation of the $U_q(\beta)$'s conditional on the Z_i 's and H_{it} 's are 0. Hence $\text{cov}\{U_q(\beta), U_{q'}(\beta)\}$ is the same as $E \text{cov}\{U_q(\beta), U_{q'}(\beta) | Z_i \text{'s} \ \& \ H_{it} \text{'s}\}$. Then, using (9), we obtain, for $q, q' \in \{1, \dots, Q\}$,

$$\begin{aligned} n^{-1} \text{cov}\{U_q(\beta), U_{q'}(\beta)\} = \\ 2^{-1} \phi(\beta) E \left(\sum_{t=0}^{K_q-1} \sum_{t'=0}^{K_{q'}-1} H_{it} H_{it'} \Lambda_t \delta_{tt'} \right) + \alpha \{ \phi(\beta) \}^2 E \left(\sum_{t=0}^{K_q-1} \sum_{t'=0}^{K_{q'}-1} H_{it} H_{it'} \Lambda_t \Lambda_{t'} \right) + o(1). \end{aligned} \quad (10)$$

The convergence ($o(1)$) was proved first by showing that the conditional covariance converges almost surely, and then applying the dominated convergence theorem.

One thing worth mentioning is that the existence of frailty implies that the the score statistic $U_q(\beta_0)$'s no longer have independent increments. (10) implies that

$$\text{cov}\{U_1(\beta_0), U_2(\beta_0) - U_1(\beta_0)\} = \alpha \{ \phi(\beta_0) \}^2 E \{ \Lambda(T_{i,01}) \Lambda(T_{i,12}) \},$$

which is positive if the frailty parameter α is positive. The independent increment structure has been a basis for many work in sequential analyses, e.g., Tsiatis, Boucher and Kim (1995), Jennison and Turnbull (1989). Now its failure means that we cannot use the usual test criteria, of the Pocock or the OF types for example. The joint distribution of the test statistics depends on the Δ_q 's and

the $\gamma_{qq'}$'s. In the present model, these parameters are dependent on the frailty α as following:

$$\Delta_q = n^{1/2}(\beta - \beta_0)[2\phi^{-1}\{E(\Lambda(T_{0q}))\}^{-1} + 4\alpha E\{(\Lambda(T_{0q}))^2\}\{E(\Lambda(T_{0q}))\}^{-2}]^{-1/2} \quad (11)$$

$$\gamma_{qq'} = \frac{E\Lambda(T_{0q}) + 2\alpha\phi E\{\Lambda(T_{0q})\Lambda(T_{0q'})\}}{[E\{\Lambda(T_{0q})\} + 2\alpha\phi E\{(\Lambda(T_{0q}))^2\}]^{1/2}[E\{\Lambda(T_{0q'})\} + 2\alpha\phi E\{(\Lambda(T_{0q'}))^2\}]^{1/2}}, \quad (12)$$

for $q, q' \in \{1, \dots, Q\}$ and $q < q'$, where ϕ is defined in (7). The element $\gamma_{q'q}$'s are required to be the same as the $\gamma_{qq'}$'s, so as to make the variance-covariance matrix symmetric in equation (6). In the case when $Q = 2$, a single parameter $\gamma = \gamma_{12}$ determines the whole variance-covariance matrix.

Note $\gamma_{qq'}$'s depend on the moments $M_{qq', d_1 d_2} = E[\{\Lambda(T_{0q})\}^{d_1}\{\Lambda(T_{0q'})\}^{d_2}]$, where $d_1, d_2 \in \{0, 1, 2\}$, $q, q' \in \{1, \dots, Q\}$. They depend on the the form of the baseline intensity function Λ_t , as well as the details of the follow-up process. While various models are possible, we in the following focus on a simplest situation, where $\text{cov}\{\Lambda(T_{0q}), \Lambda(T_{0q'})\} = 0$, $1 \leq q, q' \leq Q$, which could be assumed when the length of follow-up periods in each stage are nearly the same for all individuals (uniform follow-up plans). In this situation,

$$\Delta_q = 2^{-1}\delta\sqrt{A_q}, \quad 1 \leq q \leq Q \quad (13)$$

$$\gamma_{qq'} = \sqrt{A_q/A_{q'}}, \quad \gamma_{q'q} = \gamma_{qq'}, \quad 1 \leq q \leq q' \leq Q \quad (14)$$

where $A_q = (\alpha + (2\phi\Lambda_q)^{-1})^{-1}$, and Λ_q is a shorthand notation for $E\Lambda(T_{0q})$, $1 \leq q \leq Q$, and $\delta = n^{1/2}(\beta - \beta_0)$. Obviously, the correlation $\gamma_{qq'}$'s is an increasing function of α (non-negative). Hence,

PROPERTY 1 (P1) (Increased Correlations): *For unifrom follow-up plans, the existence of frailty leads to bigger pairwise correlations between the sequentially calculated test statistics (Wald or score) asymptotically.*

Another implication of the frailty is the following:

PROPERTY 2 (P2) (Standard Error Inflation): *The sequentially calculated test statistics (Wald or score), at each stage, have bigger asymptotic standard errors, due to frailty.*

This is because (10) implies that $\text{var}\{U_q(\beta)\}$ is an increasing function of α , and the asymptotic variance of the test statistics (Wald or score) are proportional to $\text{var}\{U_q(\beta)\}$. Note that (P2) is not restricted to the uniform follow-up plans.

In the following sections, we will investigate the stopping boundaries and the sample size planning. The implications of (P1) and (P2) on these design aspects will then be made clear. From now on we will concentrate only on the (normalized) Wald test statistic. However, up to the leading order of large sample size, things are the same for the normalized score test, since the two test statistics are asymptotically equivalent.

3. Stopping rules and sample size planning

Consider now the following stopping rule for the Q -stage analysis: For $q = 1, \dots, Q - 1$, if $|w_q(\beta_0)| \geq c_q^{(Q)}$ then stop the trial and reject H_0 at time K_q ; otherwise continue the trial and perform a test at time K_{q+1} . At time K_Q , if $|w_Q(\beta_0)| \geq c_Q^{(Q)}$ then reject H_0 ; otherwise retain H_0 . Exit boundary $\{c_1^{(Q)}, \dots, c_Q^{(Q)}\}$ is needed to preserve the overall type-I error rate, say, α_I . Sample size is also required to achieve a certain power, say, $1 - \alpha_{II}$, at the alternative hypothesis $H_a : \beta = \beta_a$.

Suppose the true parameter β is parameterized in δ as $\beta(\delta) = \beta_0 + n^{-1/2}\delta$. Define

$$\pi(\delta) = \text{pr}_{\beta(\delta)}[|w_q(\beta_0)| < c_q^{(Q)}, q = 1, \dots, Q]. \quad (15)$$

The error rate constraints are then simply

$$\pi(0) = 1 - \alpha_I \quad (16)$$

$$\pi(\delta_a) = \alpha_{II}, \quad (17)$$

with an alternative hypothesis $H_a : \beta = \beta_a = \beta(\delta_a)$. The above two equations can be used to find the exit boundary (expressed in a 1-parameter family) and the sample size (or the study duration,

if the sample size is fixed). The integration involved in calculating the probability $\pi(\delta)$ can be performed by using multivariate normal integration packages such as MULNOR (Schervish, 1984).

In the following, we consider the Pocock type boundary (Pocock, 1977), where all $c_q^{(Q)}$'s are assumed equal to some constant $c_P^{(Q)}$; as well as the OF type boundary (O'Brien and Fleming, 1979), where $c_q^{(Q)} = c_{OF}^{(Q)}(Q/q)^{1/2}$ is assumed for some constant $c_{OF}^{(Q)}$ and $q = 1, \dots, Q$. For the most commonly-used type-I error rate $\alpha_I = 0.05$, we have obtained from (16) the constants $c_P^{(Q)}$ and $c_{OF}^{(Q)}$ for $Q = 2$, as a function of the correlation $\gamma = \gamma_{12}$, by numerical integration. using the Gaussian quadrature method with 48 nodes. The results are tabulated below (Tables 1 and 2) for correlations ranging from 0.00 to 0.99, in increments of 0.01. The value of $c_P^{(Q)}$ or $c_{OF}^{(Q)}$ for a negative correlation is the same as the value for a positive correlation with the same magnitude, due to the symmetry of the integration region.

In the following we illustrate the calculation of γ based on a uniform follow-up plan defined at the end of the last section. Assume a constant intensity rate $\Lambda_t = r_0$. Then $\Lambda(T_{0q}) = r_0 T_{0q}$ where $T_{0q} := \sum_{t=0}^{K_q-1} H_t$. Assume that all subjects enter study at time 0, there is no loss to follow-up, and one interim analysis is scheduled at $t = K_1 = K_2/2$. In this case $\Lambda(T_{01}) = r_0 K_1$, and $\Lambda(T_{02}) = r_0 K_2$. Then the parameters for the asymptotic distribution of the Wald statistic are

$$\begin{aligned} \Delta_q &= n^{1/2}(\beta - \beta_0)\{2\phi^{-1}(r_0 K_q)^{-1} + 4\alpha\}, \quad q = 1, 2 \\ \text{and } \gamma &= 2^{-1/2} \left(\frac{1 + 2\alpha r_0 K_2 \phi}{1 + \alpha r_0 K_2 \phi} \right)^{1/2} \quad \text{where } \phi \text{ is defined in (7)}. \end{aligned} \quad (18)$$

The frailty parameters r_0 , β (in ϕ) and α in (18) need to be estimated *before* the study, strictly speaking. They could be estimated by the method of moments, or by a method of negative binomial regression (Lawless, 1987; Abu-Libdeh, Turnbull and Clark, 1990; Turnbull et al., 1997), based on some pilot study data set, or results from previous studies with a similar nature. One thing to notice in (18) is that the correlation, as a function of the frailty, is always bigger than the

correlation without frailty ($\alpha = 0$), which is $\gamma(\alpha = 0) = 2^{-1/2} \approx 0.7071$. Comparing with Tables 1 and 2, we see that it will always be conservative to use $c_P^{(Q)} \approx 2.18$ and $c_{OF}^{(Q)} \approx 1.98$ in testing H_0 , which corresponds to neglecting the frailty by taking $\alpha = 0$ and $\gamma = 2^{-1/2}$. If frailty is taken into account, the rejection critical values $c_P^{(Q)}$ and $c_{OF}^{(Q)}$ will be smaller, making it easier to reject H_0 for a same value of the Wald statistic. This shows a major implication of property (P1) in the last section on the stopping boundaries. (P1) implies, by the Slepian's inequality (e.g., Theorem 2.1.1 of Tong, 1980), that the existence of frailty allows the use of narrower stopping boundaries. The usual stopping boundaries obtained based on the independent increments assumption, neglecting frailty, are conservative.

In the rest of this section, we consider extensions to multi-stage analyses ($Q > 2$). The multi-dimensional numerical integration algorithms have decreasing accuracy and reliability as Q increases. However, we notice that a convenient alternative algorithm is available for uniform follow-up plans. In this situation, (13), (14) and Theorem 1 imply that $(A_q - A_{q-1})^{-1/2}[A_q^{1/2}\{w_q(\beta_0) - \Delta_q\} - A_{q-1}^{1/2}\{w_{q-1}(\beta_0) - \Delta_{q-1}\}]$, $1 \leq q \leq Q$ are independent standard normal random variables ($A_0 = 0$). This leads to the following iterative (1-dimensional) integration algorithm, in the same form of Armitage, McPherson and Rowe (1969), for $\pi(\delta)$ defined in (15):

$$\pi(\delta) = \int_{-c_Q^{(Q)}}^{c_Q^{(Q)}} g(Q, z; \delta) dz \quad (19)$$

where $g(Q, z; \delta)$ is iteratively defined as the following:

$$g(1, z; 0) = \varphi(z) := (2\pi)^{-1/2} \exp(-z^2/2), \quad (20)$$

For $1 \leq q \leq Q - 1$,

$$g(q + 1, z; 0) = \left(\frac{A_{q+1}}{A_{q+1} - A_q} \right)^{1/2} \times \int_{-c_q^{(Q)}}^{c_q^{(Q)}} g(q, u; 0) \varphi \left\{ \frac{A_{q+1}^{1/2} z - A_q^{1/2} u}{(A_{q+1} - A_q)^{1/2}} \right\}^2 du, \quad (21)$$

$$\text{and } g(Q, z; \delta) = g(Q, z; 0) \exp\{-8^{-1} A_Q \delta^2 + 2^{-1} z (A_Q)^{1/2} \delta\}. \quad (22)$$

This facilitates calculation of the stopping boundaries, powers and the sample sizes for multi-stage designs.

When ($Q = 2$), the single-parameter (γ) parameterization was very convenient for setting up concise tables for stopping boundaries, as well as calculating power or sample size in a computing algorithm. For $Q > 2$, the stopping boundary will in general depend on a Q -dimensional symmetric matrix determined from the recruitment/follow-up situation. This will lead to difficulties in summarization of the designing aspects of the interim analyses. However in a class of recruiting schemes simpler description and computation are achievable for the sequential designs.

Suppose, in addition to uniform follow-up, we have equal increments procedure, where $\Lambda_q = q\lambda$, $1 \leq q \leq Q$ for some constant λ , parameterization of Δ_q and $\gamma_{qq'}$'s can be further simplified:

$$\Delta_q = Dh_q(\rho), \quad \gamma_{qq'} = h_q(\rho)/h_{q'}(\rho), \quad \gamma_{q'q} = \gamma_{qq'}, \quad 1 \leq q \leq q' \leq Q \quad (23)$$

where $D = 2^{-1}(2\phi\lambda)^{1/2}\delta$, $h_q(\rho) = ((\rho - 0.5)(1 - \rho)^{-1} + q^{-1})^{-1/2}$ and

$$\rho = \rho(\lambda) := \gamma_{12}^2 = (2\alpha\phi\lambda + 0.5)(2\alpha\phi\lambda + 1)^{-1}. \quad (24)$$

(23) is easily obtained by noting that $A_q^{1/2} = (2\phi\lambda)^{1/2}h_q(\rho)$, $1 \leq q \leq Q$.

Hence we can in this case parameterize the power function by D and ρ ($\rho \in [0.5, 1]$). ρ contains the input of frailty parameter α . When there is no frailty, $\rho = 0.5$. Consider now the null hypothesis $\beta = \beta_0$. Note that $\delta = n^{1/2}(\beta - \beta_0)$ in D is 0, and so is D . The stopping boundaries can then be solved from (16), labeled by one parameter ρ only. Table 3 lists $c_P^{(Q)}$ and $c_{OF}^{(Q)}$ for $Q = 2, 3, 4, 5$ and ρ ranging from 0.50 to 0.90 in increments of 0.01, when $\alpha_I = 0.05$. When $Q = 1$, $c_P^{(Q)}$ and $c_{OF}^{(Q)}$ are simply $z_{\alpha_I/2} \approx 1.96$, where z_ν is the $100(1 - \nu)$ th percentile of the standard normal cumulative distribution function.

Consider now the alternative hypothesis $\beta = \beta_a$. To solve for the sample size from (17), note that (17) involves two variables D and ρ only through parametrization (23), and the sample size

enters D through $\delta = n^{1/2}(\beta - \beta_0)$. We therefore solve D from (17) as a function of ρ to obtain $D = D(\rho)$, which also (implicitly) depend on Q , α_I and α_{II} (error rates required), as well as the type T of stopping boundaries ($T = P$ or OF). Then, the definition of D below (23) leads to

$$n = 4\{D(\rho)\}^2(\beta_a - \beta_0)^{-2}(2\phi\lambda)^{-1} \quad (25)$$

where $\phi = \phi(\beta_a)$, and $\phi(\cdot)$ is defined in (7). If $Q = 1$, and $\rho = 0.5$ (no frailty), $D(\rho)$ can be solved directly as $(z_{\alpha_I/2} + z_{\alpha_{II}})$. Hence, in a fixed design without frailty, the sample size needed for a study length $Q\lambda$ is

$$n_0 = 4(z_{\alpha_I/2} + z_{\alpha_{II}})^2(\beta_a - \beta_0)^{-2}(2\phi Q\lambda)^{-1}. \quad (26)$$

n_0 is to be used as a reference sample size. The sample size required in (25) can then be expressed as $n = R_T^{(Q)}(\rho)n_0$, where the ratio $R_T^{(Q)}(\rho) = QD(\rho)^2(z_{\alpha_I/2} + z_{\alpha_{II}})^{-2}$ is tabulated at $\alpha_I = 0.05$, and $\alpha_{II} = 0.20$ (Table 4) and 0.10 (Table 5), for $Q = 2$ to 5 and $\rho = 0.50$ to 0.90 in increments of 0.01. In practice, sample size could be obtained by first finding fixed frailtyless design sample size n_0 from (26), then multiplying by a ratio $R_T^{(Q)}(\rho)$ read from Table 4 or 5, if there is an initial estimate of frailty parameter α to determine ρ . We find it very convenient to base the sample size planning on these tables. For comparison, the first row $R^{(1)}$ in those tables lists the sample size inflation ratio required in fixed designs with $\rho > 0.5$, induced by the existence of frailty.

Now we comment on the implication of properties (P1) and (P2) of the last section on the sample size planning. (P1) and (P2) have opposite implications. With fixed type-I and II error rates, (P1) alone would imply that a smaller sample size could be used with the presence of frailty. However in reality the increase of standard error, due to (R2), is often overwhelming, and a net result is that a much bigger sample size is required, due to the existence of frailty. The increment of the required sample size can be seen from Tables 4 and 5, where the ratio $R_T^{(Q)}(\rho)$'s increase with ρ , and hence also increase with the frailty parameter α .

4. Repeated confidence intervals

Repeated confidence intervals (RCIs) are a method which allows the study results to be evaluated flexibly at interim analyses without depending on the rigid stopping criteria (Jennison and Turnbull, 1984; Lai, 1984; Coe and Tamhane, 1993). Here we construct the RCIs for recurrent events data with frailty.

Note first that the boundary $\{c_q^{(Q)}\}$ in the previous section is dependent on β_0 (the value of β under H_0) through the correlation $\gamma_{qq'}$'s which depend on $\phi(\beta_0)$. We in this section explicitly express such relation as $c_q^{(Q)} = c_q^{(Q)}(\beta_0)$. (16) in the last section can then be rewritten as

$$\text{pr}_{\beta_0}[|w_q(\beta_0)| \leq c_q^{(Q)}(\beta_0), q = 1, \dots, Q] = 1 - \alpha_I.$$

Let RCIs be

$$I_q^{(Q)} = \{\beta_0 : |w_q(\beta_0)| \leq c_q^{(Q)}(\beta_0)\}, q = 1, \dots, Q. \quad (27)$$

Then

$$\text{pr}_{\beta_0}[\beta_0 \in I_q^{(Q)}, q = 1, \dots, Q] = 1 - \alpha_I.$$

Then

$$\text{pr}_{\beta_0}[\beta_0 \in I_\zeta] \geq 1 - \alpha_I \text{ for any stopping rule } \zeta.$$

Note that $w_q(\beta_0) = (\beta_q - \beta_0)\{\text{vâr}(\hat{\beta}_q)\}^{-1/2} = (\beta_q - \beta_0)/\hat{\text{sê}}(\hat{\beta}_q)$. When sample size n is large, the leading order approximation to the RCI $I_q^{(Q)}$ is determined by

$$I_q^{(Q)} = \{\beta_0 : |\beta_q - \beta_0|/\hat{\text{sê}}(\hat{\beta}_q) = |w_q(\beta_0)| \leq c_q^{(Q)}(\hat{\beta}_q)\}, q = 1, \dots, Q,$$

replacing $c(\beta_0)$ with $c(\hat{\beta}_q)$. The solution becomes

$$I_q^{(Q)} = (\hat{\beta}_q - c_q^{(Q)}(\hat{\beta}_q)\hat{\text{sê}}(\hat{\beta}_q), \hat{\beta}_q + c_q^{(Q)}(\hat{\beta}_q)\hat{\text{sê}}(\hat{\beta}_q)), q = 1, \dots, Q. \quad (28)$$

5. Minimal cost analysis

For recurrent events study planning, we often have the choice of increasing the sample size or study duration (or expected number of events per subject) to achieve a certain power. Optimal combination of sample size and duration could be determined by the minimal cost analysis. This is made possible by the sample size calculation method presented in Section 3. We assume equal increments procedure $\Lambda_q = \lambda q$, $1 \leq q \leq Q$.

Suppose the maximal cost of a study is $C_Q(n, \lambda) = C_0 n(Q\lambda + \lambda_0)$, where C_0 is a constant, and $C_0 \lambda_0$ is the minimal cost for recruiting a subject. λ_0 , termed initial duration, is the expected number of events to be observed that would cost the same as recruiting one extra subject. Note that $n = n_0 R_T^{(Q)}(\rho) \propto R_T^{(Q)}(\rho)(Q\lambda)^{-1}$ from Section 3, where $\rho = \rho(\lambda)$ is defined in (24). We have

$$C_Q(n, \lambda) \propto R_T^{(Q)}\{\rho(\lambda_0 x)\}\{1 + (Qx)^{-1}\} \quad (29)$$

where $x := \lambda/\lambda_0$. An alternative expression in terms of ρ is

$$C_Q(n, \lambda) \propto R_T^{(Q)}(\rho)\{1 + 2\phi\lambda_0\alpha Q^{-1}(1 - \rho)(\rho - 0.5)^{-1}\} \quad (30)$$

Up to a multiplicative constant, this could be calculated for each ρ from the tables of $R_T^{(Q)}(\rho)$, to search for the minimizer ρ_{op} . Then the minimizer in λ is

$$\lambda_{op} = (2\phi\alpha)^{-1}(\rho_{op} - 0.5)(1 - \rho_{op})^{-1}. \quad (31)$$

The optimal sample size is then

$$n_{op} = n_0 R_T^{(Q)}(\rho_{op}) = R_T^{(Q)}(\rho_{op})4(z_{\alpha_I/2} + z_{\alpha_{II}})^2(\beta_a - \beta_0)^{-2}(2\phi Q \lambda_{op})^{-1}. \quad (32)$$

In fixed design $Q = 1$, $R^{(1)}(\rho)$ can be analytically evaluated to be $0.5(1 - \rho)^{-1}$, the optimal points could then be solved as $\lambda_{op} = (2\alpha\phi\lambda_0)^{-1/2}\lambda_0$, $R^{(1)}(\rho_{op}) = 1 + 2\phi\alpha\lambda_{op}$ and $n_{op} = (1 + 2\phi\alpha\lambda_{op})4(z_{\alpha_I/2} + z_{\alpha_{II}})^2(\beta_a - \beta_0)^{-2}(2\phi Q \lambda_{op})^{-1}$.

6. An example

Let us use a rats experiment data set (Gail, Santner and Brown, 1980; Thompson et al., 1978) retrospectively to illustrate our method. The data set itself was really obtained from a fixed design. However we imagine that it was designed to have an interim analysis at halftime, and see what information a halftime analysis can provide in deciding whether we need to further carry out the other half of the experiment, as an illustration of our method. The data set has a relatively small sample size (48) and a relatively bigger average number of events (about 6). Further simulations will be required to test if these conditions are good enough for our proposed asymptotic method to work satisfactorily. Here the main motivation will be to use this example to illustrate the methodology.

48 female rats who remained tumor-free after sixty days of pre-treatment of a prevention drug (retinyl acetate) were randomized into two groups. In Group 1 (23 rats) they continue to receive treatment ($Z=1$), in Group 2 (25 rats) they receive placebo ($Z=0$). Rats were palpated for tumors twice a week. More details are given in Thompson et al. (1978). Times of mammary tumor diagnoses were recorded, from which our response variable Y_{it} 's are constructed. The objective of the study was to see if discontinuation of treatment leads to more tumors diagnosed. Formally, we would like to test the null hypothesis $H_0 : \beta = 0$ at level $\alpha_I = 0.05$. The original design was to follow all rats for a fixed length of time (122 days). However, imagine that an interim analysis was planned on the data gathered up to the 61th day (halftime), and we will see how the method described above can be applied. We will use the local Poisson regression model with frailty, as introduced in Section 2, and the uniform follow-up plan as described in Section 3, to calculate the correlation (18) and perform the analysis.

Based on the halftime data ($q = 1$), we get the maximum partial likelihood estimate as $\hat{\beta}_1 = -0.7549$, with the robust estimate of standard error $\hat{se}(\hat{\beta}_1) = 0.2427$. Here the subscript 1 is used to denote the first interim analysis. Note that the Z-value (or the Wald statistic) is the ratio $-0.7549/0.2427 = -3.1104$. If we decided in advance to use a Pocock's boundary, then $c_1^{(2)} = c_P^{(2)}$.

We notice from Table 1 that $c_P^{(2)}$ for any correlation γ is not as large in magnitude as our test statistic. So $|w_1(0)| = |\hat{\beta}_1|/\hat{se}(\hat{\beta}_1) \geq c_1^{(2)}$. Then we could stop the trial and reject H_0 at halftime. On the other hand, if the OF procedure was decided before hand, which is less likely to reject H_0 at an early stage, we would be comparing the Z-value with $c_1^{(2)} = 2^{1/2}c_O^{(2)}$. From looking at the Table 2 we again see that even the largest possible $c_O^{(2)}$ will make $c_1^{(2)}$ smaller than the Z-value. Therefore we decide to reject H_0 and discontinue the experiment at halftime.

The actual analysis at Day 122 gives $\hat{\beta}_2 = -0.8230$ and $\hat{se}(\hat{\beta}_2) = 0.1968$, leading to a Z-value -4.1819 .

RCIs with an overall level of confidence 95% ($\alpha_I = 0.05$) can provide a range of plausible values for β at the interim analysis, without conforming to a rigid stopping rule. In order to calculate the critical value $c_1^{(2)}$, we need to find the correlation γ from (18). The constants r_0 and α are needed from some pilot study. Since we do not have such information, two approaches could be used. One is simply use the lower bound of γ which is 0.7071 (Section 3). Another is to estimate the r_0 and α by a negative binomial regression or a method of moment estimation from the data set accumulated up to the time of the interim analysis. The second approach, unlike in the case of testing where boundaries need to be pre-specified *before* the experiment, is legitimate at present for obtaining RCIs to the leading order of large sample size. This is because the estimates of r_0 and α are used only as approximations to their true values. The first approach ($\gamma = 0.7071$) is conservative but is simpler, and will result in a slightly wider RCI. We did perform the second approach for the half-time data set and found that the resulting RCIs are very close to the conservative ones. Here we decide only to report the conservative results, corresponding to using $\gamma = 0.7071$. For RCI derived from the Pocock's procedure, we use $c_1^{(2)} = c_P^{(2)} = 2.18$ from $\gamma = 0.7071$, in place of the coefficient $c_1^{(2)}(\hat{\beta}_1)$ in (28). We obtain $I_1 = (-1.28, -0.226)$. For OF's procedure we use $c_1^{(2)} = 2^{1/2}c_O^{(2)} = (1.41)(1.98)$ and get $(-1.43, 0.0763)$. These, in the scale of of the risk ratio (e^β), become the intervals $(0.277, 0.797)$ and $(0.239, 0.927)$ respectively. These imply that the treatment effect could range from roughly

none, to reducing the frequency of tumors to about a quarter. The flexibility of RCI approach allows the decision on the continuation of the experiment being independent of the rigid stopping rules. If we decide to carry on the experiment, we can obtain a second RCI at Day 122 based on the complete data. Using a correlation of 0.7071 to obtain a most conservative interval, we get the following intervals in the scale of risk ratio (e^β). For Pocock type RCI we obtain (0.286, 0.674), while for OF type we obtain (0.298, 0.648). Notice that the OF type gives a wider RCI for the first interim analysis, but gives a narrower RCI for the later one. In conclusion, we find that the treatment effect reduces the tumor frequency to about one-third to two-thirds of the control group rats.

Now imagine that the present study is a pilot study for the purpose of estimating the sample size for the study of another drug, with the same time table of scheduled analyses, i.e., an interim analyses at Day 61 (K_1), plus a possible final analysis at Day 122 (K_2). The present pilot study provides an estimate of $r_0 = 6.04/122$ (or about 1 tumor every 20 days), as well as a frailty parameter $\alpha = 0.2665$, from a negative binomial regression (see Abu-Libdeh et al., 1990; or Turnbull et al., 1997 for example). Therefore we can use a rough value $r_0 = 6/122$ and $\alpha = 0.3$ in our sample size calculation. Suppose we are interested in detecting a drug effect of 80% in risk ratio, which corresponds to an alternative hypothesis $H_a : \beta = \beta_a = \log(0.80) = -0.2231$, with power $1 - \alpha_{II} = 0.80$. Then $\phi = \phi(\beta_a) = 0.4444$ where $\phi(\cdot)$ is defined in (7). These lead to a correlation $\gamma = 0.8498$. From Tables 1 and 2 we obtain $c_1^{(2)} = c_2^{(2)} = c_P^{(2)} = 2.133$ for the Pocock's boundary; and $c_1^{(2)} = 2^{1/2}c_O^{(2)} = 2.780$, $c_2^{(2)} = c_O^{(2)} = 1.966$ for the OF's boundary. Then we can use equation (17) to estimate the sample size. Alternatively we could use Table 4. Note that $\gamma_{12} = \gamma \approx 0.85$. $\rho = \gamma_{12}^2 \approx 0.73$ (rounded up). From (26), we obtain a reference sample size n_0 as 119. According to Table 4, sample size ratios 2.8817 and 2.7086 are needed for power 0.80, leading to adjusted sample sizes n of 343 and 323, for Pocock and OF design, respectively. If frailty was neglected ($\alpha = 0$ and $\rho = 0.5$), however, the sample size ratios will be 1.1104 and 1.0078, respectively for Pocock and OF

designs with $Q = 2$, leading to corresponding sample sizes of 132 and 120 which would be naively planned. The correct sample sizes are more than twice the naive ones. This increase of sample size is required, however, to achieve the real power of 0.80. If the naive sample size were to be used, real power can only be achieved at 0.423 and 0.416, for Pocock and OF's procedures respectively, instead of the desired one 0.80.

It is also interesting to look at the sample size needed for a fix design, if the error rates are specified to be the same as before. Suppose we plan to observe the subjects for 122 days, and assume that $r_0 K_Q$ is about 6, and the frailty α is taken as 0.3 as before. In the previous formalism we need to replace λ by $r_0 K_Q = 6$ when calculating ρ by (24). The result is $\rho \approx 0.81$. The corresponding sample size ratio $R^{(1)}$ is 2.6316. For the previously obtained reference sample size $n_0 = 119$, we get an adjusted sample size $n \approx 314$. Note that when there exists frailty ($\alpha = 0.3$), the sample size required for a fixed design is only slightly smaller than the sample size required for a sequential design. On the other hand, sequential design also allows the possibility of a shorter study period by possible stopping of the trial at halftime. These two observations suggest that in trials with recurrent event outcomes with frailty, sequential designs are recommendable.

Now we consider a cost analysis. The Type-I and II error rates are required to be 0.05 and 0.20, respectively, as before. Suppose the intial duration described in Section 5 is $\lambda_0 = 4$. $\beta_\alpha = \log(0.8)$, $\alpha = 0.3$ as before. We used the Table 4 and (30) to obtain $\rho_{op} = 0.68$, $\lambda_{op} = 2.11$ (corresponding to about 40 days follow-up each stage) and $n_{op} = 385$, for the Pocock design; and $\rho_{op} = 0.67$, $\lambda_{op} = 1.93$ (corresponding to about 40 days follow-up each stage) and $n_{op} = 374$, for the OF design. Using these results of optimal sample sizes and durations, it is straightforward to check that the OF design will have less optimal maximal cost $C_Q(n_{op}, \lambda_{op})$ —93% of that of the Pocock design.

7. Discussion

This paper is an attempt to prescribe how to perform interim analyses for recurrent events with frailty. The most general level of our approach does not impose independent increment structures

for the sequential test statistics. As a result, there may be other problems with non-independent increments of test statistics to which the present method could be applied. For example, Tables 1 and 2 only depend on the correlation, rather than the underlying mechanism by which the correlation is induced. However, computation is most convenient in the case when follow-up time variation is negligible and the iterative 1-dimensional integration technique can be applied. For equal increments procedures, parameterization can be further simplified and tables for stopping boundaries and sample size planning are provided for 2 to 5-stage analyses. The failure of independent increment structure leads to, in this case, a one-parameter family of stopping boundaries labeled by a parameter ρ depending on the frailty, which reduce to the usual stopping boundaries when $\rho = 0.5$.

The impact of the frailty on the designing aspects are explicitly investigated. The existence of frailty induces extra correlation between the sequentially calculated statistics, leading to *smaller* stopping boundary constants $c_P^{(Q)}$ and $c_{OF}^{(Q)}$ for a pre-specified type-I error rate (see Table 3). However due to the inflation of the standard error caused by the frailty, the sample size needed to achieve a certain power will be *larger* (see Tables 4 and 5).

Our methods are asymptotic and depend on the large sample approximation. A study of the agreement of the empirical and nominal type-I error rates are discussed in Cook & Lawless (1996), in the situation of constant recruitment rate. Further such studies under different parameter ranges and different recruitment plans will be helpful. Our method will probably be useful in the context when initial stage analysis involves already a relatively large number of subjects (*e.g.*, > 100), and decision on whether or not to continue the follow-up/recruitment is to be made at each stage.

There are still many opening questions left in this direction. Various recruitment procedures of practical interest may be considered in calculating the correlations. A different yet interesting question is to look at the sequential bioequivalence tests in similar problems with non-standard increment structures for the test statistics, such as the trials involving recurrent event outcomes with frailty.

In the case the *multivariate* normality does not hold but the marginal normality for each sequentially calculated score-type statistic is asymptotically normal (which usually holds under mild regularity conditions), conservative stopping boundaries may be obtained from Bonferroni-type probability inequalities, which should work well for small number of interim analyses such as 5 or 6. In the case when asymptotic normality of individual score-type statistic fails, *e.g.*, due to very small sample size at the initial analysis, Chebyshev-type inequalities (or their correlation-adjusted versions) may provide conservative stopping boundaries—the drawback is that they may be *very* conservative. These are the price to be paid for being robust in terms of the distributions of the test statistics.

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APPENDIX

LEMMA 1. *If true parameter is $\beta = \beta_0 + n^{-1/2}\delta$ (local alternative), then under mild regularity conditions, $n^{-1/2}\tilde{U}(\beta_0) \rightarrow \text{Normal}\{\tilde{I}(\beta)\delta, n^{-1}V\}$ in distribution as $n \rightarrow \infty$.*

Here $\tilde{U}(\beta_0)$ is the column of $U_q(\beta_0)$'s, V is the (asymptotic) variance-covariance matrix of $\tilde{U}(\beta_0)$, and $\tilde{I}(\beta)$ is the column of partial likelihood information $I_q(\beta)$'s defined in , where $I_q(\beta)$ can be obtained from the asymptotic limit of $n^{-1}\hat{\mathcal{I}}$ defined by (5), when restricted to the data in $t \in [0, K_q]$. We here only give the outlines of the proof. We argue that $\tilde{U}(\beta)$ is asymptotically normal with mean 0, if the true parameter is β . Then a Taylor expansion $n^{-1/2}\tilde{U}(\beta_0) = n^{-1/2}\tilde{U}(\beta) + \tilde{I}(\beta)\delta + o_p(1)$ is used to obtain Lemma 1, using the Slutsky's theorem, provided that $n^{-1/2}\tilde{U}(\beta)$ is asymptotical normal with mean zero.

To prove the asymptotic normality of $n^{-1/2}\tilde{U}(\beta)$ in the last statement, it suffices to show that $n^{-1/2}U^-(\beta)$ is asymptotically normal, where $U^-(\beta)$ is the column of difference $\{U_q(\beta) - U_{q-1}(\beta)\}$'s ($U_0(\beta) = 0$). We show this by noting that $U^-(\beta)$ can be regarded as a usual score vector of dimension q . This follows by constructing a Q -dimensional time-dependent covariate vector $\tilde{Z}_{it} = (\tilde{Z}_{it1}, \dots, \tilde{Z}_{itQ})'$, where $\tilde{Z}_{itq} = Z_i 1_{tq}$, $1_{tq} = 1$ if $t \in [K_{q-1}, K_q]$ and 0 otherwise, for $q = 1, \dots, Q$. Construct also a Q -dimensional vector $\tilde{b} = (b_1, \dots, b_Q)'$. Then $U^-(\beta) = \nabla_{\tilde{b}}\tilde{\mathcal{L}}(\tilde{b})|_{\tilde{b}=\tilde{\beta}}$, which is the score vector for the log partial likelihood

$$\tilde{\mathcal{L}}(\tilde{b}) = \log \prod_{i=1}^n \prod_{t=0}^{K-1} \left(\frac{e^{\tilde{Z}'_{it}\tilde{b}}}{\sum_{j=1}^n H_{jt} e^{\tilde{Z}'_{jt}\tilde{b}}} \right)^{Y_{it}},$$

taking value at $\tilde{b} = \tilde{\beta} = (\beta, \dots, \beta)'$. Note that $\tilde{\beta}$ corresponds to the true parameter in this formalism, since $E\nabla_{\tilde{b}}\tilde{\mathcal{L}}(\tilde{b})|_{\tilde{b}=\tilde{\beta}} = 0$.

Finally, since $U^-(\beta) = \nabla_{\tilde{b}}\tilde{\mathcal{L}}(\tilde{b})|_{\tilde{b}=\tilde{\beta}}$ has the form of a usual score vector, there are several different methods to prove it to be asymptotically normal with mean 0. A proof can be made from using a multivariate central limit theorem, by first showing that $U^-(\beta)$ is a sum of n iid random vectors plus a term of order $o_p(1)$, or from using a martingale central limit theorem, or alternatively from recognizing $\tilde{\mathcal{L}}(\tilde{b})$ as the profile likelihood for a system of n independent Poisson processes.

Table 1
 $c_P^{(2)}$ as a function of γ ($\alpha_I = 0.05$)

γ	.00	.01	.02	.03	.04	.05	.06	.07	.08	.09
0.0	2.2365	2.2365	2.2364	2.2364	2.2363	2.2363	2.2362	2.2361	2.2359	2.2358
0.1	2.2356	2.2355	2.2353	2.2350	2.2348	2.2346	2.2343	2.2340	2.2337	2.2334
0.2	2.2330	2.2327	2.2323	2.2319	2.2315	2.2310	2.2306	2.2301	2.2296	2.2291
0.3	2.2285	2.2280	2.2274	2.2268	2.2261	2.2255	2.2248	2.2240	2.2233	2.2225
0.4	2.2217	2.2209	2.2201	2.2192	2.2183	2.2173	2.2164	2.2154	2.2143	2.2132
0.5	2.2121	2.2110	2.2098	2.2086	2.2073	2.2060	2.2046	2.2032	2.2018	2.2003
0.6	2.1987	2.1971	2.1955	2.1937	2.1920	2.1901	2.1882	2.1862	2.1842	2.1821
0.7	2.1799	2.1776	2.1752	2.1728	2.1702	2.1676	2.1648	2.1619	2.1589	2.1557
0.8	2.1524	2.1490	2.1454	2.1416	2.1376	2.1334	2.1289	2.1242	2.1192	2.1139
0.9	2.1081	2.1020	2.0953	2.0880	2.0799	2.0709	2.0606	2.0485	2.0336	2.0133

Table 2
 $c_{OF}^{(2)}$ as a function of γ ($\alpha_I = 0.05$)

γ	.00	.01	.02	.03	.04	.05	.06	.07	.08	.09
0.0	1.9997	1.9997	1.9997	1.9997	1.9997	1.9996	1.9996	1.9996	1.9995	1.9994
0.1	1.9994	1.9993	1.9992	1.9991	1.9990	1.9989	1.9988	1.9987	1.9986	1.9984
0.2	1.9983	1.9981	1.9980	1.9978	1.9976	1.9975	1.9973	1.9971	1.9969	1.9966
0.3	1.9964	1.9962	1.9959	1.9957	1.9954	1.9951	1.9948	1.9946	1.9942	1.9939
0.4	1.9936	1.9933	1.9929	1.9926	1.9922	1.9918	1.9914	1.9910	1.9906	1.9902
0.5	1.9897	1.9893	1.9888	1.9883	1.9878	1.9873	1.9868	1.9862	1.9857	1.9851
0.6	1.9846	1.9840	1.9834	1.9827	1.9821	1.9814	1.9808	1.9801	1.9794	1.9787
0.7	1.9780	1.9772	1.9765	1.9757	1.9749	1.9741	1.9733	1.9725	1.9717	1.9709
0.8	1.9700	1.9692	1.9684	1.9675	1.9667	1.9659	1.9651	1.9644	1.9636	1.9629
0.9	1.9623	1.9617	1.9612	1.9607	1.9604	1.9602	1.9600	1.9600	1.9600	1.9600

Table 3
 $c_P^{(Q)}$ and $c_{OF}^{(Q)}$ as a function of ρ ; $Q = 2, 3, 4, 5$ ($\alpha_I = 0.05$)

ρ	$c_P^{(2)}$	$c_{OF}^{(2)}$	$c_P^{(3)}$	$c_{OF}^{(3)}$	$c_P^{(4)}$	$c_{OF}^{(4)}$	$c_P^{(5)}$	$c_{OF}^{(5)}$
0.50	2.1783	1.9774	2.2895	2.0040	2.3613	2.0243	2.4132	2.0401
0.51	2.1766	1.9769	2.2861	2.0022	2.3562	2.0209	2.4064	2.0350
0.52	2.1750	1.9764	2.2828	2.0004	2.3512	2.0177	2.3998	2.0303
0.53	2.1733	1.9759	2.2794	1.9987	2.3463	2.0146	2.3934	2.0258
0.54	2.1715	1.9753	2.2760	1.9969	2.3414	2.0116	2.3870	2.0216
0.55	2.1698	1.9748	2.2727	1.9953	2.3365	2.0088	2.3808	2.0177
0.56	2.1680	1.9743	2.2692	1.9936	2.3316	2.0060	2.3746	2.0140
0.57	2.1662	1.9737	2.2658	1.9920	2.3268	2.0034	2.3686	2.0104
0.58	2.1643	1.9732	2.2623	1.9905	2.3219	2.0009	2.3626	2.0071
0.59	2.1624	1.9727	2.2589	1.9889	2.3171	1.9985	2.3566	2.0040
0.60	2.1605	1.9721	2.2554	1.9874	2.3123	1.9961	2.3508	2.0010
0.61	2.1586	1.9716	2.2518	1.9860	2.3075	1.9939	2.3449	1.9981
0.62	2.1566	1.9711	2.2482	1.9845	2.3027	1.9918	2.3391	1.9955
0.63	2.1545	1.9706	2.2446	1.9831	2.2979	1.9897	2.3333	1.9929
0.64	2.1524	1.9700	2.2410	1.9818	2.2930	1.9877	2.3275	1.9905
0.65	2.1503	1.9695	2.2373	1.9805	2.2881	1.9858	2.3217	1.9882
0.66	2.1481	1.9690	2.2336	1.9792	2.2833	1.9840	2.3160	1.9860
0.67	2.1459	1.9685	2.2298	1.9779	2.2783	1.9822	2.3102	1.9840
0.68	2.1436	1.9680	2.2259	1.9767	2.2734	1.9806	2.3044	1.9820
0.69	2.1413	1.9675	2.2221	1.9755	2.2684	1.9790	2.2986	1.9802
0.70	2.1389	1.9670	2.2181	1.9744	2.2634	1.9774	2.2928	1.9784
0.71	2.1365	1.9665	2.2141	1.9733	2.2583	1.9760	2.2869	1.9768
0.72	2.1340	1.9660	2.2100	1.9722	2.2531	1.9746	2.2810	1.9752
0.73	2.1315	1.9656	2.2059	1.9712	2.2479	1.9732	2.2750	1.9737
0.74	2.1288	1.9651	2.2017	1.9702	2.2427	1.9720	2.2690	1.9724
0.75	2.1261	1.9647	2.1974	1.9692	2.2373	1.9708	2.2629	1.9711
0.76	2.1234	1.9642	2.1930	1.9683	2.2319	1.9696	2.2567	1.9698
0.77	2.1205	1.9638	2.1885	1.9674	2.2263	1.9686	2.2505	1.9687
0.78	2.1176	1.9634	2.1839	1.9666	2.2207	1.9676	2.2441	1.9676
0.79	2.1145	1.9630	2.1792	1.9658	2.2149	1.9666	2.2376	1.9667
0.80	2.1114	1.9626	2.1744	1.9651	2.2091	1.9658	2.2311	1.9658
0.81	2.1081	1.9623	2.1694	1.9644	2.2031	1.9649	2.2243	1.9649
0.82	2.1048	1.9619	2.1643	1.9638	2.1969	1.9642	2.2175	1.9642
0.83	2.1013	1.9616	2.1591	1.9632	2.1906	1.9635	2.2104	1.9635
0.84	2.0977	1.9613	2.1536	1.9626	2.1841	1.9629	2.2032	1.9629
0.85	2.0939	1.9611	2.1480	1.9621	2.1774	1.9623	2.1958	1.9623
0.86	2.0900	1.9608	2.1422	1.9617	2.1704	1.9618	2.1881	1.9618
0.87	2.0859	1.9606	2.1361	1.9613	2.1632	1.9614	2.1802	1.9614
0.88	2.0815	1.9605	2.1298	1.9609	2.1557	1.9610	2.1719	1.9610
0.89	2.0770	1.9603	2.1231	1.9607	2.1479	1.9607	2.1633	1.9607
0.90	2.0721	1.9602	2.1162	1.9604	2.1397	1.9605	2.1543	1.9605

Table 4
 $R^{(1)}, R_P^{(Q)}$ and $R_{OF}^{(Q)}$ as a function of ρ ; $Q = 2, 3, 4, 5$ ($\alpha_I = 0.05$; $1 - \alpha_{II} = 0.80$)

ρ	$R^{(1)}$	$R_P^{(2)}$	$R_{OF}^{(2)}$	$R_P^{(3)}$	$R_{OF}^{(3)}$	$R_P^{(4)}$	$R_{OF}^{(4)}$	$R_P^{(5)}$	$R_{OF}^{(5)}$
0.50	1.0000	1.1104	1.0078	1.1663	1.0174	1.2023	1.0238	1.2284	1.0284
0.51	1.0204	1.1538	1.0486	1.2337	1.0786	1.2942	1.1054	1.3452	1.1304
0.52	1.0417	1.1990	1.0911	1.3037	1.1423	1.3895	1.1904	1.4662	1.2365
0.53	1.0638	1.2460	1.1354	1.3763	1.2087	1.4884	1.2788	1.5916	1.3470
0.54	1.0870	1.2949	1.1816	1.4519	1.2779	1.5911	1.3711	1.7216	1.4623
0.55	1.1111	1.3459	1.2299	1.5307	1.3503	1.6979	1.4674	1.8567	1.5827
0.56	1.1364	1.3992	1.2803	1.6126	1.4258	1.8090	1.5680	1.9971	1.7084
0.57	1.1628	1.4548	1.3330	1.6982	1.5048	1.9248	1.6733	2.1435	1.8398
0.58	1.1905	1.5129	1.3884	1.7875	1.5877	2.0456	1.7836	2.2960	1.9777
0.59	1.2195	1.5738	1.4464	1.8810	1.6744	2.1719	1.8993	2.4552	2.1222
0.60	1.2500	1.6376	1.5072	1.9789	1.7656	2.3040	2.0206	2.6219	2.2739
0.61	1.2821	1.7047	1.5712	2.0813	1.8615	2.4424	2.1483	2.7961	2.4332
0.62	1.3158	1.7751	1.6386	2.1889	1.9622	2.5876	2.2827	2.9789	2.6013
0.63	1.3514	1.8491	1.7096	2.3021	2.0685	2.7401	2.4243	3.1708	2.7781
0.64	1.3889	1.9271	1.7844	2.4213	2.1808	2.9004	2.5738	3.3725	2.9650
0.65	1.4286	2.0095	1.8636	2.5469	2.2994	3.0694	2.7318	3.5850	3.1625
0.66	1.4706	2.0966	1.9475	2.6796	2.4250	3.2480	2.8992	3.8095	3.3716
0.67	1.5152	2.1888	2.0364	2.8200	2.5581	3.4365	3.0766	4.0466	3.5936
0.68	1.5625	2.2866	2.1310	2.9686	2.6997	3.6365	3.2654	4.2977	3.8293
0.69	1.6129	2.3906	2.2316	3.1268	2.8503	3.8487	3.4663	4.5642	4.0805
0.70	1.6667	2.5013	2.3388	3.2949	3.0112	4.0746	3.6804	4.8477	4.3482
0.71	1.7241	2.6195	2.4535	3.4742	3.1831	4.3152	3.9097	5.1497	4.6348
0.72	1.7857	2.7460	2.5764	3.6659	3.3672	4.5723	4.1552	5.4725	4.9416
0.73	1.8519	2.8817	2.7086	3.8716	3.5651	4.8478	4.4188	5.8180	5.2713
0.74	1.9231	3.0274	2.8507	4.0925	3.7782	5.1442	4.7031	6.1893	5.6268
0.75	2.0000	3.1847	3.0043	4.3306	4.0082	5.4629	5.0100	6.5892	6.0105
0.76	2.0833	3.3551	3.1706	4.5880	4.2577	5.8079	5.3423	7.0212	6.4259
0.77	2.1739	3.5397	3.3515	4.8672	4.5287	6.1815	5.7041	7.4901	6.8781
0.78	2.2727	3.7411	3.5489	5.1713	4.8246	6.5886	6.0986	7.9998	7.3711
0.79	2.3809	3.9611	3.7650	5.5037	5.1487	7.0332	6.5305	8.5568	7.9119
0.80	2.5000	4.2031	4.0027	5.8689	5.5054	7.5219	7.0063	9.1690	8.5064
0.81	2.6316	4.4699	4.2658	6.2715	5.8995	8.0606	7.5315	9.8430	9.1631
0.82	2.7778	4.7665	4.5576	6.7183	6.3377	8.6578	8.1158	10.5915	9.8938
0.83	2.9412	5.0973	4.8842	7.2172	6.8274	9.3244	8.7687	11.4254	10.7101
0.84	3.1250	5.4691	5.2515	7.7769	7.3781	10.0729	9.5035	12.3624	11.6288
0.85	3.3333	5.8899	5.6681	8.4108	8.0025	10.9198	10.3359	13.4225	12.6695
0.86	3.5714	6.3707	6.1438	9.1344	8.7166	11.8856	11.2877	14.6313	13.8593
0.87	3.8461	6.9248	6.6930	9.9676	9.5403	12.9987	12.3863	16.0246	15.2327
0.88	4.1667	7.5701	7.3342	10.9391	10.5010	14.2953	13.6676	17.6462	16.8344
0.89	4.5454	8.3328	8.0913	12.0849	11.6376	15.8259	15.1824	19.5604	18.7279
0.90	5.0000	9.2465	9.0004	13.4597	13.0003	17.6600	17.0008	21.8542	21.0009

Table 5
 $R^{(1)}$, $R_P^{(Q)}$ and $R_{OF}^{(Q)}$ as a function of ρ ; $Q = 2, 3, 4, 5$ ($\alpha_I = 0.05$; $1 - \alpha_{II} = 0.90$)

ρ	$R^{(1)}$	$R_P^{(2)}$	$R_{OF}^{(2)}$	$R_P^{(3)}$	$R_{OF}^{(3)}$	$R_P^{(4)}$	$R_{OF}^{(4)}$	$R_P^{(5)}$	$R_{OF}^{(5)}$
0.50	1.0000	1.1001	1.0071	1.1506	1.0161	1.1831	1.0222	1.2065	1.0265
0.51	1.0204	1.1433	1.0479	1.2176	1.0773	1.2743	1.1038	1.3223	1.1285
0.52	1.0417	1.1884	1.0905	1.2872	1.1410	1.3689	1.1888	1.4423	1.2348
0.53	1.0638	1.2352	1.1348	1.3595	1.2075	1.4672	1.2773	1.5667	1.3453
0.54	1.0870	1.2840	1.1810	1.4347	1.2767	1.5693	1.3696	1.6958	1.4606
0.55	1.1111	1.3349	1.2292	1.5132	1.3491	1.6754	1.4660	1.8300	1.5811
0.56	1.1364	1.3880	1.2797	1.5947	1.4246	1.7859	1.5666	1.9696	1.7069
0.57	1.1628	1.4435	1.3325	1.6800	1.5037	1.9012	1.6720	2.1152	1.8384
0.58	1.1905	1.5015	1.3878	1.7690	1.5866	2.0215	1.7824	2.2669	1.9763
0.59	1.2195	1.5623	1.4458	1.8622	1.6734	2.1473	1.8981	2.4253	2.1209
0.60	1.2500	1.6260	1.5066	1.9598	1.7646	2.2789	2.0195	2.5913	2.2727
0.61	1.2821	1.6930	1.5707	2.0620	1.8605	2.4168	2.1472	2.7648	2.4321
0.62	1.3158	1.7633	1.6380	2.1693	1.9613	2.5615	2.2817	2.9469	2.6002
0.63	1.3514	1.8372	1.7091	2.2823	2.0676	2.7136	2.4233	3.1382	2.7771
0.64	1.3889	1.9151	1.7839	2.4012	2.1800	2.8735	2.5729	3.3393	2.9640
0.65	1.4286	1.9975	1.8632	2.5266	2.2986	3.0421	2.7310	3.5513	3.1616
0.66	1.4706	2.0844	1.9471	2.6591	2.4243	3.2203	2.8984	3.7752	3.3708
0.67	1.5152	2.1766	2.0360	2.7993	2.5574	3.4085	3.0759	4.0117	3.5929
0.68	1.5625	2.2743	2.1306	2.9477	2.6991	3.6082	3.2648	4.2623	3.8286
0.69	1.6129	2.3783	2.2312	3.1057	2.8498	3.8201	3.4657	4.5284	4.0799
0.70	1.6667	2.4889	2.3385	3.2736	3.0106	4.0456	3.6799	4.8114	4.3477
0.71	1.7241	2.6071	2.4532	3.4529	3.1826	4.2860	3.9092	5.1130	4.6343
0.72	1.7857	2.7335	2.5761	3.6444	3.3667	4.5428	4.1547	5.4354	4.9412
0.73	1.8519	2.8692	2.7083	3.8500	3.5647	4.8181	4.4184	5.7805	5.2709
0.74	1.9231	3.0150	2.8504	4.0708	3.7778	5.1142	4.7027	6.1516	5.6264
0.75	2.0000	3.1723	3.0041	4.3088	4.0079	5.4329	5.0096	6.5512	6.0102
0.76	2.0833	3.3426	3.1704	4.5662	4.2574	5.7776	5.3420	6.9829	6.4257
0.77	2.1739	3.5273	3.3513	4.8454	4.5284	6.1511	5.7038	7.4516	6.8779
0.78	2.2727	3.7287	3.5487	5.1494	4.8244	6.5582	6.0984	7.9612	7.3710
0.79	2.3809	3.9487	3.7648	5.4819	5.1485	7.0028	6.5303	8.5181	7.9117
0.80	2.5000	4.1908	4.0026	5.8471	5.5052	7.4914	7.0061	9.1301	8.5062
0.81	2.6316	4.4577	4.2656	6.2497	5.8993	8.0301	7.5314	9.8042	9.1630
0.82	2.7778	4.7543	4.5576	6.6967	6.3376	8.6274	8.1157	10.5527	9.8937
0.83	2.9412	5.0852	4.8841	7.1956	6.8273	9.2941	8.7686	11.3867	10.7100
0.84	3.1250	5.4572	5.2515	7.7555	7.3780	10.0428	9.5034	12.3238	11.6287
0.85	3.3333	5.8781	5.6681	8.3896	8.0025	10.8899	10.3359	13.3841	12.6695
0.86	3.5714	6.3590	6.1438	9.1134	8.7165	11.8559	11.2877	14.5933	13.8593
0.87	3.8461	6.9133	6.6930	9.9470	9.5403	12.9694	12.3863	15.9868	15.2327
0.88	4.1667	7.5589	7.3342	10.9187	10.5010	14.2664	13.6677	17.6090	16.8344
0.89	4.5454	8.3218	8.0913	12.0650	11.6376	15.7975	15.1825	19.5238	18.7280
0.90	5.0000	9.2358	9.0004	13.4401	13.0004	17.6321	17.0008	21.8183	21.0009