Efficient panel designs for longitudinal recurrent event studies recording panel counts

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SUMMARY

Many clinical trials are designed to study outcome measures recorded as the number of events occurring during specific intervals, called panel data. In such data, the intervals are specified by a planned set of follow-up times. As the collection of panel data results in a partial loss of information relative to a record of the actual event times, it is important to gain a thorough understanding of the impact of panel study designs on the efficiency of the estimates of treatment effects and covariates. This understanding can then be used as a base from which to formulate appropriate designs by layering in other concerns, e.g. clinical constraints, or other practical considerations. We compare the efficiency of the analysis of panel data with respect to the analysis of data recorded precisely as times of recurrences, and articulate conditions for efficient panel designs where the focus is on estimation of a treatment effect when adjusting for other covariates. We build from the efficiency comparisons to optimize the design of panel follow-up times. We model the recurrent intensity through the common proportional intensity framework, with the treatment effect modeled flexibly as piecewise constant over panels, or groups of panels. We provide some important considerations for the design of efficient panel studies, and illustrate the methods through analysis of designs of studies of adenomas.

Keywords: Clinical trial; Counting process; Design of follow-up times; Interval censored; Life-history data; Panel count data; Poisson regression; Sample size.

1. INTRODUCTION

Recently, there has been a growing interest in long-term health outcomes which has translated into a popularity of longitudinal analysis. One common type of longitudinal data arises from follow-up of an event

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that may repeat over time; this is called \textit{recurrent event data} and is our focus here. Examples include recurrence of cancer tumors in the bladder, recurrence of polyps in the colon, or recurrence of events such as epileptic seizures or asthma attacks. In some situations, exact times of occurrence of events are available as participants are subjected to continuous follow-up, either because they are already hospitalized, or for ethical reasons, or because this is critical in the study context. However, most designs rely on assessments by scans or interviews, so that only the number of events between observations are known. Generally, a key question when planning a recurrent event study is how often and when individuals should be observed.

Through the widespread availability of longitudinal recurrent event data, there has been a corresponding increase in the development of methods for handling such data (Elgmati and others, 2010; Çiğşar and Lawless, 2012). Some of these developments specifically concern longitudinal counts of events (Hu and others, 2009; Zhao and others, 2011). However, few studies consider design effects (Cook, 1995; Matsui and Miyagishi, 1999; Cook and others, 2009), and no studies, to our knowledge, focus on optimal design strategies. We emphasize that such strategies are fundamental to better care, better estimators, and better utilization of funds, especially in times of fiscal constraints when national agencies implementing long-term longitudinal studies are required to justify their merit.

Due to the recent great interest and wide usage of data arising as counts of events over intervals or panels, also known as \textit{panel data}, design strategies are particularly important for the design and analysis of this type of data. Panel count data are common in clinical studies where for ethical or practical reasons only the number of episodes in an interval of time are recorded, as, for example, in the study of treatments for epilepsy (Thall and Vail, 1990). There are panel studies where in order to detect events an invasive, uncomfortable, or expensive procedure needs to be conducted. In these cases, determining the best panel follow-up times and resulting optimal efficiency of the estimators is even more critical. This is also important as such effective designs will choose more follow-up times when events are likely to occur and may then result in overall better patient management and care. In particular, we specify conditions under which the common design with regularly spaced follow-up times will be optimal.

To illustrate, we provide an example of a contemporaneous study in this context. Meyskens and others (2008) studied the prevention of colorectal adenomas in a 3-year study; adenomas were detected by colonoscopy at regular follow-up times of 18, 32, and 36 months. We will consider scenarios similar to this study to illustrate optimal design of panel follow-up times. These optimal designs utilize information available from pilot studies, often conducted to illustrate the need for the study, and will focus on collection of data at times which are more important for patient care and which provide for efficient treatment estimators.

Our principal aim is 2-fold: (1) identification of conditions for full efficiency of estimators, focusing on the treatment effect, from panel studies versus continuous follow-up and (2) optimization of panel follow-up times. Additionally, we illustrate efficiency losses for a variety of designs to demonstrate how sharply efficiencies change with different design conditions. We emphasize that these are not the only elements to be considered in study design; however, they provide foundations which, we argue, are useful as a starting point when taking into consideration other elements as availability of services for patient care, uncertainty in pilot studies, etc.

In Section 2, we derive the asymptotic relative efficiency (ARE) of estimators of treatment effects for panel versus continuous follow-up studies, provide efficiencies for several designs, and outline optimal placement of follow-up times. We illustrate the design considerations in Section 2.3, through the planning of a panel design which determines optimal placement of follow-up times for studies that mimic those reported in Meyskens and others (2008). In Section 3, we close with a summary and discussion of the methods presented.
2. ARE AND DESIGN OF FOLLOW-UP TIMES OF PANEL STUDIES

2.1 Mixed non-homogeneous Poisson processes with piecewise constant treatment effects

Efficient designs are considered here from a model-based perspective where the proportional intensity structure is employed because of its wide utility and its tractability (Andersen and Gill, 1982). To approximate smooth changes in a treatment effect over time, we consider a simple generalization of the usual proportional intensity model that allows the treatment effect to vary over panels or groups of panels, so its effect is piecewise constant over specific time segments. This might be the case when the benefit of the treatment is thought to be delayed until a certain period of exposure has been achieved, or when a treatment loses effectiveness over time.

Consider a comparison of \( k \) treatments, where \( m_j \) individuals are given treatment \( j \), and let \( M = \sum_{j=1}^{k} m_j \), the total sample size of the study. Let \( \{ N_i(t), t \geq 0 \} \) denote the counting process monitoring the occurrence of events for subject \( i, i = 1, \ldots, M \). The total observation period for all individuals is divided into \( S \) segments, defined by \( T^1, T^2, \ldots, T^S \), so segment \( s \) is \( (T^{s-1}, T^s] \), \( s = 1, \ldots, S \). Using more segments will provide greater flexibility in modeling how the treatment effect responds over time.

Each individual is observed up to time \( T_i \), referred to as the termination time (or final follow-up time) for individual \( i \). Let the observation process \( \{ Y_i(t), t \geq 0 \} \) be 1 if individual \( i \) is under study at \( t \) and 0 otherwise, and assume that \( \{ Y_i(t), t \geq 0 \} \) is independent of the counting process \( N_i(t) \). Thus, the observed counting process may be defined as \( \tilde{N}_i(t) = \int_0^t Y_i(u) \, dN_i(u), t \geq 0, t \in (0, T_i] \) for individual \( i, i = 1, \ldots, M \). The \( e_i^s \) individual-specific panel follow-up times in segment \( s \) are denoted by \( T_{i,1}^s < T_{i,2}^s < \cdots < T_{i,e_i^s}^s \), where, if individual \( i \) has not been lost to follow up, \( T_{i,e_i^s}^s = T_i \). Panel counts in segment \( s \) for individual \( i \) are denoted as \( n_{ip}^s = \tilde{N}_i(T_{i,p}^s) - \tilde{N}_i(T_{i,p-1}^s), p = 1, \ldots, e_i^s, s = 1, \ldots, S \), and the total aggregated count for individual \( i \) in segment \( s \) is \( n_{i+}^s = \sum_{p=1}^{e_i^s} n_{ip}^s \).

Define the covariate \( x_i \) as a \( k \times 1 \) treatment indicator vector for the \( i \)th individual, such that \( x_{i1} = 1 \) represents an intercept term, and \( x_{ij} = 1 \) if individual \( i \) received treatment \( j \), or 0 otherwise, \( j = 2, \ldots, k \). The \( d_z \times 1 \) vector \( z_i \) contains remaining covariates beyond treatment which are to be adjusted for in the analysis. To aid the presentation, Appendix A of supplementary material available at Biostatistics online lists all notation utilized in this discussion of efficiencies.

The counting process \( N_i(t) \) is modeled as a Poisson process with intensity function

\[
\lambda_i(t) = \nu_i \rho(t; \alpha) \exp \left\{ x_i' \left[ \sum_{s=1}^{S} \beta^s I(T^{s-1}, T_s^1(t)) \right] + z_i' \gamma \right\},
\]

given \( \nu_i \), an individual-specific random effect accounting for the common phenomenon of overdispersion; the function \( I(T^{s-1}, T_s^1(t)) \) is an indicator function for \( t \in (T^{s-1}, T_s^1] \); and \( \rho \) is a twice differentiable baseline intensity function depending on the parameter \( \alpha \) with dimension \( d_z \). The parameters \( \beta^s = (\beta^s_1, \beta^s_2, \ldots, \beta^s_k)' \) and \( \gamma \) correspond to the treatment effects in segment \( s \), and the parameters governing the effects of the covariates \( z_i \) to be adjusted for in the analysis, \( s = 1, \ldots, S \), respectively. We have parameterized the \( \beta \)’s so that treatment effects are measured relative to treatment 1. Hence, \( \beta^s_1 \) reflects the overall baseline level of the intensity function \( \lambda_i(t) \) in segment \( s \), when the \( z_i \)’s are centered, whereas \( \alpha \) describes the shape of the intensity function \( \rho(t; \alpha) \). Additionally, we may take \( E(\nu_i) = 1 \) without loss of generality; let \( \text{var}(\nu_i) = \tau \). If we denote the mean of the total aggregated counts to be \( \mu^s_{i+} = E(n_{i+}^s) \) in segment \( s \), then its variance is of the form \( \mu^s_{i+} (1 + \tau \mu^s_{i+}) \). Writing the cumulative baseline intensity function in each segment \( s \) as \( R^s_i = \int_{T^{s-1}}^{T_s^1} Y_i(t) \rho(t; \alpha) \, dt \), then \( \mu^s_{i+} = R^s_i \exp(x_i' \beta^s + z_i' \gamma) \). Similarly, defining the cumulative baseline intensity function in panel period \( p \) as \( R^s_{ip} = \int_{T_{ip}^{s-1}}^{T_{ip}^s} Y_i(t) \rho(t; \alpha) \, dt \), we have \( \mu^s_{ip} = E(n_{ip}^s) = R^s_{ip} \exp(x_i' \beta^s + z_i' \gamma) \).
Our objective is to investigate the efficiency of panel studies with respect to continuous follow-up, focusing on the estimation of the treatment effect $\beta$ while adjusting for other covariates. Because quasi-likelihood, or the use of estimating equations, is such a popular technique, and because of its high efficiency with respect to maximum likelihood estimation, we focus on the development of efficient designs based on this flexible approach. With quasi-likelihood, the mean and variance specification is sufficient to formulate estimating equations for the parameters, and also to obtain the asymptotic variance of the estimators of $\beta$, $\gamma$, and $\tau$.

We describe below the likelihood and quasi-likelihood estimators for both panel and continuous data. The likelihood over all the segments, based on either the full data or the panel data, has the form

$$
\prod_{s=1}^{S} L^s
$$

where $L^s$ corresponds to the likelihood in segment $s$, $s = 1, \ldots, S$. In the discussion below, for the purpose of simplicity in the derivation of the theorem regarding efficiency, we focus on the common form of one segment, and drop the superscript $s$; however, we provide the theorem below in its more general form based on several segments.

Let $\theta = (\beta', \gamma', \alpha', \tau')$, and let $\omega_{ipl}$ be the time of the $l$th event, from the start of the study, for the $i$th individual in panel period $p$, $i = 1, \ldots, M$, $p = 1, \ldots, e_i$, $l = 1, \ldots, n_{ip}$. The likelihood based on either the full data (subscripted by $d = f$) or the panel data (subscripted by $d = p$) factorizes as

$$
L_d(\theta) = L_{a,d}(\alpha)L(\theta), \quad d \in \{f, p\},
$$

(2.2)

where

$$
L_{a,f}(\alpha) = \prod_{i=1}^{M} \prod_{p=1}^{e_i} \prod_{l=1}^{n_{ip}} \frac{\rho(\omega_{ipl}; \alpha)}{R_i}, \quad L_{a,p}(\alpha) = \prod_{i=1}^{M} \left[ \left( \binom{n_{i+}}{n_i, \ldots, n_{i+}} \prod_{p=1}^{e_i} \left( \frac{R_{ip}}{R_i} \right)^{n_{ip}} \right) \right],
$$

(2.3)

and

$$
L(\theta) = \prod_{i=1}^{M} \int_0^{\infty} \frac{(v_i \mu_{i+})^{n_{i+}} e^{-v_i \mu_{i+}}}{n_{i+}!} p(v_i) d v_i
$$

(2.4)

is the likelihood for a mixed Poisson model based on the total counts observed for individual $i$. For example, if $v_i$ is gamma distributed, $L(\theta)$ becomes the negative binomial likelihood. Note that if there is a single panel, $L_p(\theta)$ (see (2.2)) will reduce to the simple mixed Poisson kernel, $L(\theta)$. Note too that the likelihood developed here also accommodates in straightforward manner complications in panel studies such as missing panel counts within segments, or data which are aggregated over two or more consecutive panels.

The factorization of $\lambda_i(t)$ into two components, one a function of $\alpha$, the other a function of $\beta$, $\gamma$, $\alpha$, and $\tau$ is the key to the factorization of the likelihood in (2.2). We exploit this in deriving estimators, and in computing the asymptotic efficiency of the estimator of $\beta$ (and $\alpha$) derived from $L_p$, with respect to the corresponding estimators derived from $L_f$.

Let $g_{d}$ denote the full set of estimating equations for the panel ($d = p$) or the full ($d = f$) data. The estimating equation for the covariate effect $\eta_1 = (\beta', \gamma')'$ for the panel or the full data is

$$
g_{\eta_1} = V'U_1 U_o^{-1} (n - \mu) = 0,
$$

(2.5)

where $U_1 = \text{diag}\{\mu_{i+}, \ i = 1, \ldots, M\}$, $U_o = \text{diag}\{\mu_{i+}(1 + \tau \mu_{i+}), \ i = 1, \ldots, M\}$, $n = (n_{1+}, \ldots, n_{M+})'$ is a vector of counts, and $\mu = (\mu_1, \ldots, \mu_M)'$ is the vector of their expected values; $V = (XZ)$ combines the treatment indicators in $X$ with the covariates in $Z$. Equation (2.5) arises from the usual quasi-likelihood function $(\partial \mu / \partial \eta_1) \text{var}(\eta_1)^{-1} (\eta_1 - \mu)$.
We obtain an estimating equation for $\alpha$ by combining $\partial \log L_{\alpha,d}/\partial \alpha$, $d = f, p$, with quasi-likelihood estimation, yielding
\begin{equation}
\mathbf{g}_{\alpha,d} = \frac{\partial \log L_{\alpha,d}(\alpha)}{\partial \alpha} + W'U_1U_0^{-1}(\mathbf{n} - \mathbf{\mu}) = \mathbf{0}, \tag{2.6}
\end{equation}
where $W$ is a matrix with entries
\begin{equation}
w_{ia} = \frac{\partial \log R_i}{\partial \alpha_a}, \quad i = 1, \ldots, M \text{ and } a = 1, \ldots, d. \tag{2.7}
\end{equation}

There are several choices for the estimating equation of the overdispersion parameter $\tau$, and our results concerning efficiency and design remarks in this paper are not tied to the use of any specific estimator for $\tau$. In our examples, we use the pseudo-likelihood estimator, which has been popular since its introduction by Davidian and Carroll (1987). It has performed well in simulation studies and has documented optimality properties (Nelder and Lee, 1992). The pseudo-likelihood estimating equation for $\tau$ is
\begin{equation}
g_\tau = \sum_{i=1}^{M} \frac{(n_{i+} - \mu_{i+})^2 - (1 - h_i)\mu_{i+}(1 + \tau \mu_{i+})}{(1 + \tau \mu_{i+})^2} = 0, \tag{2.8}
\end{equation}
where $h_i = \text{diag}(U_1^{1/2}V_1' (V_1'U_1V_1)^{-1}V_1'U_1^{1/2})$, $V_1 = (X'Z'W)'; h_i$ is the diagonal of the hat matrix and represents a correction to reduce small sample bias in this simple second moment equation.

Hence, when we have full data, we solve $g_f = (g'_{\eta_1}; g'_{\alpha_1}, g_\tau)' = \mathbf{0}'$ to yield an estimator of $\theta$ denoted by $\hat{\theta}$, and, when we use a panel design, the estimating equation becomes $g_p = (g'_{\eta_1}; g'_{\alpha_1}, g_\tau)' = \mathbf{0}'$ yielding the estimator $\hat{\theta}$. In the following, estimators obtained from $g_f$ are notated with a hat (e.g. $\hat{\alpha}$) while those obtained from $g_p$ are notated with a tilde ($\tilde{\alpha}$).

The information matrix for $\eta = (\beta', \gamma', \alpha')'$ has the partitioned form as follows for $d = f$ or $d = p$:
\begin{equation}
I_d = \begin{pmatrix}
V'UV & V'UW \\
W'UV & W'UW + H_d
\end{pmatrix}, \tag{2.9}
\end{equation}
with $U = U_1U_0^{-1}U_1 = \text{diag}[u_i = \mu_{i+}/(1 + \tau \mu_{i+}), i = 1, \ldots, M]$, and where the terms $H_f$ and $H_p$ are
\begin{align}
H_f &= \sum_{i=1}^{M} \sum_{p=1}^{e_i} \text{E} \left\{ \sum_{l=1}^{n_{lp}} \frac{\partial^2 \log [\rho(\omega_{ipl}; \alpha)/R_i]}{\partial \alpha \partial \alpha'} \right\} \\
H_p &= \sum_{i=1}^{M} \sum_{p=1}^{e_i} \frac{\partial^2 \log [R_{ip}/R_i]}{\partial \alpha \partial \alpha'}. \tag{2.10}
\end{align}

Theorem 1 provides the ARE of the panel treatment estimators in each segment, $\hat{\beta}^s$ and $\tilde{\alpha}$, relative to the estimators from the full data, $\hat{\beta}^s$ and $\hat{\alpha}$. It is sometimes of interest to evaluate the overall effect of a treatment over the study period, and Theorem 1 also provides the ARE of the estimator of the time-weighted mean effect of treatment $j$, $\delta_j = \sum_{s=1}^{S} \Delta^s \hat{\beta}^s_j$, where $\Delta^s = (T^s - 1 - T^s)/T^S$. The theorem is notationally cumbersome; we focus on structures which represent the efficiencies so that the main elements stand out, and for clarity, we present results for scalar $\alpha$ and a single covariate $Z$. We provide, in Appendix B of supplementary material available at Biostatistics online, a proof of Theorem 1 for the case where $\alpha$ is an arbitrary vector, and covariate $Z$ has a general structure, for a one-segment study. The derivation of the theorem for a study utilizing multiple segments follows in a straightforward manner. Additionally, to simplify the discussions herein, we adopt the following two conventions: (1) Because $\alpha$ is scalar, we denote the value $w_{i1}^s$ (see (2.7)) simply as $w_{i1}^s$. (2) We let $G_{ij}^s$ be the set indexing individuals in treatment group $j$ observed in segment $s$, $j = 1, \ldots, k$, $s = 1, \ldots, S$, and let $[\mathbf{u}]_{j+s} = \sum_{i \in G_{ij}^s} u_{i}^s$, $[\mathbf{w}]_{j+s} = \sum_{i \in G_{ij}^s} w_{i}^s u_{i}^s$. 

238
Efficient designs for recurrent event studies

\[ [uz]_{j+} = \sum_{i \in G_j} u^i_{j+} z_i. \]
Similarly, the total number of events observed for all individuals receiving treatment \( j \) in segment \( s \), \( \sum_{i \in G_j} u^i_s \), is represented by \( [n]_{j+}^s \).

**Theorem 1** (a) The ARE of \( \hat{\alpha} \) relative to \( \hat{\alpha} \) is

\[
\text{ARE}(\hat{\alpha}) = 1 - \left( 1 - \frac{H_p}{H_f} \right) \left( 1 + \frac{Q}{H_f} \right)^{-1},
\]

where \( Q = \phi_{w,w}(1 - \phi_{z,w}^2/\phi_{z,z}) \), and \( \phi_{z,w} = \sum_{s=1}^S \sum_{j=1}^k \sum_{i \in G_j} u^i_j (z_i - [uz]_{j+}^s/[u]_{j+}^s)(w^s_i - [uw]_{j+}^s/[u]_{j+}^s); \phi_{z,z} \) and \( \phi_{w,w} \) are correspondingly defined. These quantities are sums of segment and group-specific weighted variation and covariation of \( z_i \) and \( w^s_i \), with weights \( u^i_j \) depending on the mean counts \( \mu^i_j, s = 1, \ldots, S \).

(b) The ARE of \( \hat{\beta}_j^s \) relative to \( \hat{\beta}_j^s \) is

\[
\text{ARE}(\hat{\beta}_j^s) = 1 - \left( \frac{(l_j^s)^2}{l_{o,j}^s + (l_j^s)^2/\phi_{z,z}}(Q + H_p) + (l_j^s)^2 \right) \left( 1 - \frac{H_p}{H_f} \right) \left( 1 + \frac{Q}{H_f} \right)^{-1},
\]

where, for the baseline group, \( j = 1, l_{o,1}^s = 1/[u]_{j+}^s, l_{o,1}^s = [ua]_{j+}^s/[u]_{j+}^s, a = w, z \). For the treatment groups, \( j = 2, \ldots, k, l_{o,j}^s = 1/[u]_{j+}^s + 1/[u]_{j+}^s, l_{o,j}^s = [ua]_{j+}^s/[u]_{j+}^s - [ua]_{j+}^s/[u]_{j+}^s, a = w, z; r_{z,w} = \phi_{z,w}/\phi_{w,w} \phi_{z,z} \).

(c) The ARE of \( \hat{\delta}_j \) relative to \( \hat{\delta}_j \) is

\[
\text{ARE}(\hat{\delta}_j) = 1 - \left( \frac{l_j^s}{(\sum_{s=1}^S (\Delta^s)^2 l_{o,j}^s + (\sum_{s=1}^S \Delta^s l_{z,j}^s)^2/\phi_{z,z})(Q + H_p) + l_j^s} \right) \left( 1 - \frac{H_p}{H_f} \right) \left( 1 + \frac{Q}{H_f} \right)^{-1},
\]

where \( l_j = \sum_{s=1}^S \Delta^s l_{j}^s, j = 1, \ldots, k \).

### 2.1.1 Insight into conditions for high efficiency

Consider first the special case of a single segment, \( S = 1 \), and no overdispersion, \( \tau = 0 \). The parameter estimates of \( \beta \) from the full data likelihood, \( L_f \) (see (2.2)), satisfy

\[
e^{\hat{\beta}_j} = \frac{[n]_{j+}/[R(T_f; \hat{\alpha})e^{x\hat{\gamma}}]_{j+}}{e^{\hat{\beta}_j} \sum_{i \in G_j} h_{i,j+}/R(i, T_f; \hat{\alpha})e^{x\hat{\gamma}}},
\]

\( j = 2, \ldots, k \), and \( \exp(\hat{\beta}_1) = [n]_{1+}/[R(T_f; \hat{\alpha})e^{x\hat{\gamma}}]_{1+} \). Similarly, the estimates based on the panel data likelihood satisfy \( \exp(\hat{\beta}_1) = [n]_{1+}/[R(T_f; \hat{\alpha})e^{x\hat{\gamma}}]_{1+} \) and \( \exp(\hat{\beta}_j) = [n]_{j+}/[\exp(\hat{\beta}_1)]R(T_f; \hat{\alpha})e^{x\hat{\gamma}}]_{j+}, j = 2, \ldots, k \). An important simple result is that if the set of termination times \( T_f \)'s for each covariate stratum for individuals on treatment 1 are identical to those on treatment \( j \), then the estimates of \( \beta_j \) from the full and panel analyses are identical, \( \exp(\hat{\beta}_j) = [n]_{j+}/[n]_{1+}, j = 2, \ldots, k \). In this situation, the asymptotic variances of \( \hat{\beta}_j \) and \( \hat{\beta}_j \) would also be identical, so analysis of the panel counts when the design uses any number of panels is fully efficient for estimation of \( \beta_j, j = 2, \ldots, k \). Such a design is illustrated in Figure 1(a). There are two strata in each of the baseline and treatment groups, representing males and females, for illustrative purposes. Adjusting for gender in this analysis, the estimate of the treatment effect from this panel design is fully
efficient. Even though there are more male dropouts earlier in the study, this does not affect the efficiency of the treatment effect; we will illustrate later that other types of imbalance will affect this efficiency.

More generally, calculation of (2.12) for a proposed design using a range of values for true treatment effects would, of course, give an indication of efficiencies. Here, we describe conditions yielding fully efficient estimators, i.e., an ARE of unity. An important point throughout this discussion is that the form of the dependence of the counting process on $\alpha$ is left arbitrary, so these results hold for semiparametric models of the form (2.1).

1. **Joint balance.** If $l_{s,j}^j = 0$, then the panel estimator $\hat{\beta}_{s,j}^j$, $j = 2, \ldots, k$, $s = 1, \ldots, S$ is fully efficient. Intuitively, $l_{s,j}^j$ measures the similarity of the termination times and the covariates in the treatment group with respect to the baseline group. We refer to this condition as *joint balance* between the $w_j^s$’s (or termination times $T_{f,j}$’s) and the covariates $z$. Recall the simple example illustrated in Figure 1(a), where the design has equal sample sizes, there is a single covariate, gender, and no overdispersion, $\tau = 0$. The gender-specific set of termination times is identical for the baseline and treatment groups. When $\tau = 0$ and there is no missing data, the simplest case in which *joint balance* is achieved for all segments occurs when termination times for each value of the covariate are identical for the baseline and treatment groups. It is also achieved, when $\tau = 0$, when there are $r$ times as many individuals in the treatment group as in the baseline, and the termination times for each value of the covariate is an $r$-replicate in the treatment group of the corresponding values for the baseline group. In Figure 1(a), any panel design (for example, with panel follow-up times at 16, 32, 48, and 64 months and with two segments over 0–32 and 32–64 months) will lead to a fully efficient estimator of the treatment effects $\beta_j^2$, in all segments $s$, after adjusting for gender. When there are missing data, *joint balance* requires that the observation period for individuals of each gender (or, more generally, for each value of the covariate vector) be identical (or $r$-replicates) in the treatment group as for the baseline group.

The scenario $l_{s,j}^j = 0$ is most easily understood when both $l_{w,j}^s$ and $l_{z,j}^s$ are 0. Figures 1(b) and (c) illustrate designs with balance or near balance in termination times ($l_{w,j}^s$ is close to 0), while Figures 1(b), (d), and (e) illustrate designs with balance or near balance in the covariates ($l_{z,j}^s$ is close to 0); visually, the proportion of females is the same in the two treatment groups. Note that the covariate measure of $l_{z,j}^s$ does not affect ARE directly since this is modulated by $r_{z,w}$ (see (2.13)).

As suggested above, we use $l_{s,j}^j$, $s = 1, \ldots, S$ as our principal *measure of balance* for estimation of treatment effects; additionally, $l_{s,j}^j$ is partitioned into three components: $l_{w,j}^s$, which reflects imbalance in termination times, $l_{z,j}^s$, which reflects imbalance in covariates, and $r_{z,w}$ (see (2.13)), which modulates the effect of imbalance in the covariates on the ARE.

2. **Balance.** A weaker form of *balance* refers to having the same relative frequency of the termination times in each of the treatment and the baseline groups, without regard for how these are allocated over the covariates; this is denoted *balance in the termination times*. We will also consider the usual concept of *balance in the covariates*, where there are the same number of individuals in each covariate stratum, for example, the same number of males and females, in this case without regard to any differences in how the termination times by treatment are distributed over gender. We remark here immediately that *balance in the termination times* is more important than *balance in the covariates* for achieving a high ARE of the estimate of the treatment effect; this is because of the modulating effect of $r_{z,w}$ in (2.13).

3. **Overdispersion.** With overdispersion, $\tau > 0$, the panel estimator of the treatment effect is fully efficient only when $\beta_j^2 = 0$. However, we will illustrate later, that as long as *joint balance* holds (in fact, even quite approximately) the estimator of $\beta_j^2$ retains very high efficiency even if $\tau$ and $\beta_j^2$ are far from zero.

4. **Effect of $H_f$/$H_p$.** The AREs also depend on the ratio $H_p/H_f$, and this component plays a key role in determining the efficiency of the estimate of the shape parameter $\alpha$ of the baseline function (see (2.11)), and in the efficiency of estimators of the treatment effects when the design is not balanced. Both terms $H_p$ and $H_f$ derive from the first term in the likelihood $L_{a,d}(\alpha)$, where the difference in design is reflected in the analysis, and they carry the information about $\alpha$ that contrasts between making inference based on
Efficient designs for recurrent event studies

Fig. 1. Design scenarios for exploration of AREs. Females are represented in the lighter color, and males in the darker color. Table 1 provides the definition of the design of these scenarios. (a) Design $B_{t^*z}$: joint balance, (b) design $B_{tz}$: marginal balance, (c) design $B_{t}$: imbalance in $Z$, (d) design $B_{za}$: imbalance in $T_{fi}$, (e) design $B_{zb}$: more severe imbalance in $T_{fi}$, and (f) design $B$: imbalance in both $T_{fi}$ and $Z$. 

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full or panel data. They both measure the curvature of the baseline intensity function, but $H_p$ only at the
panel follow-up times while $H_f$ at all the event times. If there are many event times, particularly where
the baseline intensity function changes the most, intuitively, there is more information about $\alpha$. The ratio
increases when either the number of panels increases, as illustrated in Section 2.3, or when the panels are
set at places that maximize this ratio; based on our experience, this is where the baseline intensity function
sharply changes, as measured by the second derivative. Note that the placement of the panel follow-up
times only affects the ARE through $H_p$. Examination of this term can suggest optimal placement of the
panel follow-up times as illustrated in Section 2.3.

For some common parametric forms of the baseline intensity $\rho(t; \alpha)$, $H_f$ can be written as

$$H_f = \sum_{s=1}^S \sum_{i=1}^M \sum_{p=1}^1 \mu^p_i \psi^s_j (T^s_{i,p-1}, T^s_{i,p}; \alpha), \quad (2.16)$$

where $\psi^s_j (T^s_{i,p-1}, T^s_{i,p}; \alpha)$ is a function of the $T^s_{i,p}$'s and $\alpha$ only; $H_p$ also has the same structure with $\psi^s_j$ on
the right-hand side replaced with $\psi^s_j$. This form for $H_f$ is possible, for example, when $\rho(t; \alpha)$ is Weibull
($\alpha t^\alpha$) or exponential ($\exp(\alpha t)$). When (2.16) holds, further observations regarding the AREs can be made
as discussed in the following two remarks.

5. Size of the treatment effects. When $H_f$ has the form (2.16) and $\tau = 0$, the ARE of $\tilde{\beta}^s_j$ becomes large as
$|\beta^s_j|$ (i.e. the absolute magnitude of the effect) increases, $j = 2, \ldots, k$. If there is a single segment, $S = 1$,
the ARE of $\tilde{\beta}^s_j$ does not depend on $\beta^s_1$, the overall level of the mean count.

6. Baseline intensity estimators. The ARE of $\tilde{\alpha}$ will be high when $H_p/H_f$ is large, and $\text{ARE}(\tilde{\beta}^s_j)$ will
be high when the difference in the weighted means of the $w^s_j$'s and $z_i$'s is small. If (2.16) holds, $\tau = 0$ and
$S = 1$, these AREs do not depend on $\beta^s_1$, the overall level of the mean count. Under conditions for joint
balance, the ARE of $\tilde{\beta}^s_1$ increases with increasing values of $\sum_{j=2}^k \exp(\beta^s_j)$ and the ARE of $\tilde{\alpha}$ does not
depend on $\beta^s$.

7. Effect of $Q$. The ARE of $\tilde{\alpha}$ (2.11) will also be large when $Q$ is large. The term $Q$ denotes the weighted
variation of $w^s_j$'s rescaled by a measure of the association between the $w^s_j$'s (a function of the termination
times) and $z_i$'s. If the weighted variation of $w^s_j$'s is large or the measure of association is small, then $Q$
becomes large and so too the ARE of $\tilde{\alpha}$. Intuitively, the more variation there exists in the termination times,
the more information there will be regarding the shape of the baseline intensity (parameterized by $\alpha$).

8. Time-weighted mean treatment effect. When there is joint balance, the estimator of the time-weighted
mean treatment effect, $\tilde{\delta}_j = \sum_{i=1}^1 \Delta^s \tilde{\beta}_j^s$, where $\Delta^s = (T^S - T^s) / T^S$, will be fully efficient (2.14). This
time-weighted mean treatment effect represents the overall treatment effect over the study period. Intu-
itively, under imbalanced scenarios, imbalance in one segment may be compensated by different imbal-
bances in another segment, so that the overall estimator may become less affected by imbalance.

2.2 Efficiency under imbalanced designs

In Sections 2.2.1 and 2.2.2, we consider imbalanced designs to ascertain how sensitive efficiencies may
be to departures from the condition of joint balance when considering 1 and 2 segments.

Consider a study with two treatment groups, and a single covariate, gender, with 2, 4, and 8 equally
spaced scheduled panel follow-up times (Figure 2) over a period of 64 months. Imbalance in the data
could be interpreted conceptually as individuals abandoning the study before the 64 months, as displayed
in Figure 2, or, by staggered entry of individuals; at the scheduled panel follow-up times and at the end
of follow-up, we record information on events observed between follow-up visits. We assume a Weibull
hazard for the baseline intensity function.
In this section, we numerically study the efficiency of estimators of treatment effects under imbalanced designs, i.e. designs for which joint balance does not hold.

2.2.1 Efficiency under imbalanced designs: 1-segment. Table 1 lists six contrasting designs (labeled Bt*z, Btz, Bt, Bz, Bz_a, Bz_b, B), where the nomenclature reflects whether balance is achieved over the treatment and control groups in the covariates (z) or the termination times (t), and “∗” denotes joint balance. Figure 1 illustrates all these designs. The event times displayed by + signs in Figure 1 are one realization of the random generating process. Table 1 provides details on the numbers of individuals observed and their panel follow-up times. In Table 1, two designs achieve balance in the covariates (Bz) with different levels of imbalance in the termination times: these are denoted by Bz_a and Bz_b. All designs spread the dropouts equally at 16, 24, 32, 40, 48, and 56 months. For example, for the design with joint balance, Bt*z, where 10% (out of 60) of females and 60% (out of 60) of males drop out in each of the control and treatment groups, the loss to follow up (note that this could alternatively reflect a staggered recruitment with identical termination times) occurs as one female and six male dropouts at each of 16, 24, 32, 40, 48, and 56 months in each of these groups. For clarity, Figure 2 illustrates the loss to follow up for the control or treatment groups and the 2, 4, and 8 equally spaced panel follow-up times for the design Bt*z.

Although we investigated several parameter settings, we present here results corresponding to values which are close to estimates from an analysis of the bladder cancer data discussed several times in the literature (e.g. Dean and Balshaw, 1997; Hu and others, 2009; Zhao and others, 2011): \( \alpha = 1 \), \( \alpha \) being the shape parameter of the Weibull distribution; \( \beta_1 = -3.5 \), and \( \beta_2 = -0.5 \) for the baseline and treatment effects, respectively; \( \tau \) ranging between 0 and 2, reflecting no, and quite severe, overdispersion; and \( \gamma \) varying between –4 and 4 reflecting a very wide range of values of the covariate effect.

Generally, all the designs yield fairly high efficiencies, \( > 0.96 \), of the estimate of the treatment effect, \( \hat{\beta}_2 \) for the range of values of \( \tau \) and \( \gamma \). Efficiencies of the estimators of the parameters for the overall mean process, i.e. the parameters \( \alpha \) and \( \beta_1 \) are generally much lower than those for the treatment estimator (see Figures W1 and W2 of supplementary material available at Biostatistics online). The overall mean level of the intensity function, reflected in \( \hat{\beta}_1 \), seems to be reasonably well estimated (ARE of 0.85–1.00) when
Table 1. Scenarios considered for illustration of AREs

<table>
<thead>
<tr>
<th>Design</th>
<th>Group</th>
<th>Number of individuals (female)</th>
<th>Number of individuals (male)</th>
<th>Dropout (%)</th>
<th>Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>24</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Bt$^a$</td>
<td>Control</td>
<td>1 1 1 1 1 1 54</td>
<td>6 6 6 6 6 6 24</td>
<td>10 60</td>
<td>✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>1 1 1 1 1 1 54</td>
<td>6 6 6 6 6 6 24</td>
<td>10 60</td>
<td>✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Bt$^b$</td>
<td>Control</td>
<td>1 1 1 1 1 1 54</td>
<td>6 6 6 6 6 6 24</td>
<td>10 60</td>
<td>✓ ✓ × ×</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>6 6 6 6 6 6 24</td>
<td>6 6 6 6 6 6 24</td>
<td>60 60</td>
<td>✓ ✓ × ×</td>
</tr>
<tr>
<td>Bt$^c$</td>
<td>Control</td>
<td>1 1 1 1 1 1 14</td>
<td>3 3 3 3 3 3 142</td>
<td>10 10</td>
<td>✓ ✓ × ×</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>1 1 1 1 1 1 154</td>
<td>3 3 3 3 3 3 2</td>
<td>60 60</td>
<td>✓ ✓ × ×</td>
</tr>
<tr>
<td>Bz$^a$</td>
<td>Control</td>
<td>1 1 1 1 1 1 54</td>
<td>1 1 1 1 1 1 54</td>
<td>10 10</td>
<td>× ✓ × ×</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>6 6 6 6 6 6 24</td>
<td>6 6 6 6 6 6 24</td>
<td>60 60</td>
<td>✓ ✓ × ×</td>
</tr>
<tr>
<td>Bz$^b$</td>
<td>Control</td>
<td>1 1 1 1 1 1 54</td>
<td>1 1 1 1 1 1 54</td>
<td>10 10</td>
<td>× ✓ × ×</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>9 9 9 9 9 9 6 9 9 9 9 9 9 6</td>
<td>90 90</td>
<td>✓ ✓ × ×</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Control</td>
<td>1 1 1 1 1 1 14</td>
<td>3 3 3 3 3 3 142</td>
<td>10 60</td>
<td>× × × ×</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>24 24 24 24 24 16</td>
<td>3 3 3 3 2</td>
<td>60 10</td>
<td>× × × ×</td>
</tr>
</tbody>
</table>

The name of the scenario reflects the variable for which there is balance; "*" denotes joint balance. Bz$^a$, for example, reflects the situation where there are equal numbers of individuals in each covariate stratum over the treatment groups, but the termination times are not balanced over treatment groups; in the example, the termination times are longer in the control group.
there are at least four panels, whereas at least eight panels are required to estimate the intensity shape parameter well.

### 2.2.2 Efficiency under imbalanced designs: 2-segments.

We consider the designs discussed in Section 2.2.1 under three different situations where the segments are induced by a cut-point at 16, 24, and 32 months, and where there are one and two panels per segment; we present the AREs of the estimates of the segment-specific and time-weighted mean treatment effects in Figure 3, and Figures W3 and W4 of supplementary material available at *Biostatistics* online. Recall that for the design with joint balance, $B^* z$, the efficiency is 1 when $\tau = 0$; even in the presence of overdispersion, this design provides nearly fully efficient estimators of the treatment effect. The values of the segment-specific treatment effects, used to obtain the AREs when segment cut-points are changed, correspond to within-segment mean values of these effects from assumed continuous time-varying functional forms which are decreasing/increasing over time for $\beta^1_2 / \beta^2_2$.

Regarding imbalanced designs, efficiencies of the estimators of the treatment effects in segment 1 are high (>0.90) since the termination times in segment 1 are almost balanced (Figure 3). Efficiencies of the treatment estimators in segment 2, on the other hand, are lower than those in segment 1, with values as low as 0.65, but they increase as the cut-point for the segment is shifted closer to the end of the study (see Figure W3 of supplementary material available at *Biostatistics* online). With such a shift, the imbalance in the termination times is shared over the two segments, rather than being concentrated in segment 2; as well, the efficiency of the estimator of the treatment effect in segment 1 decreases only slightly.

The efficiency of the estimator of the time-weighted mean treatment effect is mostly driven by the level of balance in segment 2 because the estimator of the treatment effect in segment 1 tends to have high efficiency no matter the placement of the cut-point defining the segments (see Figure W4 of supplementary material available at *Biostatistics* online). Efficiencies of the estimators of segment-specific effects and time-weighted means increase as the number of panels increases.

### 2.3 Specifying panel follow-up times for estimation of baseline function: adenomas study

Since the placement of the panel follow-up times affects the ARE only through $H_p$ (see Theorem 1), optimal panel follow-up times may be found by maximizing the ratio $H_p / H_f$ for a given number of panels and using pilot information.

Here, for illustrative purposes, we will consider optimization of this ratio when $H_f$ and $H_p$ have particular forms such as (2.16), specifically, Weibull form, which may be a reasonable assumption for planning purposes. In addition, for simplicity, assume that there is a single segment ($S = 1$), that all termination times are equal, i.e. $T_{fi} = T_f$, and that the follow-up times are the same for all individuals. Since the ratio $H_p / H_f$ only depends on baseline parameters $\alpha$, when planning follow-up times for a study only the form of the baseline intensity function needs to be known from pilot investigation. In particular, for a Weibull baseline, the ratio has the form

$$
\frac{H_p}{H_f} = \frac{\alpha^2}{T_f^\alpha} \sum_{p=2}^{e} T_{p-1}^{\alpha} - T_{p}^{\alpha} \frac{\log T_{p} - \log T_{p-1})^2}{T_p^\alpha - T_{p-1}^\alpha}.
$$

Selecting $T_1, \ldots, T_f$ to maximize (2.17) for a given number $e$ provides a set of optimal panel follow-up times. As mentioned earlier, the ratio $H_p / H_f$ is key for defining the efficiency of the estimators of the baseline parameters, and, when the design is imbalanced, also for the efficiency of the estimators of treatment effects. If all termination times are equal, $T_{fi} = T_f$, then $Q = 0$, which implies $\text{ARE}(\tilde{\alpha}) = H_p / H_f$ and $\text{ARE}(\tilde{\beta}_j) = 1$, $j \geq 2$. 

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Fig. 3. AREs of $\hat{\beta}_1$ for the 2-segment model for different designs with one and two panels per segment. Parameter values are $\alpha = 1.1$, $\beta_1 = -3.5$ for the baseline intensity function; $\beta_1^2 = 0.2, 0.075, -0.050$ when the segment cut-point is at 16 (a), 24 (b), and 32 (c) months, respectively; $\beta_2^2 = -0.8, -0.925, -1.050$ when the segment cut-point is at 16, 24, and 32 months, respectively.
Table 2. Efficiencies of the estimator of the baseline parameter, \( \text{ARE}(\tilde{\alpha}) \), for different optimal and equally spaced panel follow-up times for the adenomas example

<table>
<thead>
<tr>
<th># Panels</th>
<th>Optimal follow-ups</th>
<th>Equally spaced follow-ups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up times</td>
<td>ARE((\tilde{\alpha}))</td>
</tr>
<tr>
<td>3</td>
<td>4.8, 16.5, 36.0</td>
<td>0.82</td>
</tr>
<tr>
<td>4</td>
<td>2.7, 9.2, 20.2, 36.0</td>
<td>0.89</td>
</tr>
<tr>
<td>5</td>
<td>1.7, 5.8, 12.7, 22.7, 36.0</td>
<td>0.93</td>
</tr>
<tr>
<td>6</td>
<td>1.2, 4.0, 8.6, 15.4, 24.5, 36.0</td>
<td>0.95</td>
</tr>
</tbody>
</table>

The baseline has a Weibull form and there is a single segment. Since termination times are equal, the term \( Q = 0 \), and thus \( \text{ARE}(\tilde{\alpha}) = H_p/H_f \).

Below we illustrate how to design a study with optimal panel follow-up times using two common situations involving studies of adenomas.

Suppose that the Weibull model is a reasonable model for recurrent adenomas in the colon as in Meyskens and others (2008), and one wanted to find the optimal follow-up times in a 3-year trial where pilot studies indicate that the shape of the baseline had an increasing form with \( \alpha = 1.3 \). Table 2 reports efficiencies for optimal and equally spaced panel follow-up times for different numbers of given panels. Note that in this case, since all termination times \( T_f \)’s are equal, then \( Q = 0 \) and \( \text{ARE}(\tilde{\alpha}) = H_p/H_f \). Figure 4 illustrates the ratio \( H_p/H_f \) for a three-panel design for varying values of \( T_1 \) and \( T_2 \) (first and second panel follow-up times); the Weibull baseline is also displayed in this figure. Maximizing this function using the nlmnb function in R (R Development Core Team, 2012), provides values of \( T_1 = 4.8 \) and \( T_2 = 16.5 \), to yield 85% efficiency; note though that several values near these optimal choices provide virtually the same efficiency. Choosing values of \( T_1 \) which are quite large, well beyond the early sharp changes in the intensity, for example, \( > 25 \), yields lower efficiencies regardless of the choice of \( T_2 > T_1 \).

For the follow-up times used in the study reported in Meyskens and others (2008), which were \( T_1 = 18 \) and \( T_2 = 32 \), the efficiency is only 59%. Other choices for follow-up times are also given in Table 2 for different numbers of follow-up times. Note that a design with six panels achieves quite high efficiency in estimation of baseline parameters (95%), and that by optimizing the panel follow-up times we can easily omit one or two panels: importantly, note that the equally spaced six-panel follow-up design achieves the same efficiency of 89% as the optimal four-panel follow-up design.

3. Discussion

In this investigation of the efficiency of panel designs relative to continuous follow-up for the study of recurrent events, we have focused on the estimation of a treatment effect in a semiparametric proportional intensity model. We have provided specific conditions for full efficiency, which relate principally to what we have termed joint balance in the distribution of the termination times and covariates in the baseline and treatment groups. We note that imbalance in the distribution of the covariates over treatment is less detrimental in terms of sharply reducing efficiencies than imbalance in the termination times. With panel designs of at least two panels, the efficiency of the estimator of the treatment effect is high, and those with four to eight panels give reasonable estimation of the shape of the baseline intensity function. The finite sample performance of estimators of all parameters (\( \beta, \gamma, \alpha, \tau \)) was investigated by simulation and seen to be quite good. Details on these simulations are available from the authors on request.

Detailed conditions for efficient study designs are provided in Section 2. The investigation of these conditions provides a basis for understanding the critical design aspects of panel studies. Further, the measures
Fig. 4. Exploration of the ratio $H_p/H_f$ for a Weibull intensity function $(\alpha t^{\alpha-1})$ with shape parameter $\alpha = 1.3$ (shown in (a)). The ratio $H_p/H_f$ as a function of the two-panel follow-up times $T_1$ and $T_2$ ($T_2 > T_1$) is displayed in (b).

of balance we developed here provide an indication of (i) the optimality of any design under consideration, as well as (ii) how to adapt or rebalance a design to achieve optimality when recruitment/dropout is an ongoing process. We have also illustrated how these tools may be used to derive the timing of optimal panels. We showed that such optimal placement may yield fewer panels than designs which use equally spaced follow-up times. This demonstrates how use of these methods can lead to more efficient and cost-effective study designs.

For simplicity, we have assumed here that the follow-up times align with the segment end points but this may be generalized conceptually in a straightforward manner. Computational aspects for such a generalization may be non-trivial. For example, suppose that a follow-up time corresponding to a segment end point is missed and counts are aggregated over two individual-specific panels which encompass two segments, with the treatment effect being different, say midway through this individual’s aggregated panel. The contribution to the likelihood for this aggregated panel would consist of the sum of likelihoods for all possibilities by which the aggregated count could be partitioned over the two original panels. One might
treat this as a missing data problem and adopt a Monte Carlo Expectation Maximization approach to analysis. Approximations might also be employed whereby interpolation techniques are used to partition counts over the two intervals. If there are few such situations, it is likely that standard errors and AREs from an analysis as described here but incorporating such an interpolation approximation will not be unduly affected. As well, note that since the piecewise constant intensity model is intended as a simple approximation to smooth changes in the intensity over time, in any specific analysis where such changes are relatively slow, it would be reasonable to assign values to $T_s$ where there is expected to be better agreement of follow-up times over individuals. More generally, the effects of such misalignment on AREs need further investigation.

Even though we have considered extreme imbalance for investigative purposes, any marked difference in the distribution of termination times must be carefully investigated for signs of dependency between the observation process and the recurrent event process. Here, we have assumed that the observation process, including the end of study for each individual, is independent of the process generating the events. When the termination times are induced by dropout, differential dropout in the two treatment groups raises concerns of an informative observation process. If informative dropout is not a concern, the experimenter may be able to recruit some individuals partway through the study to bring the design to near balance based on an interim analysis using the design measures developed here.

Finally, we close with the observation that the considerations herein would not provide the sole justification for choice of sample size and placement of follow-up times in a recurrent event study; however, they can be used to help guide and rationalize important decisions on these design elements.

**Supplementary material**


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**References**


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