Interim Analysis in Sequential Multiple Assignment Randomized Trials for Survival Outcomes

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SUMMARY: Sequential multiple assignment randomized trials mimic the actual treatment processes experienced by physicians and patients in clinical settings and inform the comparative effectiveness of dynamic treatment regimes. In such trials, patients go through multiple stages of treatment, and the treatment assignment is adapted over time based on individual patient characteristics such as disease status and treatment history. In this work, we develop and evaluate statistically valid interim monitoring approaches to allow for early termination of sequential multiple assignment randomized trials for efficacy targeting survival outcomes. We propose a weighted log-rank Chi-square statistic to account for overlapping treatment paths and quantify how the log-rank statistics at two different analysis points are correlated. Efficacy boundaries at multiple interim analyses can then be established using the Pocock, O'Brien Fleming, and Lan-Demets boundaries. We run extensive simulations to comparatively evaluate the operating characteristics (type I error and power) of our interim monitoring procedure based on the proposed statistic and another existing statistic. The methods are demonstrated via an analysis of a neuroblastoma dataset.

KEY WORDS: Dynamic Treatment Regimes; Efficacy Boundaries; Interim Monitoring;Inverse Probability Weighting; Log-rank Statistics; Trial Efficiency.

1. Introduction

Dynamic Treatment Regimes (DTRs), also known as adaptive treatment strategies, are decision rules that recommend when and how to adjust treatment based on the treatment history (Lavori, 2008; Chakraborty and Murphy, 2014). They are particularly effective in managing chronic diseases such as cancer, depression, and HIV, where multiple phases of treatment is common (Murphy, 2005). However, the vast array of potential DTRs can make it difficult to pinpoint the most effective regime.

Sequential Multiple Assignment Randomized Trials (SMARTs) have been proposed to mimic treatment decisions experienced by physicians and patients in clinical settings and provide a systematic approach to constructing and evaluating DTRs. In a SMART, each patient is randomly assigned to an initial treatment, and subsequent treatments at later stages are determined by patient's characteristics and intermediate outcomes observed in earlier stages (Nahum-Shani et al., 2017). Each stage in SMART corresponds to one of the critical decision points involved in the DTRs to be evaluated (Bigirumurame et al., 2022). An example is a 2-stage Neuroblastoma trial (Matthay et al., 1999), where patients were assigned to one of two initial treatments, and responders to the initial were further assigned to one of two maintenance therapies.

Although SMART is efficient for evaluating embedded DTRs, it typically takes longer to complete than traditional single-stage randomized control trials (RCTs) because of its sequential nature. The duration of SMART depends on the number of stages and the definition of intermediate and final outcomes studied in the design (Wu et al., 2021). One way to improve the efficiency of SMART is to introduce interim monitoring (IM), which is often used in RCTs (Jennsion and Turnbull, 1990; Ellenber et al., 2002) to enable early trial termination if there is compelling evidence of treatment efficacy (superiority) or lack of efficacy (futility) (Freidlin et al., 2010).

IM procedures have been adopted for time-to-event outcomes for single-stage randomized control trials (Kim and Tsiatis, 1990; Tsiatis, 1982). Tsiatis (1982) developed the asymptotic joint distribution of test statistics from multiple interim analyses while Kim and Tsiatis (1990) developed IM procedure allowing for unequal increments between repeated analyses. Gu and Lai (1999) performed interim analyses using Monte Carlo simulations that considered noncompliance, loss to follow-up, patient accrual patterns, and non-proportional hazard alternatives in clinical trial designs. Shen and Cai (2003) proposed using a weighted average of standardized linear rank statistics for inference, along with a stopping rule that allows early termination if the experimental treatment shows no advantage or is inferior to the control. Chen et al. (2003) considered both survival and disease-free survival endpoints in their IM procedure: the trial would stop early if mortality showed a significant effect at the interim, while the composite endpoint would be tested in the final analysis if the trial continued. Additionally, Broglio et al. (2014) developed methods to predict final trial results for survival outcomes based on interim data. All these approaches conduct interim analyses when a predetermined proportion of the total expected events have been observed.

Despite the wide use of interim analyses in single-stage trials, interim monitoring in SMARTs has been less studied due to the design's complexity. Recent work has focused on continuous outcomes, with Wu et al. (2021) proposing interim monitoring in SMART (IM-SMART), and Manschot et al. (2023) improving upon it to accommodate partial information. However, the interim monitoring method for time-to-event outcomes in SMART remains unclear. To address this gap, we develop various interim monitoring methods for SMARTs with survival outcomes. We adapt the log-rank test statistics proposed in Harrington and Fleming (1982) to compare survival functions among different DTRs. The development is nontrivial. First, log-rank statistics need to be carefully weighted to compensate for the systematic missingness due to sequential randomization. Second, we need to account for the

correlation between log-rank statistics at different interim monitoring time points. Lastly, estimating the variance-covariance matrix of the log-rank test statistics is complex and requires special handling. We also adopt an alternative test statistic recently proposed by Tsiatis and Davidian (2024), referred to as Tsiatis-Davidian statistic, or in short, TD statistic in tables and notation, and demonstrate that Tsiatis- Davidian statistic and the proposed weighted log-rank statistic belong to the same class of statistics.

We consider various boundaries to compare the log-rank statistics at interim time points. Pocock (1977) proposed constant boundaries across all analyses. However, interim monitoring using the Pocock boundaries tends to stop earlier and results in trials being stopped prematurely. Thus, O'Brien and Fleming (1979) suggested using decreasing boundaries, where for a trial with M analyses, the efficacy boundary at the mth interim analysis (b_m) is proportional to the boundary at the final analysis (b_M); More specifically, $b_m/b_M = \sqrt{M/m}$. One challenge in implementing these boundaries is that the covariance matrices of the test statistics depend on time, unlike the case with continuous outcomes as in Wu et al. (2021). We propose two ways to address this challenge. One is to use interim data to approximate covariance matrices at later time points and assume working independent increments. The other approach is to adopt the error spending functions proposed in Lan and Demets (1983) that offer greater flexibility, as they do not require the total number or exact timing of interim analyses to be pre-specified. In this work, for SMARTs involving time-to-event outcomes, We provide essential tools to conduct interim monitoring using the above-mentioned boundaries.

The rest of this paper is organized as follows. Section 2 describes the setting and notation for SMART design. In Section 3, we propose alternative test statistics and introduce interim monitoring procedures for SMART survival data under two SMART designs. Section 4 shows the simulation results, and Section 5 presents the analysis of Neuroblastoma study data. Finally, we provide a discussion in Section 6.

2. SMART Setting and Notation

2.1 *Setting*

In this project, for the development of the theoretical framework, we first consider a two-stage SMART design (referred hereto forth as SMART1) shown in Figure 1, where patients are initially randomized to treatment A_1 or A_2, and if they respond to the initial treatment, they are randomized to maintenance treatment B_1 or B_2 at the second stage; otherwise, they are randomized to salvage treatment C_1 or C_2. This SMART design enables the comparisons of eight embedded DTRs $A_j B_k C_l$, $j, k, l = 1, 2$, where $A_j B_k C_l$ is a decision rule prescribing to treat the patient with the initial treatment A_j, and then by the maintenance therapy B_k if the initial treatment was effective, and by the salvage treatment C_l, otherwise. We will consider a modified setting later, where non-responder (or responder) to the initial treatment do not receive further treatment (Section 3.5). The goal is to compare all embedded DTRs based on the distribution of the survival time, defined as the time from initial randomization to death.

[Figure 1 about here.]

2.2 *Observed Data*

For patient i, the generic treatment assignment indicator $I_i(x)$ equals 1 if they are assigned to treatment x, and 0 otherwise, and η_i is the indicator of entering the second stage of the study. T_{1i} is the time that patient i spent in the first stage. R_i is the response to the initial treatment. The observed time is $U_i = \min(T_i, V_i)$ with the event indicator $\delta_i = I(T_i \leqslant V_i)$, where T_i is the event time of interest, and V_i is the censoring time. Thus, the observed data for SMART1 can be represented as

$$\{I_i(A_j), \eta_i, \eta_i T_{1i}, \eta_i R_i, \eta_i R_i I_i(B_k), \eta_i(1 - R_i)I_i(C_l), U_i, \delta_i, j, k, l = 1, 2; \ i = 1, \dots, n\},$$

where variables preceded by a binary indicator are observed only when that indicator assumes value 1. For example, second stage treatment allocation $I_i(B_k)$ is observed if the patient moves to stage 2 ($\eta_i = 1$) and responds ($R_i = 1$).

2.3 *Inverse Probability Weights*

Log-rank test statistics are commonly used to compare the event time distribution across different groups. Had patients been randomly assigned to follow one of the eight DTRs, $A_j B_k C_l$, with $j, k, l = 1, 2$, the analysis would have been straightforward through the application of log-rank test for independent groups. However, Such a trial is rare, as it requires a large sample size. SMART is a more efficient design where DTRs share common paths, such as the same treatment path for responders but different paths for nonresponders. To account for this dependence and missingness due to subsequent randizations, we need to weight each patient separately using inverse probability weighting to properly utilise in the log-rank test statistics to compare embedded DTRs (Section 3). At an interim analysis, some newly enrolled participants may not have reached the second stage. To include them, we use a time-varying weight with a nuanced definition of response status. Let $D_i(s) = \eta_i I(s \geqslant T_{1i})$ be the indicator of whether the response status is observed at time s. If the response status is not observed at time s ($D_i(s) = 0$), patients assigned to A_j receive a weight of $1/\ell_j$, where ℓ_j is the randomization probability for A_j. Once the response status is determined ($D_i(s) = 1$), if patient i is a responder and assigned to B_k, the weight is further adjusted by $1/p_k$, and nonresponders assigned to C_l have their weights multiplied by $1/q_l$ to reflect the second-stage randomization, where p_k or q_l are the randomization probabilities for B_k or C_l, respectively. Therefore, following Guo and Tsiatis (2005), we have the following time-dependent weight

$$W_{jkl,i}(s) = \frac{I_i(A_j)}{\ell_j} \left[1 - D_i(s) + D_i(s) \left\{ \frac{R_i I_i(B_k)}{p_k} + \frac{(1 - R_i)I_i(C_l)}{q_l} \right\} \right] \tag{1}$$

for a patient following the DTR $A_j B_k C_l, j, k, l = 1, 2$.

2.4 *Observed and Weighted Event and At-risk Processes*

Additional notation is needed before we introduce the weighted log-rank statistics. For patient i, the observed event process $N_i(s) = I(U_i \leqslant s, \delta_i = 1)$ indicates an event at or before time s, and $N(s) = \sum_{i=1}^{n} N_i(s)$ is the total number of observed events by time s. If patient i follows a specific DTR $A_j B_k C_l$, their data will be included in the computation of the relevant log-rank statistic with the weight given in (1) to create a pseudo population where every patient follows this specific DTR. Thus, the weighted number of events $\bar{N}_{jkl}(s) = \sum_{i=1}^{n} W_{jkl,i}(s) N_i(s)$ represents the number of events at or before time s if all patients were to follow the treatment strategy $A_j B_k C_l$. Similarly, let $Y_i(s) = I(U_i \geqslant s)$ be the at-risk process for patient i and $Y(s) = \sum_{i=1}^{n} Y_i(s)$ be the total number of patients at risk at time s. $\bar{Y}_{jkl}(s) = \sum_{i=1}^{n} W_{jkl,i}(s) Y_i(s)$ is the weighted number of patients at risk by time s following the DTR $A_j B_k C_l$.

3. Interim Monitoring in SMART

3.1 *Weighted Log-rank Test Statistics*

Let $\Lambda_{jkl}(t)$ represent the cumulative hazard for the survival time of patients following the DTR $A_j B_k C_l$. Under the above setting, we would like to test the overall null hypothesis that there is no treatment effect. That is, H_0: the cumulative hazards for all DTRs are equal at any observable time, against the alternative hypothesis H_1: at least one cumulative hazard differs from others at some time point. Taking the DTR $A_1 B_1 C_1$ as the reference and comparing the cumulative hazards of other DTRs to the reference level, the null hypothesis can be written as $H_0 : \gamma(t) = 0$, where $\gamma(t) = \{\Lambda_{112}(t) - \Lambda_{111}(t), \Lambda_{121}(t) - \Lambda_{111}(t), \Lambda_{122}(t) - \Lambda_{111}(t), \Lambda_{211}(t) - \Lambda_{111}(t), \Lambda_{212}(t) - \Lambda_{111}(t), \Lambda_{221}(t) - \Lambda_{111}(t), \Lambda_{222}(t) - \Lambda_{111}(t)\}^{\intercal}$. We propose a Wald-type test statistic $T = n^{-1} Z^{\intercal} \widehat{\Sigma}^{-1} Z$. Here, $Z = (Z_{jkl})^{\intercal}$ is a 7×1 vector of weighted log-rank

(LR) statistics, where

$$Z_{jkl} = \int_0^\infty \frac{\bar{Y}_{jkl}(s)\bar{Y}_{111}(s)}{\bar{Y}_{jkl}(s) + \bar{Y}_{111}(s)} \left\{ \frac{d\bar{N}_{jkl}(s)}{\bar{Y}_{jkl}(s)} - \frac{d\bar{N}_{111}(s)}{\bar{Y}_{111}(s)} \right\}, \tag{2}$$

and $\widehat{\Sigma}$ is a consistent estimator of Σ, the asymptotic covariance matrix of $n^{-1/2}Z$. Let $Z_{jkl}(t)$ be Z_{jkl} evaluated at time t, using only the information accrued up to time t, and $Z(t) = (Z_{jkl}(t))^\intercal$. Then, the test statistic evaluated at time t is

$$T(t) = n^{-1}Z(t)^\intercal \widehat{\Sigma}^{-1}(t)Z(t), \tag{3}$$

where $\widehat{\Sigma}(t)$ is $\widehat{\Sigma}$ evaluated at time t. By the asymptotic normality of the weighted log-rank test statistic, when the null hypothesis is true, $n^{-1/2}Z(t)$ converges to a multivariate normal distribution with mean 0 and covariance matrix $\Sigma(t)$. Therefore, by multivariate Slutsky's theorem, under H_0, $T(t) \sim \chi_\nu^2$ with degrees of freedom $\nu = rank(\Sigma_0(t))$, where $\Sigma_0(t)$ is $\Sigma(t)$ evaluated under H_0.

3.2 *Interim Monitoring Procedure*

Now, we are ready to discuss interim monitoring in SMART. Let M be the total number of analyses, including the final analysis. We use t_m to represent the decision time of the mth analysis and n_m to denote the cumulative sample size up to time t_m. The test statistic in (3) at the mth analysis is denoted as $T(t_m) = n_m^{-1}Z(t_m)^\intercal\widehat{\Sigma}^{-1}(t_m)Z(t_m)$. Efficacy boundaries $b_1, \ldots, b_M$ are defined such that the trial stops at the $m^\star$-th interim analysis if the global null hypothesis is not rejected at all prior interim looks $1, \ldots, m^\star - 1$ and is rejected at the $m^\star$th look $(T(t_{m^\star}) > b_{m^\star})$. The joint distribution of $T = (T(t_1), \ldots, T(t_M))^\intercal$ is required to determine efficacy boundaries that maintain the overall type I error rate. That is,

$$\sum_{m^*=1}^M \mathrm{pr}\left(\bigcap_{m=1}^{m^*-1} T(t_m) \leqslant b_m \cap T(t_{m^*}) > b_{m^*} \mid H_0 \right) = \alpha.$$

We specify the joint distribution of T using the decomposition described in the following theorem:

THEOREM 1: *Let $Q(t_m)$ be a vector such that $T(t_m) = Q(t_m)^\intercal Q(t_m)$ for $m = 1, \ldots, M$.*

Under the null hypothesis, the stacked vector $Q = (Q(t_1), \dots, Q(t_M))^{\mathsf{T}}$ follows a multivariate

normal distribution $Q \sim MN_{\nu \times M}(0, \Psi)$, where the matrix

$$\Psi = \begin{pmatrix} \Psi_{1,1} & \cdots & \Psi_{1,M} \\ \vdots & \ddots & \vdots \\ \Psi_{M,1} & \cdots & \Psi_{M,M} \end{pmatrix}$$

with $\Psi_{m,m'} = \mathrm{cov}(Q(t_m), Q(t_{m'}))$ and $\Psi_{m,m} = I_\nu$.

The proof easily follows from the results in Dickhaus and Royen (2015). More specifically,

note that we can write $T(t) = Z(t)^{\mathsf{T}} L(t) L(t)^{\mathsf{T}} Z(t)$, where $L(t)$ is the square root of

$G(t) = n_t^{-1}(\Sigma(t))^g$. For $m = 1, \dots, M$ and for any $Q(t_m)$ satisfying $T(t_m) = Q(t_m)^{\mathsf{T}} Q(t_m)$,

there exists an orthogonal matrix $P(t_m)$ such that $Q(t_m) = P(t_m)L(t_m)^T Z(t_m)$. Therefore,

under H_0, $Q(t_m)$ has mean 0 and covariance matrix $P(t_m)P(t_m)^T = I_v$. Then following

Definition 5.1 of Dickhaus and Royen (2015), $T = (T(t_1), \dots, T(t_M))^{\mathsf{T}}$ follows a multivariate

χ^2 distribution of the Wishart type with an associated correlation matrix Ψ.

3.3 *Calculation of the Correlation Matrix Ψ*

Theorem 1 only specifies the diagonal blocks of the matrix Ψ. To calculate the whole matrix

Ψ, we apply singular value decomposition to $G(t) = n_t^{-1}(\Sigma(t))^g$, i.e., $G(t) = U(t)Q(t)U(t)^{\mathsf{T}}$.

Let $L(t) = U(t)Q(t)^{\frac{1}{2}}$ and $Q(t) = L(t)^{\mathsf{T}} Z(t)$, where $Z(t)$ is defined in Section 3.1. Then,

$G(t) = L(t) L(t)^{\mathsf{T}}$ and $T(t) = n_t^{-1} Z(t)^{\mathsf{T}} (\Sigma(t))^g Z(t) = Z(t)^{\mathsf{T}} L(t) L(t)^{\mathsf{T}} Z(t) = Q(t)^{\mathsf{T}} Q(t)$.

Thus, $T(t_m) = Q(t_m)^{\mathsf{T}} Q(t_m)$ for $m = 1, \dots, M$, and when $t_m < t_{m'}$, $\Psi_{m,m'} = \mathrm{cov}(Q(t_m), Q(t_{m'})) =$

$L(t_m)^{\mathsf{T}} \mathrm{cov}(Z(t_m), Z(t_{m'}))L(t_{m'})$. Therefore, it suffices to calculate $\widehat{\mathrm{cov}}(Z(t)) = n\widehat{\Sigma}(t)$ and

$\widehat{\mathrm{cov}}(Z(t_m), Z(t_{m'}))$. We propose to estimate these two quantities by asymptotic linearization.

Since $d\bar{N}_{jkl}(s) = \sum_{i=1} W_{jkl,i}(s)dN_i(s)$, the log-rank statistics in equation (2) can be

expressed as

$$Z_{jkl} = \sum_{i=1}^{n} \int_0^\infty \frac{\bar{Y}_{111}(s)W_{jkl,i}(s) - \bar{Y}_{jkl}(s)W_{111,i}(s)}{\bar{Y}_{jkl}(s) + \bar{Y}_{111}(s)} dN_i(s).$$

Recall $\bar{Y}_{jkl}(s)$ is defined as $\bar{Y}_{jkl}(s) = \sum_{i=1}^{n} W_{jkl,i}(s)Y_i(s)$, we have $\sum_{i=1}^{n}\{\bar{Y}_{111}(s)W_{jkl,i}(s) -$

$\bar{Y}_{jkl}(s)W_{111,i}(s)\}/\{\bar{Y}_{jkl}(s)+\bar{Y}_{111}(s)\}Y_i(s) = 0$. Let $dM_i(s) = dN_i(s) - Y_i(s)d\Lambda_0(s)$ denote the residual for patient i. Then,

$$Z_{jkl} = \sum_{i=1}^{n}\int_{0}^{\infty}\frac{\bar{Y}_{111}(s)W_{jkl,i}(s)-\bar{Y}_{jkl}(s)W_{111,i}(s)}{\bar{Y}_{jkl}(s)+\bar{Y}_{111}(s)}dM_i(s),$$

where $d\Lambda_0(s)$ is the overall hazards when H_0 is true. Under regularity conditions, $\bar{Y}_{jkl}(s)/\{\bar{Y}_{jkl}(s)+\bar{Y}_{111}(s)\}$ converges to a deterministic process, which is denoted as $\pi_{jkl}(s)$. Then, Z_{jkl} is asymptotically equivalent to the sum of n independent terms

$$\frac{1}{\sqrt{n}}Z_{jkl} = \frac{1}{\sqrt{n}}\sum_{i=1}^{n}\int_{0}^{\infty}\{(1-\pi_{jkl}(s))W_{jkl,i}(s)-\pi_{jkl}(s)W_{111,i}(s)\}dM_i(s)+o_p(1)$$

$$= \frac{1}{\sqrt{n}}\sum_{i=1}^{n}Z_{jkl,i}+o_p(1).$$

where

$$Z_{jkl,i} = \int_{0}^{\infty}\{(1-\pi_{jkl}(s))W_{jkl,i}(s)-\pi_{jkl}(s)W_{111,i}(s)\}dM_i(s).$$

It is easy to show that $Z_{jkl,i}$ has mean 0 under H_0 (Tsiatis and Davidian, 2024). Consider the vector associated with patient i, $\hat{Z}_i = (\hat{Z}_{jkl,i})^\intercal \in \mathbb{R}^7$, where

$$\hat{Z}_{jkl,i} = \int_{0}^{\infty}\frac{\bar{Y}_{111}(s)W_{jkl,i}(s)-\bar{Y}_{jkl}(s)W_{111,i}(s)}{\bar{Y}_{jkl}(s)+\bar{Y}_{111}(s)}\left\{dN_i(s)-Y_i(s)\frac{dN(s)}{Y(s)}\right\}$$

is an estimator of $Z_{jkl,i}$. Here, $\int_0^t dN(s)/Y(s)$ is the Nelson-Aalen estimator of $\Lambda_0(t)$. Let $\hat{Z}_i(t) = (\hat{Z}_{jkl,i}(t))^\intercal$ be $\hat{Z}_i$ evaluated at time t. Then, $\Sigma(t)$, which is the asymptotic covariance matrix of $n^{-1/2}Z(t)$, can be estimated by $n^{-1}\sum_{i=1}^{n}\hat{Z}_i(t)\hat{Z}_i(t)^\intercal$.

Regarding the estimation of $\text{cov}(Z(t_m), Z(t_{m'}))$ - had we known the full data at the time of interim analysis, since $\text{cov}(Z_{jkl,i}(t_m), Z_{jkl,i'}(t_{m'})) = 0$ for $i \neq i'$, and $\text{cov}(Z_{jkl,i}(t_m), Z_{jkl,i}(t_{m'})) = E(Z_{jkl,i}(t_m)Z_{jkl,i}(t_{m'}))$ could be estimated by $Z_{jkl,i}(t_m)Z_{jkl,i}(t_{m'})$, an estimator of $\text{cov}(n_m^{-1/2}Z(t_m),$ $n_{m'}^{-1/2}Z(t_{m'}))$ when $t_m < t_{m'}$ would have been obtained as $(n_m n_{m'})^{-1/2}\sum_{i=1}^{n_m}\hat{Z}_i(t_m)\hat{Z}_i(t_{m'})^\intercal$.

However, in practice, the full data is not available at the interim analysis time. In order to determine the efficacy boundaries at the interim analyses without the full data, we consider two approaches and illustrate them with $M = 2$. One approach is to assume the independent increment property and $\text{cov}(Z(t_1))/n_1 \approx \text{cov}(Z(t_2))/n_2$ when we choose t_1 such that we

expect to observe half of the events by time t_1. The second approach is to specify an error spending function $\alpha^\star(t)$ and determine the boundaries sequentially (Lan and Demets, 1983). Here, $\alpha^\star(t)$ is a strictly increasing function; boundaries b_1 and b_2 satisfy $\mathrm{pr}(T(t_1) > b_1) = \alpha^\star(t_1)$ and $\mathrm{pr}(T(t_1) \leqslant b_1, T(t_2) > b_2) = \alpha - \alpha^\star(t_1)$. According to Lan and Demets (1983), we may choose $\alpha_1^\star(t) = 2(1 - \Phi(z_{\alpha/2}/(t/L)^{1/2})$ and $\alpha_2^\star(t) = \alpha \log(1 + (e-1)t/L)$ to generate boundaries that are similar to the Pocock and OBF type boundaries with $L = 2t_1$, where Φ is the cumulative distribution function of a standard normal random variable. We will refer to these boundaries as LD-Pocock and LD-OBF respectively.

3.4 *Alternative test statistics*

Recently, Tsiatis and Davidian (2024) proposed a different test statistic based on the score test for a Cox proportional hazards model. Their statistic, abbreviated as the TD statistic, is based on $Z^{TD} = (Z_{jkl}^{TD})^\intercal$, where

$$Z_{jkl}^{TD} = \sum_{i=1}^n \int_0^\infty W_{jkl,i}(s) \left\{ dN_i(s) - Y_i(s) d\hat{\Lambda}_0^{TD}(s) \right\},$$

with $d\hat{\Lambda}_0^{TD}(s) = \sum_{j,k,l=1,2} d\bar{N}_{jkl}(s) / \sum_{j,k,l=1,2} \bar{Y}_{jkl}(s)$ being the estimated overall hazards under H_0. This statistic is equivalent to the statistic used in Li et al. (2014) under the SMART setting.

The weighted log-rank statistic defined in (2) can be written as

$$Z_{jkl} = \sum_{i=1}^n \int_0^\infty W_{jkl,i}(s) \left\{ dN_i(s) - Y_i(s) d\hat{\Lambda}_0(s) \right\},$$

where $d\hat{\Lambda}_0(s) = \{ d\bar{N}_{111}(s) + d\bar{N}_{jkl}(s) \} / \{ \bar{Y}_{111}(s) + \bar{Y}_{jkl}(s) \}$. This implies that our statistic and Tsiatis-Davidian statistic belong to the same class except that they use different estimators for the common hazard function under the null hypothesis of no difference. While Tsiatis and Davidian (2024) averages the event and risk processes across all DTRs, the LR statistic defined above averages the same over the DTR involved ($A_j B_k C_l$) and a reference DTR (more specifically, $A_1 B_1 C_1$).

3.5 *Modified SMART*

In some SMARTs, patients are initially randomized to receive treatment A_1 or A_2. Responders to the initial treatment receive maintenance treatment B_1 or B_2 at the second stage, while non-responders are not further randomized. We refer to this design as SMART2. The goal is to compare four embedded DTRs $A_j B_k$, for $j, k = 1, 2$, where $A_j B_k$ stands for "Treat with A_j initially, followed by B_k if they respond."

In this case, the observed data become $\{I_i(A_j), \eta_i, \eta_i R_i, \eta_i R_i I_i(B_k), U_i, \delta_i\}, i = 1, \ldots, n$. The observed event process is defined as $N_i(s) = I(U_i \leqslant s, \delta_i = 1)$, and the observed at-risk process becomes $Y_i(s) = I(U_i \geqslant s)$. The time-dependent weight for treatment strategy $A_j B_k$ is defined as $W_{jk,i}(s) = I_i(A_j) / \ell_j [1 - D_i(s) + D_i(s) \{R_i I_i(B_k) / p_k + (1 - R_i)\}]$. The corresponding weighted number of events by time s for $A_j B_k$ is $N_{jk}(s) = \sum_{i=1}^n W_{jk,i}(s) N_i(s)$. Similarly, we can define the weighted at-risk process $Y_{jk}(s)$.

Let $\Lambda_{jk}(t)$ be the cumulative hazard with respect to treatment strategy $A_j B_k$. The null hypothesis can be written as $H_0 : (\Lambda_{12}(t) - \Lambda_{11}(t), \Lambda_{21}(t) - \Lambda_{11}(t), \Lambda_{22}(t) - \Lambda_{11}(t))^\mathsf{T} = 0$, for any t. The weighted log-rank statistic for testing H_0 is $Z = (Z_{12}, Z_{21}, Z_{22})^\mathsf{T}$, where $Z_{jk} = \int_0^\infty \bar{Y}_{jk}(s) \bar{Y}_{11}(s) / \{\bar{Y}_{jk}(s) + \bar{Y}_{11}(s)\} \{d\bar{N}_{jk}(s) / \bar{Y}_{jk}(s) - d\bar{N}_{11}(s) / \bar{Y}_{11}(s)\}$. The Wald type test statistic can be similarly defined as in equation (3). Under H_0, $T \sim \chi_\nu^2$ with df $\nu = 3$.

4. Simulation

4.1 *Data generation*

We evaluate the performance of the proposed interim analyses for two SMART designs, SMART1 design outlined in Section 2.1 involving eight DTRs, and SMART2 design outlined in Section 3.5 involving four DTRs. For SMART1, we generated 1000 datasets, each with $n = 500$ patients arriving independently and uniformly over 5 years. Initial treatment indicator was generated from a Bernoulli distribution with equal probability ($Ber(0.5)$).

We also generated the second stage potential advancement indicator $\eta_i \sim Ber(p_\eta)$. When $\eta_i = 0$ (death in stage 1), time in stage 1 T_{1i} was generated from $Exp(\theta_j^N)$, and whereas when $\eta_i = 1$, we generated a response indicator $R_i[Ber(p_R)]$, and $T_{1i}[Exp(\theta_j)]$ with $p_R = 0.6$. For responders $(R_i = 1)$, maintenance treatment was assigned through $Ber(0.5)$. Time in stage 2, T_{2i}, was generated from $Exp(\theta_{jk}^R)$. For non-responders $(R_i = 0)$, salvage treatment was assigned with equal probability, and T_{2i} was generated from an $Exp(\theta_{jl}^{NR})$ distribution. The total survival time was then defined as $T_i = (1 - \eta_i)T_{1i} + \eta_i(T_{1i} + T_{2i})$. For the SMART2 design, the simulation was similar except that for non-responders there was no second stage treatment assignment, and their time in stage 2 was generated from $Exp(\theta_j^{NR})$. Censoring time, $V_i [Unif(0, \nu)]$, was generated independent of the survival times.

4.1.1 *Null scenarios.* The following parameters were used for the SMART1 design : $\theta_j^N = (5, 5), \theta_j = (5, 5), \theta_{jk}^R = (5, 5, 5, 5)$, and $\theta_{jl}^{NR} = (5, 5, 5, 5)$. For the SMART2 design, we used $\theta_j^N = (3, 3), \theta_j = (3, 3), \theta_{jk}^R = (2, 2, 2, 2)$, and $\theta_{jl}^{NR} = (5, 5)$. The parameter ν was controled so that censoring proportion was approximately 10%, 20%, or 40%. We also considered two values for p_η, namely, 0.90 and 0.75, the results for the latter shown in the supplementary materials. We conducted a single interim analysis when 50% of the events were observed (i.e., the information proportion was 0.5).

4.1.2 *Alternative scenarios.* Next, we evaluated the performance under four alternative scenarios. The first two scenarios pertain to the SMART1 design: (1) $\theta_j^N = (5, 5), \theta_j = (5, 5), \theta_{jk}^R = (2, 4, 3, 4), \theta_{jl}^{NR} = (3.2, 3, 2.9, 2), \nu = 2.5$; and (2) $\theta_j^N = (5, 5)$, $\theta_j = (5, 5), \theta_{jk}^R = (2.8, 4.6, 2.3, 4.9), \theta_{jl}^{NR} = (5.8, 4.3, 5.2, 6.5), \nu = 2.1$. The last two are for the SMART2 design: (3) $\theta_j^N = (3, 3), \theta_j = (3, 3), \theta_{jk}^R = (2, 3.2, 2.5, 4), \theta_{jl}^{NR} = (6, 6), \nu = 2.9$; and (4) $\theta_j^N = (3, 3), \theta_j = (3, 3), \theta_{jk}^R = (2.7, 6, 4.9, 3), \theta_{jl}^{NR} = (3.8, 7.2), \nu = 2.8$. The parameters of

SMART2 indicate that there is no further assignment for non-responders. The values of ν were selected for each scenario to control the censoring rates at approximately 20%.

4.2 *Boundary calculation*

To implement the proposed IM procedures, we need to determine the efficacy boundaries based on the distribution of the quadratic form of a multivariate normal random vector Q, with mean zero and the covariance matrix Ψ as shown in Theorem 1. Thus, the key component here is to estimate Ψ. Since in the simulations we know the true data generatiing mechanism, we approximate Ψ by generating a large SMART dataset of 10,000 individuals based on the parameters specified in the above null scenarios. We then obtain $B = 100,000$ replicates of Q vectors sampled from a multivariate normal distribution with the estimated covariance matrix. The corresponding quantiles of the empirical joint distribution of $T(t_m) = Q(t_m)^{\intercal}Q(t_m)$ for $m = 1, 2$ are taken as the efficacy boundaries. For SMART studies in practice, Ψ is estimated based on the observed data accumulated up to the interim analysis, and the covariance matrix in the final analysis can be approximated based on the interim one, as discussed in Section 3.3, resulting in either Pocock or OBF boundary. Alternatively, one can use the Lan and Demets (LD) procedure with the alpha spending function, where Ψ is estimated based on the data accumulated at each decision point. The resulting boundaries are labeled as LD-Pocock or LD-OBF boundaries. All these efficacy boundaries calculated using various approaches are presented in Table 1. The first two rows display boundaries computed using full data at the interim stage, referred to as "oracle" boundaries, while the third and fourth rows show boundaries derived by approximating the final covariance matrix using that at interim. The table reveals that, for the SMART2 design, the efficacy boundaries for the weighted log-rank and Tsiatis-Davidian statistics are similar. However, for the SMART1 design, the boundaries differ between the two, the discrepancy arising from the difference in the degrees of freedom (for SMART1 design, the weighted log-rank statistic

has seven degrees of freedom, while Tsiatis-Davidian statistic has five degrees of freedom).

We also evaluated efficacy boundaries under various other null scenarios and found that the efficacy boundaries stayed the same regardless of the settings.

[Table 1 about here.]

4.3 *Simulation Results*

To investigate the performance of our interim monitoring approach, we generated datasets with the same set of parameters above. We used two methods to estimate the covariance matrices of Z: the proposed method, which derives $\text{cov}(Z(t))$ and $\text{cov}(Z(t_m), Z(t_{m'}))$ using asymptotic linearization (Refer to Section 3.3), and a bootstrap estimator, which estimates $\text{cov}(Z(t))$ and $\text{cov}(Z(t_m), Z(t_{m'}))$ from 100 bootstrapped samples.

4.3.1 *Simulation Results: Null Scenarios.* Table 2 shows the results under the null scenario for censoring rate 20%, and 90% of the patients entering the second stage. "Rej at interim" is the estimated probability of rejection at the interim analysis, and "Rej at final" is the probability of rejection at the final analysis conditional on not being rejected at the interim analysis. We also estimated the overall rejection rate when the null hypothesis is true, denoted as "Type I Error" in Table 2. Performance under $n = 1000$ was also investigated, but the results are not shown here due to space limitations. The first row in the table is for a single analysis (regular SMART) at the conclusion of the trial and the remaining rows are for the case when there are two total analysis (single interim analysis). We observe that the type I error rates of the LR and TD statistics using the proposed covariance estimation method are well-controlled near the nominal 0.05 level across all boundary types. However, the empirical type I error rates from the bootstrap procedure are mostly inflated. We observe similar patterns under 10% censoring (Web Table 2) and 40% censoring (Web Table 3)

presented in the Supplementary material. Also presented in the supplementary materials are the results for the case when 75% of patients enter the second stage (Web Tables 4, 5 and 6). Higher censoring rates tend to result in slightly lower type I errors, making the decision more conservative. Bootstrap estimators largely yield inflated type I errors across scenarios. Moreover, TD estimators have slightly inflated type I errors than LR estimators for SMART1, especially under 10% and 20% censoring. Both estimators maintain type I errors well for SMART2. The discrepancy observed in SMART1 may be explained by the different degrees of freedom for the two statistics (7 df for LR and 5 df for TD), while both statistics have 3 df in SMART2.

[Table 2 about here.]

4.3.2 *Simulation Results: Alternative Scenarios.* Due to the inflated type I error rates observed with the bootstrapped procedure under the null scenarios, we assessed performance of the proposed interim approach using only the proposed covariance estimates for the alternative scenarios. The results are summarized in Table 3, which also includes the expected sample size $[E(n)]$ when a trial stops. We first observe that trials tend to stop earlier with the Pocock boundaries at the cost of lower power compared to a single analysis. The OBF and the LD-OBF maintain power (similar to a single analysis) across all scenarios, with a notable reduction in the average sample size . For instance, under Alternatives 1-4, the expected sample size with OBF boundaries ranges from 406 to 467, representing a reduction of 7% to 19% compared to the planned total sample size of 500. Furthermore, the TD methods achieve higher power than the LR statistic for SMART1, and the powers are similar for SMART2. This difference in power may be explained by the slightly inflated type I errors that we've observed for the TD estimator in SMART1. Additional simulations presented in the supplementary materials with censoring rates 10% (Web Table 7) and 40% (Web Table

8), and 75% of patients entering the second stage (Web Tables 9 and 10) also support similar conclusions.

[Table 3 about here.]

5. Analysis of Neuroblastoma Study Data

We applied the proposed interim monitoring method retrospectively to the Children's Cancer Group high-risk neuroblastoma study (Matthay et al., 1999, 2009). In the study, 539 patients were recruited between Jan 1991 and Apr 1996. All patients were initially treated with chemotherapy, and 379 patients without disease progression after the initial treatment participated in the first-stage randomization. These patients were randomized to autologous bone marrow transplantation (ABMT), a combination of myeloablative chemotherapy, total-body irradiation, and transplantation of autologous bone marrow purged of cancer cells ($n = 189$) or continuation chemotherapy ($n = 190$). Among them, 203 patients without disease progression after the first-stage treatment were further randomized to 13-cis-retinoic acid (cis-RA) or no further therapy (102 in cis-RA and 101 no therapy). Non-responders to the first-stage treatment did not enter the second stage of the study, and hence this study is similar to the SMART2 design considered in the previous sections. The flowchart of the Neuroblastoma trial is shown in Figure 2.

[Figure 2 about here.]

There are four embedded DTRs in this trial: 1) ABMT, cis-RA: treat with ABMT and then with cis-RA if no progression; 2) ABMT, none: treat with ABMT and receive no further therapy; 3) CC, cis-RA: treat with continuation chemotherapy and then with cis-RA if there was no disease progression; and 4) CC, none: treat with continuation chemotherapy and received no further therapy if no progression.

We reanalyzed the Neuroblastoma trial to test if there was a significant difference in

progression-free survival among the four DTRs by incorporating an interim analysis. Since the dataset did not contain enrollment time, to mimic the process of conducting an interim analysis planned a priori, we assumed the patients were enrolled uniformly in the pre-specified recruitment period (1991-1996), following the order of their study ID. Suppose the interim analysis is conducted after 50% of the events are observed (1254 days, $n =$289).

Under the null hypothesis, the Wald-type test statistic should follow a χ^2_3 distribution. The Pocock efficacy boundaries for this two-stage study, based on both the approximation and error-spending approaches, are approximately 9.1 at both stages. In contrast, the OBF efficacy boundaries are approximately 11.5 and 8, respectively; details are in Web Table 5 of the supplementary material. At the interim analysis, the weighted log-rank and Tsiatis and Davidian's test statistics, 3.34 and 3.14, respectively, are below the critical values, suggesting the trial should continue. The final test statistics are 5.80 (LR) and 6.56 (TD), which align with the interim decision not to reject the null hypothesis of no difference among the four DTRs.

We also estimated the survival curves for the four DTRs using the weighted risk set estimator of Guo and Tsiatis (2005) at both the interim and final analyses, as shown in Figure 3. The median survival times for the four treatment strategies are also reported here. We observe differences in the four curves and median survival times (e.g., 526, 440, 447, and 497 days in the interim). However, these differences are not statistically significant due to small sample sizes and large variability. Reassuringly, weighted log-rank and Tsiatis and Davidian's tests lead to the same conclusion.

[Figure 3 about here.]

6. Discussion

DTRs are widely used in managing chronic diseases, and SMART is instrumental in comparing embedded DTRs. In this paper, we proposed interim analysis procedures for SMARTs with survival outcomes based on weighted log-rank statistic and Tsiatis and Davidian's statistic. We also presented the statistical properties of the proposed test statistics and validated their use through rigorous simulation studies. Additionally, we applied the proposed methods on a neuroblastoma dataset to demonstrate the resource-saving advantage of the interim monitoring in SMARTs. Interim monitoring can potentially end the trial early without inflating type I error and maintaining statistical power.

One major issue with survival outcomes is that the covariance matrix of test statistics across analyses is not constant over time. To solve this issue, we adopted two approaches, the approximation approach and the error spending function approach. Both approaches worked well for various SMART designs in extensive simulations.

Two commonly used efficacy boundaries, the Pocock and OBF boundaries, and the Lan and Demets error spending methods were considered and evaluated in this work. The proposed interim analysis framework can easily incorporate other boundaries, such as those introduced by Haybittle (1971). The method can also be extended to accommodate additional stages and a wider range of treatment options at each stage.

7. Acknowledgements

8. Supplementary Material

The supplementary material contains available Web Appendices, Tables, and Figures referenced in Sections 4 and 5.

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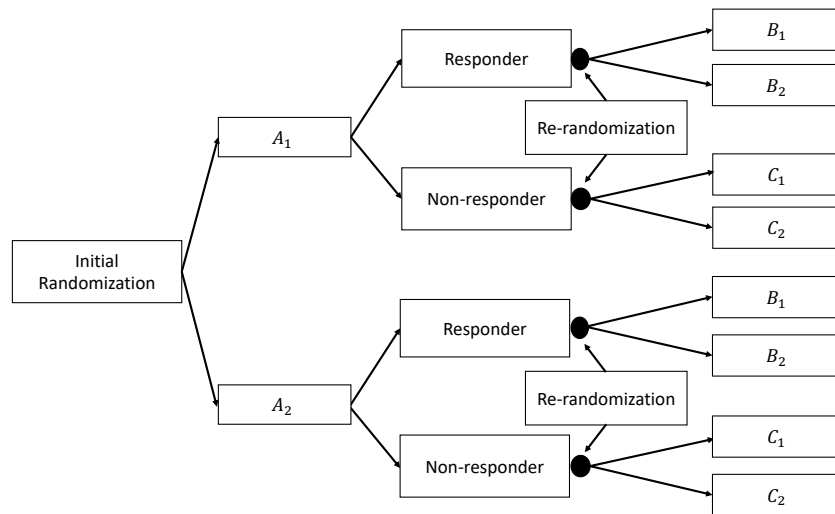
Figure 1. A SMART Design with 8 Treatment Strategies.
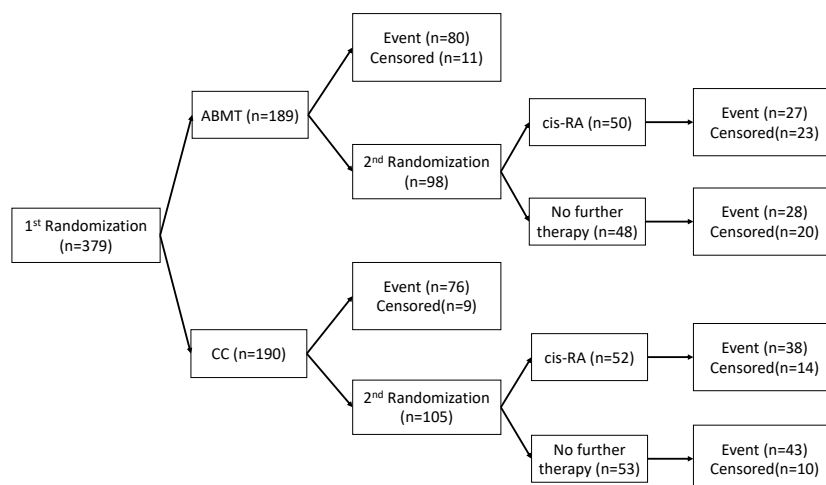
Figure 2. Flowchart of Neuroblastoma Trial; Event, progression or death.
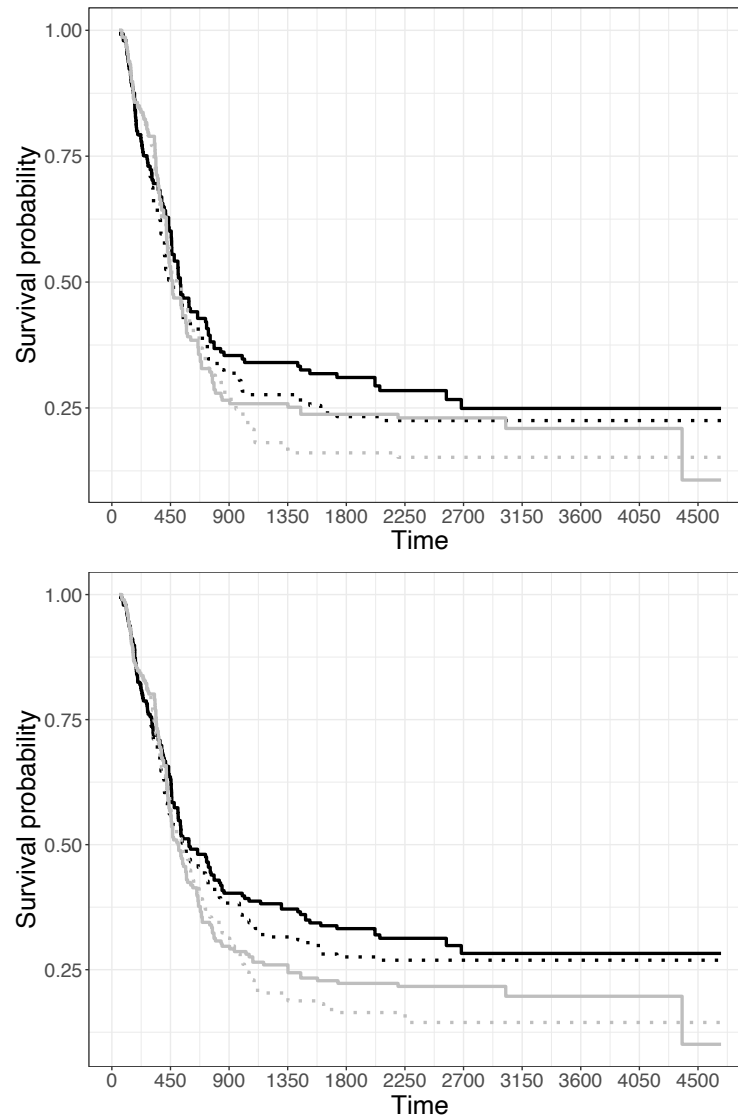
Figure 3. Survival Curves for 4 Treatment Strategies at interim (top panel) and final (bottom panel) analyses for the Neuroblastoma study. The black solid, black dotted, grey solid and grey dotted curves are survival curves for 4 treatment strategies: ABMT, cis-RA; ABMT, none; CC, cis-RA; CC, none.

Table 1

Efficacy boundaries for 2 SMART Designs. Oracle: boundaries calculated using full data at interim. LD-Pocock and LD-OBF: Pocock and OBF boundaries obtained using a particular error spending function recommended by Lan and Demets (1983). LR and TD approaches are our proposed weighted log-rank statistic and the statistic proposed in Tsiatis and Davidian (2024), respectively.

	SMART1		SMART2	
	LR	TD	LR	TD
Oracle Pocock	(15.74, 15.74)	(12.46, 12.46)	(9.03, 9.03)	(9.08, 9.08)
Oracle OBF	(20.11, 14.22)	(15.85, 11.21)	(11.43, 8.08)	(11.43, 8.08)
Pocock	(15.98, 15.98)	(12.79, 12.79)	(9.38, 9.38)	(9.42, 9.42)
OBF	(19.80, 14.00)	(15.63, 11.05)	(11.10, 7.85)	(11.07, 7.83)
LD-Pocock	(15.43, 16.14)	(12.25, 12.70)	(8.85, 9.24)	(8.87, 9.31)
LD-OBF	(20.03, 14.22)	(16.35, 11.16)	(12.61, 7.95)	(12.72, 7.95)

Table 2

Simulation results for two SMART designs under Null Scenarios with censoring rate approximately 20% and 90% patients entering stage 2. $n = 500$. M: Number of total analysis including the final. Rej at interim: rejection rate at the interim analysis. Rej at final: the probability of rejection at the final analysis condition on not rejecting at the interim analysis. Oracle: boundaries calculated using full data at interim. LR and TD: the proposed weighted log-rank and Tsiatis and Davidian (2024) statistics normalized using the proposed covariance estimates. BLR and BTD: the statistics normalized using the bootstrap covariance estimates. LD-Pocock and LD-OBF: Pocock and OBF boundaries obtained using a particular error spending function recommended by Lan and Demets (1983). Results are shown in percentages within 1 decimal place.

M	Boundary	Rejection Rate	SMART1				SMART2			
			LR	BLR	TD	BTD	LR	BLR	TD	BTD
1	NA	Type I Error	3.8	3.5	6.1	6.9	5.4	9.1	4.8	8.6
	Oracle	Rej at interim	2.3	3.2	4.3	5.8	3.0	7.0	3.1	7.1
	Pocock	Rej at final	1.8	1.7	2.8	3.1	3.0	4.3	2.9	4.5
		Type I Error	4.1	4.8	7.0	8.9	5.9	11.1	6.0	11.3
	Oracle	Rej at interim	0.3	0.6	1.6	1.7	1.3	3.2	1.1	2.7
	OBF	Rej at final	3.7	3.2	4.8	6.7	4.2	6.9	4.1	7.2
		Type I Error	4.0	3.8	6.4	8.3	5.5	9.9	5.2	9.8
	Pocock	Rej at interim	2.2	2.9	4.0	4.9	2.8	5.9	2.7	6.4
		Rej at final	1.5	1.6	2.7	2.7	2.7	4.2	2.8	4.3
2		Type I Error	3.7	4.5	6.6	7.5	5.4	9.9	5.5	10.5
	OBF	Rej at interim	0.5	0.7	1.7	2.2	1.4	3.6	1.4	3.3
		Rej at final	3.8	3.6	5.0	6.6	4.9	7.7	4.5	7.6
		Type I Error	4.3	4.3	6.6	8.7	6.2	11.1	5.8	10.7
	LD-Pocock	Rej at interim	3.0	3.8	4.6	6.2	3.3	7.2	3.4	7.8
		Rej at final	1.4	1.4	2.4	2.7	2.8	4.2	2.7	4.1
		Type I Error	4.4	5.1	6.9	8.7	6.0	11.1	6.0	11.6
	LD-OBF	Rej at interim	0.3	0.6	1.4	1.5	1.0	2.1	0.8	2.3
		Rej at final	3.7	3.2	5.1	6.7	4.7	7.6	4.3	7.5
		Type I Error	4.0	3.8	6.4	8.1	5.7	9.6	5.1	9.7

Table 3
Simulation results for SMART1 and SMART2 under alternative scenarios with a censoring rate of approximately 20%, n = 500.M: Number of total analysis including the final. Rej at interim: rejection rate at the interim analysis. Rej at final: the probability of rejection at the final analysis condition on not rejecting at the interim analysis. Oracle: boundaries calculated using full data at interim. LR and TD: the proposed weighted log-rank and Tsiatis and Davidian (2024) statistics normalized using the proposed covariance estimates. LD-Pocock and LD-OBF: Pocock and OBF boundaries obtained using a particular error spending function recommended by Lan and Demets (1983). All results (except E(n)) are shown in percentages rounded to integers.

M	Boundary	Rejection Rate	SMART1				SMART2			
			Alt1		Alt2		Alt3		Alt4	
			LR	TD	LR	TD	LR	TD	LR	TD
1	NA	Power	78	82	92	95	70	70	91	91
	Oracle	Rej at interim	33	42	47	60	28	28	50	49
		Rej at final	60	64	78	82	53	51	75	76
		Power	73	79	88	93	66	65	88	87
		E(n)	431	413	402	375	441	441	395	398
	OBF	Rej at interim	16	26	26	43	14	16	31	32
		Rej at final	73	76	88	91	65	63	86	85
		Power	78	82	91	95	70	69	90	90
		E(n)	466	446	446	409	471	468	435	432
	Pocock	Rej at interim	32	40	45	57	26	26	47	46
		Rej at final	59	64	78	81	49	49	73	73
		Power	72	78	88	92	63	62	86	85
2		E(n)	434	415	406	380	446	446	402	404
	OBF	Rej at interim	17	27	27	45	16	17	33	35
		Rej at final	74	76	89	91	65	65	86	86
		Power	79	83	92	95	70	71	91	91
		E(n)	465	443	443	406	467	465	431	427
	LD-Pocock	Rej at interim	34	43	49	62	29	29	51	50
		Rej at final	57	63	77	89	50	49	73	73
		Power	72	79	88	92	64	64	87	86
		E(n)	428	410	399	371	440	440	393	395
	LD-OBF	Rej at interim	16	24	26	40	11	11	26	24
		Rej at final	73	77	88	91	66	66	87	87
		Power	78	82	91	95	70	70	90	90
		E(n)	466	450	445	416	478	478	446	449