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ESTIMATING SURVIVAL DISTRIBUTIONS FOR TIME-VARYING SMART DESIGNS

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Treatment of complex diseases such as cancer, HIV, leukemia and depression usually follows complex treatment sequences. In two-stage randomization designs, patients are randomized to first-stage treatments, and upon response, a second randomization to the second-stage treatments is done. The clinical goal in such trials is to achieve a response such as complete remission of leukemia, 50% shrinkage of solid tumor or increase in CD4 count in HIV patients. These responses are presumed to predict longer survival. The focus in two-stage randomization designs with survival endpoints is on estimating survival distributions and comparing different treatment policies. In this article, we propose a parametric approach for estimating survival distributions in time-varying SMART designs. To evaluate the performance of our approach, a simulation study is conducted. The results of the simulation study reveal that the new approach gives survival probabilities that are less biased and more precise than the nonparametric methods. The new method is applied to a data set from a leukemia clinical trial.

Key words: Survival distributions, Time-varying SMART designs, Treatment sequences, Two-stage randomization designs.

1. Introduction

Treatment and management of chronic illnesses such as cancer, leukemia and HIV often require multiple courses of treatment. The clinical goal in such trials is to achieve a response such as complete remission of leukemia, 50% shrinkage of solid tumor or increase in CD4 count in HIV patients. These responses are presumed to predict longer survival. Dynamic treatment regimes, also known as dynamic treatment strategies or treatment policies, have become popular in the conduct of cancer trials (Lokhnygina and Helterbrand, 2007). These designs use a sequence of decision rules that link the observed patient's history with treatment recommendations. In two-stage randomization designs, for instance in cancer clinical trials, patients are initially randomized to an induction treatment followed by another randomization to a maintenance regimen provided that the patient responds to the induction therapy and consents to further study. These designs are sometimes referred to as sequential multiple assignment randomized trials (SMART). The focus in two-stage randomization designs with survival endpoints is on estimating survival distributions and comparing the different treatment policies.

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We differentiate between two SMART designs. SMART designs with outcome assessments at fixed time points are referred to as standard SMART designs (Dai and Shete, 2016). In such a SMART design, we take the time to response to be the same for every individual in the study. This is because the time to measure response to the first stage treatments is fixed for every individual, for example at six months. In a time-varying SMART design, individuals are randomized to the second stage treatments as soon as a response is observed. This means that the response times for the individuals vary. There are, however, advantages for this type of design especially in cancer trials where medications have some side effects. Prolonged intake of such medications in the first stage even when a response has been observed may lead to several side effects and thereby making patients refuse second stage treatments. Also, this type of design may lead to reduction in costs (Dai and Shete, 2016).

Over the past two decades, several methods for estimating and comparing survival distributions for two-stage randomization designs have been developed (Kidwell and Wahed, 2013; Guo and Tsiatis, 2005; Wahed and Tsiatis, 2004; Lunceford, Davidian and Tsiatis, 2002). Wahed (2010) developed a parametric method for estimating and comparing survival distributions for standard SMART designs. However, his approach does not extend to time-varying SMART designs. In this article, we propose a parametric approach for estimating survival distributions in time-varying SMART designs.

2. Model framework

Consider a two-stage randomization design where patients are first randomized to receive treatment A with levels A_1 and A_2, and individuals who respond and consent to further study are randomized to the second treatment with levels, say, B_1 and B_2. For simplicity we shall henceforth use the word "response" to indicate response to previous treatment and consent to second randomization. The strategy $A_jB_k,\ j,k = 1,2$, entails treating with A_j followed by B_k if the patient responds to the first treatment. Non-responders are not randomized to the second stage treatments as in the CALGB 19808 study (Kolitz et al., 2010) which motivated this work. Our objective is to estimate and compare survival distributions for the different treatment policies. For this scope, we conceptualize the problem using potential outcomes (Rubin, 1974). This does not mean that focus is on causal inference but we use potential outcomes as a vehicle for formalizing the problem.

In reality, each individual follows only one treatment strategy, we observe only one outcome for the specific treatment strategy. However, in theory individuals in the population can follow any treatment policy A_jB_k, that is, for each individual in the population one can envision one outcome for each possible strategy. Each individual has his/her set of potential outcomes and the entire set of possible outcomes for each individual is referred to as his/her counterfactuals.

Here, we shall focus on data from patients who received induction therapy A_1, since data from patients who received different induction therapies are independent. Data from patients who received A_2 are analyzed in a similar manner. Interest is on estimating survival distributions for treatment policies A_1B_1 and A_1B_2. We assume that associated with subject i is a set of random variables

$$\left\{R_i^*, (1-R_i^*)T_{0i}, R_i^*T_i^R, R_i^*T_{1i}^*, R_i^*T_{2i}^*\right\},$$

where R_i^* is the response status if patient i was assigned to A_1. $R_i^* = 1$ if patient i responds to treatment A_1, $R_i^* = 0$ otherwise. T_i^R is the time from initial randomization to response for patient

i defined only when $R_i^* = 1$; T_{0i} is the survival time for a patient who do not respond to first stage treatment. T_{1i}^* is the time from second randomization to death if patient i receives B_1, and similarly T_{2i}^* is the time from second randomization to death if patient i receives B_2 instead. If patient i is assigned to A_1B_k, his/her survival time would be

$$T_{ki} = (1 - R_i^*)T_{0i} + R_i^*(T_i^R + T_{ki}^*), \quad k = 1, 2.$$

We note that we can only observe T_{1i} or T_{2i}, hence T_{ki} are potential outcomes. If $R_i^* = 0$ then $T_{1i} = T_{2i} = T_{0i}$.

Let T_k denote the survival time for the population if all participants were assigned to the treatment strategy A_1B_k. Inference on features of these distributions address directly the intent-to-treat question of interest. Using data from the two-stage design we estimate the distribution of T_k.

Without right censoring, the observed data can be represented as a set of independent and identically distributed (iid) random vectors $(R_i^*, R_i^*T_i^R, R_i^*Z_i, T_i)$, for $i = 1, \ldots, n$, where Z_i is an indicator for the B treatment defined only if $R_i^* = 1$. We have $Z_i = 1$ if patient i is assigned to B_1 and $Z_i = 0$ if assigned to B_2. The observed survival time, T_i, is related to the potential outcomes as follows:

$$T_i = (1 - R_i^*)T_{0i} + R_i^* \left\{T_i^R + Z_iT_{1i}^* + (1 - Z_i)T_{2i}^*\right\}. \tag{1}$$

To incorporate right censoring, let C_i be the time to censoring for the ith patient. The observed data can then be represented as independent and identically distributed vectors $(R_i, R_iZ_i, R_iT_i^R, U_i, \Delta_i)$, where $\Delta_i = I(T_i < C_i)$ is the failure indicator, $U_i = \min(T_i, C_i)$ is the observed time to either death or censoring. $R_i = 0$ if patient i is censored without having had a response to treatment A_1, otherwise $R_i = R_i^*$.

We assume that the second stage randomization is made independently of the other potential outcomes, that is

$$\pi_z = P(Z_i = 1|R_i = 1, T_i^R, T_{1i}, T_{2i}, C_i) = P(Z_i = 1|R_i = 1).$$

We note that π_z, defined only if $R_i = 1$, is the probability of being randomized to the B treatment and it is typically fixed by design.

3. Nonparametric methods

Several nonparametric estimators have been proposed. The most popular ones are the weighted risk set estimator (WRSE) of Guo and Tsiatis (2005), and the inversely weighted estimators proposed by Lunceford et al. (2002) which we shall refer to as the LDT estimator.

3.1 LDT estimator

The LDT estimator (Lunceford et al., 2002) is derived using the inverse weighting technique (Robins, Rotnitzky and Zhao, 1994). Consider the estimation of the survival distributions for the treatment policy A_1B_k, that is, $S_{1k}(t) = 1 - P(T_{1k} \leq t) = 1 - F_{1k}$, for $k = 1, 2$. For simplicity, consider A_1B_1. In two-stage designs, difficulties arise from subjects who are not consistent with the treatment policy of interest. In this case we treat them as missing. If all the patients are assigned to A_1B_1 and there is no censoring, meaning $U_i = T_i = T_{1i}$, the natural estimator for $F_{11}(t)$ is $n^{-1}\sum_{i=1}^n I(U_i \leq t)$.

With censoring and second stage randomization upon response, only a subset of patients would have their observed survival time and actual treatment received being consistent with A_1B_1 since some patients are randomized to A_1B_2. Lunceford et al. (2002) proposed an estimator based on inverse probability weighting (Robins et al., 1994) to weight observations in this subset in such a way that the distribution of the weighted observations mimic that in an ideal case. Let $W_{1i} = 1 - R_i + R_i Z_i/\pi_z$ be the weight function. When the ith patient is consistent with treatment policy A_1B_1, W_{1i} acts as a weight. Non-responders consistent with A_1B_1 represent themselves and they get a weight of 1, that is, $W_{1i} = 1$. Each responder consistent with A_1B_1 represents $1/\pi_z$ remitting or consenting individuals who could have been potentially assigned to B_1 and gets a weight of $1/\pi_z$. Responders not consistent with the policy A_1B_1 get a weight of 0.

This weighting scheme motivates the estimator

$$\hat{F}^1_{1k}(t) = n^{-1} \sum_{i=1}^{n} \frac{\Delta_i W_{ki}}{\hat{K}(U_i)} I(U_i \le t), \quad k = 1, 2, \tag{2}$$

where $\hat{K}(U_i)$ is the Kaplan–Meier estimator for the censoring distribution given by $\hat{K}(U_i) = \prod_{u \le t}\{1 - dN^c(u)/Y(u)\}$, with $N^c = \sum_{i=1}^{n} I(U_i \le u, \Delta_i = 0)$ and $Y(u) = \sum_{i=1}^{n} I(U_i \ge u)$.

Instead of dividing by n in (2), a second estimator can be obtained by dividing by a probabilistically adjusted sample size:

$$\hat{F}^*_{1k}(t) = \left\{ \sum_{i=1}^{n} \frac{\Delta_i W_{ki}}{\hat{K}(U_i)} \right\}^{-1} \sum_{i=1}^{n} \frac{\Delta_i W_{ki}}{\hat{K}(U_i)} I(U_i \le t), \quad k = 1, 2. \tag{3}$$

From (3), the survival distributions for A_1B_k are estimated using

$$\hat{S}_{1k}(t) = 1 - \hat{F}^*_{1k}(t),$$

and the variance is estimated by

$$\widehat{\mathrm{Var}}(\hat{S}_{1k}(t)) = \frac{1}{n} \left\{ \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i W_{ki}}{\hat{K}(U_i)} \{ I(U_i \le t) - \hat{F}^*_{1k} \}^2 + \int_0^L \frac{dN^c(u)}{\hat{K}(u) Y(u)} \hat{E}\{ L^*_{1ki}(t,u) \}^2 \right\},$$

where L is the restricted lifetime which is smaller than the maximum follow-up of the study,

$$E\{ L^*_{1ki}(t,u) \}^2 = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(U_i)} \left[W_{ki} \{ I(U_i \le t) - \hat{F}^*_{1k}(t) \} - \hat{G}^*_{1k}(t,u) \right]^2 I(U_i \ge u),$$

and

$$\hat{G}^*_{1k}(t,u) = \{ n \hat{S}(u) \}^{-1} \sum_{i=1}^{n} \frac{\Delta_i W_{ki}}{\hat{K}(U_i)} \left\{ \{ I(U_i \le t) - \hat{F}^*_{1k}(t) \} \right\} I(U_i \ge u).$$

More details on the variance derivation can be found in the appendix of Lunceford et al. (2002).

3.2 Weighted risk set estimator

The derivation of the WRSE estimator relies heavily on the counting processes. For a one-stage study with survival endpoints, the cumulative hazard rate can be estimated by the Aalen-Nelson estimator

$$\hat{\Lambda}(t) = \int_0^t \frac{dN(u)}{Y(u)},$$

where $N(u) = \sum_{i=1}^{n} I(U_i \leq u, \Delta_i = 1)$ denotes the number of deaths up to and including time u, and $Y(u) = \sum_{i=1}^{n} I(U_i \geq u)$ is the number of patients at risk at time u. The WRSE is here showed for A_1B_1, as the development of the estimator for A_1B_2 follows similarly. Consider the case when all individuals are assigned to A_1B_1 in which case the observed death or censoring time is $U_{1i} = \min(T_{1i}, C_i)$. Let $N_{1i}(u) = I(U_{1i} \leq u, \Delta_i = 1)$ and $Y_{1i}(u) = I(U_{1i} \geq u)$, then the cumulative hazard estimator becomes

$$\hat{\Lambda}_{11}(t) = \int_0^t \frac{\sum_{i=1}^{n} dN_{1i}(u)}{\sum_{i=1}^{n} Y_{1i}(u)}.$$

In reality, some of the patients who could have received B_1 received instead B_2 after randomization to the second stage. $N_{1i}(u)$ and $Y_{1i}(u)$ cannot be observed directly and the WRSE propose to incorporate inverse weighting where the weight function depending on u is defined as $W_i(u) = 1 - R_i(u) + R_i(u)Z_i/\pi_z$, where $R_i(u)$ is the response status at time u. $R_i(u) = 0$ if at time u a response has not been achieved for patient i but patient i is still consistent with A_1B_1 and gets a weight of 1. For a patient i with $R_i(u) = 1$ and $Z_i = 0$, a weight of 0 is assigned since this patient is no longer consistent with the treatment strategy A_1B_1. For a responder assigned to B_1, this patient is consistent with A_1B_1 and gets a weight of $1/\pi_z$ at time u. This patient represents $1/\pi_z$ individuals who could have been potentially assigned to B_1. The weight function $W_i^*(u) = 1 - R_i(u) + R_i(u)(1 - Z_i)/(1 - \pi_z)$ is used for A_1B_2 and a similar argument is made.

The difference between the LDT and the WRSE is that the WRSE uses time dependent weights. A patient who is a responder and is randomized to B_2 gets a weight of 0 under the LDT at any time u including the time before the second randomization. This leads to a loss in efficiency. On the contrary, the WRSE includes this subset of patients and assigns a weight $W_i = 1$ at any time u before the second randomization; thereafter the weight changes to $W_i = 0$.

The cumulative hazard estimator for A_1B_1 using the above weight function is

$$\hat{\Lambda}_{11}(t) = \int_0^t \frac{\sum_{i=1}^{n} W_i(u) dN_i(u)}{\sum_{i=1}^{n} W_i(u) Y_i(u)},$$

where $N_i(u) = I(U_i \leq u, \Delta_i = 1)$ and $Y_i(u) = I(U_i \geq u)$. The survival estimator is

$$\hat{S}_1(t) = \exp\left\{ - \int_0^t \frac{\sum_{i=1}^{n} W_i(u) dN_i(u)}{\sum_{i=1}^{n} W_i(u) Y_i(u)} \right\}.$$

The variance is given by

$$\widehat{\mathrm{Var}}(S_{A_1B_1}(t)) = n^{-1} \{S_{A_1B_1}(t)\}^2 \hat{\sigma}^2,$$

where

$$\hat{\sigma}^2 = n^{-1} \sum_{i=1}^{n} \left(\int_0^t \frac{W_i(u) \left[dN_i(u) - Y_i(u) \frac{\sum_{i=1}^{n} W_i(u) dN_i(u)}{\sum_{i=1}^{n} W_i(u) Y_i(u)} \right]}{n^{-1} \sum_{i=1}^{n} W_i(u) Y_i(u)} \right)^2.$$

4. Parametric mixture approach

Wahed (2010) developed a likelihood based method for estimating the survival means for adaptive treatment strategies upon which inferences are made to compare different treatment policies. The

development of this approach is also based on counterfactuals. We now describe Wahed's (2010) approach in a design where we consider first stage treatments A_j, $j = 1, 2$, and second stage treatments B_k, $k = 1, 2$. Let

$$T_{jki} = (1 - R_{ji})T_{j0i} + R_{ji}T^{**}_{jki}, \quad j, k = 1, 2,$$

and the observed survival time is

$$T_i = \sum_{i=1}^{n} X_{ji} \left\{(1 - R_{ji})T_{j0i} + R_{ji}Z_{ki}T^{**}_{jki}\right\}, \quad j, k = 1, 2,$$

where X_{ji} is the first treatment indicator and T^{**}_{jki} is the overall survival time for the ith patient assigned to treatment policy A_jB_k. Note that this survival time is different from T^{*}_{jk} defined in the previous section. T^{**}_{jki} is the total survival time from first randomization to an event while T^{*}_{jk} is the time from second randomization to an event. Define $X_2 = 1 - X_1$ and $Z_2 = 1 - Z_1$. It is further assumed that, by design, the randomization probabilities are independent of the observed data.

To construct the likelihood for the observed data, probability models are assumed for the counterfactual times. Let $E[h(T^{**}_{jki})] \equiv \gamma_{jk}$, $j = 1, 2$, $k = 0, 1, 2$, where $h(\cdot)$ is some function based on the data. Noting that the survival time for the treatment policy A_jB_k is a mixture of two survival counterfactual variables, the expected value for the treatment policy A_jB_k can be written as

$$\mu_{jk} = (1 - \pi_{rj})\gamma_{j0} + \pi_{rj}\gamma_{jk}, \quad j = 1, 2; k = 1, 2, \tag{4}$$

where π_{rj} is the proportion of responders in arm A_j, $j = 1, 2$. Let $X_{ji} \sim$ Bernoulli(π_{xj}), $R_{ji}|X_{ji} \sim$ Bernoulli(π_{rj}), $Z_{ki}|R_i \sim$ Bernoulli(π_{zk}), $T^{**}_{jk} \sim f(\cdot; \theta_{jk})$, $j, k = 1, 2$, and $T_{j0} \sim f(\cdot; \theta_{j0})$, $j = 1, 2$. π_{xj} is the proportion of subjects assigned to A_j, $j = 1, 2$, and π_{zk} is the proportion of subjects assigned to B_k, $k = 1, 2$. We define $\pi_{z2} = 1 - \pi_{z1}$ and $\pi_{x2} = 1 - \pi_{x1}$. Let r_i be a realization of R_i and δ be a realization of Δ. With right censoring, the observed data are $D_i = (X_{1i}, R_iZ_{1i}, U_i, \Delta_i)$ and the full likelihood is

$$L(\theta, \pi; \{D_i\}_{i=1}^{n}) = L^1\left(\pi; \{x_{1i}, r_i, r_iz_{1i}\}_{i=1}^{n}\right) L^2\left(\theta; \{x_{1i}, r_i, r_iz_{1i}, u_i, \delta_i\}_{i=1}^{n}\right),$$

with $\pi = (\pi_{r1}, \pi_{r2}, \pi_{x1}, \pi_{z1})$, $\theta = (\theta_{jk}\ j = 1, 2; k = 0, 1, 2)$,

$$L^1(\pi; \{x_{1i}, r_i, r_iz_{1i}\}_{i=1}^{n}) = \prod_{i=1}^{n} b(x_{1i}; \pi_{x1}) \prod_{j=1}^{2} \{b(r_i; \pi_{rj})b(z_{1i}; \pi_{z1})\}^{x_{ji}},$$

where $b(\cdot; p)$ is the probability mass function for a Bernoulli random variable with success probability p, and

$$L^2(\theta; \{x_{1i}, r_i, r_iz_{1i}, u_i, \delta_i\}_{i=1}^{n}) = \prod_{i=1}^{n} \prod_{j=1}^{2} \left(\left[\prod_{k=1}^{2} \{f_{jk}(u_i; \theta_{jk})^{\delta_i} S_{jk}(u_i; \theta_{jk})^{1-\delta_i}\}^{z_{ki}} \right]^{r_i} \right.$$
$$\left. \times \{f_{jk}(u_i; \theta_{j0})^{\delta_i} S_{j0}(u_i; \theta_{j0})^{1-\delta_i}\}^{1-r_i} \right)^{x_j i}.$$

The likelihood factorizes into two components: the likelihood contribution for π and the likelihood contribution for θ. To estimate survival distributions for the treatment strategies one replaces the means in (4) with survival functions to get

$$\mathcal{S}_{jk}(u) = (1 - \pi_{rj})S_{j0}(u) + \pi_{rj}S_{jk}(u), \quad j, k = 1, 2.$$

This is a well known result from the theory of mixture distributions (McLachlan and McGiffin, 1993).

5. Parametric approach for time-varying SMART designs

The approach for estimating survival distributions developed by Wahed (2010) is not suitable for time-varying SMART designs. Consider the treatment A_1 (the results are similar for treatment A_2). Wahed (2010) defined using counterfactuals the survival time for patient i, if assigned to A_1B_k, as

$$T_{ki} = (1 - R_i)T_{0i} + R_iT^{**}_{ki}, \quad k = 1, 2.$$

This way of definition is not appropriate for two-stage time-varying SMART designs. In addition to T^{**}_{ki}, we need to consider another variable for responders, T^R_i, which is the time to response for the ith patient in the first stage. Since time to the first-stage response varies among the responders, it must be accounted for in the likelihood. In a time-varying SMART design the survival time should be defined as

$$T_{ki} = (1 - R_i)T_{0i} + R_i(T^R_i + T^*_{ki}), \quad k = 1, 2.$$

The observed survival time in this case is the sum of two random variables for the responders. One cannot put a single distribution on a sum as that could be theoretically incorrect. The density function of a sum of two random variables is given by the convolution of their density functions. To solve this problem, we propose a parametric approach for the estimation of survival functions of treatment policies A_jB_k in the presence of a time-varying SMART design. This work follows the lines of Wahed (2010), extending some of the theory therein to a more general setting.

5.1 Density of T_k

Let $\tilde{T}_{ki} = T^R_i + T^*_{ki}$, then $T_{ki} = (1 - R_i)T_{0i} + R_i\tilde{T}_{ki}$, for $k = 1, 2$. Let r be a realization of R, $r \in (0, 1)$. Then we can write, for $k = 1, 2$,

$$\begin{aligned} F_{T_k} &= P(T_k \le t) = P([(1 - r)T_0 + r\tilde{T}_k] \le t) \\ &= \sum_{r \in (0,1)} P([(1 - r)T_0 + r\tilde{T}_k] \le t | R = r)P(R = r) \\ &= P(T_0 \le t)P(R = 0) + P(\tilde{T}_k \le t)P(R = 1) \\ &= (1 - \pi_r)P(T_0 \le t) + \pi_r P(\tilde{T}_k \le t), \end{aligned}$$

where $P(R = 1) = \pi_r$. This leads to

$$f_{T_k}(t) = (1 - \pi_r)f_0(t) + \pi_r f_k(t), \quad k = 1, 2,$$

where $f_0(t)$ and $f_k(t)$ are the density functions of T_0 and $\tilde{T}_k$, respectively.

We note that $f_{\tilde{T}_k}(t)$ is obtained from a convolution of T^R and T_k^*. Using the relationship between a mixture density and the survival function (McLachlan and McGiffin, 1993), the survival function for treatment policy A_1B_k is given as

$$S_{T_k}(t) = (1-\pi_r)S_0(t) + \pi S_k(t),$$

where $S_0(t)$ and $S_k(t)$ are the survival functions of T_0 and $\tilde{T}_k$, respectively.

Example: Exponential Model
Suppose that

$$\begin{aligned} T^R &\sim \lambda_R \exp(-\lambda_R t), \quad \lambda_R > 0, \\ T_k^* &\sim \lambda_k \exp(-\lambda_k t), \quad \lambda_k > 0, k = 1, 2. \end{aligned}$$

We are interested in the density of $\tilde{T}_k$:

$$\begin{aligned} f_{\tilde{T}_k}(\tilde{z}) &= \int_0^{\tilde{z}} \lambda_R \lambda_k e^{-\lambda_R t} e^{-\lambda_k(\tilde{z}-t)} dt \\ &= \int_0^{\tilde{z}} \lambda_R \lambda_k e^{-\lambda_R t} e^{-\lambda_k \tilde{z} + \lambda_k t} dt \\ &= \lambda_R \lambda_k e^{-\lambda_k \tilde{z}} \int_0^{\tilde{z}} e^{-(\lambda_R - \lambda_k)t} dt \\ &= \frac{\lambda_R \lambda_k}{\lambda_k - \lambda_R} e^{-\lambda_R \tilde{z}} + \frac{\lambda_R \lambda_k}{\lambda_R - \lambda_k} e^{-\lambda_k \tilde{z}}, \quad \lambda_R, \lambda_k > 0, z \geq 0. \end{aligned}$$

Likewise, we can obtain the distribution function

$$\begin{aligned} F_{\tilde{T}_k}(\tilde{z}) &= P(\tilde{T}_k \leq \tilde{z}) \\ &= \frac{\lambda_R \lambda_k}{\lambda_k - \lambda_R} \int_0^{\tilde{z}} \left(e^{-\lambda_R t} - e^{-\lambda_k t} \right) dt \\ &= 1 + \frac{\lambda_R}{\lambda_k - \lambda_R} e^{-\lambda_k \tilde{z}} - \frac{\lambda_k}{\lambda_k - \lambda_R} e^{-\lambda_R \tilde{z}}. \end{aligned}$$

Consequently, the survival function for $\tilde{T}_k$ is

$$\begin{aligned} S_{\tilde{T}_k}(\tilde{z}) &= 1 - F_{\tilde{T}_k}(\tilde{z}) \\ &= 1 - \left[1 + \frac{\lambda_R}{\lambda_k - \lambda_R} e^{-\lambda_k \tilde{z}} - \frac{\lambda_k}{\lambda_k - \lambda_R} e^{-\lambda_R \tilde{z}} \right] \\ &= \frac{\lambda_k}{\lambda_k - \lambda_R} e^{-\lambda_R \tilde{z}} + \frac{\lambda_R}{\lambda_R - \lambda_k} e^{-\lambda_k \tilde{z}}. \end{aligned}$$

5.2 Likelihood and survival function

Suppose that the time-to-event is subject to right censoring. We assume that everyone's response status is always observed. To estimate the parameters needed for the survival distribution, we

construct the likelihood for the observed data in a two-stage design. The joint distribution of the data can be obtained as

$$
\begin{aligned}
&f(U_i = u_i, \Delta_i = \delta_i, R_i Z_i = r_i z_i | R_i = r_i) P(R_i = r_i) \\
&= f(U_i = u_i, \Delta_i = \delta_i | R_i Z_i = r_i z_i, R_i = r_i) P(R_i Z_i = r_i z_i | R_i = r_i) P(R_i = r_i) \\
&= \begin{cases}
f(U_{0i} = u_i, \Delta_i = \delta_i | R_i Z_i = 0, R_i = 0) P(R_i Z_i = 0 | R_i = 0) P(R_i = 0), & \text{if } R_i = 0 \\
f(U_{1i} = u_i, \Delta_i = \delta_i | R_i Z_i = 1, R_i = 1) P(R_i Z_i = 1 | R_i = 1) P(R_i = 1), & \text{if } R_i = 1, Z_i = 1 \\
f(U_{2i} = u_i, \Delta_i = \delta_i | R_i Z_i = 0, R_i = 1) P(R_i Z_i = 0 | R_i = 1) P(R_i = 1), & \text{if } R_i = 1, Z_i = 0
\end{cases} \\
&= \begin{cases}
(1 - \pi_r) f_0(u_i)^{\delta_i} S_0(u_i)^{1-\delta_i} \\
\pi_r \pi_z f_1(u_i)^{\delta_i} S_1(u_i)^{1-\delta_i} \\
\pi_r (1 - \pi_z) f_2(u_i)^{\delta_i} S_2(u_i)^{1-\delta_i},
\end{cases}
\end{aligned}
$$

where $P(Z_i = 1 | R_i = 1) = \pi_z$ which is the probability of being randomized to B_1 in the second stage. Clearly, $P(Z_i = 0 | R_i = 1) = 1 - \pi_z$ is the probability to be randomized to B_2.

Let O_i denote the observed data $(r_i, r_i z_i, u_i, \delta_i)$ for patient i. Then the full likelihood is

$$
\begin{aligned}
L(\theta, \pi; O) = \prod_{i=1}^{n} &[(1 - \pi_r) f_0(u_i)^{\delta_i} S_0(u_i)^{1-\delta_i}]^{1-r_i} \\
&\times \{[\pi_r \pi_z f_1(u_i)^{\delta_i} S_1(u_i)^{1-\delta_i}]^{z_i} \cdot [\pi_r (1 - \pi_z) f_2(u_i)^{\delta_i} S_2(u_i)^{1-\delta_i}]^{1-z_i}\}^{r_i},
\end{aligned}
$$

where $O = (O_1, O_2, ..., O_n)$, $\pi = (\pi_r, \pi_z)$ and $\theta = (\theta_R, \theta_k)$, $k = 1, 2$. The likelihood factorizes into two parts, with one part depending only on the parameters π and the other part on the parameters θ:

$$
\begin{aligned}
L_1(\pi; O) &= (1 - \pi_r)^{\sum_{i=1}^n (1 - r_i)} \cdot \pi_r^{\sum_{i=1}^n z_i r_i} \cdot \pi_z^{\sum_{i=1}^n z_i r_i} \cdot (1 - \pi_z)^{\sum_{i=1}^n r_i (1 - z_i)} \cdot \pi_r^{\sum_{i=1}^n r_i (1 - z_i)} \\
&= (1 - \pi_r)^{\sum_{i=1}^n (1 - r_i)} \cdot \pi_r^{\sum_{i=1}^n z_i r_i + \sum_{i=1}^n r_i - \sum_{i=1}^n z_i r_i} \cdot \pi_z^{\sum_{i=1}^n z_i r_i} \cdot (1 - \pi_z)^{\sum_{i=1}^n r_i (1 - z_i)} \\
&= (1 - \pi_r)^{\sum_{i=1}^n (1 - r_i)} \cdot \pi_r^{\sum_{i=1}^n r_i} \cdot \pi_z^{\sum_{i=1}^n z_i r_i} \cdot (1 - \pi_z)^{\sum_{i=1}^n r_i (1 - z_i)}.
\end{aligned}
$$

The corresponding log-likelihood is

$$
\begin{aligned}
l_1(\pi; O) &= \log L_1(\pi; O) \\
&= \sum_{i=1}^{n} (1 - r_i) \log(1 - \pi_r) + \sum_{i=1}^{n} r_i \log \pi_r + \sum_{i=1}^{n} z_i r_i \log \pi_z + \sum_{i=1}^{n} r_i (1 - z_i) \log(1 - \pi_z),
\end{aligned}
$$

and

$$
\begin{aligned}
\frac{\partial l_1(\pi; O)}{\partial \pi_r} &= \frac{-\sum_{i=1}^n (1 - r_i)}{1 - \pi_r} + \frac{\sum_{i=1}^n r_i}{\pi_r}, \\
\frac{\partial l_1(\pi; O)}{\partial \pi_z} &= \frac{\sum_{i=1}^n z_i r_i}{\pi_z} - \frac{\sum_{i=1}^n r_i (1 - z_i)}{1 - \pi_z}.
\end{aligned} \tag{5}
$$

Setting the two score equations from (5) to zero we get

$$
\hat{\pi}_r = \frac{\sum_{i=1}^n r_i}{n}, \qquad \hat{\pi}_z = \frac{\sum_{i=1}^n r_i r_i}{\sum_{i=1}^n r_i}, \tag{6}
$$

which are maximum likelihood estimators (MLEs) from $L_1(\pi; O)$. The likelihood for θ is

$$L_2(\theta; O) = \prod_{i=1}^{n} [f_0(u_i)^{\delta_i} S_0(u_i)^{1-\delta_i}]^{1-r_i} \{[f_1(u_i)^{\delta_i} S_1(u_i)^{1-\delta_i}]^{z_i} \cdot [f_2(u_i)^{\delta_i} S_2(u_i)^{1-\delta_i}]^{1-z_i}\}^{r_i},$$

and the log-likelihood, $l_2(\theta; O) = \log L_2(\theta; O)$, becomes

$$l_2(\theta; O) = \sum_{i=1}^{n} \{(1-r_i)\log f_0(u_i)^{\delta_i} S_0(u_i)^{1-\delta_i} + r_i z_i \log f_1(u_i)^{\delta_i} S_1(u_i)^{1-\delta_i} + r_i(1-z_i)\log f_2(u_i)^{\delta_i} S_2(u_i)^{1-\delta_i}\}.$$

To estimate the survival distributions for the treatment policy $A_1 B_k$, we propose using

$$\hat{S}_{A_1 B_k}(u) = (1-\hat{\pi}_r)\hat{S}_0(u) + \hat{\pi}_r \hat{S}_k(u), \quad k = 1, 2,$$

where $\hat{S}_0(u)$ and $\hat{S}_k(u)$ are obtained by replacing the MLEs of θ in the parametric survival functions of $S_0(u)$ and $S_k(u)$. Estimating survival distributions for treatment policy $A_2 B_k$ follows analogously.

Example: Exponential Model

Assuming the exponential distribution we have

$$\begin{aligned} f_0(u) &= \lambda_0 e^{-\lambda_0 u}, \\ f_1(u) &= \frac{\lambda_R \lambda_1}{\lambda_1 - \lambda_R} e^{-\lambda_R u} + \frac{\lambda_R \lambda_1}{\lambda_R - \lambda_1} e^{-\lambda_1 u}, \\ f_2(u) &= \frac{\lambda_R \lambda_2}{\lambda_2 - \lambda_R} e^{-\lambda_R u} + \frac{\lambda_R \lambda_2}{\lambda_R - \lambda_2} e^{-\lambda_2 u}, \end{aligned}$$

and the log-likelihood becomes

$$\begin{aligned} l(\theta; O_i) = \sum_{i=1}^{n} \Bigg\{ & (1-r_i)\log[\lambda_0 e^{-\lambda_0 u_i}]^{\delta_i} [e^{-\lambda_0 u_i}]^{1-\delta_i} \\ & + r_i z_i \log \left[\frac{\lambda_R \lambda_1}{\lambda_1 - \lambda_R} e^{-\lambda_R u_i} + \frac{\lambda_R \lambda_1}{\lambda_R - \lambda_1} e^{-\lambda_1 u_i} \right]^{\delta_i} \left[\frac{\lambda_1}{\lambda_1 - \lambda_R} e^{-\lambda_R u_i} + \frac{\lambda_R}{\lambda_R - \lambda_1} e^{-\lambda_1 u_i} \right]^{1-\delta_i} \\ & + r_i(1-z_i)\log \left[\frac{\lambda_R \lambda_2}{\lambda_2 - \lambda_R} e^{-\lambda_R u_i} + \frac{\lambda_R \lambda_2}{\lambda_R - \lambda_2} e^{-\lambda_2 u_i} \right]^{\delta_i} \left[\frac{\lambda_2}{\lambda_2 - \lambda_R} e^{-\lambda_R u_i} + \frac{\lambda_R}{\lambda_R - \lambda_2} e^{-\lambda_2 u_i} \right]^{1-\delta_i} \Bigg\}. \end{aligned}$$

Since the full likelihood factorizes into two parts, each part can be maximized separately. The maximum likelihood estimates for $L_1(\pi; O)$ are given in (6) above. $L_2(\theta; O)$ can be maximized numerically since the estimates of the parameters from the convolution do not have closed-form solutions. Assuming an exponential distribution for $k = 1$ leads to

$$\hat{S}_{A_1 B_1}(u) = (1-\hat{\pi}_r) e^{-\hat{\lambda}_0 u} + \hat{\pi}_r \left(\frac{\hat{\lambda}_1}{\hat{\lambda}_1 - \hat{\lambda}_R} e^{-\hat{\lambda}_R u} + \frac{\hat{\lambda}_R}{\hat{\lambda}_R - \hat{\lambda}_1} e^{-\hat{\lambda}_1 u} \right).$$

5.3 Large sample properties

Consider the case when $k = 1$, that is, when estimating survival curve for treatment policy A_1B_1

$$\hat{S}_{A_1B_1}(u) = (1 - \hat{\pi}_r)\hat{S}_0(u) + \hat{\pi}_r\hat{S}_1(u), \quad \text{for } u \in [0, \tau].$$

Let $\hat{\phi} = (\hat{\pi}_r, \hat{\theta})$ and $G(u)$ denote the vector of partial derivatives with respect to each parameter in $\phi = (\pi_r, \theta)$. Also define $V = \text{Var}(\hat{\phi})$ to be the variance-covariance matrix for the MLEs. Then, by the delta method, we have that

$$\hat{S}_{A_1B_1}(u) \;\dot{\sim}\; N(S_{A_1B_1}(u), \Sigma(u)),$$

where $\Sigma(u) = G(u)VG(u)^T$. We estimate $\Sigma(u)$ by replacing $\phi = (\pi_r, \theta)$ with $\hat{\phi} = (\hat{\pi}_r, \hat{\theta})$. This leads to $\hat{\Sigma} = \hat{G}\hat{V}\hat{G}^T$, where $\hat{V}$ is the estimated variance-covariance matrix of $\hat{\phi}$.

Example: Exponential Model

Using the delta method, we compute the variance of $\hat{S}_{A_1B_1}$ when exponential distributions are assumed. Taking partial derivatives with respect to the parameters, we get

$$\begin{aligned}
d_1 &= \frac{\partial S_{A_1B_1}(u)}{\partial \pi_r} = -e^{-\lambda_0 u} + \left(\frac{\lambda_1}{\hat{\lambda}_1 - \lambda_R}e^{-\lambda_R u} + \frac{\lambda_R}{\lambda_R - \lambda_1}e^{-\lambda_1 u}\right),\\
d_2 &= \frac{\partial S_{A_1B_1}(u)}{\partial \lambda_0} = -u(1 - \pi_r)e^{-\lambda_0 u},\\
d_3 &= \frac{\partial S_{A_1B_1}(u)}{\partial \lambda_R} = \frac{\lambda_1}{(\lambda_1 - \lambda_R)^2}e^{-\lambda_R u} - \frac{\lambda_1 u}{\lambda_1 - \lambda_R}e^{-\lambda_R u} - \frac{\lambda_1}{(\lambda_R - \lambda_1)^2}e^{-\lambda_1 u},\\
d_4 &= \frac{\partial S_{A_1B_1}(u)}{\partial \lambda_1} = \frac{\lambda_R}{(\lambda_R - \lambda_1)^2}e^{-\lambda_1 u} - \frac{\lambda_R}{(\lambda_1 - \lambda_R)^2}e^{-\lambda_R u} - \frac{\lambda_R u}{\lambda_R - \lambda_1}e^{-\lambda_1 u}.
\end{aligned}$$

Now, given $G = (d_1, d_2, d_3, d_4)$, we obtain

$$\Sigma = G\begin{pmatrix} \text{Var}(\hat{\pi}_r) & 0 & 0 & 0 \\ 0 & \text{Var}(\hat{\lambda}_0) & 0 & 0 \\ 0 & 0 & \text{Var}(\hat{\lambda}_R) & \text{Cov}(\hat{\lambda}_R, \hat{\lambda}_1) \\ 0 & 0 & \text{Cov}(\hat{\lambda}_1, \hat{\lambda}_R) & \text{Var}(\hat{\lambda}_1) \end{pmatrix} G^T.$$

We plug in $\hat{\phi}$ to obtain $\hat{G} = (\hat{d}_1, \hat{d}_2, \hat{d}_3, \hat{d}_4)$. $V = \text{Var}(\hat{\phi})$ is estimated by the observed Fisher information matrix.

6. Simulation study

To study the performance of the proposed estimator, a simulation study was conducted and a comparison with other estimators was made. The generation of the datasets was done following a two-stage SMART design with two first stage treatments and two second stage treatments. We focused on data from A_1 as data from A_1 and A_2 are independent. All simulations were done in R.

Different simulation scenarios were considered with different response rates. R_i was taken to be a Bernoulli distribution with $P(R_i = 1) = \pi_r$, and $\pi_r \in (0.5, 0.7)$ so as to achieve between 50% and 70% of individuals responding to the first stage intervention. T_{0i} was generated from an exponential

Table 1. Simulation results for $\pi_r = 0.5$.

				TVS				WRSE					LDT			
c	n	t	$S_1(u)$	$\hat{S}_1(u)$	SE	Bias	CP	$\hat{S}_1(u)$	SE	Bias	CP	RE	$\hat{S}_1(u)$	SE	Bias	CP
20%	100	1	0.851	0.859	0.021	0.01	95.2	0.855	0.035	0.00	95.7	0.370	0.851	0.038	0.00	95.6
		3	0.638	0.642	0.041	0.00	95.4	0.648	0.051	0.01	94.7	0.652	0.640	0.057	0.00	95.1
		6	0.434	0.439	0.048	0.01	94.2	0.453	0.057	0.02	93.7	0.715	0.439	0.067	0.01	93.4
		8	0.340	0.347	0.049	0.01	94.6	0.367	0.058	0.03	92.2	0.736	0.350	0.068	0.01	93.1
		12	0.211	0.223	0.047	0.01	94.6	0.241	0.055	0.03	92.5	0.778	0.220	0.064	0.01	89.4
	300	1	0.851	0.854	0.013	0.00	96.1	0.852	0.021	0.00	95.0	0.370	0.850	0.022	0.00	95.6
		3	0.638	0.637	0.024	0.00	95.9	0.643	0.030	0.01	95.7	0.637	0.639	0.034	0.00	96.6
		6	0.434	0.432	0.028	0.00	95.9	0.447	0.034	0.01	94.2	0.707	0.441	0.039	0.01	94.8
		8	0.340	0.339	0.029	0.00	95.0	0.358	0.034	0.02	93.9	0.723	0.350	0.040	0.01	94.5
		12	0.211	0.213	0.027	0.00	94.6	0.232	0.032	0.02	90.5	0.728	0.223	0.038	0.01	92.7
40%	100	1	0.851	0.860	0.022	0.01	95.3	0.855	0.036	0.00	95.6	0.385	0.838	0.038	0.01	89.9
		3	0.638	0.643	0.042	0.01	94.6	0.648	0.052	0.01	94.6	0.672	0.607	0.060	0.03	86.0
		6	0.434	0.444	0.051	0.01	94.7	0.452	0.060	0.02	92.9	0.737	0.387	0.070	0.05	77.4
		8	0.340	0.355	0.054	0.02	95.2	0.368	0.062	0.03	93.1	0.769	0.292	0.071	0.05	75.3
		12	0.211	0.238	0.055	0.03	95.1	0.243	0.061	0.03	90.7	0.847	0.150	0.061	0.06	62.1
	300	1	0.851	0.854	0.013	0.00	94.2	0.853	0.021	0.00	95.8	0.387	0.839	0.022	0.01	86.2
		3	0.638	0.637	0.025	0.00	94.9	0.643	0.030	0.01	94.0	0.653	0.607	0.036	0.03	78.5
		6	0.434	0.433	0.029	0.00	95.1	0.447	0.035	0.01	94.1	0.718	0.392	0.043	0.04	72.9
		8	0.340	0.342	0.029	0.00	94.6	0.358	0.037	0.02	93.3	0.729	0.293	0.044	0.05	68.6
		12	0.211	0.219	0.030	0.01	94.8	0.235	0.037	0.02	92.1	0.731	0.158	0.041	0.05	59.6

Table 2. Simulation results for $\pi_r = 0.7$.

				TVS				WRSE					LDT			
c	n	t	$S_1(u)$	$\hat{S}_1(u)$	SE	Bias	CP	$\hat{S}_1(u)$	SE	Bias	CP	RE	$\hat{S}_1(u)$	SE	Bias	CP
20%	100	1	0.906	0.912	0.018	0.01	94.8	0.908	0.029	0.00	95.4	0.374	0.906	0.031	0.00	95.6
		3	0.746	0.747	0.037	0.00	94.9	0.755	0.048	0.01	94.7	0.623	0.748	0.052	0.00	95.0
		6	0.553	0.552	0.050	0.00	94.1	0.573	0.060	0.02	93.3	0.710	0.562	0.068	0.01	93.3
		8	0.449	0.450	0.053	0.00	94.6	0.476	0.063	0.03	92.3	0.739	0.461	0.071	0.01	92.4
		12	0.288	0.296	0.054	0.01	94.0	0.322	0.062	0.03	92.5	0.769	0.302	0.071	0.01	90.0
	300	1	0.906	0.908	0.010	0.00	94.4	0.907	0.017	0.00	94.4	0.372	0.906	0.018	0.00	94.4
		3	0.746	0.746	0.022	0.00	94.8	0.754	0.028	0.01	93.3	0.596	0.751	0.031	0.01	93.3
		6	0.553	0.551	0.029	0.00	95.5	0.573	0.035	0.02	92.2	0.697	0.567	0.039	0.01	92.2
		8	0.449	0.448	0.031	0.00	95.0	0.475	0.037	0.03	91.8	0.726	0.468	0.042	0.02	91.8
		12	0.288	0.290	0.031	0.00	94.4	0.320	0.037	0.03	89.6	0.717	0.310	0.042	0.02	89.6
40%	100	1	0.906	0.912	0.018	0.01	94.2	0.908	0.030	0.00	95.1	0.392	0.892	0.032	0.01	87.6
		3	0.746	0.747	0.039	0.00	94.2	0.753	0.049	0.01	95.0	0.651	0.712	0.055	0.03	83.4
		6	0.553	0.556	0.053	0.00	94.2	0.576	0.063	0.02	92.8	0.744	0.506	0.072	0.05	77.0
		8	0.449	0.456	0.059	0.01	94.0	0.481	0.067	0.03	91.6	0.770	0.395	0.076	0.05	73.8
		12	0.288	0.310	0.062	0.02	94.2	0.328	0.071	0.04	91.0	0.806	0.215	0.072	0.07	61.8
	300	1	0.906	0.908	0.011	0.00	95.2	0.908	0.017	0.00	95.0	0.391	0.895	0.019	0.01	86.3
		3	0.746	0.745	0.022	0.00	95.2	0.753	0.029	0.01	94.0	0.626	0.719	0.033	0.03	80.3
		6	0.553	0.552	0.031	0.00	94.1	0.572	0.037	0.01	93.4	0.723	0.513	0.043	0.04	75.4
		8	0.449	0.450	0.034	0.00	93.2	0.474	0.040	0.03	92.0	0.747	0.401	0.047	0.50	72.3
		12	0.288	0.296	0.036	0.01	94.2	0.319	0.043	0.03	91.4	0.738	0.224	0.047	0.06	57.0

distribution with a mean of 3 years for those with $R_i = 0$. The second stage indicator was generated from a Bernoulli distribution with $P(Z_i = 1) = \pi_z$, and π_z was set to be 0.5 in all simulations. We generated T_i^R from an exponential distribution with a mean of 5 years for the responders to the first stage treatment. For those with $Z_i = 1$, T_{1i}^* was generated from an exponential distribution with a mean of 7 years and T_{2i}^* was generated from an exponential distribution with a mean of 8 years. The observed survival time, T_i, was obtained using equation (1). The right censoring time, C_i, was generated from a uniform distribution, $U(0, v)$, such that 20% and 40% of the sample were censored. Finally, the observed time was defined as $U_i = \min(T_i, C_i)$. The DTR package was used for estimating the WRSE and the LDT estimator (Tang and Melguizo, 2005). For our estimator, an ad-hoc R function was written and maximized using the `optim` function in R. To facilitate exposition, we denote our parametric approach for time-varying SMART designs as TVS. We also denote the censoring rate by c and time by t.

Tables 1 and 2 show the results of the simulation study. The results for our estimator are given under the TVS columns. We report the standard errors (SE), absolute bias, and 95% coverage probabilities (CP) for the three estimators for treatment policy A_1B_1. Relative efficiency (RE) is also reported between our parametric estimator and the WRSE. The relative efficiency is calculated as the sample variance of our estimator divided by the sample variance of the WRSE for estimating the survival function. Guo and Tsiatis (2005) established that the WRSE is more efficient as compared to the LDT estimator. For this reason, we only computed the relative efficiency of our estimator and the WRSE. Two different censoring and response rates are considered.

The results of this simulation study show that our estimator is more precise compared to its nonparametric counterparts. This is shown by the small standard errors across all the simulation scenarios. The LDT estimator has the largest standard errors among the estimators. Our estimator is more efficient than the other two estimators. This result is not surprising. Inferences based on parametric distributions are more precise provided the parametric assumptions are valid (Collett, 2015). The coverage probabilities of our method are close to the nominal level, the same applies to the WRSE. The coverage probabilities of the LDT estimator are highly affected by the change in censoring rates. In cases where the censoring rate is high, that is, 40%, the coverage probabilities are way below the desired nominal level.

In terms of biasedness, all three methods performed fairly well with the exception of the LDT estimator in the case of 40% censoring. Increasing the censoring rate from 20% to 40% for the LDT estimator leads to an increase in bias. There is, however, a minimal increase in bias for the other two estimators when the censoring rate was increased. The bias vanished with increase in the sample size, as expected. Our parametric estimator has the least bias among the three methods, and when the sample size is 300, the bias of our method diminishes. Changing the response rates changes the survival estimates. In general all three methods yield similar survival estimates. The differences in the survival estimates is profound for the LDT when the censoring rate is 40%. With a lower censoring rate, the survival estimates from the three methods are mostly similar.

7. Application: CALGB 19808 study

We apply our methodology to the Cancer and Leukemia Group B 19808 (CALGB 19808) study (Kolitz et al., 2010, 2014). In the CALGB 19808 study, 302 patients were randomized to receive

Table 3. Application results.

t	Policy	$\hat{S}(t)^{exp}_{TVS}$	SE^{exp}	$\hat{S}(t)^{gom}_{TVS}$	SE^{gom}	$\hat{S}(t)_{WRSE}$	SE
0.03	ADEP-rIL-2	0.9952	0.0006	0.9845	0.0026	0.9868	0.0092
	ADEP-OBS	0.9952	0.0006	0.9844	0.0027	0.9868	0.0092
	ADE-rIL-2	0.9953	0.0006	0.9847	0.0027	0.9801	0.0114
	ADE-OBS	0.9953	0.0006	0.9847	0.0030	0.9801	0.0114
1.30	ADEP-rIL-2	0.8114	0.0186	0.6356	0.0402	0.6302	0.0407
	ADEP-OBS	0.8007	0.0188	0.6249	0.0429	0.5964	0.0436
	ADE-rIL-2	0.8146	0.0188	0.6427	0.0430	0.6157	0.0433
	ADE-OBS	0.8034	0.0189	0.6315	0.0420	0.6210	0.0422
4.10	ADEP-rIL-2	0.5233	0.0352	0.4422	0.0438	0.4286	0.0449
	ADEP-OBS	0.4890	0.0334	0.4079	0.0422	0.3815	0.0463
	ADE-rIL-2	0.5337	0.0356	0.4571	0.0419	0.4144	0.0471
	ADE-OBS	0.4988	0.0338	0.4221	0.0446	0.3624	0.0452
8.00	ADEP-rIL-2	0.3186	0.0389	0.3676	0.0262	0.3547	0.0445
	ADEP-OBS	0.2663	0.0325	0.3153	0.0435	0.3199	0.0452
	ADE-rIL-2	0.3344	0.0389	0.3888	0.0331	0.3787	0.0470
	ADE-OBS	0.2796	0.0329	0.3341	0.0311	0.3407	0.0450

induction chemotherapy regimens consisting of cytosine arabinoside (Ara-C;A), daunorubicin (D), and etoposide (E) without (ADE) or with (ADEP) PSC-833 (P). The study was done to patients under the age of 60 with newly diagnosed acute myeloid leukemia. To be eligible, the patients should not have been previously treated for leukemia and be under the age of 60. The study was designed to compare the two induction chemotherapy regimens, ADE and ADEP, with both treatments given at their highest clinically feasible doses.

For the first stage, the main objective of the trial was to determine whether use of the Pgp-modulating agent PSC-833 in the ADEP regimen improved overall survival and disease-free survival compared to ADE only. The randomization between ADE and ADEP was done at 1:1 ratio. The analysis of the first stage data is reported in Kolitz et al. (2010). In both treatment arms, 75% of the patients achieved complete remission (CR). Complete remission was defined using the National Cancer Institute Workshop criteria (Cheson et al., 1990). The 75% who achieved complete remission were further randomized to the second stage treatments, namely recombinant interleukin-2 (rIL-2) and no rIL-2 (observation).

Table 3 shows the results of fitting our method to the CALGB 19808 study. This analysis is based on the overall survival. For the first component in the survival mixture model (S_0), we assumed either the exponential or the Gompertz distributions. Under the columns $\hat{S}(t)^{exp}_{TVS}$ and $\hat{S}(t)^{gom}_{TVS}$, we report the survival estimates when the exponential or the Gompertz distribution is used for the non-responders. The second component, $(T_i^R + T^*_{ki})$, is the convolution of exponential distributions. The results when a Gompertz distribution was used provide a better fit with similar estimates to the WRSE. The fit with an exponential distribution is poor. It tends to overestimate the survival probability in the middle of

the curve and the discrepancy is profound.

8. Conclusion

We can differentiate between two types of SMART designs. In some SMART designs, the response is measured at one time point. In other SMART designs, the response is measured at different time points in the first stage. The time to response then differs from patient to patient. This makes the observed survival times differ in these two types of designs. In the latter, the observed survival times are a sum of two random survival times for the responders. This makes it theoretically flawed to just assume a single survival model for the sum. The density of a sum of two random variables is always given by a convolution. In this paper, we proposed using a convolution-based density function in modelling the total times for responders. Maximum likelihood estimation was used and the results are compared to the nonparametric estimates from the WRSE. The proposed approach is not restricted to only convolutions of the exponential distribution but can be generalized to other distributions using numerical methods based on the discrete Fourier transforms or other approximations. The `distr` package provides a platform where such probability densities can be computed.

We note that the way the survival time is defined in a standard SMART design makes it easier for the parametric analysis to be conducted as it avoids the use of convolutions. The way the survival time is defined for responders in time-varying SMART designs poses a challenge in the analysis.

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