STATISTICAL ISSUES IN THE DESIGN AND ANALYSIS OF SEQUENTIALLY RANDOMIZED TRIALS

by

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Adaptive treatment strategies are comprehensive methods for treating chronic diseases according to patients’ needs and responses. They are useful in the treatment of diseases such as cancer or AIDS, where the treatment is frequently modified to adapt to the patients’ health status. In the first part of this dissertation, we consider two commonly used randomization designs in clinical trial, namely, up-front randomized trial and sequentially randomized trial used to compare treatment strategies. Up-front randomization is the classical method of randomization where patients are randomized at the beginning of the study to pre-specified strategies. On the other hand, in sequentially randomization trials, patients are randomized sequentially to available treatment options over the duration of the therapy as they become eligible to receive them. We compare the efficiency of the traditional up-front randomized trials to that of sequentially randomized trials for comparing adaptive treatment strategies both analytically and numerically based on a continuous outcome.

In the second part of the dissertation, we consider analyzing right-censored survival data from two-stage sequentially randomized trials. In such analysis, it is often of interest to use median residual lifetime as the summary parameter to assess the treatment effectiveness. However, estimation of the median residual lifetime from sequentially randomized trials is not as straightforward because of its sequential randomization structure. We propose methods for estimating strategy-specific median residual life function from a two-stage sequentially randomized trial. Two types of estimators are proposed by inverting the inverse-probability-weighted estimated survival function and by using inverse-probability-weighted estimating
equation function. We provide methods for estimating variances of these estimators and compare them through a simulation study. Our simulation study shows that both methods produce approximately unbiased estimators in large samples. We demonstrate our methods by applying them to a sequentially randomized leukemia clinical trial data set.

Diseases such as cancer, leukemia, depression, and AIDS are major causes of morbidity and mortality in the United States. Medical research in the recent times has focused on finding optimal treatment strategies to manage or eradicate these diseases to reduce individual and community burdens. Statistical methodologies proposed in this dissertation will help appropriately design and analyze trials to develop effective treatment strategies and thus will be of significant use for improving public health in the United States and around the world.

**Keywords:** Adaptive Treatment Strategies, Dynamic Treatment Regime, Inverse Probability Weighting, Sequential Randomization, Two-Stage Randomization Design, Median Residual Life Function.
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PREFACE

I would like to express my sincere gratitude to my dissertation advisor, Dr. Abdus Wahed, for help and support through the whole process of producing this dissertation. I truly believe that I'm fortunate to have him as an advisor. Without his help, I couldn't finish this dissertation. Also, without his understanding, I couldn't stay with my husband in Virginia during this dissertation study. I would also like to thank my committees and all faculty members in this department for their time and support. Finally, I would like to thank my family and friends, above all, my husband Jeongheon Lee for all his love and support.
1.0 INTRODUCTION

1.1 ADAPTIVE TREATMENT STRATEGY (ATS)

Adaptive treatment strategies are comprehensive methods for treating chronic diseases according to patients’ needs and responses. They are useful in the treatment of diseases such as cancer or AIDS, where the treatment is frequently modified to adapt to the patients’ health status. For example, in the treatment of acute myeloid leukemia, it is of interest to know whether growth factor infusion should be used following induction chemotherapy, or whether a mono-therapy or a combination therapy should be used as maintenance following remission. Usually, these questions are addressed locally by comparing the treatments at specific stages of the disease. However, a locally optimum treatment (e.g. the best induction for archiving remission) may not be the best globally (e.g. extended overall survival). Therefore, instead of considering each treatment separately, ATSs are formed to consider all treatment options at once for the purpose of the analysis. For example, in the treatment of leukemia, one ATS might be “treat with induction chemotherapy and add a growth factor; if remission is achieved, treat with a combination maintenance therapy; if remission is not achieved, declare that patient to be a treatment failure”. Another such strategy can just avoid the growth factor. Treatment options at each evaluation time determine the possible ATSs.
1.2 RANDOMIZATIONS IN CLINICAL TRIALS

Up-front randomized trial (URT) and sequentially randomized trial (SRT) are two methods to randomize patients to different strategies in order to compare treatment strategies. Up-front randomization is the classical method of randomization which randomizes patients at the beginning of the study to pre-specified strategies. Sequential randomization randomizes patients sequentially to possible treatments as they become eligible to receive subsequent treatment. An illustration of URT and SRT with two stages of treatment is presented in Figure 1.

Suppose $A_i$ denotes the $i^{th}$ induction treatment, $B_k$ is the $k^{th}$ maintenance treatment for the responders and $C_l$ is the $l^{th}$ alternative treatment for the non-responders. For simplicity, we assume that there are two varieties of $A$, $B$ and $C$, and thus $j$, $k$ and $l$ can take values 1 and 2. In practice, the alternative treatment $C$ can be one of the induction treatments that were not received by the patients at stage 1 (see Thall et al. [2007]). In some terminal illnesses, such as leukemia in elder patients, if a response (remission) is not achieved with an induction, no further treatment is given to reduce the treatment-related mortality and therefore $C$ can be regarded as no treatment. In this case, patients without response to the induction treatment do not receive any further treatment.

As can be seen from Figure 1(a), in URT, patients are randomized upon entry to all possible treatment strategies (a total of 8, in this case), realizing that some of the patients will not receive the intended maintenance or alternative treatment. For example, patient randomized to $A_1B_1C_1$ will receive $B_1$ only if they respond to $A_1$ and $C_1$ only if they do not respond to $A_1$. Thus, even if randomized with equal probability, for example, to $A_1B_1C_1$ and $A_1B_1C_2$, the actual number of patients receiving $C_1$ and $C_2$ can be very different depending on the number of patients not responding to $A_1$ in the two arms. URT is simple to conduct and the traditional method of analysis can be easily applied to analyze the data from such trials. Statistical analysis for comparing strategies follows standard method of multiple treatment trials.

In SRT (Figure 1(b)), patients are randomized to one of the two first-stage treatments $A_1$ or $A_2$ at entry. Once a patient achieves response, he/she is randomized to the second-
stage treatments $B_1$ or $B_2$ and to $C_1$ or $C_2$ if not. As can be seen, patients responding to the induction treatment can be randomized to two maintenance treatments $B_1$ or $B_2$ by maintaining balance if desired. Similarly, if desired a balance in the number of patients between two alternative treatments $C_1$ and $C_2$ can be attained. SRTs are often referred to as SMART (Sequential Multiple Assignment Randomized Trials, Murphy [2005]). Even though more complex statistical methods are required to compare treatment strategies, SRT follows the traditional principle of randomizing patients at the time of ascertaining eligibility.

1.3 MEDIAN RESIDUAL LIFE FUNCTION

A MERL function is the median of the remaining life time at a specific time point. For overall survival $T$, median residual lifetime at time $t_0$ is defined as:

$$\theta(t_0) = \text{median}(T - t_0 | T \geq t_0),$$

where $\text{median}(X|Y)$ stands for the median of the conditional distribution of $X$ given condition $Y$. In other words, $\theta(t_0)$ is the median time for those who survived beyond time $t_0$ in the population. The median residual lifetime is stable since it is not affected by outliers such as very long durations of survival time. In the case with the censored data, the use of a median for the residual lifetime not only exhibits a better location estimate than its mean but also shows less sensitivity to skewed distributions. The minimum of observed survival probability of the residual life distribution should be smaller than the 0.5, so that the median residual lifetime can be defined under censoring (Schmittlein et al. [1981]).

Various methods have been proposed in the literature to estimate the median residual lifetimes for one and two sample cases. Haines et al. [1974] introduced a general concept of the $\alpha$-percentile residual life function ($0 < \alpha < 1$). Schmittlein et al. [1981] established a general concept of MERL function exploring non-uniqueness of the corresponding lifetime distribution. Csörgő et al. [1987] proposed a 100$(1 - p)$th percentile residual lifetime estimator for complete data, whereas Chung [1989] extended this idea to censoring cases. The nonparametric estimator of 100$(1 - p)$th percentile residual lifetime was proposed by Feng.
Figure 1: Illustrations of (a) URT and (b) SRT with two stages of treatment.

Jeong et al. [2008] introduced a test statistic to compare two median residual lifetimes at a certain time point.
1.4 OBJECTIVE

The primary objective of this dissertation is two-fold: (a) compare the efficiency of the traditional up-front randomized trials to that of sequentially randomized trials for comparing adaptive treatment strategies and (b) propose methods for estimating strategy-specific median residual life function. We use the probability-adjusted survival estimator to estimate median residual life function.

To achieve the first goal, we construct unbiased estimators under both URT and SRT, and compared their analytical and estimated variances. We present the results in Chapter 3. We then propose two forms of estimators for the median residual lifetime from sequentially randomized trials. These are obtained by inverting the estimated survival function and using the estimating functions. The results are presented in Chapter 4.
2.0 METHODOLOGY REVIEWS

In the following, we review some of techniques used in this dissertation.

2.1 KAPLAN-MEIER ESTIMATOR

The Kaplan-Meier Estimator is a nonparametric method used to estimate a survival curve from lifetime data. Life time data is usually right censored and hence the empirical distribution function does not directly apply to the estimation of the survival distribution. Let $S(t)$ be the survival probability exceeding a time $t$. The Kaplan-Meier estimator is formulated as follows from the sample data containing $N$ observed times (event/censoring times).

$$\hat{S}(t) = \prod_{t_i < t} \frac{n_i - d_i}{n_i}, i = 1 \ldots N,$$

where $t_i$’s are event times, $n_i$ is the number of survivors excluding censored cases at time $t_i$ and $d_i$ is the number of events occurred at time $t_i$. The variance of this estimator is generally approximated using the Greenwood formula:

$$\text{var}(\hat{S}(t)) = \hat{S}^2(t) \sum_{t_i < t} \frac{d_i}{n_i(n_i - d_i)}.$$

The Kaplan-Meier estimator is known to be unbiased in large samples and is asymptotically normally distributed with mean $S(t)$ and variance that can be estimated by the above formula.
2.2 INVERSE-PROBABILITY-WEIGHTED ESTIMATOR

The idea of inverse-probability-weighting originates from the survey sampling where the inverse of the probability of sampling an individual unit is used as weight for that unit to construct unbiased estimators (Horvitz et al. [1952]). The idea can be extended to the estimation of survival curve in the presence of censoring. When censoring is considered independent of the observed data, the complete observation can be viewed as independent sample of the whole data. Thus, only the complete observations can be used to empirically estimate the survival functions with individual probability of not being censored as the reciprocal of weights.

Let \( U_i = \min(T_i, C_i) \) be the observed survival time, \( \Delta_i = I(T_i < C_i) \) be the event indicator where \( T_i \) is the event time and \( C_i \) is the potential censoring time for the \( i^{th} \) patient that for a fixed time \( t \). The inverse probability of censoring weighted estimator of \( S(t) \) is given by

\[
\hat{S}_{IPW}(t) = n^{-1} \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(U_i)} I(U_i > t)
\]

where \( \hat{K}(U_i) \) is the Kaplan-Meier estimator for censoring.
3.0 UP-FRONT VS. SEQUENTIAL RANDOMIZATION IN CLINICAL TRIALS

3.1 INTRODUCTION

Recently, SRTs have drawn considerable attention as an effective way of comparing ATSs. Analytical methods for comparing treatment strategies from SRTs are available in the literature (Lunceford et al. [2002], Murphy [2005], Robins et al. [1994], Wahed and Tsiatis [2004]). However, there is no literature on how SRT compares to URT in terms of statistical inference - particularly with respect to the efficiency of the estimators and the power of statistical hypothesis testing. In Wolbers et al. [2008], by using an estimator from Lunceford et al. [2002], several URTs were compared with a single SRT to show how new induction and maintenance treatments are beneficial over the existing treatment combinations. In their work, authors show that SRT is better than URT with respect to efficient use of information about patients. However, comparison does not include the efficiency of estimators.

In this chapter, we derive estimators of the mean of a continuous outcome for URT and SRT with two-stage designs by using the inverse-probability-weighting (IPW) (Robins et al. [1994]). Then we aim to evaluate the performance of the estimators for URT and SRT in terms of the efficiency of the estimators and the power of statistical hypothesis testing. Assumptions and notation used in this chapter are described in section 3.2. Inferential procedures in URT and SRT are discussed in section 3.3. We present the results of a simulation study in section 3.4.
3.2 NOTATION AND ASSUMPTIONS

Suppose there are two induction treatments $A_j$, $j = 1, 2$, two maintenance treatments for responders $B_k$, $k = 1, 2$, and two alternative treatments for non-responders $C_l$, $l = 1, 2$.

Let us define $Y$ to be the outcome variable of interest. We will treat $Y$ as being continuous; however, the methodology can be applied analogously to binary responses. We will define the estimands in terms of patient-specific counterfactual variables (Holland [1986]). Let $Y_i(A_j B_k)$ denote the outcome of the individual $i$ if he/she actually received the treatment sequence $A_j B_k$ (Receive $A_j$, respond, and then receive $B_k$). Similarly, let $Y_i(A_j C_l)$ be the outcome of the same patient if he/she had received the sequence $A_j C_l$. Note that under the possible options for induction and maintenance, there are 8 such outcomes possible. In practice, only one of the sequences will be followed by one individual. Therefore, only one of these 8 outcomes will be observed if $R_i$ denotes the response status ($R_i = 1$ for response, 0 for no response) for the patient $i$ in the population, then the outcome $Y$ for the patients $i$ under strategy $A_j B_k C_l$ can be written as

$$Y_i(A_j B_k C_l) = R_i Y_i(A_j B_k) + (1 - R_i) Y_i(A_j C_l), j, k, l = 1, 2.$$  \hspace{1cm} (3.1)

To represent a generic individual, for simplicity, we will drop $i$ from the variable notation, wherever possible.

Our goal is to estimate

$$\mu_{jkl} = \mathbb{E}\{Y(A_j B_k C_l)\}.$$  

Note that conditioning on $R$, $\mu_{jkl}$ can be expressed as

$$\mu_{jkl} = \pi_{R_j} \mu_{A_j B_k} + (1 - \pi_{R_j}) \mu_{A_j C_l},$$

where $\mu_{A_j B_k} = \mathbb{E}\{Y(A_j B_k)\}$, $\mu_{A_j C_l} = \mathbb{E}\{Y(A_j C_l)\}$ and $\pi_{R_j}$ is the probability of response to induction treatment $A_j$. All the variables $Y(A_j B_k), Y(A_j C_l)$ and $Y(A_j B_k C_l), j, k, l = 1, 2$ are counterfactuals, as they all cannot be observed for the same individual. Regardless of the design of the study, that is, whether URT or SRT, the observed data can be written as $\{I_i(A_j), R_i, R_i I_i(B_k), (1 - R_i) I_i(C_l), Y_i, j, k, l = 1, 2\}$, $i = 1, 2, ..., n$, where $Y_i$ is the observed
outcome for the $i^{th}$ patient, $I_i(X)$ is the indicator function for treatment $X$. $I_i(X) = 1$ if the $i^{th}$ patient was assigned to receive treatment $X$, and 0, otherwise.

### 3.3 ESTIMATION IN UP-FRONT AND SEQUENTIALLY RANDOMIZED TRIALS

In this section, we construct unbiased estimators for $\mu_{jkl}$ under the two randomized designs, URT and SRT, and derive their variances in order to compare their efficiency.

#### 3.3.1 Estimation in Up-front Randomized Trials

In URT, patients are randomized at the beginning into 8 eligible strategies. Therefore, the estimator for the mean outcome $\mu_{jkl}$ in URT is given by the sample mean of the outcome for patients randomized to the strategy $A_jB_kC_l$. Specifically,

$$\hat{\mu}_{jkl}^{URT} = \frac{\sum_{i=1}^{n} Y_i I_i(A_jB_kC_l)}{\sum_{i=1}^{n} I_i(A_jB_kC_l)} = \frac{\sum_{i=1}^{n} Y_i I_i(A_jB_kC_l)}{n_{jkl}},$$

where $I_i(A_jB_kC_l) = I_i(A_j)\{R_i I_i(B_k) + (1 - R_i)I_i(C_l)\}$ and $n_{jkl} = \sum_{i=1}^{n} I_i(A_jB_kC_l)$. The variance of this estimator is given by

$$\text{Var}(\hat{\mu}_{jkl}^{URT}) = \frac{\text{Var}\{Y(A_jB_kC_l)\}}{n_{jkl}}.$$  

Now, by the law of conditioned variance,

$$\text{Var}\{Y(A_jB_kC_l)\} = \text{Var}[\text{E}\{Y(A_jB_kC_l)|R\}] + \text{E}[\text{Var}\{Y(A_jB_kC_l)|R\}]. \quad (3.2)$$

First, consider the first part of the right-hand side in Eq. (3.2). Using Eq. (3.1),

$$\text{E}\{Y(A_jB_kC_l)|R\} = R\text{E}\{Y(A_jB_k)|R\} + (1-R)\text{E}\{Y(A_jC_l)|R\} = R\mu_{A_jB_k} + (1-R)\mu_{A_jC_l},$$
Note that \( E[\{Y(A_jB_kC_l|R)\}] = \pi \mu_{A_jB_k} + (1 - \pi) \mu_{A_jC_l} \). Then, its variance would be

\[
\text{Var}[E\{Y(A_jB_kC_l|R)\}] = E[\{E\{Y(A_jB_kC_l|R)\}\}^2] - \{\pi \mu_{A_jB_k} + (1 - \pi) \mu_{A_jC_l}\}^2
\]

\[
= E[\{RE(Y(A_jB_k)|R) + (1 - R)E(Y(A_jC_l)|R)\}^2]
- \{\pi \mu_{A_jB_k} + (1 - \pi) \mu_{A_jC_l}\}^2
\]

\[
= E\{R\mu_{A_jB_k}^2 + (1 - R)\mu_{A_jC_l}^2\} - \{\pi \mu_{A_jB_k} + (1 - \pi) \mu_{A_jC_l}\}^2
\]

\[
= \pi \mu_{A_jB_k}^2 + (1 - \pi) \mu_{A_jC_l}^2 - \{\pi \mu_{A_jB_k} + (1 - \pi) \mu_{A_jC_l}\}^2. \quad (3.3)
\]

Similarly for the second term,

\[
\text{Var}\{Y(A_jB_kC_l|R)\} = \text{Var}\{RY(A_jB_k) + (1 - R)Y(A_jC_l)|R\}
\]

\[
= E\{(RY(A_jB_k) + (1 - R)Y(A_jC_l))^2|R\}
- [RE\{Y(A_jB_k)|R\} + (1 - R)E\{Y(A_jC_l)|R\}]^2
\]

\[
= R[E\{Y(A_jB_k)^2|R\} + (1 - R)E\{Y(A_jC_l)^2|R\}]^2
- R[E\{Y(A_jB_k)^2|R\}]^2 - (1 - R)[E\{Y(A_jC_l)^2|R\}]^2.
\]

\[
= R(\sigma_{A_jB_k}^2 + \mu_{A_jB_k}^2) + (1 - R)(\sigma_{A_jC_l}^2 + \mu_{A_jC_l}^2)
- R\mu_{A_jB_k}^2 - (1 - R)\mu_{A_jC_l}^2,
\]

whose expected value is given by

\[
E[\text{Var}\{Y(A_jB_kC_l|R)\}] = \pi (\sigma_{A_jB_k}^2 + \mu_{A_jB_k}^2) + (1 - \pi)(\sigma_{A_jC_l}^2 + \mu_{A_jC_l}^2)
- \pi \mu_{A_jB_k} - (1 - \pi)\mu_{A_jC_l}^2. \quad (3.4)
\]

Then, by combining Eq. (3.3) and Eq. (3.4), the variance of \( \hat{\mu}^{URT}_{jkl} \) is

\[
\text{Var}(\hat{\mu}^{URT}_{jkl}) = \frac{1}{n_{jkl}} \left\{ \pi (\sigma_{A_jB_k}^2 + \mu_{A_jB_k}^2) + (1 - \pi)(\sigma_{A_jC_l}^2 + \mu_{A_jC_l}^2)
- \pi \mu_{A_jB_k} - (1 - \pi)\mu_{A_jC_l}^2 \right\}. \quad (3.5)
\]

When randomization is done with equal probability to 8 different strategies, then \( n_{jkl} \approx n/8 \) and the variance in Eq. (3.5) can be written as

\[
\frac{8}{n} \left\{ \pi (\sigma_{A_jB_k}^2 + \mu_{A_jB_k}^2) + (1 - \pi)(\sigma_{A_jC_l}^2 + \mu_{A_jC_l}^2)
- \pi \mu_{A_jB_k} + (1 - \pi)\mu_{A_jC_l}^2 \right\}. \quad (3.6)
\]

The variance of the estimator \( \hat{\mu}^{URT}_{jkl} \) can be estimated by the sample variance for individual groups.
3.3.2 Estimation with Inverse-probability-weighting in Sequentially Randomized Trials

SRT randomizes patients first into one of the two treatments \((A_1, A_2)\), then depending on the response, further randomizes to \(B\) or \(C\) treatments. Responders are randomized to \(B_1\) or \(B_2\) while non-responders to \(C_1\) or \(C_2\). Consider only patients who received \(A_j\) \((j=1\) or \(2)\). Using the idea of inverse-probability-weighting (IPW) (Robins et al. [1994]), an unbiased estimator for \(\mu_{jkl}\) can be expressed as the average of the weighted outcome of responders and non-responders as follows

\[
\hat{\mu}_{jkl}^{SRT} = \frac{1}{n_j} \sum_{i=1}^{n_j} \left\{ \frac{R_i I_i(B_k)}{P_k} + \frac{(1-R_i)I_i(C_l)}{Q_l} \right\} Y_i, \quad (3.7)
\]

where \(P_k\) and \(Q_l\) are the probability of the responders receiving \(B_k\) and non-responders receiving \(C_l\), respectively, and \(n_j\) is the number of patients assigned to \(A_j\) at the entry, i.e., \(n_j = \sum_{i=1}^{n} I_i(A_j)\). The fact that \(\hat{\mu}_{jkl}^{SRT}\) is unbiased can be shown by using the consistency assumption (Cole [2009]). In terms of the counterfactuals and the observed data, the consistency assumption can be written as

\[
Y_i = \sum_{i=1}^{n} I_i(A_j) \left\{ R_i \sum_{k=1}^{n} I_i(B_k) Y_i(A_j B_k) + (1-R_i) \sum_{l=1}^{n} I_i(C_l) Y_i(A_j C_l) \right\}. \quad (3.8)
\]

The consistency assumption states that a patient’s counterfactual outcome under a given strategy equals the observed outcome under treatment assignment consistent to the same strategy. Now, under Eq. (3.8), Eq. (3.7) can be written as

\[
\hat{\mu}_{jkl}^{SRT} = \frac{1}{n_j} \sum_{i=1}^{n_j} \left\{ \frac{R_i I_i(B_k)}{P_k} Y_i(A_j B_k) + \frac{(1-R_i)I_i(C_l)}{Q_l} Y_i(A_j C_l) \right\}. 
\]
Unbiasedness of this estimator can be shown by using the sequential randomization assumption as follows

\[
E[\hat{\mu}_{jkl}^{SRT}] = \frac{1}{n_j} \sum_{i=1}^{n_j} E \left[ \frac{R_i I_i(B_k)}{P_k} Y_i(A_j B_k) + \frac{(1 - R_i) I_i(C_l)}{Q_l} Y_i(A_j C_l) \right]
\]

\[
= \frac{1}{n_j} \sum_{i=1}^{n_j} \left[ \frac{1}{P_k} E \{ R_i Y_i(A_j B_k) E[I(B_k)|R_i, Y_i(A_j B_k)] \} + \frac{1}{Q_l} E \{ (1 - R_i) Y_i(A_j C_l) E[I(C_l)|R_i, Y_i(A_j C_l)] \} \right]
\]

\[
= \frac{1}{n_j} \sum_{i=1}^{n_j} \left[ \frac{1}{P_k} E [R_i Y_i(A_j B_k) P_k] + \frac{1}{Q_l} E [(1 - R_i) Y_i(A_j C_l) Q_l] \right]
\]

\[
= \frac{1}{n_j} \sum_{i=1}^{n_j} E[R_i Y_i(A_j B_k) + (1 - R_i) Y_i(A_j C_l)]
\]

\[
= \frac{1}{n_j} \sum_{i=1}^{n_j} E[Y_i(A_j B_k C_l)]
\]

\[= \mu_{jkl},\]

where the sequential randomization assumption was used from going to the third line from the second, which states that the probability of receiving a treatment given the history of the observed data does not depend on counterfactuals. In the case of receiving treatment \(B_k\), this assumption can be written as \(I_i(B_k) \perp \{Y_i(A_j B_k), Y_i(A_j C_l)\}|R_i\).

The variance of \(\hat{\mu}_{jkl}^{SRT}\) is obtained in a similar manner as \(\text{Var}(\hat{\mu}_{jkl}^{URT})\). Let \(\hat{\mu}_{jkl}^{SRT} = (1/n_j) \sum_{i=1}^{n_j} H_i\) where \(H_i = \{\{Y_i(A_j B_k)R_i I_i(B_k)\}/P_k + \{Y_i(A_j C_l)(1 - R_i) I_i(C_l)\}/Q_l\}.\) Then the variance of \(\hat{\mu}_{jkl}^{SRT}\) can be expressed as

\[\text{Var}(\hat{\mu}_{jkl}^{SRT}) = \frac{\text{Var}(H)}{n_j},\]

where \(H = \sum_{i=1}^{n} H_i\).

Now,

\[\text{Var}(H) = E \left[ \text{Var}\{H|R, Y(A_j B_k), Y(A_j C_l)\} \right] + \text{Var} \left[ E\{H|R, Y(A_j B_k), Y(A_j C_l)\}\right]. \quad (3.9)\]

Starting with the conditional variance,

\[\text{Var}(H|R, Y(A_j B_k), Y(A_j C_l)) = R(Y(A_j B_k))^2 \frac{(1 - P_k)}{P_k} + (1 - R)(Y(A_j C_l))^2 \frac{(1 - Q_l)}{Q_l}.\]

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The expected value of the conditional variance

\[
\text{E}\{\text{Var}(H|R, Y(A_jB_k), Y(A_jC_l))\} = \frac{R}{P_k} Y(A_jB_k) \text{E}\{I(B_k)|R, Y(A_jB_k)\}
+ \frac{(1-R)}{Q_l} Y(A_jC_l) \text{E}\{I(C_l)|R, Y(A_jC_l)\}
= RY(A_jB_k) + (1-R)Y(A_jC_l)
= Y(A_jB_kC_l),
\]
the variance of which is

\[
\text{Var}[\text{E}(H|R, Y(A_jB_k), Y(A_jC_l))] = \pi (\sigma^2_{A_jB_k} + \mu^2_{A_jB_k}) + (1-\pi)(\sigma^2_{A_jC_l} + \mu^2_{A_jC_l})
- \left(\pi \mu_{A_jB_k} + (1-\pi)\mu_{A_jC_l}\right)^2. \tag{3.11}
\]

By combining Eq. (3.10) and Eq. (3.11) together, the overall variance of \(\hat{\mu}_{jkl}^{SRT}\) is

\[
\text{Var}(\hat{\mu}_{jkl}^{SRT}) = \frac{1}{n_j} \left[ \pi (\sigma^2_{A_jB_k} + \mu^2_{A_jB_k}) \frac{(1-P_k)}{P_k}
+ (1-\pi)(\sigma^2_{A_jC_l} + \mu^2_{A_jC_l}) \frac{(1-Q_l)}{Q_l}
+ \pi (\sigma^2_{A_jB_k} + \mu^2_{A_jB_k}) + (1-\pi)(\sigma^2_{A_jC_l} + \mu^2_{A_jC_l})
- \left\{\pi \mu_{A_jB_k} + (1-\pi)\mu_{A_jC_l}\right\}^2 \right]
= \frac{1}{n_j} \left[ \pi (\sigma^2_{A_jB_k} + \mu^2_{A_jB_k}) \frac{1}{P_k}
+ (1-\pi)(\sigma^2_{A_jC_l} + \mu^2_{A_jC_l}) \frac{1}{Q_l}
- \left\{\pi \mu_{A_jB_k} + (1-\pi)\mu_{A_jC_l}\right\}^2 \right]. \tag{3.12}
\]
For the equal probability of the maintenance treatment (i.e. \( P_k = Q_l = 1/2 \)), the variance of the estimator is

\[
\text{Var}(\hat{SRT}_{jkl}) = \frac{1}{n_j} \left[ 2 \left\{ \pi(\sigma^2_{A_jB_k} + \mu^2_{A_jB_k}) + (1 - \pi)(\sigma^2_{A_jC_l} + \mu^2_{A_jC_l}) \right\} - \left\{ \pi \mu_{A_jB_k} + (1 - \pi) \mu_{A_jC_l} \right\}^2 \right]
\]

### 3.3.3 Estimation with Probability-adjusted-weights in Sequentially Randomized Trials

Another estimator commonly used in SRT is the probability-adjusted inverse-probability-weighted estimator (Lunceford et al. [2002]). We will call this estimator as the probability-adjusted estimator, thereafter. The probability-adjusted estimator is expressed as

\[
\hat{\mu}_{jkl}^{\text{SRTPA}} = \left[ \sum_{i=1}^{n_j} \left\{ \frac{R_i I_i(B_k)}{P_k} + \frac{(1 - R_i) I_i(C_l)}{Q_l} \right\} \right]^{-1} \sum_{i=1}^{n_j} \left\{ \frac{R_i I_i(B_k)}{P_k} + \frac{(1 - R_i) I_i(C_l)}{Q_l} \right\} Y_i
\]

\[
= \sum_{i=1}^{n_j} W_{ki} Y_i + \sum_{i=1}^{n_j} W_{li} Y_i
\]

\[
= G_{nk} + G_{nl},
\]

where

\[
W_{ki} = \frac{Q_l R_i I_i(B_k)}{Q_l \sum_{i=1}^{n_j} R_i I_i(B_k) + P_k \sum_{i=1}^{n_j} (1 - R_i) I(C_l)},
\]

and

\[
W_{li} = \frac{P_k (1 - R_i) I_i(C_l)}{P_k \sum_{i=1}^{n_j} R_i I_i(C_l) + Q_l \sum_{i=1}^{n_j} (1 - R_i) I(B_k)}.
\]

Note that

\[
\text{E}\{W_{ki} | R_i, Y(A_jB_k)\} \approx \frac{Q_l R_i P_k}{Q_l P_k \sum_{i=1}^{n_j} R_i + Q_l P_k \sum_{i=1}^{n_j} (1 - R_i)} \approx \frac{R_i}{n_j}.
\]

Therefore, \( \text{E}(W_{ki}) \approx \pi/n_j \) and similarly, \( \text{E}(W_{li}) \approx (1 - \pi)/n_j \).

Unbiasedness of this estimator is shown as follows. We can write

\[
\text{E}(\hat{\mu}_{jkl}^{\text{SRTPA}}) = \text{E}(G_{nk}) + \text{E}(G_{nl}). \tag{3.13}
\]
For the first part of Eq. (3.13),

\[
E(G_{nk}) = E \left( \sum_{i=1}^{n_j} W_{ki} Y_i \right) \quad \text{(By consistency assumption)}
\]

\[
= E \left\{ \sum_{i=1}^{n_j} W_{ki} Y_i (A_j B_k) \right\}
\]

\[
= E \left[ \sum_{i=1}^{n_j} Y_i (A_j B_k) E \{ W_{ki} | R_i, Y_i (A_j B_k) \} \right]
\]

\[
\approx E \left\{ \sum_{i=1}^{n_j} \frac{R_i}{n_j} Y_i (A_j B_k) \right\}
\]

\[
= \frac{1}{n_j} \sum_{i=1}^{n_j} E \{ R_i E \{ Y_i (A_j B_k) | R_i \} \}
\]

\[
= \frac{1}{n_j} \sum_{i=1}^{n_j} \mu_{A_j B_k}
\]

\[
= \pi \mu_{A_j B_k}.
\]

Similarly, \(E(G_{nl}) = (1 - \pi) \mu_{A_j C_l}\). Then we have

\[
E(\hat{\mu}_{jkl}^{\text{SRTPA}}) = \pi \mu_{A_j B_k} + (1 - \pi) \mu_{A_j C_l} = \mu_{A_j B_k C_l}.
\]

To derive the variance of \(\hat{\mu}_{jkl}^{\text{SRTPA}}\), we note that

\[
\text{Var}(\hat{\mu}_{jkl}^{\text{SRTPA}}) = \text{Var}(G_{nk}) + \text{Var}(G_{nl}) + 2\text{cov}(G_{nk}, G_{nl}). \quad (3.14)
\]

Consider the first part of the Eq. (3.14) first,

\[
\text{Var}(G_{nk}) = \text{Var} \left( \sum_{i=1}^{n_j} W_{ki} Y_i \right)
\]

\[
= \text{Var} \left\{ \sum_{i=1}^{n_j} W_{ki} Y_i (A_j B_k) \right\}
\]

\[
= \sum_{i=1}^{n_j} \text{Var} \{ W_{ki} Y_i (A_j B_k) \}.
\]
Then,

\[
\text{Var}\{W_{ki}Y_i(A_j B_k)\} = \text{Var}\{\text{E}\{W_{ki}Y_i(A_j B_k)\|R_i, Y_i(A_j B_k)\}\} \\
+ \text{E}\{\text{Var}\{W_{ki}Y_i(A_j B_k)\|R_i, Y_i(A_j B_k)\}\} \\
\approx \text{E}\left\{\left(\frac{R_i Y_i(A_j B_k)}{n_j}\right)^2\right\} - \text{E}\left\{\frac{R_i Y_i(A_j B_k)}{n_j}\right\}^2 \\
+ \text{E}[Y_i^2(A_j B_k)\text{Var}\{W_{ki}\|R_i, Y_i(A_j B_k)\}].
\]

The conditional variance of $W_{ki}$ can be approximated as

\[
\text{Var}\{W_{ki}\|R_i, Y_i(A_j B_k)\} \approx \text{E}\{W_{ki}^2\|R_i, Y_i(A_j B_k)\} - \frac{R_i}{n_j^2} \\
\approx \text{E}\left[\frac{R_i I_i(B_k)Q_i^2/n_j^2}{\left\{Q_i\sum \frac{R_i I_i(B_k)Q_i^2/n_j^2}{P_k} + P_k\sum (1-R_i)I_i(C_i)\right\}^2} - \frac{R_i}{n_j^2}\right] \\
\approx \text{E}\left[\frac{R_i I_i(B_k)Q_i^2/n_j^2}{\left\{Q_i\pi P_k + P_k(1-\pi)Q_i\right\}^2} - \frac{R_i}{n_j^2}\right] \\
\approx \frac{R_i}{n_j^2} \left(1 - \frac{R_i}{P_k}\right). \\
\]

Therefore,

\[
\text{Var}\{W_{ki}Y_i(A_j B_k)\} \approx \frac{1}{n_j^2} \left\{\pi(\sigma_{A_j B_k}^2 + \mu_{A_j B_k}^2) - \pi^2 \mu_{A_j B_k}^2\right\} \\
+ \text{E}\left\{Y_i^2(A_j B_k) \frac{1 - P_k}{P_k}\right\} \\
\approx \frac{1}{n_j^2} \left\{\pi(\mu_{A_j B_k}^2) - \pi^2 \mu_{A_j B_k}^2\right\} \\
+ \frac{1}{n_j^2} \left\{\left(\frac{1 - P_k}{P_k}\right)\pi(\sigma_{A_j B_k}^2 + \mu_{A_j B_k}^2)\right\} \\
= \frac{\pi}{n_j^2} \left\{\left(\frac{1 - P_k}{P_k}\right)\left(\sigma_{A_j B_k}^2 + \mu_{A_j B_k}^2\right) - \pi^2 \mu_{A_j B_k}^2\right\} \\
= \frac{\pi}{n_j^2} \left\{\frac{1}{P_k}(\sigma_{A_j B_k}^2 + \mu_{A_j B_k}^2) - \pi^2 \mu_{A_j B_k}^2\right\}.
\]
Similarly,\[
\text{Var}\{W_i Y(A_j C_i)\} \approx \frac{1 - \pi}{n_j^2} \left\{ \frac{1}{Q_l} (\sigma^2_{A_j C_i} + \mu^2_{A_j C_i}) - (1 - \pi)\mu^2_{A_j C_i} \right\}.
\]

For the covariance term,\[
\text{Cov}(G_{nk}, G_{nl}) = \text{E}(G_{nk}, G_{nl}) - \text{E}(G_{nk})\text{E}(G_{nl})
\]
\[
= \text{E} \sum_{i=1}^{n_j} \sum_{j=i}^{n_j} (W_{ki}W_{lj}Y_iY_j) - \pi \mu_{A_j B_k} (1 - \pi) \mu_{A_j C_i}
\]
\[
= \frac{n_j(n_j - 1)}{n_j^2} \{\pi \mu_{A_j B_k} (1 - \pi) \mu_{A_j C_i} \} - \pi \mu_{A_j B_k} (1 - \pi) \mu_{A_j C_i}
\]
\[
= - \frac{1}{n_j} \pi \mu_{A_j B_k} (1 - \pi) \mu_{A_j C_i}.
\]

Therefore, the variance for probability-adjusted SRT is
\[
\text{Var}(\hat{\mu}^{\text{SRTPA}}_{jkl}) \approx \frac{1}{n_j} \left\{ \frac{\pi}{F_k} (\sigma^2_{A_j B_k} + \mu^2_{A_j B_k}) + \frac{(1 - \pi)}{Q_l} (\sigma^2_{A_j C_i} + \mu^2_{A_j C_i})
\]
\[
- \left( \pi \mu_{A_j B_k} + (1 - \pi) \mu_{A_j C_i} \right)^2 \right\}. \tag{3.15}
\]

For the equal probability of the maintenance treatment, the variance of the estimator is
\[
\text{Var}(\hat{\mu}^{\text{SRTPA}}_{jkl}) \approx \frac{1}{n_j} \left\{ 2 \left( \pi (\sigma^2_{A_j B_k} + \mu^2_{A_j B_k}) + (1 - \pi) (\sigma^2_{A_j C_i} + \mu^2_{A_j C_i}) \right)
\]
\[
- \left( \pi \mu_{A_j B_k} + (1 - \pi) \mu_{A_j C_i} \right)^2 \right\}.
\]

From Eq. (3.12) and Eq. (3.15), we see that, for sufficiently large \( n \), the variance of the IPW and probability-adjusted estimators have the same variance. Therefore, when comparing SRT to URT, we will use the probability-adjusted estimator. The variance in Eq. (3.15) can be estimated by replacing the parameters with the corresponding sample estimates. For example,
\[
\hat{\sigma}^2_{A_j B_k} = \frac{\sum_{i=1}^{n_j} I(B_k) \left\{ Y - \frac{\sum_{i=1}^{n_j} I(B_k) Y}{\sum_{i=1}^{n_j} I(B_k)} \right\}}{\sum_{i=1}^{n_j} I(B_k) - 1}.
\]
An analogous estimator can be used for $\hat{\sigma}_A^2$. Instead of estimating sample variances individually, we use the fact that estimators ($\hat{\mu}_{jkl}^{SRT}$ and $\hat{\mu}_{jkl}^{SRTPA}$) are the solutions to the estimating equations

$$\sum_{i=1}^{n} \psi_i(\hat{\mu}_{jkl}^{SRT}) = \sum_{i=1}^{n_j} \left[ \left\{ \frac{R_i I_i(B_k)}{P_k} + \frac{(1 - R_i)I_i(C_{kl})}{Q_l} \right\} Y_i - \mu_{jkl}^{SRT} \right] = 0,$$

and

$$\sum_{i=1}^{n} \psi_i(\hat{\mu}_{jkl}^{SRTPA}) = \sum_{i=1}^{n_j} \left[ \left\{ \frac{R_i I_i(B_k)}{P_k} + \frac{(1 - R_i)I_i(C_{kl})}{Q_l} \right\} (Y_i - \mu_{jkl}^{SRTPA}) \right] = 0,$$

respectively. Then, the variances could be estimated by so-called sandwich variance estimator.

$$\text{var}(\hat{\mu}_{jkl}^{SRT}) = \left( \frac{1}{n_j} \right) \frac{B(\hat{\mu}_{jkl}^{SRT})}{A(\hat{\mu}_{jkl}^{SRT})^2},$$

where $A_n(x)$ is the empirical estimate of $A(x) = -\mathbb{E} \left[ \frac{\partial}{\partial \mu} \{ \psi_i(\mu) \} \right] |_{\mu=x} = 1$ and $B_n(x) = \sum \psi_i^2(x) / n_j$. Similarly, $\text{Var}(\hat{\mu}_{jkl}^{SRTPA})$ also can be estimated.

The covariance of the two estimators can be estimated in a similar manner. For example, for $\hat{\mu}_{111}$ and $\hat{\mu}_{112}$, the covariance is

$$\text{cov}(\hat{\mu}_{111}^{SRT}, \hat{\mu}_{112}^{SRT}) = n_1^{-2} \sum \psi_i(\hat{\mu}_{111}^{SRT}) \psi_i(\hat{\mu}_{112}^{SRT}).$$
3.3.4 Hypothesis Testing

To test hypotheses regarding the strategy-specific means, we construct test statistics based on Wald-type tests. For example, to test the difference among $\mu_{111}$, $\mu_{112}$, $\mu_{121}$ and $\mu_{122}$, constructed test statistic as follows:

$$\hat{\mu} = \begin{bmatrix} \hat{\mu}_{111} & \hat{\mu}_{112} & \hat{\mu}_{121} & \hat{\mu}_{122} \end{bmatrix}$$

$$C = \begin{bmatrix} 1 & 0 & -1 & 0 \\ 0 & 1 & 0 & -1 \\ 1 & -1 & 0 & 0 \end{bmatrix}$$

$$\Sigma = \begin{bmatrix}
\text{var}(\hat{\mu}_{111}) & \text{cov}(\hat{\mu}_{111}, \hat{\mu}_{112}) & \text{cov}(\hat{\mu}_{111}, \hat{\mu}_{121}) & \text{cov}(\hat{\mu}_{112}, \hat{\mu}_{122}) \\
\text{cov}(\hat{\mu}_{112}, \hat{\mu}_{111}) & \text{var}(\hat{\mu}_{112}) & \text{cov}(\hat{\mu}_{112}, \hat{\mu}_{121}) & \text{cov}(\hat{\mu}_{112}, \hat{\mu}_{122}) \\
\text{cov}(\hat{\mu}_{121}, \hat{\mu}_{111}) & \text{cov}(\hat{\mu}_{121}, \hat{\mu}_{112}) & \text{var}(\hat{\mu}_{121}) & \text{cov}(\hat{\mu}_{121}, \hat{\mu}_{122}) \\
\text{cov}(\hat{\mu}_{122}, \hat{\mu}_{111}) & \text{cov}(\hat{\mu}_{122}, \hat{\mu}_{112}) & \text{cov}(\hat{\mu}_{122}, \hat{\mu}_{121}) & \text{var}(\hat{\mu}_{122})
\end{bmatrix}$$

$$Z^2 = \hat{\mu}^T \times \hat{C}^T \times [\hat{C} \times \Sigma \times \hat{C}^T]^{-1} \times \hat{C} \times \hat{\mu},$$

where $T$ stands for transpose of a matrix. This statistic can be approximated by a $\chi^2$ distribution with 3 degree of freedom under the null hypothesis of no difference. Similarly, test statistics for other hypotheses testing can be constructed.

3.4 SIMULATION STUDY

The true population in the simulation can be described in terms of the distribution of counterfactual variables. For each individual $i$ in the population, assume that $Y_i(A_jB_k)$ and $Y_i(A_jC_l)$ are individually normally distributed with mean $\mu_{A_jB_k}$ and variance $\sigma_{A_jB_k}^2$, and mean $\mu_{A_jC_l}$ and variance $\sigma_{A_jC_l}^2$ respectively, $j, k, l = 1, 2$. The response indicator $R_i$ was assumed to follow a Bernoulli distribution with probability of success $\pi_{R_1}$ for the initial treatment $A_1$ and $\pi_{R_2}$ for $A_2$. 

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We repeatedly (1000) sampled data from this population by using two forms of designs. In the URT design, $n$ individuals are randomized with equal probability to 8 different strategies $A_1B_1C_1,A_1B_1C_2,\ldots,A_2B_2C_2$. In the SRT, we randomized $n$ patients first to two induction treatments $A_1$ and $A_2$ with probabilities $\pi_{A_1}$ and $\pi_{A_2}$ respectively ($\pi_{A_1}+\pi_{A_2}=1$). For simplicity, we use $\pi_A=\pi_{A_1}=\pi_{A_2}=1/2$, throughout the study. In both designs, the observed outcome was generated from the counterfactual distributions using the formula (3.8). The response status $R_i$ for the $i^{th}$ patient was generated according to a Bernoulli distribution with probability of success $\pi$. When $R_i=1$, we randomly assigned the patient to $B_1(B_2)$ with probability $P_1(P_2)$ ($P_1+P_2=1$). Similarly, patients with $R_i=0$ where randomized to $C_1(C_2)$ with probability $Q_1(Q_2)$ ($Q_1+Q_2=1$).

We considered many different simulation scenarios by varying the values of population parameters $\mu_{A_1B_k}$, $\sigma_{A_1B_k}^2$, $\mu_{A_2C_l}$, $\sigma_{A_2C_l}^2$, $\pi_{R_1}$, $\pi_{R_2}$, $P_k$ and $Q_l$, $j, k, l = 1, 2$. On the other hand, the first treatment assignment probability, $\pi_A$ is set to $1/2$ for all scenarios. Therefore, number of samples for both first treatments $A_1$ and $A_2$ are equal.

The first four scenarios represented here assumes that $\mu_{A_1B_k}=\mu_{A_2C_l}=15$, $j, k, l = 1, 2$, and $\sigma_{A_1B_k}^2 = 6$, $j, k = 1, 2$, and $\sigma_{A_2C_l}^2 = 8$, $j, l = 1, 2$. In these situations, the eight strategy means are all equal to 15, i.e., $\mu_{A_1B_1C_1} = \mu_{A_1B_1C_2} = \mu_{A_1B_2C_1} = \mu_{A_1B_2C_2} = \mu_{A_2B_1C_1} = \mu_{A_2B_1C_2} = \mu_{A_2B_2C_1} = \mu_{A_2B_2C_2} = 15$. In our first simulation scenario, we assumed $\pi_{R_1} = \pi_{R_2} = P_1 = Q_1 = 1/2$. Then $\pi_{R_1}$ and $\pi_{R_2}$ are adjusted to see the change for other scenarios.

Table 1 summarizes the results of the simulation under designs from scenario 1-4, where all the strategy means are identical. The table lists the estimated strategy-specific means (Est.), Monte Carlo standard error (SE), and the relative bias (RB %). It also provides the coverage probability (CP) of 95% confidence interval based on normality assumptions.

In addition, the table provides type I error rates for testing three hypotheses, namely $H_1$: strategy means are identical for strategies sharing the same first stage treatment $A_1$ ($\mu_{A_1B_1C_1} = \mu_{A_1B_1C_2} = \mu_{A_1B_2C_1} = \mu_{A_1B_2C_2}$), $H_2$: strategy means are identical for strategies sharing the same first stage treatment $A_2$ ($\mu_{A_2B_1C_1} = \mu_{A_2B_1C_2} = \mu_{A_2B_2C_1} = \mu_{A_2B_2C_2}$) and $H_3$: strategy means are identical for all strategies ($H_3$ : $\mu_{A_1B_1C_1} = \mu_{A_1B_1C_2} = \mu_{A_1B_2C_1} = \mu_{A_1B_2C_2} = \mu_{A_2B_1C_1} = \mu_{A_2B_1C_2} = \mu_{A_2B_2C_1} = \mu_{A_2B_2C_2}$).

From the results in Table 1, we see that both URT and SRT produce unbiased estima-
tors of strategy means under the same sample size. Absolute relative biases were less than 0.7% for URT estimator and less than 0.5% for probability-adjusted estimator from the SRT. Standard errors of estimators are generally larger for the URT estimators as compared to the probability-adjusted estimator. In most cases, URT estimator fails to meet nominal coverage level for the 95% Wald confidential interval. On the other hand, probability-adjusted estimator provides coverage probabilities close to the nominal level. In most cases, rejection rates for the true null hypothesis match the nominal type I error rate of 5% for the probability-adjusted estimator in the SRT design, whereas for URT, the observed type I error rate were always larger than the nominal level. This was true irrespectively of the hypotheses being tested. And adjusting response rate does not change the results.

In the next four scenarios, we assume that \( \mu_{A_jB_1} = 15, \mu_{A_jC_1} = 20, \mu_{A_jB_2} = 22, \mu_{A_jC_2} = 15, \) \( j=1,2, \) and \( \sigma^2_{A_jB_k} = 6, j,k=1,2, \) and \( \sigma^2_{A_jC_l} = 8, j,l=1,2 \) to test alternative hypothesis that all strategies have different means. In Tables 2(a) and 2(b), we assume that \( \pi_{R_1} = \pi_{R_2} = P_1 = Q_1 = 1/2 \) with sample sizes 150 and 200, respectively. In the next two scenarios (Tables 2(c) and 2(d)), response rates, \( \pi_{R_1} \) and \( \pi_{R_2} \) are adjusted to 0.1, 0.5 and 0.8 with \( n = 200. \)

Table 2 provides the powers for testing hypotheses to detect mean difference in addition to estimated strategy-specific means (Est.), MC standard error (SE), the relative bias (RB %) and the coverage probability (CP) of 95% confidence interval. Here, we use the same three hypotheses defined in Table 1. As can be seen from Table 2, both estimators are approximately unbiased. Relative biases were less than 0.8% for URT estimator and less than 0.6% for probability-adjusted estimator from the SRT. Standard errors of probability-adjusted estimator in SRT are smaller than the estimator in URT. And the probability-adjusted estimator in SRT achieves the nominal level of coverage probabilities and almost over 95% of power of the hypothesis to detect mean difference while coverage probabilities of the estimator in URT are less than the nominal level and its power is about 70%. Similar to the Table 1, adjusting response rate does not change the results. We note that both show better performance, such as smaller relative bias, smaller standard errors, smaller power and higher coverage probabilities with larger sample size.

Table 3 shows how the proportions of treatment assignment of \( B_k \) or \( C_l \) affect the estimates. Small probability of receiving \( B_k \) (i.e., \( P_k \leq 0.5 \)) makes the variance of the \( \hat{\mu}_{j1k} \) larger.
and large proportion of receiving $B_k$ (i.e., $P_k \geq 0.5$) makes the variance of $\mu_{j2k}$ larger. This is analogous to the $Q_l$. From this scenario, we note that the probability-adjusted estimators in SRT for $B_k$ have smaller standard errors when $P_k > 0.5$ during the simulation study. This applied to the $C_l$ with $Q_l$ similarly.

Overall, the simulation studies showed that the both estimators are approximately unbiased. The performance of the probability-adjust estimator in SRT was better than the estimator in URT in terms of unbiasedness, efficiency and power.

### 3.5 DISCUSSION

In this chapter, we have compared the estimators in up-front and sequential randomization trials using a statistical inferential approach. The estimator in URT can be obtained directly. For SRT, we employed the IPW estimator (Robins et al. [1994]) and the probability-adjusted estimator (Lunceford et al. [2002]). Using the sequential randomization assumption, we showed unbiasedness of estimators. Our simulation results indicated that all estimators are approximately unbiased. However, the probability-adjusted estimator in SRT has smaller standard errors and higher power than the estimator in URT. During this study, we also noted that the efficiency of the estimators could be related to the maintenance treatment proportion. Because the assigned sample size for a specific treatment strategy is affected by this proportion. In conclusion, the probability-adjusted estimator in sequential randomized trial performed better than the estimator in up-front randomized trial in terms of efficiency of the estimators and the power of statistical hypothesis testing.
Table 1: Simulation results of estimation with the same means

(a) $n = 150$, $\pi_A = 0.5$, $\pi_{R1} = 0.5$, $\pi_{R2} = 0.5$, $P_k = 0.5$, $Q_l = 0.5$

<table>
<thead>
<tr>
<th>Policy</th>
<th>Estimator in SRT</th>
<th>Probability-adjusted estimator in SRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Est.</td>
<td>SE</td>
</tr>
<tr>
<td>$A_1B_1C_1$ 15.0</td>
<td>15.0</td>
<td>1.42</td>
</tr>
<tr>
<td>$A_1B_2C_2$ 15.0</td>
<td>14.9</td>
<td>1.42</td>
</tr>
<tr>
<td>$A_2B_2C_3$ 15.0</td>
<td>15.0</td>
<td>1.41</td>
</tr>
<tr>
<td>$A_1B_2C_2$ 15.0</td>
<td>15.0</td>
<td>1.41</td>
</tr>
<tr>
<td>$A_2B_1C_1$ 15.0</td>
<td>15.0</td>
<td>1.76</td>
</tr>
<tr>
<td>$A_2B_1C_2$ 15.0</td>
<td>15.0</td>
<td>1.76</td>
</tr>
<tr>
<td>$A_2B_2C_3$ 15.0</td>
<td>15.0</td>
<td>1.77</td>
</tr>
<tr>
<td>$A_2B_2C_3$ 15.0</td>
<td>15.0</td>
<td>1.76</td>
</tr>
</tbody>
</table>

|          |          | 0.057$^3$ | 0.053$^4$ |

(b) $n = 150$, $\pi_A = 0.5$, $\pi_{R1} = 0.1$, $\pi_{R2} = 0.5$, $P_k = 0.5$, $Q_l = 0.5$

<p>| | | | |</p>
<table>
<thead>
<tr>
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<th></th>
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</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(c) $n = 150$, $\pi_A = 0.5$, $\pi_{R1} = 0.5$, $\pi_{R2} = 0.9$, $P_k = 0.5$, $Q_l = 0.5$

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<table>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(d) $n = 150$, $\pi_A = 0.5$, $\pi_{R1} = 0.2$, $\pi_{R2} = 0.9$, $P_k = 0.5$, $Q_l = 0.5$

<p>| | | | |</p>
<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

$^1H_1 : \mu_{A_1B_1C_1} = \mu_{A_1B_1C_2} = \mu_{A_1B_2C_1} = \mu_{A_1B_2C_2} = \mu_{A_2B_2C_1} = \mu_{A_2B_2C_2}$

$^2H_2 : \mu_{A_2B_1C_1} = \mu_{A_2B_1C_2} = \mu_{A_2B_2C_1} = \mu_{A_2B_2C_2}$

$^3H_3 : \mu_{A_1B_1C_1} = \mu_{A_1B_1C_2} = \mu_{A_1B_2C_1} = \mu_{A_1B_2C_2} = \mu_{A_2B_2C_1} = \mu_{A_2B_2C_2}$
Table 2: Simulation results of estimation with the different means

(a) $n = 150$, $\pi_A = 0.5$, $\pi_{R1} = 0.5$, $\pi_{R2} = 0.5$, $P_k = 0.5$, $Q_l = 0.5$

<table>
<thead>
<tr>
<th>Policy</th>
<th>True</th>
<th>Est.</th>
<th>SE</th>
<th>RB(%)</th>
<th>CP</th>
<th>Power</th>
<th>Est.</th>
<th>SE</th>
<th>RB(%)</th>
<th>CP</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1B_1C_1$</td>
<td>17.5</td>
<td>17.5</td>
<td>1.94</td>
<td>0.1</td>
<td>0.88</td>
<td>17.6</td>
<td>1.47</td>
<td>-0.6</td>
<td>0.91</td>
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<td>0.91</td>
<td>15.1</td>
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<td>0.93</td>
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<td>2.03</td>
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<td>1.39</td>
<td>0.1</td>
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<tr>
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(b) $n = 200$, $\pi_A = 0.5$, $\pi_{R1} = 0.5$, $\pi_{R2} = 0.5$, $P_k = 0.5$, $Q_l = 0.5$

<table>
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<tr>
<th>Policy</th>
<th>True</th>
<th>Est.</th>
<th>SE</th>
<th>RB(%)</th>
<th>CP</th>
<th>Power</th>
<th>Est.</th>
<th>SE</th>
<th>RB(%)</th>
<th>CP</th>
<th>Power</th>
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<td>17.5</td>
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<td>1.05</td>
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<td>15.0</td>
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<td>0.94</td>
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<td></td>
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<td>$A_2B_2C_1$</td>
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<td>0.92</td>
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<td>18.5</td>
<td>1.68</td>
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<td>1.11</td>
<td>0.1</td>
<td>0.94</td>
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(c) $n = 200$, $\pi_A = 0.5$, $\pi_{R1} = 0.5$, $\pi_{R2} = 0.8$, $P_k = 0.5$, $Q_l = 0.5$

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<th>Policy</th>
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<th>SE</th>
<th>RB(%)</th>
<th>CP</th>
<th>Power</th>
<th>Est.</th>
<th>SE</th>
<th>RB(%)</th>
<th>CP</th>
<th>Power</th>
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<tbody>
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<td>17.5</td>
<td>1.05</td>
<td>-0.1</td>
<td>0.94</td>
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<td>15.1</td>
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<td>0.91</td>
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<td>0.93</td>
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<td>-0.1</td>
<td>0.95</td>
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</tr>
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<td>15.0</td>
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<td>-0.0</td>
<td>0.94</td>
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<td>0.95</td>
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<td>0.99</td>
<td>0.1</td>
<td>0.95</td>
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</table>

(d) $n = 200$, $\pi_A = 0.5$, $\pi_{R1} = 0.1$, $\pi_{R2} = 0.5$, $P_k = 0.5$, $Q_l = 0.5$

<table>
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<tr>
<th>Policy</th>
<th>True</th>
<th>Est.</th>
<th>SE</th>
<th>RB(%)</th>
<th>CP</th>
<th>Power</th>
<th>Est.</th>
<th>SE</th>
<th>RB(%)</th>
<th>CP</th>
<th>Power</th>
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<tbody>
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<td>1.53</td>
<td>0.5</td>
<td>0.93</td>
<td>15.0</td>
<td>1.10</td>
<td>0.3</td>
<td>0.94</td>
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</tr>
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<td>-0.1</td>
<td>0.94</td>
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<td>$A_1B_2C_2$</td>
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<tr>
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<td>17.6</td>
<td>1.27</td>
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</table>

1 $H_1$: $\mu_{A_1B_1C_1} = \mu_{A_1B_1C_2} = \mu_{A_1B_2C_1} = \mu_{A_1B_2C_2}$, $H_2$: $\mu_{A_2B_1C_1} = \mu_{A_2B_1C_2} = \mu_{A_2B_2C_1} = \mu_{A_2B_2C_2}$, $H_3$: $\mu_{A_3B_1C_1} = \mu_{A_3B_1C_2} = \mu_{A_3B_2C_1} = \mu_{A_3B_2C_2}$
Table 3: Simulation results of estimation by adjusting probability of maintenance treatment

\( n = 200, \pi_A = 0.5, \pi_{R1} = \pi_{R2} = 0.5, P_k = 0.9, Q_t = 0.5 \)

<table>
<thead>
<tr>
<th>Policy</th>
<th>True</th>
<th>Est.</th>
<th>SE</th>
<th>RB(%)</th>
<th>CP</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( A_1B_1C_1 )</td>
<td>17.5</td>
<td>17.5</td>
<td>1.51</td>
<td>0.2</td>
<td>0.95</td>
<td>17.5</td>
</tr>
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<td>0.95</td>
<td>15.0</td>
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<tr>
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<td>21.0</td>
<td>21.0</td>
<td>1.42</td>
<td>-0.2</td>
<td>0.92</td>
<td>21.0</td>
</tr>
<tr>
<td>( A_1B_2C_2 )</td>
<td>18.5</td>
<td>18.5</td>
<td>1.58</td>
<td>-0.2</td>
<td>0.94</td>
<td>18.3</td>
</tr>
<tr>
<td>( A_2B_1C_1 )</td>
<td>17.5</td>
<td>17.5</td>
<td>1.60</td>
<td>-0.3</td>
<td>0.94</td>
<td>17.5</td>
</tr>
<tr>
<td>( A_2B_1C_2 )</td>
<td>15.0</td>
<td>15.0</td>
<td>1.52</td>
<td>0.3</td>
<td>0.94</td>
<td>15.1</td>
</tr>
<tr>
<td>( A_2B_2C_1 )</td>
<td>21.0</td>
<td>21.0</td>
<td>1.52</td>
<td>-0.2</td>
<td>0.93</td>
<td>21.0</td>
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<tr>
<td>( A_2B_2C_2 )</td>
<td>18.5</td>
<td>18.5</td>
<td>1.68</td>
<td>0.1</td>
<td>0.93</td>
<td>18.4</td>
</tr>
</tbody>
</table>

Estimator in URT

0.721

0.753

0.855

Power

0.969

26
4.0 NONPARAMETRIC INFERENCE ON MEDIAN RESIDUAL LIFE FUNCTION IN SEQUENTIALLY RANDOMIZED TRIALS

4.1 INTRODUCTION

Sequentially randomized trials (SRT) are effective methods for comparing ATSs. In SRT, patients are randomized sequentially to treatment options as the trial progresses and patients move from one stage to another.

Figure 2: An example of Sequentially Randomization Trial from Cancer and Leukemia group B

Figure 2 shows an example of SRT with two stages, drawn from a leukemia study protocol from CALGB co-operative group. At entry, patients are randomized to one of the two first-stage treatments standard chemotherapy($A_1$) or standard chemotherapy plus granulocyte-macrophage colony-stimulating factor(GM-CSF)($A_2$). Once the patient achieves complete
In remission, he/she is randomized to the second-stage treatments cytrabine($B_1$) or cytrabine plus mitoxantrone($B_2$). This SRT allows comparison of 4 treatment strategies $A_jB_k$, $j, k = 1, 2$, where the strategy $A_jB_k$ is defined as “Treat with $A_j$ followed by $B_k$ if a response to $A_j$ is observed” ([Lunceford et al. [2002]]). Note that a patient belonging to any of the following scenarios is considered to be treated with strategy $A_jB_k$ (consistent with strategy $A_jB_k$) :

1. Patient received $A_j$, and did not respond.
2. Patient received $A_j$, responded, and received $B_k$ at the second stage.

The objective would be to assess which of these four strategies $A_jB_k$, $j, k = 1, 2$ results in the best benefit for the patients. In survival analysis, the best benefit would be measured by longest survival time. The sample mean is the most common statistics in terms of summarizing the survival distributions. Survival probabilities at a fixed point of time or median survival are also used to summarize the data.

The estimation of mean survival time in SRT, especially in two-stage design, has been discussed extensively in the literature. Lunceford et al. [2002] proposed estimators for the survival distribution and mean restricted survival time under different treatment strategies using the concept of inverse-probability-weighting (IPW) ([Robins et al. [1994]]). Locally efficient estimators for survival distribution in two-stage design settings were introduced by Wahed and Tsiatis [2004], Wahed et al. [2006] for complete and right censored cases. The improvement in efficiency of these estimators was achieved through the use of additional information from auxiliary covariates. Guo [2005] proposed a weighted risk set estimator (WRSE) for the survival distribution. Even though the sample mean is the most commonly used index to summarize a distribution, this may not be a good summary representative of the overall distribution when the data are highly skewed. In such a case, percentiles can be a good index outlining the distribution instead of means.

In addition to percentile of the distribution (including median), the median residual life function (MERL function) is frequently used for the time-to-event data. A MERL function is the median of the remaining life time at a specific time point. For overall survival $T$, the median residual lifetime at time $t_0$ is defined as

$$\theta(t_0) = \text{median}(T - t_0 | T \geq t_0),$$
where \( \text{median}(X|Y) \) stands for the median of the conditional distribution of \( X \) given \( Y \). In other words, \( \theta(t_0) \) is the median time for those who survived beyond time \( t_0 \) in the population. The median residual lifetime is stable since it is not affected by outliers such as very long durations of survival time. In the case with censored data, the use of a median for the residual lifetime not only exhibits a better location estimate than its mean but also shows less sensitivity to skewed distributions. The minimum of observed survival probability of the residual life distribution should be smaller than the 0.5, so that the median residual lifetime can be defined under censoring (Schmittlein et al. [1981]).

Various methods have been proposed in the literature to estimate the median residual lifetimes for one and two sample cases. Haines et al. [1974] introduced a general concept of the \( \alpha \)-percentile residual life function \((0 < \alpha < 1)\). Schmittlein et al. [1981] established a general concept of MERL function exploring non-uniqueness of the corresponding life distribution. Csörgő et al. [1987] proposed a 100\((1 - p)\)th percentile residual lifetime estimator for complete data, whereas Chung [1989] extended this idea to censoring cases. The nonparametric estimator of 100\((1 - p)\)th percentile residual lifetime was proposed by Feng et al. [1991], where inverse function of the Kaplan-Meier curve was used. Jeong et al. [2008] introduced a test statistic to compare two median residual lifetimes at a fixed time point. However, these methods cannot be applied to estimate median residual lifetime for treatment strategies in two-stage designs as they do not account for sequential randomization structure.

In this study, we aim to develop methods for nonparametric estimation of strategy-specific median residual lifetime from two-stage randomization designs. Our method uses the marginal mean models for survival data introduced by Lunceford et al. [2002] for sequentially randomized trials. We also use inverse-probability weighted estimating equations directly for this purpose.

Notation used throughout this chapter is described in Section 4.2. Estimation of MERL function using different approaches is discussed in Section 4.3. We present a simulation study to demonstrate the performance of proposed methods in Section 4.4. Then, we apply these methods to a leukemia data set in Section 4.5.
4.2 NOTATION AND ASSUMPTIONS

We consider the two-stage design described in the previous section. Our development of methods borrows the idea of counterfactual variables from the causal inference literature (Holland [1986]). Consider only the population that receives $A_1$ as the initial treatment (development for the population receiving $A_2$ is analogous). For the $i^{th}$ individual in the population, let $R_i$ be the response indicator: $R_i = 1$ if a response to the first-stage treatment is achieved, 0 otherwise. If the patient did not respond, his/her survival time is denoted by $T_{NRi}$. Let $T_{ki}^*$ be the post-response survival time for patient $i$ if the patient had responded and received $B_k$ as the maintenance treatment. Let $T_{ai}$ be the time to the starting of the second-stage treatment, if the $i^{th}$ patient proceeded to the second stage. Thus, under the strategy $A_1B_k$, the overall survival time for patients $i$ can be defined as

$$T_{ki} = (1 - R_i)T_{NRi} + R_i(T_{ai} + T_{ki}^*), \quad k = 1, 2.$$  

Note that, $T_1$ and $T_2$ both cannot be observed for the same patient since a patient either does not receive any maintenance treatment, or receives only one of the two maintenance treatments, $B_1$ or $B_2$. For such, these variables are referred to as potential outcomes or counterfactuals (Holland [1986]). The interest lies in estimating the MERL function for the strategy $A_1B_k$ or equivalently for the overall survival $T_{ki}$. Now, the survival time for the $i^{th}$ patient, $T_i$, if observed for the $i^{th}$ individual, can be expressed in terms of $T_1$ and $T_2$ by means of the consistency assumption (Cole [2009]) as follows.

$$T_i = Z_{ki}T_{ki} + Z_{2i}T_{2i}, \quad (4.1)$$

where $Z_{ki}$ is the $B_k$ treatment assignment indicator, i.e. $Z_{ki} = 1$ if the $i^{th}$ patient was assigned to treatment $B_k$, 0 otherwise. Note that, Eq. (4.1) can alternatively be expressed as,

$$T_i = (1 - R_i)T_{NRi} + R_i \{T_{ai} + Z_{1i}T_{1i}^* + Z_{2i}T_{2i}^* \}.$$  

Unfortunately, $T_i$ also may not be observed for the $i^{th}$ individual, since it may be censored. The observed data from a two-stage design described in Figure. 2 can be denoted
by \((R_i, R_iZ_{ki}, U_i, \Delta_i)\) \(i = 1...n, k = 1, 2\), where \(R_i\) and \(Z_{ki}\) are as defined before, \(\Delta_i\) is the complete case indicator, and \(U_i\) is the event (survival or censoring) time. If \(C_i\) is used to denote the censoring time for the \(i^{th}\) individual in the sample, then \(U_i = \min(T_i, C_i)\) and \(\Delta_i = I(T_i < C_i)\). Note that, in practice, patients may be censored prior to a response being observed; such patients are historically treated as non responders in the analysis. We assume that censoring does not depend on \(T_i\) or any other observed or counterfactual data. Denote by \(K(t)\) the survival distribution function of censoring time \(C_i\), i.e., \(K(t) = P(C_i \geq t)\). Let \(\pi_1 = P(Z_{1i} = 1|R_i = 1)\) and \(\pi_2 = 1 - \pi_1\) denote the probability of receiving treatment \(B_1\) or \(B_2\), respectively. Further let \(S_k(t) = P(T_k > t)\) denote the survival probability at time \(t\) under strategy \(A_1B_k\) for \(k = 1, 2\).

Again, our goal is to find an estimator of the MERL function under strategy \(A_1B_k\) for \(k = 1, 2\). In other words, we would like to estimate \(\theta_k(t_0)\), where

\[
\theta_k(t_0) = \text{median}(T_k - t_0|T_k > t_0). \tag{4.2}
\]

### 4.3 ESTIMATION OF THE MEDIAN RESIDUAL LIFE FUNCTION

We first express \(\theta_k(t_0)\) as a function of \(S_k(t_0)\) so that the median residual lifetime can be estimated indirectly from the estimated survival curve. The MERL function defined in Eq. (4.2) can be expressed as \(P(T_k - t_0 \geq \theta_k(t_0)|T_k \geq t_0) = \frac{1}{2}\), thereby suggesting that

\[
\theta_k(t_0) = S_k^{-1}\left[\frac{1}{2}S_k(t_0)\right] - t_0, \tag{4.3}
\]

where \(S_k^{-1}(u)\) is the inverse of the survival function at \(u\), i.e., \(S_k^{-1}(u) = \inf\{t : S_k(t) < u\}\). Thus, one way to estimate \(\theta_k(t_0)\) is to estimate the survival distribution \(S_k(t_0)\) and use Eq. (4.3) to obtain \(\hat{\theta}_k(t_0)\) as

\[
\hat{\theta}_k^{(1)}(t_0) = \hat{S}_k^{-1}\left[\frac{1}{2}\hat{S}_k(t_0)\right] - t_0, \tag{4.4}
\]

where \(\hat{S}_k(t)\) is a consistent estimator of \(S_k(t)\) (Feng et al. [1991], Jeong et al. [2008]). As long as the largest observation in the sample is uncensored, the MERL function can be appropriately estimated.
One way to estimate the survival curve for a given strategy $A_1B_k$ is the probability-adjusted inverse-probability-weighted estimator defined as:

$$\hat{S}_k(t_0) = \left\{ \frac{\sum_{i=1}^{n} \Delta_i Q_{ki}}{\hat{K}(U_i)} \right\}^{-1} \left\{ \frac{\sum_{i=1}^{n} \Delta_i Q_{ki}}{\hat{K}(U_i)} I(U_i > t_0) \right\},$$

where, $\hat{K}(U_i)$ is the Kaplan-Meier estimator of $K(t)$ and $Q_{ki} = 1 - R_i + \frac{R_i Z_{ki}}{n_k}$, $k = 1, 2$ is the weight function. This function assigns appropriate weight to each observation that is consistent with the strategy $A_1B_k$. In the estimation of the survival function $S_k$, every uncensored $U_i$ is weighted by $\frac{1}{\hat{K}(U_i)}$ to reflect the fact that there were $\frac{P(C_i \leq U_i)}{P(C_i > U_i)} = \frac{1}{\hat{K}(U_i)} - 1$ expected censored individuals in the population at time $U_i$. Therefore, the response for an uncensored individual counts for him/herself and additional censored individual $\frac{1}{\hat{K}(U_i)} - 1$.

The weights $Q_{ki}$ are defined based on the fact that patients who did not respond are consistent with both strategies $A_1B_1$ and $A_1B_2$, and those who responded, only a portion of them are treated with $A_1B_1$ ($A_1B_2$) with probability $\pi_1$ ($\pi_2$). Thus, for the treatment strategy $A_1B_1$, $Q_{1i} = 0$ if individual $i$ received $B_2$ treatment (i.e., $R_i = 1$ and $Z_i = 0$), while $Q_{1i} = 1$ if $R_i = 0$, and $Q_{1i} = \pi_i^{-1}$ if $R_i = 1$ and $Z_i = 1$ to reflect the weights due to randomization. Similarly, when an individual receives a treatment which is consistent with the treatment strategy $A_1B_2$, $Q_{2i}$ acts as a weight.

Lunceford et al. [2002] showed that the estimator $\hat{S}_k(t_0)$ defined by Eq. (4.5) is a consistent and asymptotically normal estimator with mean $S_k(t_0)$ and variance $\sigma_k^2(t_0)$ that can be estimated by

$$\hat{\sigma}_k^2(t_0) = \frac{1}{n} \left[ \frac{1}{n} \sum_{i=1}^{n} \Delta_i Q_{ki} \left\{ I(U_i > t_0) - 1 + \hat{S}_k(t_0) \right\}^2 \right. + \left. \int_{0}^{L} \frac{dN^c(u)}{\hat{K}(u)Y(u)} \hat{E}\{L_{ki}(t, u)\}^2 \right] \frac{1}{\hat{K}(U_i) Y(U_i)}.$$
where
\[
\int_0^L \frac{dN^c(u)}{K(u)Y(u)} \hat{E}\{L_{ki}(t, u)\}^2
= \sum_{j=1}^n \left\{ \frac{1 - \Delta_j}{K(U_j)Y(V_j)} \left\{ \frac{1}{n} \sum_{i=1}^n \Delta_i \left\{ Q_{ki}(I(U_i > t_0) - 1 + \hat{S}_k(t_0)) \right\} \right\}^2 \right. \\
- \left. \hat{G}_k(t, U_i) \right\} \frac{2I(U_i \geq u)}{K(U_i)},
\]

\[
\hat{G}_{ki}(t, u) = \frac{1}{nS(u)} \left\{ \sum_{i=1}^n \Delta_i Q_{ki}(I(U_i > t_0) - 1 + \hat{S}_k(t_0)) \frac{I(U_i \geq u)}{K(U_i)} \right\}.
\]

Here, \( N^c(u) = \sum N_i^c(u) = \sum I(U_i < u, \Delta_i = 0) \) and \( Y(u) = \sum Y_i(u) = \sum I(U_i \geq u) \).

### 4.3.1 Survival Function Based Estimator

Substituting Eq. (4.5) in Eq. (4.4), we obtain the first estimator for the MERL function. This estimator will be referred to as survival function based (SFB) estimator, \( \hat{\theta}_k^{(1)}(t_0) \). To calculate the variance of this estimator, we first note that \( \hat{\theta}_k^{(1)}(t_0) \) satisfies
\[
\hat{S}_k(t_0 + \hat{\theta}_k^{(1)}(t_0)) - \frac{1}{2} \hat{S}_k(t_0) = 0.
\]

Let us denote the left hand side of the above equation by \( \psi_k(\hat{\theta}_k^{(1)}(t_0)) \). Expanding \( \psi_k(\hat{\theta}_k^{(1)}(t_0)) \) around \( \theta_k(t_0) \), we obtain,
\[
\psi_k(\hat{\theta}_k^{(1)}(t_0)) \approx \psi_k(\theta_k(t_0)) + (\hat{\theta}_k^{(1)}(t_0) - \theta_k(t_0)) \frac{\delta \psi_k(\theta_k(t_0))}{\delta \theta_k(t_0)}.
\]

Assuming sufficient regularity, it follows that variance of \( \hat{\theta}_k(t_0) \) could be approximated by
\[
\text{Var}(\hat{\theta}_k^{(1)}) \approx \frac{\text{var}[\psi_k(\hat{\theta}_k^{(1)}(t_0))]}{\left[ \frac{\delta \psi_k(\theta_k(t_0))}{\delta \theta_k(t_0)} \right]^2}.
\]

Note that,
\[
\frac{\delta \psi_k(\theta)}{\delta \theta} = -f_k(t_0 + \theta),
\]

leading to
\[
\text{Var}(\hat{\theta}_k^{(1)}(t_0)) \approx \frac{\text{var}[\psi_k(\hat{\theta}_k^{(1)}(t_0))]}{f_k^2(t_0 + \hat{\theta}_k^{(1)}(t_0))}, \quad (4.6)
\]

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where $f_k(\cdot)$ is the density function of $T_k$, which can be estimated by using nonparametric smoothing technique such as the kernel density estimator. To estimate the variance in Eq. (4.6), we first note that $\psi_k(\hat{\theta}_k^{(1)}(t_0))$ can be written as

\[
\left\{ \sum_{i=1}^{n} \frac{\Delta_i Q_{ki}}{K(U_i)} \right\}^{-1} \left\{ \sum_{i=1}^{n} \frac{\Delta_i Q_{ki}}{K(U_i)} h\{U_i; \hat{\theta}_k^{(1)}(t_0)\} \right\},
\]

where $h\{U_i; \theta\} = I(U_i > \theta + t_0) - \frac{1}{2} I(U_i > t_0)$. Following Lunceford et al. [2002], we obtain a consistent estimator of $\text{Var}(\hat{\psi}_k(\hat{\theta}_k^{(1)}(t_0)))$ as follows:

\[
\text{var}(\hat{\psi}_k(\hat{\theta}_k^{(1)}(t_0))) = \frac{1}{n} \left[ \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i Q_{ki}}{K(U_i)} \left\{ h(U_i) \right\}^2 + \int_{0}^{L} \frac{dN^c(u)}{K(u)Y(u)} \hat{E}\{L_{ki}(t,u)\}^2 \right],
\]

(4.7)

where

\[
\int_{0}^{L} \frac{dN^c(u)}{K(u)Y(u)} \hat{E}\{L_{ki}(t,u)\}^2 = \sum_{j=1}^{n} \left\{ \frac{1 - \Delta_j}{K(U_j)Y(V_j)} \left\{ \frac{1}{n} \sum_{i=1}^{n} \Delta_i \left\{ Q_{ki}(h\{U_i; \hat{\theta}_k^{(1)}(t_0)\}) \right\} \right. \\
- \hat{G}_k(t,U_i) \left\}^2 \frac{I(U_i \geq u)}{K(U_i)} \right\},
\]

\[
\hat{G}_{ki}(t,u) = \frac{1}{nS(u)} \left\{ \sum_{i=1}^{n} \Delta_i Q_{ki}(h\{U_i; \hat{\theta}_k^{(1)}(t_0)\}) \frac{I(U_i \geq u)}{K(U_i)} \right\}.
\]

Eq.(4.7), along with an inverse-probability-weighted kernel density estimator of $f_k$, can then be used in Eq.(4.6) to estimate the variance of $\hat{\theta}_k^{(1)}(t_0)$. 

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4.3.2 Estimating Equation Based Approach

An alternative method of estimating the MERL function at time $t_0$ would be to directly solve an appropriate estimating equation of the form

$$\sum_{i=1}^{n} \psi_i(\theta_k(t_0)) = 0,$$

(4.8)

where $\psi_i(\theta) = \frac{\Delta Q_k}{K(U_i)} [I(U_i > t_0 + \theta) - \frac{1}{2} I(U_i > t_0)].$ Note that $K(\cdot)$ is unknown and hence it must be estimate by some consistent method. Since this equation is not linear in $\theta$, we can use numerical methods such as the Secant method or Newton-Raphson method to solve the equation for $\theta$. We used the Secant method for this purpose to avoid computing numerical derivative in the Newton-Raphson method. The solution to Eq.(4.8) will be referred to as $\hat{\theta}_k^{(2)}(t_0)$.

To estimate the variance, we will use the so-called sandwich estimator. (4.8). Explicitly,

$$\text{var}(\hat{\theta}_k^{(2)}(t_0)) = \left( \frac{1}{n} \right) \frac{B(\hat{\theta}_k^{(2)}(t_0))}{A(\hat{\theta}_k^{(2)}(t_0))^2},$$

where $A(\theta) = \hat{S}_k(t_0 + \theta)$ and $B(\theta) = \left\{ \sum_{i=1}^{n} \frac{\Delta Q_k}{K(U_i)} \right\}^{-1} \sum_{i=1}^{n} \{\psi_i(\theta)\}^2$.

4.4 SIMULATION STUDY

We conducted a simulation study to evaluate the proposed methods. Since initial treatment $A_1$ and $A_2$ are assigned by randomization, we only designed simulation studies for the induction treatment $A_1$. We generate $n$ independent sets of observations described as follows.

Indicator of patient’s response $R$ was generated from a Bernoulli ($\pi_R$) distribution, where $\pi_R$ was varied between 0.1 and 0.7. For responders ($R = 1$), the $B_1$ treatment assignment indicator $Z_1$ was generated from Bernoulli ($\pi_1$) distribution. We then defined $Z_2 = 1 - Z_1$.

For non-responders ($R = 0$), we generated survival time $T_{NR}$ from exponential distribution with mean $\lambda = 0.5$. For responders, a response time $T_a$ was generated from exponential ($\alpha = 0.1$). Patients receiving maintenance treatment $B_k$, post remission survival time $T_k^*$ was generated from three-parameter Weibull distribution as $T_k^* = \left( \frac{1}{\rho} \right) (-exp(-\beta_k log(1 - u)))^{(\frac{1}{\rho})}$.
, \( k = 1, 2 \). Following Jeong et al. [2008], the parameter values for \( \rho \) and \( \eta \) are set to 0.2 and 2, respectively, and \( \beta_1 = 0.6 \) and \( \beta_2 = 0.9 \). Therefore, the survival time for the \( i^{th} \) patient, \( T_i = (1 - R_i)T_{NRi} + R_i\{T_{ai} + Z_{1i}T^*_{1i} + Z_{2i}T^*_{2i}\} \). The censoring time \( C_i \) was taken from a uniform distribution between 0 and \( \theta_C \) to reflect about 30% of censoring and assumed independent of all other variables. The observed survival \( U_i \) is \( \min(T_i, C_i) \) and the complete case indicator \( \Delta_i \) is \( I(T_i < C_i) \).

Under different simulation scenarios obtained under different combination of parameters, we generated 1000 samples of size \( n \) (200 and 500) and then estimated median residual lifetime at 183 and 365 days.

In Table 4 and Table 5, we summarize estimators of the median residual lifetimes (Estimates) and standard error (S.E.) for these estimators, along with 95% coverage probability of estimates (CP). Table 4 gives the results from scenarios where patients were assigned to the maintenance treatment with equal allocation. As can be seen, estimates and coverage probabilities were similar for the SFB and EEB. For the SFB and EEB estimators, the coverage probabilities in most cases achieved by the nominal level. These estimators were approximately unbiased as shown by the small observed biases. Standard errors for the EEB estimators were larger than the SFB estimators.

The cases with unequal probability of assignment to maintenance treatment are shown in Table 5. Here 30% of the responders were assigned to \( B_1 \) while 70% to \( B_2 \). Performance of the estimators, coverage probabilities and standard errors remain similar to the case where the randomization was done with equal probability in Table 5. In this scenario, estimators corresponding to the maintenance treatment with higher probability of randomization had smaller standard errors compared to the strategy which shared the other maintenance treatment. Specifically, standard errors for \( A_1B_1 \) was larger than that for \( A_1B_2 \) with 30% of responders being assigned to \( B_1 \). This is expected since this form of randomization increases the effective sample size of strategy \( A_1B_2 \) and reduces the number of patients followed in the strategy \( A_1B_1 \).

In both Tables 4 and 5, both estimators gained efficiency with increasing sample size. Standard errors of the estimators and Monte Carlo standard errors were close to each other, implying consistency of variance estimators for both methods.
Overall, the estimator from SFB method has smaller standard errors than the EEB estimator, and EEB estimator shows higher coverage rate than the SFB estimator.

4.5 ANALYSIS OF LEUKEMIA CALGB 8923 TRIAL

In this section, we apply the methods described in previous sections to estimate the median residual lifetime of patients treated with various treatment strategies. The data is collected from a two-stage randomized clinical trial conducted by the Cancer and Leukemia Group B (CALGB). This is a double-blinded placebo-controlled trial designed to examine the effects of infusions of granulocyte-macrophage colony-stimulating factor (GM-CSF) following induction chemotherapy in acute myelogenous leukemia (AML) patients. Patients are initially randomized to GM-SCF (n =193) or placebo (n=195) following treatment with standard chemotherapy. Patients who achieved remission and consented to second stage treatment (79 out of 193 in GM-CSF and 90 out of 195 in the placebo group) were re-randomized into one of the intensification therapies: cytarabine (intensification I) and cytarabine+mitoxantrone (Intensification II). In this process, 37 patients were assigned to intensification I in the GM-CSF group whereas 45 were assigned to the same intensification in the placebo group. The remaining patients in each group received intensification II. Therefore, there are 4 possible treatment strategies in this trial, namely, GM-CSF/I, GM-CSF/II, Placebo/I, and Placebo/II, where for example, “GM-CSF/I” stands for “add GM-CSF by infusion after chemotherapy followed by maintenance cytarabine, if respond to chemotherapy with GM-CSF infusion”.

In Table 6, we presented the estimators of the median residual lifetime at specific time points for the treatment strategies, GM-CSF/I, GM-CSF/II, Placebo/I and Placebo/II, using the SFB [Eq. (4.4)] and EEB [Eq. (4.8)] methods. The median residual lifetimes at three different time points of 150, 250, and 350 days were estimated. From the results presented in Table 6, the estimates under both methods SFB and EEB were similar to each other, although the standard errors of the EEB estimates were larger compared to the SFB estimates. Estimated MERL was smallest for strategy GM-CSF/I whereas it was largest for
Table 4: Simulation results of estimation of MERL at two time points with $\pi_Z = 0.5$

<table>
<thead>
<tr>
<th>n</th>
<th>$\pi_R$</th>
<th>$t_0$</th>
<th>Method</th>
<th>Strategy</th>
<th>$\theta(t_0)$ Estimates</th>
<th>S.E.</th>
<th>MC S.E.</th>
<th>C.P.</th>
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</thead>
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<td>183</td>
<td>0.4</td>
<td></td>
<td>SFB</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$A_1B_2$</td>
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<td>0.92</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EEB</td>
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<td></td>
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<td></td>
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<td></td>
<td>365</td>
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<td>SFB</td>
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<td>0.4</td>
<td></td>
<td>SFB</td>
<td>$A_1B_1$</td>
<td>341.9 332.3 51.25 51.68</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>$A_1B_2$</td>
<td>285.6 283.6 47.58 44.42</td>
<td>0.94</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EEB</td>
<td>$A_1B_1$</td>
<td>341.9 340.7 61.29 52.47</td>
<td>0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$A_1B_2$</td>
<td>285.6 289.8 52.33 44.52</td>
<td>0.98</td>
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<td></td>
</tr>
<tr>
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<td>365</td>
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<td>SFB</td>
<td>$A_1B_1$</td>
<td>262.9 253.7 56.70 55.26</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>$A_1B_2$</td>
<td>209.5 205.1 48.63 48.33</td>
<td>0.93</td>
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<td></td>
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<td></td>
<td></td>
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<td>262.9 270.0 69.62 57.97</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>$A_1B_2$</td>
<td>209.5 214.9 54.11 49.47</td>
<td>0.96</td>
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</tbody>
</table>

38
Table 5: Simulation results of estimation of MERL at two time points with $\pi_Z = 0.3$

<table>
<thead>
<tr>
<th>N</th>
<th>$\pi_R$</th>
<th>$t_0$</th>
<th>Method</th>
<th>Strategy</th>
<th>$\theta(t_0)$</th>
<th>Estimates</th>
<th>S.E.</th>
<th>MC S.E.</th>
<th>C.P.</th>
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<tr>
<td>200</td>
<td>0.4</td>
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<td>265.3</td>
<td>61.47</td>
<td>66.04</td>
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<td>$A_1B_2$</td>
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<td>280.4</td>
<td>71.66</td>
<td>87.88</td>
<td>0.93</td>
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<td>$A_1B_2$</td>
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<td>42.80</td>
<td>38.93</td>
<td>0.96</td>
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<tr>
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<td>$A_1B_1$</td>
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<td>$A_1B_2$</td>
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<td>189.6</td>
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<td>46.31</td>
<td>0.91</td>
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<td>74.32</td>
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<td>40.55</td>
<td>38.73</td>
<td>0.95</td>
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<td>214.0</td>
<td>46.30</td>
<td>39.53</td>
<td>0.97</td>
</tr>
<tr>
<td>500</td>
<td>0.7</td>
<td>183</td>
<td>SFB</td>
<td>$A_1B_1$</td>
<td>273.9</td>
<td>270.8</td>
<td>40.19</td>
<td>42.62</td>
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<td>$A_1B_2$</td>
<td>239.9</td>
<td>235.8</td>
<td>24.34</td>
<td>25.34</td>
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</tr>
<tr>
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<td>EEB</td>
<td>$A_1B_1$</td>
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<td>275.4</td>
<td>46.67</td>
<td>43.25</td>
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<td>237.4</td>
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<td>25.25</td>
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<tr>
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<td>$A_1B_1$</td>
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<td>234.1</td>
<td>52.10</td>
<td>53.73</td>
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<td>$A_1B_2$</td>
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<td>193.7</td>
<td>28.47</td>
<td>29.14</td>
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<td>$A_1B_1$</td>
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<td>244.9</td>
<td>62.80</td>
<td>57.57</td>
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<tr>
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<td>$A_1B_2$</td>
<td>193.4</td>
<td>196.9</td>
<td>32.27</td>
<td>29.67</td>
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</tr>
<tr>
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<td>SFB</td>
<td>$A_1B_1$</td>
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<td>258.9</td>
<td>49.04</td>
<td>48.26</td>
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<td>$A_1B_2$</td>
<td>210.4</td>
<td>207.6</td>
<td>25.54</td>
<td>25.31</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>EEB</td>
<td>$A_1B_1$</td>
<td>262.1</td>
<td>268.5</td>
<td>58.73</td>
<td>52.75</td>
<td>0.96</td>
</tr>
<tr>
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<td>$A_1B_2$</td>
<td>210.4</td>
<td>209.7</td>
<td>28.80</td>
<td>25.19</td>
<td>0.96</td>
</tr>
</tbody>
</table>
Table 6: Estimated median residual lifetime for CALGB 8923 data at different days

<table>
<thead>
<tr>
<th>Strategy</th>
<th>t0 (days)</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SFB</td>
</tr>
<tr>
<td>GM-CSF/I</td>
<td>150</td>
<td>290.0 (21.07)</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>260.0 (23.93)</td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>233.0 (26.92)</td>
</tr>
<tr>
<td>GM-CSF/II</td>
<td>150</td>
<td>288.0 (21.66)</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>233.0 (22.80)</td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>192.0 (27.08)</td>
</tr>
<tr>
<td>Placebo/I</td>
<td>150</td>
<td>313.0 (27.08)</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>285.0 (27.59)</td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>271.0 (31.55)</td>
</tr>
<tr>
<td>Placebo/II</td>
<td>150</td>
<td>401.0 (45.47)</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>395.0 (47.62)</td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>500.0 (68.60)</td>
</tr>
</tbody>
</table>

the strategy Placebo/II at all three time points. When the time of interest increased, median residual lifetimes decreased, except for the strategy “do not give GM-CSF after chemotherapy, and when a response is observed treat with second maintenance”. The estimates of the median residual lifetimes over time are presented in Figure 3 for all four treatment strategies. It shows the evolution of the median residual lifetime over the duration of the trial.

For all strategies, the median residual lifetimes initially increased, most likely due to the effect of initial treatment. After about 50 days, the median residual lifetimes began to decrease for the strategies GM-CSF/I, GM-CSF/II and Placebo/I. Placebo/II shows the increasing median residual lifetimes throughout which may be due to the fact that some of the patients survived extremely long under this strategy. This result has been consistent with the findings from previous studies based on mean survival or survival curve (Lunceford et al. [2002]; Wahed and Tsiatis [2004]) where it has been showed that the infusion with GM-CSF was not beneficial to patients in terms of overall survival.
Figure 3: Survival function based median residual lifetimes for CALGB 8923 data with number of the patients at risk for each strategy

4.6 DISCUSSION

In this chapter, two methods were proposed to estimate the median residual life function for sequentially randomized trials. First, we estimated the median residual lifetime indirectly from the estimated survival curve. The survival curve estimation was done based on the inverse-probability-weighting. One important limitation of this estimator is that we need to estimate the density function to estimate the variance. In addition to SFB method, the median residual lifetime can also be estimated by directly solving the estimating equation of the median residual lifetime.

As can be seen from our simulation study, the SFB and EEB estimators are approximately unbiased. The estimator from SFB method has smaller standard errors than the EEB estimator which leads to higher coverage rates for the latter. Future research in this area might consider including covariates in the estimation process. Other important research might include developing test statistics to compare MERL across different strategies.
We first have compared up-front and sequential randomization designs as prospective designs for comparing dynamic treatment strategies. Most previous studies investigated these methods but few compared them with respect to efficiency. Our simulation results indicated that the sequential randomization provides better estimator for ATS’s compared to up-front randomization designs. Specifically, sequential randomization is better than up-front randomization in terms of efficiency of the estimators and the power of statistical hypothesis testing. In the latter half of the study, we proposed nonparametric estimation methods to estimate the MERL function for SRT. One estimator for MERL function was obtained by using probability-adjusted estimator (Lunceford et al. [2002]). The other estimator was obtained by directly solving the estimating equation. We demonstrated our methods by applying to a Leukemia clinical trial data set. Our simulation study shows that SFB and EEB estimators for SRT are approximately unbiased in large samples.

One advantage of the SFB methods is that it can be calculated directly from the survival curve estimator. One limitation of this approach is that it requires density estimation for the purpose of estimating its variance. On the other hand, EEB estimator although less efficient, does not require any such limitation.
APPENDIX

PROGRAMS WRITTEN IN MATLAB©

A.1 UP-FRONT AND SEQUENTIAL RANDOMIZATION IN CLINICAL TRIALS

clear all;

% ==============================================================
% Function to find nearest value
% ==============================================================
function K = fOne(U,tk,Ku);

n = length(U);
for i=1:n
    index = find(U(i)==tk);
    if length(index)==0
        [val1 index] = min(abs(U(i)-tk));
    end
    K(i) = Ku(index(1));
end

% ==============================================================
% Function to find Kaplan Meier Estimator
% ==============================================================
% ==============================================================

function [K S] = kmest(U,D)
    D1 = 1-D;
    n = length(D);
    [K,x] = ecdf(U,'censoring',D,'function','survivor');
    [S,x1] = ecdf(U,'censoring',D1,'function','survivor');
    K = f0ne(U,x,K);
    S = f0ne(U,x1,S);
    for j = 2:n
        if K(j) == 0 K(j) = K(j-1); end
        if S(j) == 0 S(j) = S(j-1); end
    end
    K = K';
    S = S';
% ==============================================================
% Function to find Density function
% ==============================================================

function [Den1_R0 Den1_t0_R0] = denS(U_R0, Q, D1_R0, t0)
    n_R0 = length(U_R0);
    [den1_R0,x1] = ksdensity(U_R0,'weights',Q,'censoring',D1_R0,'npoints',n_R0);
    Den1_R0 = f0ne(U_R0,x1,den1_R0);
    Den1_t0_R0 = f0ne(t0,U_R0,Den1_R0);

function f = secfunc1(p1)
    load FileforSecant
    f = (sum((D./K.*Q1.*((U>t0+p1)-0.5.*(U>t0))))/sum(D./K.*Q1));
% ==============================================================
% Function to call secant function
% ==============================================================
function f = secfunc1(p1)
load FileforSecant
f = (sum((D./K.*Q1.*((U>t0+p1)-0.5.*(U>t0))))/sum(D./K.*Q1));

% Function to find Inverse Survival
% Function to calculate Coverage Probabilities

function [S_half1_pmb Sinv1_pmb Sinv1_pmb_t0 S_half1_pmb_t0] = S_find(S1pmb, U_pmb, t0)
    S_half1_pmb = 0.5*S1pmb;
    Sinv1_pmb = fOne(S_half1_pmb,S1pmb,U_pmb);
    Sinv1_pmb_t0 = fOne(t0,U_pmb,Sinv1_pmb);
    S_half1_pmb_t0 = fOne(t0,U_pmb,S_half1_pmb);

function [Var331 Var332 Se331 Se332 Cp331 Cp332] = CP1(Den31_t0, Den32_t0, D, K, Q1, Q2, U, t0, Theta31, Theta32, mu31, mu32)
n = length(U);
    AA31 = Den31_t0^2;
    AA32 = Den32_t0^2;
    BB31 = sum(((D./K.*Q1.*((U>t0+Theta31)-0.5.*(U>t0))).^2)/n;
    BB32 = sum(((D./K.*Q2.*((U>t0+Theta32)-0.5.*(U>t0))).^2)/n;
    Var331 = (BB31/AA31)/n;
    Var332 = (BB32/AA32)/n;
    Se331 = sqrt(Var331);
    Se332 = sqrt(Var332);
CL_L331 = Theta31 - 1.96* Se331;
CL_U331 = Theta31 + 1.96* Se331;
CL_L332 = Theta32 - 1.96* Se332;
CL_U332 = Theta32 + 1.96* Se332;
Cp331 = (mu31 >= CL_L331) * (CL_U331 >= mu31);
Cp332 = (mu32 >= CL_L332) * (CL_U332 >= mu32);

% ==============================================================
% Begin Main codes
% ==============================================================
clear all;
nos = 100; % iterations
nT = 200; % sample size
%%% make effect size small like 0.25? 0.1

piA = 0.5; % for Treatment A
piR1 = 0.5; % response for A1
piR2 = 0.5; % response for A2
piB = 0.5; % proportion for B
piC = 0.5; % proportion for C
% % % % % % same true mean
% m11d = 15;
% m1d1 = 15;
% m12d = 15;
% m1d2 = 15;
% m21d = 15;
% m2d1 = 15;
% m22d = 15;
% m2d2 = 15;
different true mean

\[ m_{11d} = 15; \]
\[ m_{1d1} = 20; \]
\[ m_{12d} = 22; \]
\[ m_{1d2} = 15; \]
\[ m_{21d} = 15; \]
\[ m_{2d1} = 20; \]
\[ m_{22d} = 22; \]
\[ m_{2d2} = 15; \]

\[ n_1 = \pi_A n_T; \]  \(\%\) # of people in A1

\[ n_2 = (1-\pi_A) n_T; \]  \(\%\) # of people in A2

\[ v_1 = 6; \]
\[ v_2 = 8; \]

for \(k = 1 :\text{nos}\)

\[ U_{01} = \text{rand}(n_1,1); \]
\[ U_{02} = \text{rand}(n_2,1); \]
\[ U_1 = \text{rand}(n_1,1); \]
\[ U_2 = \text{rand}(n_1,1); \]
\[ V_1 = \text{rand}(n_1,1); \]
\[ V_2 = \text{rand}(n_1,1); \]
\[ V_{21} = \text{rand}(n_2,1); \]
\[ V_{22} = \text{rand}(n_2,1); \]
\[ U_{21} = \text{rand}(n_2,1); \]
\[ U_{22} = \text{rand}(n_2,1); \]

\%  \text{------------------------------------------------------}
\%  For A1
\%  \text{------------------------------------------------------}

for \(i = 1 :n_1\)

\% indicator for receiving second treatment

if \(V_1(i) < \pi_R1 \) \(R_1(i) = 1;\)
else R1(i) = 0;
end

% indicator for second treatment method (responders piB, non-responders piC)
if U1(i) < piB Z1(i) = 1;
else Z1(i) = 0;
end
if U2(i) < piC Z3(i) = 1;
else Z3(i) = 0;
end

% indicator for 4 groups in URT
if U01(i) < 0.25 X1(i) = 1;
else X1(i) = 0;
end
if (0.25 <= U01(i)) && (U01(i) < 0.5) X2(i) = 1;
else X2(i) = 0;
end
if (0.5 <= U01(i)) && (U01(i) < 0.75) X3(i) = 1;
else X3(i) = 0;
end
if U01(i) >= 0.75 X4(i) = 1;
else X4(i) = 0;
end

% distribution of observed data
y11d = randn(n1,1)*v1 + m11d;
y1d1 = randn(n1,1)*v2 + m1d1;
y12d = randn(n1,1)*v1 + m12d;
y1d2 = randn(n1,1)*v2 + m1d2;

% split data into 4 different groups in URT
y111(i) = (R1(i)*y11d(i) + (1-R1(i))*y1d1(i))*X1(i);
\[ y_{11}(i) = (R_1(i) \cdot y_{11d}(i) + (1-R_1(i)) \cdot y_{1d2}(i)) \cdot X_2(i); \]
\[ y_{121}(i) = (R_1(i) \cdot y_{12d}(i) + (1-R_1(i)) \cdot y_{1d1}(i)) \cdot X_3(i); \]
\[ y_{122}(i) = (R_1(i) \cdot y_{12d}(i) + (1-R_1(i)) \cdot y_{1d2}(i)) \cdot X_4(i); \]

% total observed data in SRT with counterfactuals
\[ y_{\text{tot}}(i) = R_1(i) \cdot (Z_1(i) \cdot y_{11d}(i) + (1-Z_1(i)) \cdot y_{12d}(i)) + (1-R_1(i)) \cdot (Z_3(i) \cdot y_{1d1}(i) + (1-Z_3(i)) \cdot y_{1d2}(i)); \]

% divide into 4 groups based on second treatment agreement and
% treatment method in SRT
\[ W_{111}(i) = \frac{((R_1(i) \cdot Z_1(i))/\pi_B) + (((1-R_1(i)) \cdot Z_3(i)))}{\text{piC}}; \% \text{IPW} \]
\[ W_{112}(i) = \frac{((R_1(i) \cdot Z_1(i))/\pi_B) + (((1-R_1(i)) \cdot (1-Z_3(i))))}{(1-\text{piC})}; \]
\[ W_{121}(i) = \frac{((R_1(i) \cdot (1-Z_1(i)))/(1-\text{piB})) + (((1-R_1(i)) \cdot Z_3(i)))}{\text{piC}}; \]
\[ W_{122}(i) = \frac{((R_1(i) \cdot (1-Z_1(i)))/(1-\text{piB})) + (((1-R_1(i)) \cdot (1-Z_3(i))))}{(1-\text{piC})}; \]

\[ (((1-R_1(i)) \cdot (1-Z_3(i))))/(1-\text{piC})}; \]

\[ y_{1_2}(i) = (((R_1(i) \cdot Z_1(i))/\pi_B) + (((1-R_1(i)) \cdot Z_3(i))) \cdot y_{\text{tot}}(i); \]
\[ y_{2_2}(i) = (((R_1(i) \cdot Z_1(i))/\pi_B) + (((1-R_1(i)) \cdot (1-Z_3(i))))/(1-\text{piC})}; \]
\[ y_{3_2}(i) = (((R_1(i) \cdot (1-Z_1(i)))/(1-\text{piB})) + (((1-R_1(i)) \cdot Z_3(i))) \cdot y_{\text{tot}}(i); \]
\[ y_{4_2}(i) = (((R_1(i) \cdot (1-Z_1(i)))/(1-\text{piB})) + \]
\[ (((1-R_1(i)) \cdot (1-Z_3(i))))/(1-\text{piC})}; y_{\text{tot}}(i); \]
%%%indicator for second treatment method
if U21(i) < \piB Z2(i) = 1;
else Z2(i) = 0;
end
if U22(i) < \piC Z4(i) = 1;
else Z4(i) = 0;
end

%%%indicator for 4 groups in design 1
if U02(i) < 0.25 X1(i) = 1;
else X1(i) = 0;
end
if (0.25 <= U02(i)) && (U02(i) < 0.5) X2(i) = 1;
else X2(i) = 0;
end
if (0.5 <= U02(i)) && (U02(i) < 0.75) X3(i) = 1;
else X3(i) = 0;
end
if U02(i) >= 0.75 X4(i) = 1;
else X4(i) = 0;
end

%%%distribution of observed data
y21d = randn(n2,1)*v1 + m21d;
y2d1 = randn(n2,1)*v2 + m2d1;
y22d = randn(n2,1)*v1 + m22d;
y2d2 = randn(n2,1)*v2 + m2d2;

%%%split data into 4 different groups in URT for rest of R
y211(i) = ((R2(i))*y21d(i) + (1-R2(i))*y2d1(i))*X1(i);
y212(i) = ((R2(i))*y21d(i) + (1-R2(i))*y2d2(i))*X2(i);
y221(i) = ((R2(i))*y22d(i) + (1-R2(i))*y2d1(i))*X3(i);
y222(i) = ((R2(i))*y22d(i) + (1-R2(i))*y2d2(i))*X4(i);
\[
\begin{align*}
\text{total observed data in SRT with counterfactuals} \\
y_{\text{tot}_2a(i)} &= (R2(i))*(Z2(i)*y_{21d(i)} + (1-Z2(i))*y_{22d(i)}) + \\
&\quad (1-R2(i))*(Z4(i)*y_{2d1(i)} + (1-Z4(i))*y_{2d2(i)});
\end{align*}
\]
\[
\text{divide into 4 groups based on second treatment agreement and} \\
\text{treatment method in SRT} \\
W211(i) &= (((R2(i))*Z2(i))/\piB) + (((1-R2(i))*Z4(i))/\piC)); \\
\text{IPW} \\
W212(i) &= (((R2(i))*Z2(i))/\piB) + (((1-R2(i))*(1-Z4(i)))/(1-\piC))); \\
W221(i) &= (((R2(i))*(1-Z2(i))/(1-\piB)) + \\
&\quad (((1-R2(i))*Z4(i))/\piC)); \\
W222(i) &= (((R2(i))*(1-Z2(i))/(1-\piB)) + \\
&\quad (((1-R2(i))*(1-Z4(i)))/(1-\piC))); \\
y_{1_2_2a(i)} &= (((R2(i))*Z2(i))/\piB) + (((1-R2(i))*Z4(i))/\piC)) \times y_{\text{tot}_2a(i)}; \\
y_{2_2_2a(i)} &= (((R2(i))*Z2(i))/\piB) + \\
&\quad (((1-R2(i))*(1-Z4(i)))/(1-\piC))\times y_{\text{tot}_2a(i)}; \\
y_{3_2_2a(i)} &= (((R2(i))*(1-Z2(i))/(1-\piB)) + \\
&\quad (((1-R2(i))*Z4(i))/\piC)) \times y_{\text{tot}_2a(i)}; \\
y_{4_2_2a(i)} &= (((R2(i))*(1-Z2(i))/(1-\piB)) + \\
&\quad (((1-R2(i))*(1-Z4(i)))/(1-\piC)))\times y_{\text{tot}_2a(i)};
\end{align*}
\]
end

\[
\begin{align*}
\text{%remoove all zeros from each outcome vector in SRT} \\
\text{index111} &= \text{find}(y_{111}); y_{1_n1} = y_{111}(\text{index111}); \\
\text{index112} &= \text{find}(y_{112}); y_{2_n1} = y_{112}(\text{index112}); \\
\text{index121} &= \text{find}(y_{121}); y_{3_n1} = y_{121}(\text{index121}); \\
\text{index122} &= \text{find}(y_{122}); y_{4_n1} = y_{122}(\text{index122}); \\
\text{index211} &= \text{find}(y_{211}); y_{1_n1_2a} = y_{211}(\text{index211}); \\
\text{index212} &= \text{find}(y_{212}); y_{2_n1_2a} = y_{212}(\text{index212});
\end{align*}
\]
index221 = find(y221); y3_n1_2a = y221(index221);
index222 = find(y222); y4_n1_2a = y222(index222);

%% counting elements after removing zeros
size1 = length(y1_n1);
size2 = length(y2_n1);
size3 = length(y3_n1);
size4 = length(y4_n1);
size1_2a = length(y1_n1_2a);
size2_2a = length(y2_n1_2a);
size3_2a = length(y3_n1_2a);
size4_2a = length(y4_n1_2a);

% estimate means
% ==============================================================
%
% mean from URT
m111(k) = mean(y1_n1);
m112(k) = mean(y2_n1);
m121(k) = mean(y3_n1);
m122(k) = mean(y4_n1);
m211(k) = mean(y1_n1_2a);
m212(k) = mean(y2_n1_2a);
m221(k) = mean(y3_n1_2a);
m222(k) = mean(y4_n1_2a);

% mean in SRT
nmu111(k) = mean(y1_2);
nmu112(k) = mean(y2_2);
nmu121(k) = mean(y3_2);
nmu122(k) = mean(y4_2);
nmu211(k) = mean(y1_2_2a);
nmu212(k) = mean(y2_2_2a);
nmu221(k) = mean(y3_2_2a);
nmu222(k) = mean(y4_2_2a);

%%% mean in SRT probability adjusted
mu111(k) = sum(y1_2)/sum(W111);
mu112(k) = sum(y2_2)/sum(W112);
mu121(k) = sum(y3_2)/sum(W121);
mu122(k) = sum(y4_2)/sum(W122);
mu211(k) = sum(y1_2_2a)/sum(W211);
mu212(k) = sum(y2_2_2a)/sum(W212);
mu221(k) = sum(y3_2_2a)/sum(W221);
mu222(k) = sum(y4_2_2a)/sum(W222);

%%% variance for estimators

%%% sample variance for URT
s111_1(k) = (sum((y1_n1 - m111(k)).^2)/(size1-1));
s112_1(k) = (sum((y2_n1 - m112(k)).^2)/(size2-1));
s121_1(k) = (sum((y3_n1 - m121(k)).^2)/(size3-1));
s122_1(k) = (sum((y4_n1 - m122(k)).^2)/(size4-1));
s111_1_2a(k) = (sum((y1_n1_2a - m211(k)).^2)/(size1_2a-1));
s112_1_2a(k) = (sum((y2_n1_2a - m212(k)).^2)/(size2_2a-1));
s121_1_2a(k) = (sum((y3_n1_2a - m221(k)).^2)/(size3_2a-1));
s122_1_2a(k) = (sum((y4_n1_2a - m222(k)).^2)/(size4_2a-1));

%%% M-est for var. in SRT
B111(k) = (sum((W111.*y_tot-nmu111(k)).^2)/n1^2);
B112(k) = (sum((W112.*y_tot-nmu112(k)).^2)/n1^2);
B121(k) = (sum((W121.*y_tot-nmu121(k)).^2)/n1^2);
\[ B_{122}(k) = \frac{\text{sum}((W_{122} \cdot y_{tot} - n\mu_{122}(k))^2)}{n_1^2}; \]
\[ B_{211}(k) = \frac{\text{sum}((W_{211} \cdot y_{tot_2a} - n\mu_{211}(k))^2)}{n_2^2}; \]
\[ B_{212}(k) = \frac{\text{sum}((W_{212} \cdot y_{tot_2a} - n\mu_{212}(k))^2)}{n_2^2}; \]
\[ B_{221}(k) = \frac{\text{sum}((W_{221} \cdot y_{tot_2a} - n\mu_{221}(k))^2)}{n_2^2}; \]
\[ B_{222}(k) = \frac{\text{sum}((W_{222} \cdot y_{tot_2a} - n\mu_{222}(k))^2)}{n_2^2}; \]

\% covariance for SRT
\[ C_{12\_2}(k) = \frac{\text{sum}((W_{111} \cdot y_{tot} - n\mu_{111}(k)) \cdot (W_{112} \cdot y_{tot} - n\mu_{112}(k)))}{n_1^2}; \]
\[ C_{13\_2}(k) = \frac{\text{sum}((W_{111} \cdot y_{tot} - n\mu_{111}(k)) \cdot (W_{121} \cdot y_{tot} - n\mu_{121}(k)))}{n_1^2}; \]
\[ C_{14\_2}(k) = \frac{\text{sum}((W_{111} \cdot y_{tot} - n\mu_{111}(k)) \cdot (W_{122} \cdot y_{tot} - n\mu_{122}(k)))}{n_1^2}; \]
\[ C_{23\_2}(k) = \frac{\text{sum}((W_{112} \cdot y_{tot} - n\mu_{112}(k)) \cdot (W_{121} \cdot y_{tot} - n\mu_{121}(k)))}{n_1^2}; \]
\[ C_{24\_2}(k) = \frac{\text{sum}((W_{112} \cdot y_{tot} - n\mu_{112}(k)) \cdot (W_{122} \cdot y_{tot} - n\mu_{122}(k)))}{n_1^2}; \]
\[ C_{34\_2}(k) = \frac{\text{sum}((W_{121} \cdot y_{tot} - n\mu_{121}(k)) \cdot (W_{122} \cdot y_{tot} - n\mu_{122}(k)))}{n_1^2}; \]
\[ C_{12\_2\_2a}(k) = \frac{\text{sum}((W_{211} \cdot y_{tot_2a} - n\mu_{211}(k)) \cdot (W_{212} \cdot y_{tot_2a} - n\mu_{212}(k)))}{n_2^2}; \]
\[ C_{13\_2\_2a}(k) = \frac{\text{sum}((W_{211} \cdot y_{tot_2a} - n\mu_{211}(k)) \cdot (W_{221} \cdot y_{tot_2a} - n\mu_{221}(k)))}{n_2^2}; \]
\[ C_{14\_2\_2a}(k) = \frac{\text{sum}((W_{211} \cdot y_{tot_2a} - n\mu_{211}(k)) \cdot (W_{222} \cdot y_{tot_2a} - n\mu_{222}(k)))}{n_2^2}; \]
\[ C_{23\_2\_2a}(k) = \frac{\text{sum}((W_{212} \cdot y_{tot_2a} - n\mu_{212}(k)) \cdot (W_{221} \cdot y_{tot_2a} - n\mu_{221}(k)))}{n_2^2}; \]
\[ C_{24\_2\_2a}(k) = \frac{\text{sum}((W_{212} \cdot y_{tot_2a} - n\mu_{212}(k)) \cdot (W_{222} \cdot y_{tot_2a} - n\mu_{222}(k)))}{n_2^2}; \]
\[ C_{34\_2\_2a}(k) = \frac{\text{sum}((W_{221} \cdot y_{tot_2a} - n\mu_{221}(k)) \cdot (W_{222} \cdot y_{tot_2a} - n\mu_{222}(k)))}{n_2^2}; \]

\% M-est for var. in SRTPA
\[ BM_{111}(k) = \frac{\text{sum}((W_{111} \cdot (y_{tot} - \mu_{111}(k)))^2)}{(n_1 \cdot \text{sum}(W_{111})^2)}; \]
\[ BM_{112}(k) = \frac{\text{sum}((W_{112} \cdot (y_{tot} - \mu_{112}(k)))^2)}{(n_1 \cdot \text{sum}(W_{112})^2)}; \]
\[ BM_{121}(k) = \frac{\text{sum}((W_{121} \cdot (y_{tot} - \mu_{121}(k)))^2)}{(n_1 \cdot \text{sum}(W_{121})^2)}; \]
\[ BM_{122}(k) = \frac{\text{sum}((W_{122} \cdot (y_{tot} - \mu_{122}(k)))^2)}{(n_1 \cdot \text{sum}(W_{122})^2)}; \]
BM211(k) = (sum((W211.*(y_tot_2a-mu211(k))).^2)/(n2*sum(W211)^2));
BM212(k) = (sum((W212.*(y_tot_2a-mu212(k))).^2)/(n2*sum(W212)^2));
BM221(k) = (sum((W221.*(y_tot_2a-mu221(k))).^2)/(n2*sum(W221)^2));
BM222(k) = (sum((W222.*(y_tot_2a-mu222(k))).^2)/(n2*sum(W222)^2));

%% covariance for SRTPA
C12_3(k) = sum((W111.*(y_tot-mu111(k))).*(W112.*(y_tot-mu112(k))))/(n1^2);
C13_3(k) = sum((W111.*(y_tot-mu111(k))).*(W121.*(y_tot-mu121(k))))/(n1^2);
C14_3(k) = sum((W111.*(y_tot-mu111(k))).*(W122.*(y_tot-mu122(k))))/(n1^2);
C23_3(k) = sum((W112.*(y_tot-mu112(k))).*(W121.*(y_tot-mu121(k))))/(n1^2);
C24_3(k) = sum((W112.*(y_tot-mu112(k))).*(W122.*(y_tot-mu122(k))))/(n1^2);
C34_3(k) = sum((W121.*(y_tot-mu121(k))).*(W122.*(y_tot-mu122(k))))/(n1^2);

C12_3_2a(k) = sum((W211.*(y_tot_2a-mu211(k))).*(W212.*(y_tot_2a-mu212(k))))/(n2^2);
C13_3_2a(k) = sum((W211.*(y_tot_2a-mu211(k))).*(W221.*(y_tot_2a-mu221(k))))/(n2^2);
C14_3_2a(k) = sum((W211.*(y_tot_2a-mu211(k))).*(W222.*(y_tot_2a-mu222(k))))/(n2^2);
C23_3_2a(k) = sum((W212.*(y_tot_2a-mu212(k))).*(W221.*(y_tot_2a-mu221(k))))/(n2^2);
C24_3_2a(k) = sum((W212.*(y_tot_2a-mu212(k))).*(W222.*(y_tot_2a-mu222(k))))/(n2^2);
C34_3_2a(k) = sum((W221.*(y_tot_2a-mu221(k))).*(W222.*(y_tot_2a-mu222(k))))/(n2^2);
%% to test 8 strategies
new_contrast = [1 0 -1 0 0 0 0 ; 0 1 0 -1 0 0 0 ; ... 
   1 -1 0 0 0 0 0 ; 0 0 0 1 0 -1 0; 0 0 0 0 1 0 -1; 
   0 0 0 1 -1 0 0];

%% testing in URT
new_mean1 = [m111(k) m112(k) m121(k) m122(k) m211(k) m212(k) 
   m221(k) m222(k)];

%% var-cov matrix for URT
new_cov1 = [s111_1(k)/size1 0 0 0 0 0 0 0; 
   0 s112_1(k)/size2 0 0 0 0 0 0; ... 
   0 0 s121_1(k)/size3 0 0 0 0 0; 0 0 s122_1(k)/size4 0 0 0 0; ... 
   0 0 0 0 s111_1_2a(k)/size1_2a 0 0 0; 
   0 0 0 0 0 s112_1_2a(k)/size2_2a 0 0; ... 
   0 0 0 0 0 0 s121_1_2a(k)/size3_2a 0; 
   0 0 0 0 0 0 0 s122_1_2a(k)/size4_2a];

% ts_tot_1(k) = new_mean1*new_contrast'*
% inv(new_contrast*new_cov1*new_contrast')*new_contrast*new_mean1';

%% testing in SRTPA
new_mean = [mu111(k) mu112(k) mu121(k) mu122(k) mu211(k) 
   mu212(k) mu221(k) mu222(k)];

new_cov = [BM111(k) C12_3(k) C13_3(k) C14_3(k) 0 0 0 0 ; 
   C12_3(k) BM112(k) C23_3(k) C24_3(k) 0 0 0 0 ; ... 
   C13_3(k) C23_3(k) BM121(k) C34_3(k) 0 0 0 0; 
   C14_3(k) C24_3(k) C34_3(k) BM122(k) 0 0 0 0 ; ... 
   0 0 0 0 BM211(k) C12_3_2a(k) C13_3_2a(k) C14_3_2a(k); 
   0 0 0 0 C12_3_2a(k) BM212(k) C23_3_2a(k) C24_3_2a(k); ... 
   0 0 0 0 C13_3_2a(k) C23_3_2a(k) BM221(k) C34_3_2a(k); 
   0 0 0 0 C14_3_2a(k) C24_3_2a(k) C34_3_2a(k) BM222(k)];

% ts_tot_3(k) = new_mean*new_contrast'*
inv(new_contrast*new_cov*new_contrast')*new_contrast*new_mean';

%% A1, A2 testing
%% mean matrices
mean_1 = [m111(k) m112(k) m121(k) m122(k)]; % URT A1
mean_2 = [nmul11(k) nmu112(k) nmu121(k) nmu122(k)]; % SRT A1
mean_3 = [mul11(k) mul12(k) mul21(k) mul22(k)]; % SRTPA A1
mean_1_2a = [m211(k) m212(k) m221(k) m222(k)]; % URT A2
mean_2_2a = [nmul21(k) nmu212(k) nmu221(k) nmu222(k)]; % SRT A2
mean_3_2a = [mul21(k) mul212(k) mul221(k) mul222(k)]; % SRTPA A2
contrast = [1 0 -1 0;0 1 0 -1; 1 -1 0 0];
%% Var-Cov matrix for URT
v_cov_1 = [s111_1(k)/size1 0 0 0; 0 s112_1(k)/size2 0 0;...
0 0 s121_1(k)/size3 0; 0 0 s122_1(k)/size4];
v_cov_1_2a = [s111_1_2a(k)/size1_2a 0 0 0;
0 0 s121_1_2a(k)/size3_2a 0; 0 0 s122_1_2a(k)/size4_2a];
%% Var-Cov matrix for SRT
v_cov_2 = [B111(k) C12_2(k) C13_2(k) C14_2(k); C12_2(k) B112(k) C13_2(k) C14_2(k);
C13_2(k) C12_2(k) B121(k) C23_2(k); C14_2(k) C12_2(k) B221(k) C24_2(k);
C24_2(k) C23_2(k) B122(k)];
v_cov_2_2a = [B211(k) C12_2_2a(k) C13_2_2a(k) C14_2_2a(k); C12_2_2a(k) B212(k) C23_2_2a(k) C24_2_2a(k);
C13_2_2a(k) C23_2_2a(k) B221(k) C24_2_2a(k); C14_2_2a(k) C24_2_2a(k) C34_2_2a(k) B222(k)];
%% Var-Cov matrix for SRTPA
v_cov_3 = [BM111(k) C12_3(k) C13_3(k) C14_3(k); C12_3(k)
BM12(k) C23_3(k) C24_3(k); C13_3(k) C23_3(k) BM121(k) C34_3(k); C14_3(k) C24_3(k)
v_cov_3_2a = [BM211(k) C12_3_2a(k) C13_3_2a(k) C14_3_2a(k); C12_3_2a(k) BM212(k) C23_3_2a(k) C24_3_2a(k);...
C13_3_2a(k) C23_3_2a(k) BM221(k) C34_3_2a(k); C14_3_2a(k) C24_3_2a(k) C34_3_2a(k) BM222(k)];

%% Test Statistics
%% URT A1
ts_1(k) = mean_1*contrast'*inv(contrast*v_cov_1*contrast')*contrast*mean_1';

%% SRTPA A1
ts_3(k) = mean_3*contrast'*inv(contrast*v_cov_3*contrast')*contrast*mean_3';

%% URT A2
ts_1_2a(k) = mean_1_2a*contrast'*inv(contrast*v_cov_1_2a*contrast')*contrast*mean_1_2a';

%% SRTPA A2
ts_3_2a(k) = mean_3_2a*contrast'*inv(contrast*v_cov_3_2a*contrast')*contrast*mean_3_2a';

% =================================
% comparing test statistics with chi-sq critical values
% =================================

% for URT
if abs(ts_1(k)) >= 7.82
    count1(k) = 1;
else
    count1(k) = 0;
end
if abs(ts_1_2a(k)) >= 7.82
    count1_2a(k) = 1;
else
    count1_2a(k) = 0;
end
if abs(ts_tot_1(k)) >= 14.02
    count_tot_1(k) = 1;
else count_tot_1(k) = 0;
end

%% for SRTPA
if abs(ts_tot_3(k)) >= 14.02
    count_tot_3(k) = 1;
else count_tot_3(k) = 0;
end
if abs(ts_3(k)) >= 7.82
    count3(k) = 1;
else count3(k) = 0;
end
if abs(ts_3_2a(k)) >= 7.82
    count3_2a(k) = 1;
else count3_2a(k) = 0;
end

%%=========================================================================% Coverage probabilities
%%=========================================================================%
%% true means for A1
t_mu111 = piR1*m11d + (1-piR1)*m1d1;
t_mu112 = piR1*m11d + (1-piR1)*m1d2;
t_mu121 = piR1*m12d + (1-piR1)*m1d1;
t_mu122 = piR1*m12d + (1-piR1)*m1d2;

%% true means for A2
t_mu211 = piR2*m21d + (1-piR2)*m2d1;
t_mu212 = piR2*m21d + (1-piR2)*m2d2;
t_mu221 = piR2*m22d + (1-piR2)*m2d1;
t_mu222 = piR2*m22d + (1-piR2)*m2d2;

%% Confidence interval in URT
U_CL111 = m111 - 1.96*sqrt(s111_1/size1);
U_CU111 = m111 + 1.96*sqrt(s111_1/size1);
U_CL112 = m112 - 1.96*sqrt(s112_1/size2);
U_CU112 = m112 + 1.96*sqrt(s112_1/size2);
U_CL121 = m121 - 1.96*sqrt(s121_1/size3);
U_CU121 = m121 + 1.96*sqrt(s121_1/size3);
U_CL122 = m122 - 1.96*sqrt(s122_1/size4);
U_CU122 = m122 + 1.96*sqrt(s122_1/size4);
U_CL211 = m211 - 1.96*sqrt(s111_1_2a/size1_2a);
U_CU211 = m211 + 1.96*sqrt(s111_1_2a/size1_2a);
U_CL212 = m212 - 1.96*sqrt(s112_1_2a/size2_2a);
U_CU212 = m212 + 1.96*sqrt(s112_1_2a/size2_2a);
U_CL221 = m221 - 1.96*sqrt(s121_1_2a/size3_2a);
U_CU221 = m221 + 1.96*sqrt(s121_1_2a/size3_2a);
U_CL222 = m222 - 1.96*sqrt(s122_1_2a/size4_2a);
U_CU222 = m222 + 1.96*sqrt(s122_1_2a/size4_2a);

%% Coverage probability in URT
U_CP111 = (t_mu111 >= U_CL111) .* (t_mu111 <= U_CU111);
U_CP112 = (t_mu112 >= U_CL112) .* (t_mu112 <= U_CU112);
U_CP121 = (t_mu121 >= U_CL121) .* (t_mu121 <= U_CU121);
U_CP122 = (t_mu122 >= U_CL122) .* (t_mu122 <= U_CU122);
U_CP211 = (t_mu211 >= U_CL211) .* (t_mu211 <= U_CU211);
U_CP212 = (t_mu212 >= U_CL212) .* (t_mu212 <= U_CU212);
U_CP221 = (t_mu221 >= U_CL221) .* (t_mu221 <= U_CU221);
U_CP222 = (t_mu222 >= U_CL222) .* (t_mu222 <= U_CU222);
%%% Confidence interval in SRTPA
CL111 = mu111 - 1.96*sqrt(BM111);
CU111 = mu111 + 1.96*sqrt(BM111);
CL112 = mu112 - 1.96*sqrt(BM112);
CU112 = mu112 + 1.96*sqrt(BM112);
CL121 = mu121 - 1.96*sqrt(BM121);
CU121 = mu121 + 1.96*sqrt(BM121);
CL122 = mu122 - 1.96*sqrt(BM122);
CU122 = mu122 + 1.96*sqrt(BM122);
CL211 = mu211 - 1.96*sqrt(BM211);
CU211 = mu211 + 1.96*sqrt(BM211);
CL212 = mu212 - 1.96*sqrt(BM212);
CU212 = mu212 + 1.96*sqrt(BM212);
CL221 = mu221 - 1.96*sqrt(BM221);
CU221 = mu221 + 1.96*sqrt(BM221);
CL222 = mu222 - 1.96*sqrt(BM222);
CU222 = mu222 + 1.96*sqrt(BM222);

%%% coverage probability in SRTPA
CP111 = (t_mu111 >= CL111).* (t_mu111 <= CU111);
CP112 = (t_mu112 >= CL112).* (t_mu112 <= CU112);
CP121 = (t_mu121 >= CL121).* (t_mu121 <= CU121);
CP122 = (t_mu122 >= CL122).* (t_mu122 <= CU122);
CP211 = (t_mu211 >= CL211).* (t_mu211 <= CU211);
CP212 = (t_mu212 >= CL212).* (t_mu212 <= CU212);
CP221 = (t_mu221 >= CL221).* (t_mu221 <= CU221);
CP222 = (t_mu222 >= CL222).* (t_mu222 <= CU222);

% latex(P2,'%.3f')
% savefile1 = ['VC55' num2str(piR1*10) '51.mat'];
% save(savefile1, 'P*')
% save savefile Policy
% msave('VC5551.mat','P*');
% save VC55581.mat Policy*

% end
% end
% end
% diary vc_table_out11

PPi = [piA piR1 piR2 piB piC ];
PPower = [sum(count_tot_1)/nos sum(count_tot_3)/nos];
P1 = [ mean(m111') sqrt(mean(s111_1)/size1) 
  ((t_mu111 - mean(m111'))/t_mu111)*100 mean(U_CP111') sum(count1)/nos...
  mean(mu111') sqrt(mean(BM111)) ((t_mu111 - mean(mu111'))/t_mu111)*100 mean(CP111') sum(count3)/nos;...
  mean(m122') sqrt(mean(s122_1)/size4) ((t_mu211 - mean(m211'))/t_mu211)*100 mean(U_CP211') sum(count1_2a)/nos...
  mean(mu211') sqrt(mean(BM211)) ((t_mu222 - mean(mu222'))/t_mu222)*100 mean(CP211') sum(count3_2a)/nos;...]

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mean(mu211') sqrt(mean(BM211)) ((t_mu211 - mean(mu211'))/t_mu211)*
100 mean(CP211') sum(count3_2a)/nos;

mean(m212') sqrt(mean(s112_1_2a)/size2_2a)
((t_mu212 - mean(m212'))/t_mu212)*100 mean(U_CP212') sum(count3_2a)/nos;

mean(mu212') sqrt(mean(BM212)) ((t_mu212 - mean(mu212'))/t_mu212)*
100 mean(CP212') sum(count3_2a)/nos;

mean(m221') sqrt(mean(s121_1_2a)/size3_2a)
((t_mu221 - mean(m221'))/t_mu221)*100 mean(U_CP221') sum(count1_2a)/nos;

mean(mu221') sqrt(mean(BM221)) ((t_mu221 - mean(mu221'))/t_mu221)*
100 mean(CP221') sum(count3_2a)/nos;

mean(m222') sqrt(mean(s122_1_2a)/size4_2a)
((t_mu222 - mean(m222'))/t_mu222)*100 mean(U_CP222') sum(count1_2a)/nos;

mean(mu222') sqrt(mean(BM222)) ((t_mu222 - mean(mu222'))/t_mu222)*
100 mean(CP222') sum(count3_2a)/nos];

P2 =
[mean(nmu111') sqrt(mean(B111)) ((t_mu111 - mean(nmu111'))/t_mu111)*100;
mean(nmu112') sqrt(mean(B112)) ((t_mu112 - mean(nmu112'))/t_mu112)*100;
mean(nmu121') sqrt(mean(B121)) ((t_mu121 - mean(nmu121'))/t_mu121)*100;
mean(nmu122') sqrt(mean(B122)) ((t_mu122 - mean(nmu122'))/t_mu122)*100;
mean(nmu211') sqrt(mean(B211)) ((t_mu211 - mean(nmu211'))/t_mu211)*100;
mean(nmu212') sqrt(mean(B212)) ((t_mu212 - mean(nmu212'))/t_mu212)*100;
mean(nmu221') sqrt(mean(B221)) ((t_mu221 - mean(nmu221'))/t_mu221)*100;
mean(nmu222') sqrt(mean(B222)) ((t_mu222 - mean(nmu222'))/t_mu222)*100];

%diary off

disp('pi0 & piR1 & piR2 & piB1 & piB2 & piC1 & piC2')
latex(PPi,'%.1f')
latex(PPower,'%.3f')

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disp('True & Estimates & SE & RelativeBias & CP & Power')
latex(P1,'%.2f')
sum(count_tot_1)/nos
sum(count_tot_3)/nos
latex(P2,'%.2f')
%% True values are same under null no matter what response rates are
%% applied

A.2 NONPARAMETRIC INFERENCE ON MEDIAN RESIDUAL LIFE
FUNCTION IN SEQUENTIALLY RANDOMIZED TRIALS

clear all;

%same functions needed from previous code
%parameters
% ==============================================================
% Leukemia data set analysis
% ==============================================================
Pi_z = 0.5; % equally assigned to both maintenance treatments
t0 = 250; % time of interest
trtA = 1; %depend on induntion treatment option
% trtA = 2;
[id trt1 resp resp_time consent sec_rand_time trt2 death U age wbc] = textread('C:\calgb1_.txt','%d %d %d %d %d %d %d %d %d %d %f ');
R = resp.*consent;
if trt2 == 2
    trt2 = 0;
end
Z = trt2;
D = death; % 0 for censored
n = length(D);
for i=1:n
    if (Z(i)==2)
        Z(i) = 0;
    else Z(i) = Z(i);
    end
    if D(i)==0
        D1(i)=1;
    else D1(i)=0;
    end
end
D1=D1';

% for first or second treatment option in induction treatment
index_vector = find(trt1==trtA);
R = R(index_vector);
Z = Z(index_vector);
D = D(index_vector);
D1 = D1(index_vector);
U = U(index_vector);
resp_time = resp_time(index_vector);

n = length(D);

% Kaplan-Meier Estimators
[K,x] = ecdf(U,'censoring',D,'function','survivor');
[S,x1] = ecdf(U,'censoring',D1,'function','survivor');
K = fOne(U,x,K);
S = fOne(U,x1,S);

for j = 1:n
    if K(j) == 0 K(j) = K(j-1); end
    if S(j) == 0 S(j) = S(j-1); end
end

% weight functions
Q2=1-R + ((R.*(1-Z))/(1- Pi_z));
Q1=1-R + ((R.*Z)/Pi_z);
Cens = D./K';
K = K';
save FileforSecant D K Q1 Q2 U t0 n;

% Secant method to find Theta
[Theta31,fncvalue,err,hist] = secant1('secfunc1',0,500,1.0e-16,1.0e-16,10000);
[Theta32,fncvalue,err,hist] = secant1('secfunc2',0,500,1.0e-16,1.0e-16,10000);
K = K';

% Survival for each time point;
for j = 1:n
    S01 = Cens.*Q1.*(U>U(j));
    S02 = Cens.*Q2.*(U>U(j));
    S1(j) = sum(S01)/sum(Cens.*Q1);
    S2(j) = sum(S02)/sum(Cens.*Q2);
end
S1_t0 = fOne(t0,U,S1);
S2_t0 = fOne(t0,U,S2);

S_half1 = 0.5*S1;
S_half2 = 0.5*S2;
S_half1_t0 = fOne(t0,U,S_half1);
S_half2_t0 = fOne(t0,U,S_half2);

%Find S inverse for 0.5*S(t)
Sinv1 = fOne(S_half1, S1, U);
Sinv2 = fOne(S_half2, S2, U);
Sinv1_t0 = fOne(t0,U,Sinv1);
Sinv2_t0 = fOne(t0,U,Sinv2);

%kernel density to find density of S
[den1,xi1] = ksdensity(U,’weights’,Q1,’censoring’,D1,’npoints’,n);
[den2,xi2] = ksdensity(U,’weights’,Q2,’censoring’,D1,’npoints’,n);
Den21 = fOne(U,xi1,den1);
Den22 = fOne(U,xi2,den2);
Den21_t0 = fOne(t0,U,Den21);
Den22_t0 = fOne(t0,U,Den22);

% MERL Theta 1
for j = 1:n
    Theta11(j) = Sinv1(j) - U(j);
    Theta12(j) = Sinv2(j) - U(j);
end
Theta11_t0 = fOne(t0,U,Theta11);
Theta12_t0 = fOne(t0,U,Theta12);

% density for theta 1 +t0 and theta3+t0
Den31_the = fOne(Theta31+t0,U,Den21);
Den32_the = fOne(Theta32+t0,U,Den22);
Den11_the_new = fOne(Theta11_t0+t0, U,Den21);
Den12_the_new = fOne(Theta12_t0+t0, U,Den22);

U_new1 = U' + Theta11;
U_new2 = U' + Theta12;

[den1_new,x1_new] = ksdensity(U_new1,'npoints',n,
'weights',Q1);
[den2_new,x2_new] = ksdensity(U_new2,'npoints',n,
'weights',Q2);
Den11_the = fOne(U_new1,x1_new,den1_new);
Den12_the = fOne(U_new2,x2_new,den2_new);

% /* Y(u) and Y(u)^-1
for j = 1:n
    Y(j) = sum(U >= U(j));
    Y_inv(j) = (sum(U >= U(j))).^-1;
end

%Aalan-Nelson Est.
for j = 1:n
    if (U(j) < t0) & (D(j) ==1)
\[ \text{ANe}(j) = \sum(\text{Y_inv}(j)) \]
end
end

\% finding variances
for j = 1:n
    for k = 1:n
        \[ G11(j, k) = \frac{\sum(\text{Cens} \cdot \text{Q1} \cdot ((U \geq U(j) - 0.5 \cdot (U > U(j))) \cdot (U \geq U(k)))}{n \cdot \text{S}(k)} \]
        \[ G12(j, k) = \frac{\sum(\text{Cens} \cdot \text{Q2} \cdot ((U \geq U(j) - 0.5 \cdot (U > U(j))) \cdot (U \geq U(k)))}{n \cdot \text{S}(k)} \]
        \[ E11(j, k) = \frac{\sum(\text{Cens} \cdot ((U \geq U(j) - 0.5 \cdot (U > U(j))) - G11(j, k))^2 \cdot (U \geq U(k)))}{n} \]
        \[ E12(j, k) = \frac{\sum(\text{Cens} \cdot ((U \geq U(j) - 0.5 \cdot (U > U(j))) - G12(j, k))^2 \cdot (U \geq U(k)))}{n} \]
        \[ G21(j, k) = \frac{\sum(\text{Cens} \cdot \text{Q1} \cdot (U > U(j)) \cdot (U \geq U(k)))}{n \cdot \text{S}(k)} \]
        \[ G22(j, k) = \frac{\sum(\text{Cens} \cdot \text{Q2} \cdot (U > U(j)) \cdot (U \geq U(k)))}{n \cdot \text{S}(k)} \]
        \[ E21(j, k) = \frac{\sum(\text{Cens} \cdot ((U \geq U(j) - G21(j, k))^2 \cdot (U \geq U(k)))}{n} \]
        \[ E22(j, k) = \frac{\sum(\text{Cens} \cdot ((U \geq U(j) - G22(j, k))^2 \cdot (U \geq U(k)))}{n} \]
    end
end

V_second11(j) = \sum((1-D)' \cdot E11(j,:) / (K.*Y))
V_second12(j) = \sum((1-D)' \cdot E12(j,:) / (K.*Y))
V_second21(j) = \sum((1-D)' \cdot E21(j,:) / (K.*Y))
V_second22(j) = \sum((1-D)' \cdot E22(j,:) / (K.*Y))
V_first11(j) = \sum(\text{Cens} \cdot ((U \geq U(j) - 0.5 \cdot (U > U(j))) \cdot (U \geq U(k))) / (K.*Y))
\[ V_{\text{first}12}(j) = \text{sum}(\text{Cens} \cdot ((Q2 \cdot ((U>U_{\text{new}1}(j)) - 0.5 \cdot (U>U(j)))^2))/n; \]

\[ V_{\text{first}21}(j) = \text{sum}(\text{Cens} \cdot ((Q1 \cdot (U>U(j))-S1(j))^2))/n; \]

\[ V_{\text{first}22}(j) = \text{sum}(\text{Cens} \cdot ((Q2 \cdot (U>U(j))-S2(j))^2))/n; \]

\[ \text{var}11(j) = (V_{\text{first}11}(j) + V_{\text{second}11}(j))/n; \]

\[ \text{var}12(j) = (V_{\text{first}12}(j) + V_{\text{second}12}(j))/n; \]

\[ \text{var}21(j) = (V_{\text{first}21}(j) + V_{\text{second}21}(j))/n; \]

\[ \text{var}22(j) = (V_{\text{first}22}(j) + V_{\text{second}22}(j))/n; \]

\[ \text{Var}11(j) = \text{var}11(j)/(\text{Den}11_{\text{the}}(j)^2); \]

\[ \text{Var}12(j) = \text{var}12(j)/(\text{Den}12_{\text{the}}(j)^2); \]

\[ \text{Var}21(j) = \text{var}21(j)/(4*(\text{Den}21(j)^2)); \]

\[ \text{Var}22(j) = \text{var}22(j)/(4*(\text{Den}22(j)^2)); \]

\[ \text{Se}11(j) = \sqrt{\text{Var}11(j)}; \]

\[ \text{Se}12(j) = \sqrt{\text{Var}12(j)}; \]

\[ \text{Se}21(j) = \sqrt{\text{Var}21(j)}; \]

\[ \text{Se}22(j) = \sqrt{\text{Var}22(j)}; \]

\[ \text{CL}_L_{11}(j) = \Theta_{11}(j) - 1.96 \cdot \text{Se}11(j); \]

\[ \text{CL}_U_{11}(j) = \Theta_{11}(j) + 1.96 \cdot \text{Se}11(j); \]

\[ \text{CL}_L_{12}(j) = \Theta_{12}(j) - 1.96 \cdot \text{Se}12(j); \]

\[ \text{CL}_U_{12}(j) = \Theta_{12}(j) + 1.96 \cdot \text{Se}12(j); \]

\[ \text{CL}_L_{21}(j) = \Theta_{11}(j) - 1.96 \cdot \text{Se}21(j); \]

\[ \text{CL}_U_{21}(j) = \Theta_{11}(j) + 1.96 \cdot \text{Se}21(j); \]

\[ \text{CL}_L_{22}(j) = \Theta_{12}(j) - 1.96 \cdot \text{Se}22(j); \]

\[ \text{CL}_U_{22}(j) = \Theta_{12}(j) + 1.96 \cdot \text{Se}22(j); \]

\[ \text{end} \]

\[ \text{Se}11_{t0} = fOne(t0,U,\text{Se}11); \]

\[ \text{Se}12_{t0} = fOne(t0,U,\text{Se}12); \]

\[ \text{Se}21_{t0} = fOne(t0,U,\text{Se}21); \]
Se22_t0 = fOne(t0, U, Se22);

CL_L11_t0 = fOne(t0, U, CL_L11);
CL_U11_t0 = fOne(t0, U, CL_U11);
CL_L12_t0 = fOne(t0, U, CL_L12);
CL_U12_t0 = fOne(t0, U, CL_U12);

% sandwich estimator for theta 1
AA1 = Den11_the_new.^2;
AA2 = Den12_the_new.^2;
BB1 = sum(((Cens.*Q1.*((U>t0+Theta11_t0)-0.5.*(U>t0))).^2)/
          (sum(Cens.*Q1)));
BB2 = sum(((Cens.*Q2.*((U>t0+Theta12_t0)-0.5.*(U>t0))).^2)/
          (sum(Cens.*Q2)));
Var31 = (BB1/AA1)/n;
Var32 = (BB2/AA2)/n;
Se31 = sqrt(Var31);
Se32 = sqrt(Var32);

% sandwich estimator for theta 3 from secant
AA31 = Den31_the.^2;
AA32 = Den32_the.^2;
BB31 = sum(((Cens.*Q1.*((U>t0+Theta31)-0.5.*(U>t0))).^2)/
          (sum(Cens.*Q1)));
BB32 = sum(((Cens.*Q2.*((U>t0+Theta32)-0.5.*(U>t0))).^2)/
          (sum(Cens.*Q2)));
Var331 = (BB31/AA31)/n;
Var332 = (BB32/AA32)/n;
Se331 = sqrt(Var331);
Se332 = sqrt(Var332);
\[ K = K'; \]

\[
\psi_{11} = \frac{D}{K} \cdot Q_1 \cdot (U > t_0) \cdot R \cdot (\text{resp}_t \leq t_0) \cdot Z; \\
\psi_{12} = \frac{D}{K} \cdot Q_1 \cdot (U > t_0) \cdot (1 - R) \cdot (\text{resp}_t \leq t_0) \cdot Z; \\
\psi_{31} = \frac{D}{K} \cdot Q_2 \cdot (U > t_0) \cdot R \cdot (\text{resp}_t \leq t_0) \cdot Z; \\
\psi_{32} = \frac{D}{K} \cdot Q_2 \cdot (U > t_0) \cdot (1 - R) \cdot (\text{resp}_t \leq t_0) \cdot Z; \\
\psi_{21} = \frac{D}{K} \cdot R \cdot (\text{resp}_t \leq t_0); \\
\psi_{22} = \frac{D}{K} \cdot (1 - R) \cdot (\text{resp}_t \leq t_0); \\
\]

% Variance by M-estimation

```matlab
A1 = [\text{Den11_the_new} 0; 0 -1]; \\
B1 = [\text{sum(\psi_{11}^2)/n \ sum(\psi_{11} \cdot \psi_{21}/n; \ sum(\psi_{11} \cdot \psi_{21}/n \\
sum(\psi_{21}^2)/n]]; \\
inva1 = inv(A1); \\
V1 = (inva1*B1*inva1')./n; \\
A2 = [\text{Den12_the_new} 0; 0 -1]; \\
B2 = [\text{mean(\psi_{11}^2)} \text{mean(\psi_{12} \cdot \psi_{22}); \ mean(\psi_{12} \cdot \psi_{22} \\
mean(\psi_{22}^2)}]; \\
inva2 = inv(A2); \\
V2 = (inva2*B2*inva2')./n; \\
new_var = V1+V2;
```
out = [Theta11_t0 Se11_t0 Se31 Theta31 Se331 Theta41_t0 Se41];
out1= [Theta12_t0 Se12_t0 Se32 Theta32 Se332 Theta42_t0 Se42];
ltx(out,'%.2f')
ltx(out1,'%.2f')

% ================
% Simulation study for Median Residual Life Function
% ================

A = 3.5;
Pi_r = 0.4;
Pi_z = 0.5;
t0 = 365;
nu = 2;
rho = 0.2;
%1000 iterations and sample size
nos = 1000;
n = 200;

% values for different scenrios
% mu31 = 267; mu32 = 235; %183, 0.4, 0.5
mu31=234.3; mu32=193.4; %365, 0.4, 0.5

% mu31 = 341.9; mu32 = 285.6; %183 0705
% mu31 = 262.9; mu32 = 209.5; %365 0705

% mu31 = 273.9; mu32 = 239.9; %183 0403
for l = 1:nos
    % C for Censoring~Uni(0,A);
    c = rand(n,1);
    C = A*c;
    ind1 = 0;
    ind2 = 0;
    index2 = 0;
    index3 = 0;
    index4 = 0;
    r = rand(n,1);
    z = rand(n,1);
    % **Generating R from b(1,Pi_r) for Consent indicator;
    R = zeros(n,1);
    Z = zeros(n,1);
    Tnr = zeros(n,1);
    Ta = zeros(n,1);
    T1 = zeros(n,1);
    T2 = zeros(n,1);
    for i = 1:n
        % indicator for receiving second treatment
        if r(i) < Pi_r
            R(i,1) = 1;
        else
            R(i,1) = 0;
        end
for i = 1:n
    if R(i) == 1
        % Generating Z from bin(1, Pi_z) for trt B1 indicator;
        if z(i) < Pi_z
            Z(i,1) = 1;
        else
            Z(i,1) = 0;
        end
    else
        Z(i,1) = -1;
    end
end

ind1 = find(R==0);
ind2 = find(R==1);
Tnr(ind1) = expinv(rand(length(ind1),1),0.5);
% failure times are exponential(exp(beta1)) under R=0
Ta(ind2) = expinv(rand(length(ind2),1),0.1);
% failure times are exponential(exp(beta1)) under R=1
u11 = rand(length(ind2),1);
u12 = rand(length(ind2),1);
T1(ind2) = (1/rho).*(-exp(-0.6).*log(1-u11)).^(1/nu);
T2(ind2) = (1/rho).*(-exp(-0.9).*log(1-u12)).^(1/nu);
T = ((R.*((Z).*((Ta + T1) + (1-Z).*((Ta + T2)) + (1-R).*Tnr)));
Tr = R.*Ta + (1-R).*Tnr;
U = min(T,C);
D = (T <= C); % 1 for not censoring
data = [U R Z D Tr Ta Tnr];
data = sortrows(data);
U = data(:,1);
R = data(:,2);
Z = data(:,3);
D = data(:,4);
Tr = data(:,5);
Ta = data(:,6);
Tnr = data(:,7);
D(n,1) = 1;
D1 = 1-D;
U = U*365.25;
Tr = Tr*365.25;
Ta = Ta*365.35;
Tnr = Tnr*365.25;

% weight
Q1 = (1-R) + ((R.*Z)./(Pi_z));
Q2 = (1-R) + ((R.*(1-Z))./(1-Pi_z));

% KMe
[K,sk] = kmest(U,D);
[S,ss] = kmest(U,D1);

% save files for EEB method
save FileforSecant D K Q1 Q2 U t0 n;

%=========================================================================
% SSB method & Taylor
%=========================================================================

% SampleSize adjusted survival estimates for each time point;
S1 = 0; S2 = 0;
for j = 1:n
S1(j) = 1-sum(D./K.*Q1.*(U<=U(j)))/sum(D./K.*Q1);
S2(j) = 1-sum(D./K.*Q2.*(U<=U(j)))/sum(D./K.*Q2);
end

%   S1 = S_1(:,l);
%   S2 = S_2(:,l);
S1_t0 = fOne(t0,U,S1);
S2_t0 = fOne(t0,U,S2);

[S_half1 Sinv1 Sinv1_t0(l) S_half1_t0] = S_find(S1, U, t0);
[S_half2 Sinv2 Sinv2_t0(l) S_half2_t0] = S_find(S2, U, t0);
[Den21 Den21_t0] = denS(U, Q1, D1, t0);
[Den22 Den22_t0] = denS(U, Q2, D1, t0);

% **MERL Theta 1 and 2**;
Theta11_t0(l) = Sinv1_t0(l) - t0;
Theta12_t0(l) = Sinv2_t0(l) - t0;
Theta21_t0(l) = S_half1_t0/Den21_t0;
Theta22_t0(l) = S_half2_t0/Den22_t0;

% density for theta1+t0
Den11_the_new = fOne(Theta11_t0(l)+t0, U,Den21);
Den12_the_new = fOne(Theta12_t0(l)+t0, U,Den22);

%theta plus t0
U_new1_t0 = t0 + Theta11_t0(l);
U_new2_t0 = t0 + Theta12_t0(l);

% Y(u) and Y(u)^-1
Y = 0; Y_inv = 0;
for j = 1:n
    Y(j) = sum(U >= U(j));
    Y_inv(j) = (sum(U >= U(j))).^-1;
end
%
% Var and CP by Lunceford

[Se11(l) Cp11(l)] = CP5(D, K, Q1, U, U_new1_t0, t0, S, Y, Theta11_t0(l), mu31, Den11_the_new);
[Se12(l) Cp12(l)] = CP5(D, K, Q2, U, U_new2_t0, t0, S, Y, Theta12_t0(l), mu32, Den12_the_new);
[Se21(l) Cp21(l)] = CP6(D, K, Q1, U, t0, S, Y, Theta11_t0(l), mu31, Den21_t0, S1_t0);
[Se22(l) Cp22(l)] = CP6(D, K, Q2, U, t0, S, Y, Theta12_t0(l), mu32, Den22_t0, S2_t0);
%
% Var and CP by Sandwich for theta 1

[Var31 Var32 Se31(l) Se32(l) Cp31(l) Cp32(l)] =
CP1(Den11_the_new, Den12_the_new, D, K, Q1, Q2, U, t0, Theta11_t0(l), Theta12_t0(l), mu31, mu32);

%%%======================================================================
%%% EEB method
%%%======================================================================

%%% estimates for MERL times by EEB

[Theta31(l),fncvalue31(l),err,hist] =
secant1('secfunc1',0,400,1.0e-16,1.0e-16,10000);
[Theta32(l),fncvalue32(l),err,hist] =
secant1('secfunc2',0,400,1.0e-16,1.0e-16,10000);

%%% Density for theta3 + t0

Den31_t0 = fOne(Theta31(l)+t0,U,Den21);
Den32_t0 = fOne(Theta32(l)+t0,U,Den22);

%%% Var and CP for theta 3 from secant by sandwich

[Var331 Var332 Se331(l) Se332(l) Cp331(l) Cp332(l)] = ...
CP1(Den31_t0, Den32_t0, D, K, Q1, Q2, U, t0, Theta31(l), Theta32(l), mu31, mu32);

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end

Out = [mean(Theta11_t0) mean(Se11) sqrt(var(Theta11_t0)) mean(Cp11) ;
mean(Theta12_t0) mean(Se12) sqrt(var(Theta12_t0)) mean(Cp12);
mean(Theta11_t0) mean(Se31) sqrt(var(Theta11_t0)) mean(Cp31) ;
mean(Theta12_t0) mean(Se32) sqrt(var(Theta12_t0)) mean(Cp32) ;
mean(Theta21_t0) mean(Se21) sqrt(var(Theta21_t0)) mean(Cp21) ;
mean(Theta22_t0) mean(Se22) sqrt(var(Theta22_t0)) mean(Cp22) ;
mean(Theta31) mean(Se331) sqrt(var(Theta31)) mean(Cp331) ;
mean(Theta32) mean(Se332) sqrt(var(Theta32)) mean(Cp332) ;
mean(Theta41_t0) mean(Se41) sqrt(var(Theta41_t0)) mean(Cp41) ;
mean(Theta42_t0) mean(Se42) sqrt(var(Theta42_t0)) mean(Cp42)];
out = latex(Out, '\%.2f')

[mean(Se51) mean(Se52)]

% save MERL_0812_R0705_N200_T183.mat
%Relative bias
RB11 = ((mu31 - mean(Theta11_t0))/mu31)*100;
RB12 = ((mu32 - mean(Theta12_t0))/mu32)*100;
RB31 = ((mu31 - mean(Theta31))/mu31)*100;
RB32 = ((mu32 - mean(Theta32))/mu32)*100;
RB41 = ((mu31 - mean(Theta41_t0))/mu31)*100;
RB42 = ((mu32 - mean(Theta42_t0))/mu32)*100;

Out1 = [RB11 RB12 RB31 RB32 RB41 RB42];
out1 = latex(Out, '\%.1f')
BIBLIOGRAPHY


