STATISTICAL INFERENCES FOR TWO-STAGE TREATMENT REGIMES FOR TIME-TO-EVENT AND LONGITUDINAL DATA

by

Sachiko Miyahara

B.A. in Statistics, University of Connecticut, 1998

M.S. in Statistics, University of Connecticut, 2000

Submitted to the Graduate Faculty of

the Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2009

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This dissertation was presented

by

Sachiko Miyahara

It was defended on

July 16, 2009

and approved by

Dissertation Advisor:

Abdus Wahed Ph.D

Assistant Professor

Department of Biostatistics

Graduate School of Public Health

University of Pittsburgh

Committee Member:

Sati Mazumdar Ph.D

Professor

Department of Biostatistics

Graduate School of Public Health

University of Pittsburgh

Committee Member:

Yu Cheng Ph.D

Assistant Professor

Department of Statistics

School of Arts and Sciences

University of Pittsburgh

Committee Member:

Stephen Wisniewski Ph.D

Associate Professor

Department of Epidemiology

Graduate School of Public Health

University of Pittsburgh

STATISTICAL INFERENCES FOR TWO-STAGE TREATMENT REGIMES FOR TIME-TO-EVENT AND LONGITUDINAL DATA

Sachiko Miyahara, PhD

University of Pittsburgh, 2009

Adaptive treatment regime is a set of rules that governs the assignment of time-varying treatment based on observed covariates and intermediate response. Treatment choices are made sequentially as patients make transition from one health state to another. Specifically, in two stage randomization designs, patients are randomized to one of the initial treatments, and at the end of the first stage, they are randomized to one of the second stage treatments depending on the outcome of the initial treatment. The goal is to find the best treatment regime which produces the best terminal outcome. For time-to-event data, the best outcome is the longest survival time, and for longitudinal data, the best outcome is greatest reduction (or increase) in some scores such as reduction 24-item Hamilton Rating Scale of Depression ($HRSD_{24}$) score. For time-to-event data, we propose a weighted Kaplan-Meier estimator based on the method of inverse-probability weighting and compare its properties to that of the standard Kaplan-Meier estimator, and two other existing methods such as marginal mean model based estimator and weighted risk set estimator. For longitudinal data, outcome such as $HRSD_{24}$ scores are collected repeatedly to monitor the progress of the subject. We propose three methods incorporating inverse probability weighting, mixed models, multiple imputations, and pattern mixture models to assess the effect of treatment regimes on the longitudinal $HRSD_{24}$ scores. Methods are compared through simulation studies with an application to a depression study. Assessing the effect of treatment regimes on longitudinally observed outcome data is important in Public Health since clinicians will be able to identify effective treatment regimes for treating chronic diseases. Proposed statistical methods pro-

vide useful tools for unbiased estimation of the effects of treatment regimes from sequentially randomized designs. Availability of these methods will help advance the research in AIDS, cancer, depression, hepatitis and other disease areas.

Keywords: Dynamic Treatment Regimes, Adaptive Treatment Strategies, Weighted Kaplan-Meier Estimator, Inverse Weighting, Mixed Models, Missing Data, Repeated Measurement.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

First, I would like to thank my advisor, Dr. Wahed, for his support to complete this thesis. His patience and willingness to help his students are quite exceptional. I truly appreciated how he took his time to answer my questions or reviewed our papers so quickly even when he was very busy. Second, I thank my committee members, Dr. Mazumdar, Dr. Yu, and Dr. Wisniewski for their insightful comments and suggestions. Third, I thank my classmates, Yoko Tanaka, Meredith Lotz Wallace, Ya-Hsiu Chuang, Wenzhu Bi, Jinnie Ko and Kelly Im for the friendship. We shared hard (and sometimes sleepless) times together, as well as so many happy moments throughout our PhD life at the University of Pittsburgh. Next, I thank my parents for being very understandable and supportive even though my decision to study in the United States was not their first preference. Finally, I thank Nico for his continuous encouragement and intelligent advices. His ability to observe things from many different perspectives helped me in countless occasions.

1.0 INTRODUCTION

1.1 ADAPTIVE TREATMENT REGIME

Adaptive treatment regime, also known as dynamic treatment regime, is a set of rules that governs the assignment of time-varying treatment based on observed covariates and intermediate response. Treatment choices are made sequentially as patients make transition from one health state to another. The goal is to find the best treatment regime which produces the best terminal outcome, where the best outcome can be the longest survival time or greatest reduction in some scores such as Hamilton Rating Scale of Depression (HRSD_{24}) score. As such, this idea of adaptive treatment regimes appeals the clinicians treating complex diseases such as cancer, AIDS, and depression.

Sequentially randomized trials are often used to investigate the effect of adaptive treatment regimes. For example, suppose there are two treatment options A_1 and A_2 at the first stage and two treatment options for both responders (B_1 and B_2) and non-responders (B_1' and B_2') at the second stage. In sequentially randomized designs, patients are randomized to A_1 or A_2 followed by another randomization at the second stage, to B_1 or B_2 if the patient is a responder or to B_1' or B_2' if the patient is a non-responder. With this design, one can investigate a total of eight treatment regimes, namely, $A_jB_kB_l', j, k, l = 1, 2$ where $A_jB_kB_l'$ stands for "Treat with A_j followed by B_k if respond, by B_l' if otherwise." Number of treatment options in second stage may vary between responders and non-responders. For example, in a leukemia trial described in Stone et al. [1], patients not responding to the initial stage treatment were not treated any further (see Chapter 3).

Statistical inference on treatment regimes using a summary outcome measure has been well-studied in literature. For example, estimation of a mean response based on observational

longitudinal data are proposed in Murphy, Van Der Laan and Robins [2] and Murphy [3]. Methods for survival outcomes were considered in Lunceford et al. [4], Wahed and Tsiatis [5, 6], Guo and Tsiatis [7], Hernan et al. [8], Lokhnygina and Helterbrand [9]. Thall et al. [10] adapts a Bayesian approach to model the time to failure and compare two-stage adaptive treatment regimes.

1.2 GOALS AND ORGANIZATION

In this thesis, we worked on two different areas of estimations within the framework of adaptive treatment regimes in two-stage designs. One area is the estimation of survival distributions. The goal in this case is to estimate the survival distribution of the patient population following a specific regime based on the data collected through a two-stage randomization design. The other area is the estimation of treatment effect when the data are collected longitudinally. In this case, the goal is to assess the treatment effect over time for each treatment regime.

In Chapter 1, we introduced the idea of adaptive treatment regimes, and in Chapter 2, survival analysis, mixed models, and missing data methods are reviewed as they will be our common tools for developing methods for adaptive treatment regimes. In Chapter 3, we propose a weighted Kaplan Meier estimator for two-stage treatment regimes. In order to accommodate the loss due to the second randomization, a standard Kaplan Meier estimator was modified using the inverse-probability weighting method. Through simulation studies, the proposed methods were examined in large sample properties, and we compared the result with the ones from two existing estimators. In Chapter 4, we propose two methods to assess the effect of treatment regimes on longitudinal outcome data in two-stage designs. First method is referred to as two-step method since the overall treatment effects for all regimes are estimated in two steps. At the first step, the effect for each treatment sequence is estimated using mixed model techniques, and at the second step, the effects of treatment regimes are estimated by taking their weighted averages. The second method uses a multiple imputation approach to reconstruct observations for subjects who did not follow the regime

of interest. This method involves one extra step of multiple imputations and hence will be referred to as three-step method. The proposed methods were examined through simulation studies. In Chapter 5 we propose a method adapting pattern mixture models to assess the effects of treatment regimes when the data are not missing at random and have a monotone missing pattern. First, the data were stratified by the missing data pattern within each group of observed treatment sequence. Then the parameter of interest was estimated within each strata, and the treatment sequence effects were estimated by taking the weighted averages. Finally the overall treatment regime effects were estimated by combining the estimated treatment sequence effects with the empirical missing data response rate. The simulation studies were conducted to examine the performance of the proposed method.

2.0 METHODOLOGY REVIEWS

Methods used for the following chapters are reviewed in this chapter. In sub-section 2.1, we present an overview of standard Kaplan-Meier and Nelson-Aalen methods for estimating survival distribution. An overview of mixed models is included in sub-section 2.2. Finally, in sub-section 2.3, different types of missing data, multiple imputation methods, and pattern mixture models are explained.

2.1 KAPLAN-MEIER AND NELSON-AALEN ESTIMATORS

Methods for analyses of right censored data includes Kaplan-Meier, Nelson-Aalen, and Cox proportional hazard models. The Kaplan Meier estimator [11], also known as Product Limit estimator, is one of the most common method for estimating survival distribution of right censored data. Let $S(t)$ be the survival rate at time t, the Kaplan-Meier estimator is expressed as follows

$$\widehat{S}(t) = \begin{cases} 1, & t < t_1 \\ \Pi_{t_m \leq t}\big(1 - \frac{d_m}{Y_m}\big), & t \geq t_1 \end{cases}$$

where $d_m = \sum_{i=1}^{n} \Delta_i I(V_i = t_m)$, $Y_m = \sum_{i=1}^{n} I(V_i \geq t_m)$, V_i is the observed time to event (i.e. a minimum of time to event T_i and a censored time C_i), and $t_m, m = 1, 2, \ldots,$ are the distinct ordered failure times. The variance of Kaplan-Meier estimator can be estimated by Greenwood formula [12] as follows

$$\widehat{V}\left[\widehat{S}(t)\right] = \hat{S}(t)^2 \sum_{t_m \leq t} \frac{d_m}{Y_m(Y_m - d_m)}.$$

Another simple and common method for estimating survival distribution is the Nelson-Aalen estimator [13], the estimated survival distribution can be expressed as follows

$$\widehat{S}(t) = Exp[-\widehat{H}(t)]$$

where the cumulative hazard is estimated by

$$\widehat{H}(t) = \begin{cases} 0, & t < t_1 \\ \Pi_{t_m \leq t}\left(\frac{d_m}{Y_m}\right), & t \geq t_1 \end{cases}$$

The estimated variance of the Nelson-Aalen estimator is as follows

$$\sigma^2_H(t) = \Pi_{t_m \leq t} \frac{d_m}{{Y_m}^2}$$

Both Kaplan-Meier and Nelson-Aalen estimators appear in Chapter 3.

2.2 ANALYSIS OF LONGITIDINAL DATA

By longitudinal data, one usually refers to data measured repeatedly over time from the same individual. Compared to the cross-sectional data, such data have an advantage of allowing investigators to examine the average treatment effect over time. Mixed models [14, 15, 16] is one of the most common method for the analysis of longitudinal data since it can take the within-subject correlation into account.

There are three advantages of fitting mixed models. First, one model can estimate the overall treatment effect, and the same model can also provide treatment effects at each time point. Second, we can select the covariance structure for the repeated measurements. Finally, the mixed models can handle missing data if the missing is not at random. Since we adapt a mixed model approach in Chapter 4, we review the mixed models in following sub-sections.

2.2.1 COVARIANCE STRUCTURE

A wide range of covariance structures are available. Here we selected to introduce three most common structures: General, First-order Autoregressive, and Compound Symmetry. For $i = 1, ...n$, let Y_{im} be the repeatedly measured outcomes for the i^{th} subject at the m^{th} time point, $m = 1, ...M$. We define Y_i to be the vector of observations from the i^{th} individual and R_i to be the covariance matrix of Y_i. Assuming the number of repeated measures is four, the covariance structures are as follows

1. General

$$R_i = \begin{bmatrix} \sigma_1^2 & \theta_{12} & \theta_{13} & \theta_{14} \\ \theta_{21} & \sigma_2^2 & \theta_{22} & \theta_{24} \\ \theta_{31} & \theta_{32} & \sigma_3^2 & \theta_{34} \\ \theta_{41} & \theta_{42} & \theta_{43} & \sigma_4^2 \end{bmatrix},$$

   where θ_{ij}=θ_{ji}

2. First-order Auto Regressive

$$R_i = \begin{bmatrix} \sigma^2 & \sigma^2\rho & \sigma^2\rho^2 & \sigma^2\rho^3 \\ \sigma^2\rho & \sigma^2 & \sigma^2\rho & \sigma^2\rho^2 \\ \sigma^2\rho^2 & \sigma^2\rho & \sigma^2 & \sigma^2\rho \\ \sigma^2\rho^3 & \sigma^2\rho^2 & \sigma^2\rho & \sigma^2 \end{bmatrix}.$$

3. Compound Symmetry

$$R_i = \begin{bmatrix} \sigma^2 & \theta & \theta & \theta \\ \theta & \sigma^2 & \theta & \theta \\ \theta & \theta & \sigma^2 & \theta \\ \theta & \theta & \theta & \sigma^2 \end{bmatrix}.$$

where $\sigma^2 > \theta$

The first structure assumes that the variances at different time points are different as well as the covariances. The advantage of this structure is that it requires a minimum assumption about the covariance structure; however, the number of parameters can be large. For example, the number of repeated measures is four, 10 parameters are to be estimated. The second structure assumes that a relationship between the closer follow-ups has stronger correlation than the further follow-ups. The variance over time is assumed to remain constant. The most simple structure is the third one. The assumption is that the variance at each time point is the same, and the covariance is set equal as well. This assumption may not be realistic for some data, but it only requires to estimate two parameters compared to 10 parameters in the general structure.

2.2.2 RANDOM COEFFICIENTS MODEL

In general there are three categories of mixed models: random effects model, covariance pattern model, and random coefficient model. For the random effect model, we assume that certain effects are drawn from certain distributions and these effects add additional variation to the data in addition to the residual variation. The covariance pattern model allows us to fit fixed models with repeated measurements and a pattern of correlations between observations is directly estimated. For the random coefficient model, we assume

that a covariate effect introduce additional variation. For example, if the intercept and slopes are treated as random, these parameter themselves are assumed to have their own distributions. Therefore, we can fit a model with subject-specific intercept and slopes. The random coefficient mixed model can be expressed as follows

$$Y_{im} = V_i^T \alpha + \beta t_{im} + H_i^T \eta_i + \epsilon_{im}, \tag{2.1}$$

where Y_{im} is the outcome vector, V_i is the fixed covariate vector, α is the parameter estimates of the fixed covariates, β is the parameter estimate for random effects, t_{im} indicates time, H_i is the vector of random effects, and η_i's are random vectors of parameters for each subject and we assume that η_i is distributed as multivariate normal with mean 0 and variance-covariance matrix G. We also assume ϵ_{im} follows a Normal distribution with mean 0 and variance σ_e^2. For details on random coefficient models, we refer the reader to Brown and Prescott [17]. In Chapter 4, we adapt the random coefficients model to assess the effect of treatment regimes on longitudinal outcome data in two-stage designs.

2.3 MISSING DATA REVIEW

2.3.1 THREE PATTERNS OF MISSING DATA

According to Rubin [18], there are three different types of missing data mechanism: (1) Missing Completely at Random (MCAR), (2) Missing at Random (MAR), and (3) Not Missing at Random (NMAR). First let us define G as the missing data indicator vector, Y be the outcome matrix which includes observed outcome Y_{obs} and missing outcome Y_{mis}, and ϕ is the unknown parameter associated with missing data. MCAR and MAR can be expressed as

1. MCAR: f(G|Y, ϕ) = f(G|ϕ) for all Y and ϕ
2. MAR: f(G|Y, ϕ) = f(G|Y_{obs}, ϕ) for all Y_{mis} and ϕ,

In words, if missing data do not depend on the outcomes, the data are classified as MCAR. If missing data depends on Y_{obs} and ϕ, the data are considered as MAR, and if the missing data depend on Y_{mis}, the data are NMAR.

The NMAR data in a longitudinal study occur when subjects drop out from the study because of their health-related outcomes. For example, if a subject receive a treatment at baseline and if it is not effective (i.e. the outcomes continuously showed that he/she was not responding to the treatment), the subject might choose not to participate in the study any further. This type of dropout needs to be distinguished from random dropouts.

2.3.2 IMPUTATION METHODS

When missing data are NMAR, standard methods for analyzing continuous outcome data such as GEE or Mixed Models produce biased results [19]. For such data, the pattern mixture models [20] and the selection models [21] are the two most common methods. Since the pattern mixture models have an advantage that we do not have to specify the distribution of missing patterns, in this chapter, we focus on this approach. Since we selected to use random-coefficient models in Section 5.3, we review random-coefficient pattern mixture models below.

The random-coefficient pattern mixture models can be fitted in three-steps: stratified the

data by the missing time points, fit a random coefficient model per stratified data, find the estimate for the parameter of interest, and finally combine the estimates by multiplying with the proportion of each missing data pattern. This model can be expressed as a factorized likelihood. For i^{th} subject where $i = 1, ..n$, let Y_i be the vector of continuous outcomes, G_i is the missing data indicator, X_i is the fixed covariate design matrix, and β_i is the coefficient of random effect. The joint likelihood of Y_i, G_i and β_i can be factorized as follows

$$[Y_i, G_i, \beta_i | X_i] = [Y_i | X_i, \beta_i, G_i][\beta_i | X_i, G_i][G_i | X_i], \tag{2.2}$$

where $[Y_i|X_i, \beta_i, G_i]$ models the repeated outcomes stratified by missing data pattern, $[\beta_i|X_i, G_i]$ models the within-subject variation due to random effect, and $[G_i|X_i]$ models the proportion of subjects in each missing data pattern.

Little [20] introduces one special type of random-coefficient pattern mixture models. It is called Random-effect-dependent drop-out model, and we assume that the missing pattern depends only on X_i and β_i. In this model, the joint likelihood is simplified to

$$[Y_i, G_i, \beta_i | X_i] = [Y_i | \beta_i][\beta_i | X_i, G_i][G_i | X_i]. \tag{2.3}$$

and each component of the joint likelihood assumed to have the following distributions

$$[Y_i|\beta_i] \sim N_M\left(\begin{bmatrix} 1 & t_{i1} \\ \vdots & \vdots \\ 1 & t_{iM} \end{bmatrix} \begin{bmatrix} \beta_{i0} \\ \beta_{i1} \end{bmatrix}, \sigma_e^2 \mathbf{I} \right),$$

$$[\beta_i | X_i = x, G_i = g] \sim N_2(\beta_x^{(g)}, \Gamma),$$

and

$$[G_i | X_i = x] \sim Multinomial(\pi_x),$$

where β_i^T=(β_{i0}, β_{i1}) is the random intercept and slope, X_i is the fixed effect variable, such as an indicator for treatment group, π_x is the vector of proportions of subjects with $X = x$ within the subjects who fall in different missing patterns. Once π_x and $\beta_x^{(g)}$ are estimated, the overall treatment effect can be combined as follows

$$E(\beta | X_i = x) = \sum_{g=1}^{M} \pi_x^{(g)} \beta_x^{(g)}. \tag{2.4}$$

In Chapter 5, we adapt the random coefficient drop-out model to assess the effects of treatment regimes when the data are not missing at random.

3.0 WEIGHTED KAPLAN-MEIER ESTIMATOR FOR TWO-STAGE TREATMENT REGIMES

3.1 INTRODUCTION

Dynamic treatment regime is a set of rules that governs the assignment of time-varying treatments based on intermediate response to prior treatments and covariates. For example, in the treatment of depression, one two-stage dynamic treatment regime might consist of the following sequence of rules: (a) start treating the patient with Citalopram (CIT), (a1) evaluate the patient after 12 weeks of treatment with CIT, (b1) if the patient's 16-item Quick Inventory of Depressive Symptomatology (QIDS-C_{16}) score is less than or equal to 5, keep the patient on CIT for another 8 weeks (b2) otherwise, switch the patient to Buspirone (BUP) for 12 weeks. A slightly different dynamic treatment regime might augment CIT with BUP in the second stage when QIDS-C_{16} score after the first stage of treatment is not below 5 (Figure 1). The goal in the treatment of depression is, for example, to reduce the QIDS-C_{16} score. Therefore, one objective is to find the treatment regime that results in the best possible outcome (e.g. minimum QIDS-C_{16} score) for a given subject. Knowing the best patient-specific treatment regime beforehand allows the physician to choose the best treatment options based on patient's medical history. In practice, it is difficult to find the best set of rules due to high inter-individual variability in patient characteristics. However, if there are only a fixed number of regimes, then one might be interested in estimating the effect of these regimes on overall outcome and compare the regimes based on corresponding treatment effect. There are different statistical designs that allow estimation of regime-specific treatment efficacy: (1) Single stage randomization design - randomize patients to all possible treatment regimes upon entry into the trial, (2) Multiple separate trials for the first

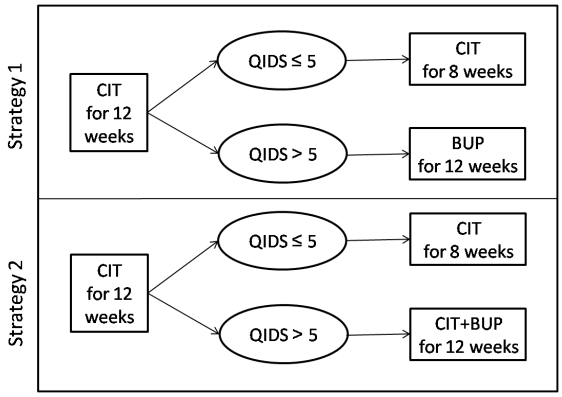

Figure 1: Example of two two-stage regimes in chronic depression treatment

and second stages, and (3) Sequential Multiple Assignment Randomized Trials (SMART) [22]. The first method is easy to conduct; however, it is expensive in terms of cost and sample size while the second method renders issues related to patient comparability between trials. Contrary to the first two methods, SMART has more attractive features: the design randomizes eligible patients to available treatment options at each stage, allows estimation of interaction effect between the first and second stage treatments, and perhaps requires fewer subjects than that would have been required using either of the first two methods.

SMART designs are straightforward to implement. Patients entering into the trial are randomized to the initial treatment options. Those proceeding to the next stage are randomized to available treatment options based on their intermediate response to the initial treatment, and so on. For example, suppose there are two treatment options A_1 and A_2 at the first stage and two treatment options for both responders (B_1 and B_2) and non-responders (B_1' and B_2') at the second stage. In SMART, patients are randomized to A_1 or A_2 followed by another randomization at the second stage, to B_1 or B_2 if the patient is a responder or to B_1' or B_2' if the patient is a non-responder. Number of treatment options in second stage may vary between responders and non-responders. For example, in a leukemia trial described in Stone et al. [1], patients not responding to the initial stage treatments were not treated any further (see Section 6). The goal of SMART design is to estimate the effect of different regimes of interest.

In many chronic diseases such as leukemia and AIDS, the goal is to extend the length of life (survival time). For analyzing survival data from SMAR trials, two methods have been proposed in the literature, namely, marginal mean model approach [2], used by Lunceford et al. [4] in the two-stage setting in the form of estimating equations, and a weighted risk set (WRS) estimator proposed in Guo and Tsiatis [7]. The Lunceford et al. estimator (which will be referred to as MM estimator) uses the method of inverse weighting [23]. The WRS estimator is a modified Nelson-Aalen [13] estimator, where the method of inverse weighting is used to create weighted counting processes. Both WRS and MM estimators were shown to be asymptotically unbiased and normally distributed.

Kaplan-Meier estimator [11] is one of the most commonly used method of estimating survival curves. It is tempting to apply this estimator to the subgroup of patients following a particular regime. Wahed and Tsiatis [6] showed that such estimator is biased since it does not account for the second randomization. In this article we propose an weighted version of the standard Kaplan-Meier (SKM) estimator in order to account for the second randomization in the two-stage SMART design. We follow Lunceford et al. [4] and Lokhnygina and Helterband [9] to form weights based on the method of inverse probability weighting and use them to construct weighted event and at-risk processes to be used in the Kaplan-Meier estimator. We compare the properties of weighted Kaplan-Meier (WKM) estimator to that of the SKM, MM, and the WRS estimators through simulation.

The article is organized as follows. In Section 3.2, we describe the set-up and notation used throughout this article. Section 3.3 gives a review of existing methods: the MM and WRS estimators. In Section 3.4, we introduce the weighted Kaplan-Meier estimator. The results from a simulation study are reported in Section 3.5, followed by the application to a leukemia data set in Section 3.6. We conclude with some remarks in Section 3.7.

3.2 SET-UP AND NOTATION

Consider treatment regimes consisting of two stages of treatments. A patient could receive A_1 or A_2 as initial treatment, and then upon response to the initial treatment could be treated

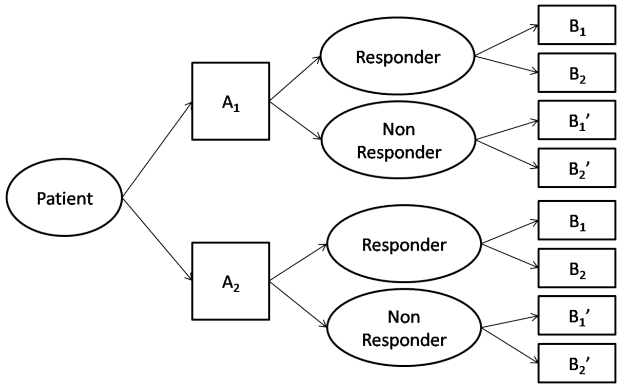

Figure 2: Example of two-stage randomization design

with either B_1 or B_2. Patients not responding to the initial treatment could receive either B_1' or B_2' in the second stage. With these options, there are a total of eight treatment regimes, namely, $A_jB_kB_l', j, k, l = 1, 2$ where $A_jB_kB_l'$ stands for "Treat with A_j followed by B_k if respond, by B_l' if otherwise." Suppose T_{jkl} denote the survival time of a patient treated under regime $A_jB_kB_l'$. The goal is to estimate the survival distribution of the patient population following a specific regime based on the data collected through a two-stage randomization design. In other words, we are interested in estimating $S_{jkl}(t) = Pr(T_{jkl} > t)$, for a given t. In a two-stage randomization design (Figure 2) initially patients are randomized to two treatment groups, namely, A_1 and A_2. The patients are then followed for intermediate response. Those for whom a response is observed are then randomized to B_1 or B_2 and non-responders are randomized to B_1' or B_2'. Patients are followed until death, withdrawal, or termination of the study.

Consider data from patients who are assigned to the A_1 treatment group. For $i = 1, 2, ..n$, the i^{th} subject's observed data can be presented as $\{T_i^R, R_i, R_iZ_{1i}, (1 - R_i)Z_{2i}, V_i, \Delta_i\}$ where T_i^R is the time of intermediate response assessment, R_i is the indicator for response status to the initial treatment A_1(R_i=1 if the subject responded to A_1; 0, otherwise), Z_{1i} represents the second treatment assignment for responders (Z_{1i}=1 if the subject receives B_1; 0, otherwise), Z_{2i} represents the second treatment assignment for non-responders (Z_{2i}=1 if the subject receives B_1'; 0, otherwise), V_i is the time to death (T_i) or time to censoring (C_i) from initial

randomization whichever occurs first, and Δ_i is the indicator for complete (uncensored) survival time, i.e, $\Delta_i = I(C_i \geq T_i)$.

Note that, for fixed j, k, and l, the survival time T_{jkl} is not observed for all patients in the study. It is only observed for those who were on A_j, responded to A_j and received B_k or did not respond to A_j and received B'_l. Thus the challenge would be to estimate the distribution of T_{jkl} based on the observed survival times which are subjected to right censoring. We assume independent censoring, i.e.,

$$C_i \perp (T_i, X_{1i}, R_i, Z_{1i}, Z_{2i}).$$

Let $\pi_{B_1} = \Pr(Z_{1i} = 1|R_i = 1)$, and $\pi_{B'_1} = \Pr(Z_{2i} = 1|R_i = 0)$ denote the randomization probabilities for B_1 and B'_1 respectively. Assume that these randomization probabilities are independent of observed data prior to the second randomization except for the intermediate response status.

3.3 ESTIMATION

3.3.1 MARGINAL MEAN MODEL

Lunceford et al. [4] introduces three estimators based on estimating equations formed using marginal mean model for regime-specific survival times. Their methods use the observations that are consistent with a specific regime to estimate the regime-specific survival probabilities; however, to account for the second randomization and right censoring, each observation is weighted by the inverse probability of observing complete data. Consider the regime $A_1B_1B'_1$ and the observations from the A_1 treatment group only. Patients receiving A_1 and receiving B_1 after responding to A_1, or B'_1 after becoming resistant (non-responder) to A_1 are consistent with the treatment regime $A_1B_1B'_1$. On the other hand, patients who received B_2 after responding to A_1 or B'_2 after becoming resistant to A_1 did not follow this regime. However these patients were equally eligible to receive B_1 or B'_1 as appropriate. Thus the data from those who followed the regime $A_1B_1B'_1$ need to be weighted for the loss of information due to some patients receiving treatments other than the regime under consideration.

Following the idea of inverse-probability weighting, each patient randomized to B_1 then receives a weight $1/\pi_{B_1}$ (inverse of the randomization probability) and those randomized to B_1' receives a weight of $1/\pi_{B_1'}$. Thus each observation within A_1 arm receives a weight of

$$\frac{R_i Z_{1i}}{\pi_{B_1}} + \frac{(1-R_i)Z_{2i}}{\pi_{B_1'}} \tag{3.1}$$

for the purpose of estimating quantities related to the regime $A_1B_1B_1'$. We will denote this by $Q_{A_1B_1B_1'}$.

Besides the information loss due to patients being assigned to a treatment group that is not dictated by the regime, we also lose information due to some patients being right-censored. To account for that Lunceford et al. [4] used another layer of inverse-probability weights leading to the following weight for each observation:

$$\frac{\Delta_i}{K(V_i)} Q_{A_1B_1B_{1i}'}$$

where $K(t) = P(C_i \geq t)$ where C_i is the censored time. But $K(t)$ is unknown and needs to be estimated from the data, leading to the estimated weight:

$$W_{A_1B_1B_{1i}'} = \frac{\Delta_i}{\hat{K}(V_i)} Q_{A_1B_1B_{1i}'}$$

where $\hat{K}(V_i)$ is the product limit estimator of censoring survival distribution. Weights for the other regimes can be constructed in a similar fashion.

With weights defined in this fashion, the MM estimator for the survival probability for regime $A_1B_kB_l'$ is given by

$$\widehat{S}^{MM}_{A_1B_kB_l'}(t) = 1 - \widehat{F}^{MM}_{A_1B_kB_l'}(t)$$

where

$$\widehat{F}^{MM}_{A_1B_kB_l'}(t) = \frac{\sum_{i=1}^n W_{A_1B_kB_{li}'} I(V_i \leq t)}{\sum_{i=1}^n W_{A_1B_kB_{li}'}}, \quad k,l = 1,2.$$

We note that this estimator uses only the observations belonging to the A_1 treatment group. But one could also impose another layer of weight for the first randomization (see the discussion section). Following Lunceford et al. [4], it can be shown that the MM estimator

is asymptotically normally distributed with mean $S_{A_1B_kB'_l}(t)$ and a variance that can be estimated by

$$\begin{aligned}\widehat{Var}[\hat{S}^{MM}_{A_1B_kB'_l}(t)] &= n^{-1}\Big[n^{-1}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(V_i)}\{Q_{A_1B_kB'_{li}}(I(V_i\le t)-\hat{F}^{MM}_{A_1B_kB'_l}(t)\}^2 \\ &+ \int_0^L \frac{dN^c(u)}{\hat{K}(u)Y(u)}\hat{E}\{L_{A_1B_kB'_l}(t,u)\}^2\Big]\end{aligned}$$

where

$$\hat{E}\{L_{A_1B_kB'_l}(t,u)\} = n^{-1}\sum_{i=1}^{n}\Delta_i[Q_{A_1B_kB'_{li}}\{I(V_i\le t)-\hat{F}^{MM}_{A_1B_kB'_l}(t)\}-\hat{G}_{A_1B_kB'_l}(t,u)]^2\frac{I(V_i\ge u)}{\hat{K}(V_i)},$$

and

$$\hat{G}_{A_1B_kB'_l}(t,u) = \{n\hat{S}(u)\}^{-1}\sum_{i=1}^{n}\Delta_i Q_{A_1B_kB'_{li}}\{I(V_i\le t)-\hat{F}^{MM}_{A_1B_kB'_l}(t)\}\frac{I(V_i\ge u)}{\hat{K}(V_i)},$$

where $\hat{S}(u)$ is the product limit estimator of survival distribution.

3.3.2 WEIGHTED RISK SET ESTIMATOR

Another method of estimation is to use Nelson-Aalen estimator. Since the observations that are consistent with the regime $A_1B_kB'_l$ are not a random sample from the corresponding population, again a weighted approach needs to be adapted. If everyone in the sample were treated according to the regime $A_1B_kB'_l$ for fixed k and l, then the Nelson-Aalen estimator [13] of $S_{A_1B_kB'_l}(t)$ would have been defined as :

$$\widehat{S}_{A_1B_kB'_l}(t) = \exp\left\{-\int_0^t \frac{\sum_{i=1}^n dN_i(u)}{\sum_{i=1}^n Y_i(u)}\right\},$$

where $N_i(u) = I(\Delta_i = 1, T_i \le u)$ is the indicator of whether the i^th individual fails prior to time u, and $Y_i(u) = I(V_i \ge u)$ is the indicator of whether the subject is at risk at time u. Since not all patients are treated according to the regime $A_1B_kB'_l$, a weighted version of the Nelson-Aalen estimator is calculated as follows:

$$\widehat{S}^{WRS}_{A_1B_kB'_l}(t) = \exp\left\{-\int_0^t \frac{\sum_{i=1}^n Q_{A_1B_kB'_{li}}dN_i(u)}{\sum_{i=1}^n Q_{A_1B_kB'_{li}}Y_i(u)}\right\}.$$

Another version of this estimator with time-varying weight appeared in Guo and Tsiatis [7] where the weight was allowed to depend on the time of response assessment. Since this estimator is a special case of the estimator proposed in Guo and Tsiatis [7], we can follow the argument therein to show that the WRS estimator is asymptotically normally distributed with mean $S_{A_1B_kB_l'}(t)$ and variance that can be estimated by:

$$\widehat{Var}(\widehat{S}^{WRS}_{A_1B_kB_l'}(t)) = n^{-1}\left\{\widehat{S}^{WRS}_{A_1B_kB_l'}(t)\right\}^2\hat{\sigma}^2$$

where

$$\hat{\sigma}^2 = n^{-1}\sum_{i=1}^{n}\left(\int_0^t \frac{Q_{A_1B_kB_{li}'}\left[dN_i(u) - Y_i\left\{\frac{\sum_{i=1}^n Q_{A_1B_kB_{li}'}dN_i(u)}{\sum_{i=1}^n Q_{A_1B_kB_{li}'}Y_i(u)}\right\}\right]}{n^{-1}\sum_{i=1}^n Q_{A_1B_kB_{li}'}Y_i(u)}\right)^2.$$

3.4 PROPOSED METHOD

If everyone in the sample were treated with the regime $A_1B_kB_l'$, the survival rate at time t for the regime $A_1B_kB_l'$ could be estimated using the Kaplan-Meier estimator as follows:

$$\widehat{S}_{A_1B_kB_l'}(t) = \begin{cases} 1, & t < t_1 \\ \Pi_{t_m \le t}\left(1 - \frac{d_m}{Y_m}\right), & t \ge t_1 \end{cases}$$

where $d_m = \sum_{i=1}^n \Delta_i I(V_i = t_m)$, $Y_m = \sum_{i=1}^n I(V_i \ge t_m)$, $t_m, m = 1, 2, \ldots,$ are the distinct ordered failure times. However, as mentioned in the previous section, some patients will potentially receive treatment inconsistent with the regime $A_1B_kB_l'$, and we need to adjust for the loss of these patients. Taking a similar approach to the MM and WRS estimators, we propose the weighted Kaplan Meier estimator:

$$\widehat{S}_{A_1B_kB_l'}(t) = \begin{cases} 1, & t < t_1 \\ \Pi_{t_m \le t}\left(1 - \frac{d_m^w}{Y_m^w}\right) & t \ge t_1 \end{cases}$$

where $d_m^w = \sum_{i=1}^n \Delta_i I(V_i = t_m) Q_{A_1B_kB_{li}'}$, and $Y_m^w = \sum_{i=1}^n I(V_i \ge t_m) Q_{A_1B_kB_{li}'}$. Thus we have weighted the death process and the at risk process by the inverse of the probability of randomization. Xie and Liu [24] has proposed a similar method to construct weighted Kaplan-Meier

estimator to adjust for covariate imbalance between randomized or non-randomized groups. It can be shown that the WKM estimator is unbiased, and the proof is outlined in Section 3.4.1.

The variance of this estimator is obtained through slight modification of the Greenwood formula [12] as suggested in Xie and Liu [24] as follows:

$$\widehat{Var}[\widehat{S}_{A_1B_kB'_l}(t)] = [\widehat{S}_{A_1B_kB'_l}(t)]^2 \sum_{m:t_m \le t} \frac{1 - \hat{s}_{A_1B_kB'_{lm}}}{\widehat{M}_{A_1B_kB'_{lm}} \widehat{s}_{A_1B_kB'_{lm}}},$$

where

$$\widehat{M}_{A_1B_kB'_{lm}} = \left(\sum_{i=1}^{n} Q_{A_1B_kB'_{li}} I(V_i \ge t_m) \right)^2 / \sum_{i=1}^{n} \left\{ Q_{A_1B_kB'_{li}} I(V_i \ge t_m) \right\}^2,$$

and $\widehat{s}_{A_1B_kB'_{lm}} = 1 - d^w_m / Y^w_m, m = 1, 2, ...$ The derivation of this variance is outlined in Section 3.4.2.

3.4.1 UNBIASSEDNESS OF $\hat{S}(t)$

We follow Xie and Liu [24] to show the unbiasedness of weighted Kaplan-Meier estimator. First, we define $s_{A_1B_kB'_lm} = S_{A_1B_kB'_l}(t_m)/S_{A_1B_kB'_l}(t_{m-1})$ to be the probability of survived beyond time t_m given treat the patient has survived until t_{m-1}, and unbiased estimator of which is given by $\hat{s}_{A_1B_kB'_lm} = 1 - d^w_m / y^w_m$. The proof of unbiasedness depends on the assumption that at any time point t_m, there is a positive number of subjects at risk for those who followed a specific regime, e.g. $A_1B_1B'_1$.

$$\begin{aligned}
E_m(1 - \hat{s}_{A_1B_1B'_{1m}}) &= E_m \left[\frac{\sum_{i=1}^n \Delta_i I(V_i = t_m) Q_{A_1B_1B'_{1i}}}{\sum_{i=1}^n I(V_i \ge t_m) Q_{A_1B_1B'_{1i}}} \right] \\
&= E_m \left\{ E_m \left[\frac{\sum_{i=1}^n \Delta_i I(V_i = t_m) Q_{A_1B_1B'_{1i}}}{\sum_{i=1}^n I(V_i \ge t_m) Q_{A_1B_1B'_{1i}}} \Big| Z_{1i}, Z_{2i}, R_i, i, \ s.t.\ V_i \ge t_m \right] \right\} \\
&= E_m \left[(1 - s_{A_1B_1B'_{1m}}) \frac{\sum_{i=1}^n I(V_i \ge t_m) Q_{A_1B_1B'_1 i}}{\sum_{i=1}^n I(V_i \ge t_m) Q_{A_1B_1B'_{1i}}} \right] \\
&= 1 - s_{A_1B_1B'_{1m}}
\end{aligned}$$

where E_m indicates a conditional expectation given the information up to time t_m. The conditional expected values for the other regimes, $E_m(1 - \hat{s}_{A_1B_kB'_{lm}})$ with $k, l = 1, 2$, can be

constructed similarly with the regime-specific assumption. Now using the method of successive conditional expectations, we show that E($\hat{S}_{A_1B_kB'_l}(t)$)=$S_{A_1B_kB'_l}(t)$. For convenience, we use a simplified notation and let $Q_{A_1B_kB'_l} = Q$, $\hat{S}_{A_1B_kB'_l}(t) \equiv \hat{S}(t)$, $S_{A_1B_kB'_l}(t) \equiv S(t)$, $\hat{s}_{A_1B_kB'_{lm}} \equiv \hat{s}_m$, and $s_{A_1B_kB'_l}(t) \equiv s(t)$. Let t_q be the maximum observed death time prior to t, then $\hat{S}(t)$=$\prod_{m=1}^{q} \hat{s}_m$ and we have

$$\begin{aligned} E[\hat{S}(t)] &= E[\hat{s}_1...\hat{s}_{q-1}E_q(\hat{s}_q)] = E[\hat{s}_1...\hat{s}_{q-1}s_q] \\ &= s_qE[\hat{s}_1...\hat{s}_{q-2}E_q(\hat{s}_{q-1})] = ... \\ &= s_1...s_{q-1}s_q = S(t). \end{aligned}$$

Thus, the WKM is an unbiased estimator.

3.4.2 VARIANCE OF $\hat{S}(t)$

Let Var_m denotes the variance conditional on information up to but not including time t_m. Then,

$$\begin{aligned} Var_m(\hat{s}_m) &= Var_m(1 - \frac{\sum_{i=1}^{n} \Delta_i I(V_i = t_m)Q_i}{\sum_{i=1}^{n} I(V_i \geq t_m)Q_i}) \\ &= \frac{\sum_{i=1}^{n} Var_m(\Delta_i I(V_i = t_m)Q_i)}{(\sum_{i=1}^{n} I(V_i \geq t_m)Q_i)^2} \\ &= \frac{\sum_{i=1}^{n} I(V_i = t_m)Q_i^2 Var_m(\Delta_i : I(V_i = t_m))}{(\sum_{i=1}^{n} I(V_i \geq t_m)Q_i)^2} \\ &= \frac{\sum_{i=1}^{n} I(V_i \geq t_m)Q_i^2 s_m(1 - s_m)}{(\sum_{i=1}^{n} I(V_i \geq t_m)Q_i)^2} \\ &= \frac{s_m(1 - s_m)}{M_m} \end{aligned} \tag{3.2}$$

where $1/M_m$ is $\sum_{i=1}^{n} I(V_i \geq t_m){Q_i}^2/(\sum_{i=1}^{n} I(V_i \geq t_m)Q_i)^2$. Now,

$$\begin{aligned}
E[\hat{S}(t)]^2 &= \prod_{m=1}^{q} E_m[\hat{s}_m^2] \\
&= \prod_{m=1}^{q} (E_m(\hat{s}_m^2) + Var_m(\hat{s}_m)) \\
&= \prod_{m=1}^{q} \left(s_m^2 + \frac{s_m(1-s_m)}{M_m} \right) \quad \text{using (3.2)} \\
&= \prod_{m=1}^{q} \left(s_m^2 + s_m^2 \frac{1-s_m}{M_m s_m} \right) \\
&= \prod_{m=1}^{q} s_m^2 \left(1 + \frac{1-s_m}{M_m s_m} \right) \\
&= s_1^2 \ldots s_q^2 \prod_{m=1}^{l} \left(1 + \frac{1-s_m}{M_m s_m} \right) \\
&= (S(t))^2 \prod_{m=1}^{q} \left(1 + \frac{1-s_m}{M_m s_m} \right).
\end{aligned}$$

Finally, $Var[\hat{S}(t)]$ can be derived as

$$\begin{aligned}
Var[\hat{S}(t)] &= (S(t))^2 \prod_{m=1}^{q} \left(1 + \frac{1-s_m}{M_m s_m} \right) - S^2(t). \\
&\approx (S(t))^2 \sum_{m=1}^{q} \frac{1-s_m}{M_m s_m} \qquad (3.3)
\end{aligned}$$

The assumption here is that $\max_i I(V_i \geq t_m)Q_i / \sum_{i=1}^{n} I(V_i \geq t_m)Q_i \to 0$ so that we can ignore terms of order greater than M_m^{-1} in (3.3).

3.5 SIMULATION STUDY

A simulation study was conducted to examine the performance of the proposed estimator and its large sample properties. The results were compared to those of the other estimators. The data were generated following the two-stage SMART design with two initial treatments and two separate pairs of second-stage treatments depending on the outcome of the initial treatment, as shown in Figure 2. Since the data from subjects who were randomized to A_1

are independent of those who received A_2, only A_1 treatment path was considered for the simulation.

The proposed and existing estimators were examined in three different scenarios. In the first scenario, we generated the datasets with an equal randomization rate for the second stage treatments for both responders and non-responders. Using the notation in Section 2, Z_{1i} and Z_{2i} were drawn from a Bernoulli distribution with a mean of 0.5. In the second scenario, Z_{1i} and Z_{2i} were drawn from a Bernoulli distribution with a mean of 0.3 and 0.5, respectively. Finally, in the third scenario, all responders receive the same second stage treatment (B_1) while the non-responders are equally randomized to one of the two second stage treatments. Therefore, Z_{1i} was set to 1 for all responders, and Z_{2i} was drawn from a Bernoulli distribution with a mean of 0.5.

We generated 2000 datasets with 200 and 500 observations in each, and 40% and 70% response rates were selected to represent the lower and higher response rates. Each dataset contained the variables T^R, R, Z_1, Z_2, Δ, and V as described in Section 2. For the i^{th} patient, the time to response to the initial treatment (T_i^R) was generated from an Exponential(0.7) distribution, restricted at 2 years. For convinience, the time to not respond (T_i^{NR}) is set equal to T_i^R. The time to death from the second randomization ($T^*_{A_1B_{ki}}$ or $T^*_{A_1B'_{li}}$, $k, l = 1, 2$) was drawn from a Uniform distribution with a range of 0 to (1+0.5T_i^R)*1.5 for the sequence of treatments A_1B_1, 0 to (1+0.5T_i^R)*1 for the A_1B_2 treatment, 0 to (0.75+0.25T_i^{NR})*0.75 for the $A_1B'_1$ treatment, and 0 to (0.75+0.25T_i^{NR})*0.5 for the $A_1B'_2$ treatment. In the absence of censoring, the observed survival time is then $T_i = R_iT_i^R + R_i[Z_{1i}T^*_{A_1B_{1i}} + (1 - Z_{1i})T^*_{A_1B_{2i}}] + (1 - R_i)T_i^{NR} + (1 - R_i)[Z_{2i}T^*_{A_1B'_{1i}} + (1 - Z_{2i})T^*_{A_1B'_{2i}}]$. The time to censoring (C_i) is created as a sum of T_i^R and a random value generated from a Uniform distribution between 0 and $(5 - T_i^R)$ years. Finally, the observed time to event (V_i) was set to a minimum of T_i and C_i, and the death indicator (Δ_i) was set to 1 if T_i was less than C_i, 0 otherwise. In all scenarios, the total percentage of censoring was 29.5% for the 40% response rate, and 37.4% for the 70% rate.

Although, in the first and second scenario, there were 4 possible regimes, we only present the results for regimes $A_1B_1B'_1$ and $A_1B_1B'_2$. The results follow the same trend for the other regimes. Table 1 provides the results for simulation scenario 1, where responders and

non-responders were assigned to the second stage treatments with equal probability. For this case, all four estimators were approximately unbiased with similar standard errors. The relative bias varied from 0 to 0.06. However the coverage probabilities for the 95% confident interval were closest to the nominal level for the WKM estimator most of the time, followed by the SKM estimator. With the increase in sample size from 200 to 500, both relative bias and the standared errors were reduced with improvement in the coverage probability.

Table 2 summarizes the results for simulation scenario 2, where the second stage randomization rates were set to be unequal for the responders and non-responders. The three estimators (WKM, WRS, and MM) performed very similarly, and the estimates in this scenario were very close to the ones in scenario 1. The standard errors increased naturally for covering the higher percentage of loss due to the lower randomization rate to B_1. The SKM estimator, however, produced estimates with higher relative bias and significantly lower coverage rates compared to scenario 1. The differences in the results were more obvious for the regime $A_1B_1B_2'$, for which the relative bias was as high as 0.07 and the coverage probability for 95% confidence interval as as low as 85.6%.

Table 3 lists the results from simulation scenario 3, where the responders received the same second stage treatment, but the non-responders were equally randomized to one of the two second stage treatments. Again the three inverse-probability-weighted methods (WKM, WRS, and MM) provided very close estimates; however, the standard errors for WKM and WRS were slightly smaller than those for the MM estimator. The coverage rates for the WKM and WRS estimators were lower compared to the rates for the MM estimator. The SKM performed quite poorly, indicated by a range of relative bias between 0.04 to 0.17. The coverage rate dropped dramatically and the highest rate was only 75.9%.

In conclusion, the simulation studies showed that the WKM estimator is approximately unbiased in three different randomization scenarios. The performance of the WKM was very similar to the other two existing estimators MM and WRS. The SKM, on the other hand, was only unbiased when the second randomization rate was equal between responders and non-responders. When the SKM was applied to the scenarios with the unequal randomization rates, the relative bias increased significantly. This result showed that the modified survival estimators with the inverse-probability weighting method are necessary to estimate

the survival distribution for the multiple stage design with unequal randomization rates.

3.6 ANALYSIS OF CALGB DATA

The four estimators were applied to a dataset from Cancer and Leukemia Group B (CALGB). The study was a two-stage double-blind placebo-controlled randomized clinical trial, and a total of 388 elderly patients with acute myelogenous leukemia were enrolled. At the first stage, 193 patients were randomized to one of the two initial treatments GM-CSF (A_1), and 195 were randomized to the Placebo group (A_2). At the second stage, 37 GM-CSF responders and 45 Placebo responders were randomized to the maintenance therapy I (B_1), and 42 GM-CSF responders and 45 Placebo responders were randomized to the maintenance therapy II (B_2). Since the non-responders (114 patients in GM-CSF, and 105 in Placebo) were not randomized at the second stage, the weight function from (3.1) for the regime A_1B_k is written as

$$Q_{A_1B_{ki}} = \frac{R_i Z_{1i}}{\pi_{B_k}} + (1 - R_i), \quad k = 1, 2.$$

Thus there are a total of four treatment regimes for this study: (a) Treat with GM-CSF and a standard chemotherapy, follow by the maintenance therapy I if respond to the initial treatment (b) Treat with GM-CSF and a standard chemotherapy, follow by the maintenance therapy II if respond to the initial treatment, (c) Treat with Placebo and a standard chemotherapy, follow by the maintenance therapy I if respond to the initial treatment, and (d) Treat with Placebo and a standard chemotherapy, follow by the maintenance therapy II if respond to the initial treatment. All four methods discussed in previous sections were applied to the CALGB 8923 data, and the survival distributions for the four regimes were estimated. The results are shown in Figure 3.

Figure 3 shows that the three methods (WKM, MM, and WRS) provide very similar estimates for the survival curve under different regimes. However, the SKM estimator provides estimates which were always lower to those obtained from other methods. Figure 4 provides the survival estimates for four regimes in CALGB data using WKM approach. It is evident

Table 1: **Simulation Scenario 1: Even Second Stage Randomization Rate of $\mathbf{P}(Z_1)$=0.5 and $\mathbf{P}(Z_2)$=0.5.** *Monte Carlo Mean, Standard Error, Relative Bias, and Coverage Rate (based on 95% C.I.) for estimating survival probabilities at time t for the two regimes $A_1B_1B_1'$ and $A_1B_1B_2'$. n=200 and 500, P(response)=0.4 and 0.7, and t=0.5 and 1.0 year.*

				Regime $A_1B_1B_1'$				Regime $A_1B_1B_2'$			
n	t	P(r)	Method	S(t)	MC Mean (SE)	Relative Bias	Coverage Rate(%)	S(t)	MC Mean (SE)	Relative Bias	Coverage Rate(%)
200	0.5	0.4	SKM	0.81	0.81(0.039)	0.00	92.3	0.75	0.75(0.043)	0.00	92.8
			WKM		0.81(0.039)	0.00	92.3		0.75(0.043)	0.00	92.8
			WRS		0.81(0.039)	0.00	91.7		0.75(0.043)	0.00	92.5
			MM		0.81(0.039)	0.00	92.7		0.75(0.043)	0.00	92.8
		0.7	SKM	0.86	0.86(0.035)	0.00	92.8	0.83	0.83(0.038)	0.00	93.3
			WKM		0.86(0.035)	0.00	92.8		0.83(0.038)	0.00	93.3
			WRS		0.86(0.035)	0.00	92.5		0.83(0.037)	0.00	93.2
			MM		0.86(0.035)	0.00	92.7		0.83(0.038)	0.00	93.1
	1.0	0.4	SKM	0.49	0.51(0.051)	0.04	92.9	0.46	0.47(0.051)	0.02	93.6
			WKM		0.51(0.051)	0.04	92.9		0.47(0.051)	0.02	93.7
			WRS		0.52(0.051)	0.06	92.5		0.48(0.051)	0.04	93.3
			MM		0.51(0.051)	0.04	92.5		0.47(0.051)	0.02	93.1
		0.7	SKM	0.60	0.62(0.050)	0.03	94.7	0.58	0.60(0.050)	0.03	94.3
			WKM		0.62(0.050)	0.03	94.7		0.60(0.050)	0.03	94.3
			WRS		0.62(0.050)	0.03	94.2		0.60(0.050)	0.03	93.7
			MM		0.61(0.050)	0.02	94.1		0.59(0.050)	0.02	94.0
500	0.5	0.4	SKM	0.81	0.81(0.025)	0.00	92.1	0.75	0.75(0.027)	0.00	93.2
			WKM		0.81(0.025)	0.00	92.8		0.75(0.027)	0.00	93.2
			WRS		0.81(0.025)	0.00	92.1		0.75(0.027)	0.00	93.1
			MM		0.81(0.025)	0.00	92.3		0.75(0.028)	0.00	93.2
		0.7	SKM	0.86	0.86(0.022)	0.00	93.9	0.83	0.83(0.024)	0.00	95.0
			WKM		0.86(0.022)	0.00	93.9		0.83(0.024)	0.00	95.0
			WRS		0.86(0.022)	0.00	93.7		0.83(0.024)	0.00	95.0
			MM		0.86(0.022)	0.00	93.8		0.83(0.024)	0.00	94.8
	1.0	0.4	SKM	0.49	0.51(0.032)	0.04	90.6	0.46	0.47(0.032)	0.02	91.8
			WKM		0.51(0.032)	0.04	90.6		0.47(0.032)	0.02	91.8
			WRS		0.51(0.032)	0.04	90.2		0.47(0.032)	0.02	91.4
			MM		0.51(0.033)	0.04	90.9		0.47(0.033)	0.02	92.0
		0.7	SKM	0.60	0.61(0.032)	0.02	92.3	0.58	0.59(0.032)	0.02	93.5
			WKM		0.61(0.032)	0.02	92.3		0.59(0.032)	0.02	93.5
			WRS		0.61(0.031)	0.02	92.0		0.59(0.032)	0.02	93.2
			MM		0.61(0.032)	0.02	92.7		0.59(0.032)	0.02	93.4

Table 2: **Simulation Scenario 2: Uneven Second Stage Randomization Rate of $\mathbf{P}(Z_1)$=0.3 and $\mathbf{P}(Z_2)$=0.5.** *Monte Carlo Mean, Standard Error, Relative Bias, and Coverage Rate (based on 95% C.I.) for estimating survival probabilities at time t for the two regimes $A_1B_1B_1'$ and $A_1B_1B_2'$. n=200 and 500, P(response)=0.4 and 0.7, and t=0.5 and 1.0 year.*

				Regime $A_1B_1B_1'$				Regime $A_1B_1B_2'$			
n	t	P(r)	Method	S(t)	MC Mean (SE)	Relative Bias	Coverage Rate(%)	S(t)	MC Mean (SE)	Relative Bias	Coverage Rate(%)
200	0.5	0.4	SKM	0.81	0.79(0.044)	0.02	93.8	0.75	0.72(0.049)	0.04	93.1
			WKM		0.81(0.044)	0.00	93.6		0.75(0.049)	0.00	94.3
			WRS		0.81(0.044)	0.00	93.3		0.75(0.049)	0.00	94.1
			MM		0.81(0.042)	0.00	92.1		0.75(0.047)	0.00	92.9
		0.7	SKM	0.86	0.84(0.043)	0.02	94.0	0.83	0.80(0.047)	0.04	94.0
			WKM		0.86(0.042)	0.00	93.8		0.83(0.046)	0.00	94.9
			WRS		0.86(0.042)	0.00	93.2		0.83(0.046)	0.00	94.9
			MM		0.86(0.040)	0.00	91.8		0.83(0.043)	0.00	93.9
	1.0	0.4	SKM	0.49	0.48(0.056)	0.02	93.1	0.46	0.43(0.055)	0.07	89.7
			WKM		0.51(0.059)	0.04	93.5		0.47(0.059)	0.02	93.3
			WRS		0.52(0.058)	0.04	93.5		0.48(0.059)	0.04	92.9
			MM		0.51(0.057)	0.06	92.5		0.47(0.058)	0.02	93.1
		0.7	SKM	0.60	0.58(0.059)	0.03	93.4	0.58	0.55(0.060)	0.05	90.8
			WKM		0.61(0.061)	0.02	93.9		0.59(0.062)	0.02	94.8
			WRS		0.62(0.060)	0.03	93.7		0.60(0.062)	0.03	94.4
			MM		0.61(0.059)	0.02	93.2		0.59(0.060)	0.02	93.7
500	0.5	0.4	SKM	0.81	0.79(0.028)	0.02	93.5	0.75	0.72(0.031)	0.04	88.9
			WKM		0.81(0.028)	0.00	94.2		0.75(0.031)	0.00	94.4
			WRS		0.81(0.028)	0.00	94.0		0.75(0.031)	0.00	94.4
			MM		0.81(0.027)	0.00	93.0		0.75(0.030)	0.00	92.8
		0.7	SKM	0.86	0.84(0.028)	0.02	93.4	0.83	0.80(0.030)	0.04	88.2
			WKM		0.86(0.027)	0.00	94.8		0.83(0.029)	0.00	96.4
			WRS		0.86(0.027)	0.00	94.7		0.83(0.029)	0.00	96.3
			MM		0.86(0.026)	0.00	93.4		0.83(0.027)	0.00	94.7
	1.0	0.4	SKM	0.49	0.47(0.035)	0.04	92.0	0.46	0.43(0.035)	0.07	85.6
			WKM		0.51(0.037)	0.04	92.7		0.47(0.037)	0.02	93.1
			WRS		0.51(0.037)	0.04	92.2		0.47(0.037)	0.02	92.8
			MM		0.51(0.037)	0.04	92.2		0.47(0.037)	0.02	92.6
		0.7	SKM	0.60	0.57(0.038)	0.05	89.2	0.58	0.55(0.038)	0.05	85.9
			WKM		0.61(0.039)	0.02	94.3		0.59(0.039)	0.02	94.9
			WRS		0.61(0.039)	0.02	93.9		0.59(0.039)	0.02	94.6
			MM		0.61(0.038)	0.02	93.3		0.59(0.038)	0.02	93.8

Table 3: **Simulation Scenario 3: Uneven Second Stage Randomization Rate of $\mathbf{P}(Z_1)$=1.0 and $\mathbf{P}(Z_2)$=0.5.** *Monte Carlo Mean, Standard Error, Relative Bias, and Coverage Rate (based on 95% C.I.) for estimating survival probabilities at time t for the two regimes $A_1B_1B_1'$ and $A_1B_1B_2'$. n=200 and 500, P(response)=0.4 and 0.7, and t=0.5 and 1.0 year.*

				Regime $A_1B_1B_1'$				Regime $A_1B_1B_2'$			
n	t	P(r)	Method	S(t)	MC Mean (SE)	Relative Bias	Coverage Rate(%)	S(t)	MC Mean (SE)	Relative Bias	Coverage Rate(%)
200	0.5	0.4	SKM	0.81	0.84(0.031)	0.04	75.9	0.75	0.80(0.034)	0.07	65.2
			WKM		0.81(0.035)	0.00	90.3		0.75(0.038)	0.00	91.4
			WRS		0.81(0.035)	0.00	89.9		0.75(0.038)	0.00	91.4
			MM		0.81(0.037)	0.00	91.8		0.75(0.041)	0.00	92.8
		0.7	SKM	0.86	0.88(0.025)	0.02	79.4	0.83	0.86(0.026)	0.04	69.0
			WKM		0.86(0.028)	0.00	90.7		0.83(0.030)	0.00	89.9
			WRS		0.86(0.028)	0.00	90.9		0.83(0.030)	0.00	89.9
			MM		0.86(0.030)	0.00	92.3		0.83(0.033)	0.00	92.1
	1.0	0.4	SKM	0.49	0.57(0.043)	0.16	54.6	0.46	0.54(0.043)	0.17	46.3
			WKM		0.51(0.044)	0.04	90.8		0.47(0.044)	0.02	92.6
			WRS		0.52(0.044)	0.06	90.2		0.48(0.044)	0.04	92.3
			MM		0.51(0.046)	0.04	91.8		0.47(0.046)	0.02	93.2
		0.7	SKM	0.60	0.66(0.037)	0.05	64.7	0.58	0.65(0.038)	0.12	59.6
			WKM		0.62(0.039)	0.02	91.8		0.60(0.039)	0.03	91.9
			WRS		0.62(0.039)	0.02	91.5		0.60(0.039)	0.03	91.7
			MM		0.62(0.041)	0.02	93.2		0.60(0.042)	0.03	93.5
500	0.5	0.4	SKM	0.81	0.84(0.020)	0.04	57.0	0.75	0.80(0.022)	0.07	34.6
			WKM		0.81(0.022)	0.00	90.1		0.75(0.024)	0.00	90.3
			WRS		0.81(0.022)	0.00	89.9		0.75(0.024)	0.00	90.2
			MM		0.81(0.023)	0.00	92.5		0.75(0.026)	0.00	92.3
		0.7	SKM	0.86	0.88(0.016)	0.02	65.8	0.83	0.86(0.017)	0.04	44.1
			WKM		0.86(0.018)	0.00	90.8		0.83(0.019)	0.00	91.4
			WRS		0.86(0.018)	0.00	90.7		0.83(0.019)	0.00	91.4
			MM		0.86(0.019)	0.00	92.8		0.83(0.021)	0.00	94.3
	1.0	0.4	SKM	0.49	0.57(0.027)	0.16	18.4	0.46	0.54(0.027)	0.17	11.6
			WKM		0.51(0.028)	0.04	88.0		0.47(0.028)	0.02	88.5
			WRS		0.51(0.028)	0.04	87.7		0.47(0.028)	0.02	88.1
			MM		0.51(0.029)	0.04	90.6		0.47(0.029)	0.02	89.0
		0.7	SKM	0.60	0.66(0.024)	0.10	35.4	0.58	0.64(0.024)	0.10	26.9
			WKM		0.61(0.025)	0.02	89.4		0.59(0.025)	0.02	90.7
			WRS		0.61(0.025)	0.02	89.0		0.59(0.025)	0.02	90.3
			MM		0.61(0.026)	0.02	90.9		0.59(0.026)	0.02	92.3

that none of the regime is clearly superior to the other three regimes.

3.7 DISCUSSION

We proposed the weighted Kaplan-Meier estimator to estimate the survival distribution for different treatment regimes from SMART designs. The inverse of the second stage randomization rate was used as a weight in order to account for the loss of information from those who were randomized to a treatment other than the regime dictated. One advantage of using this method is that the implementation is straightforward compared to the existing methods. In addition, the method can provide survival estimates at time points where there are only censored cases in the risk set. In contrast, the MM method provides zero as the survival estimate after the last event case is observed. Therefore, when one is interested in finding the survival rates at the later stage of follow-up times, the weighted Kaplan-Meier method may be more appropriate.

As briefly mentioned in Section 3.3.1, it is possible to add another layer of weight for the first randomization. In this case, patients receiving initial treatment, for example, A_1 would additionally be weighted by $1/\pi_{A_1 i}$, where $\pi_{A_1 i}$ can be estimated by a propensity score for receiving the treatment A_1. The score may be calculated using a logistic regression model including the covariate information. For estimating quantities related to the regime $A_1 B_1 B_1'$, the weight in (3.1) would be changed to

$$Q^*_{A_1 B_1 B_1'} = \frac{X_i}{\pi_{A_1 i}} Q_{A_1 B_1 B_1'},$$

where $X_i = 1$, if patient receives A_1; 0, otherwise. This would allow gaining efficiency for the estimators by accounting for the information loss due to some patients receiving A_2 at the beginning.

Further research in this area includes generalizing the WKM estimator to account for the variable intermediate response time.

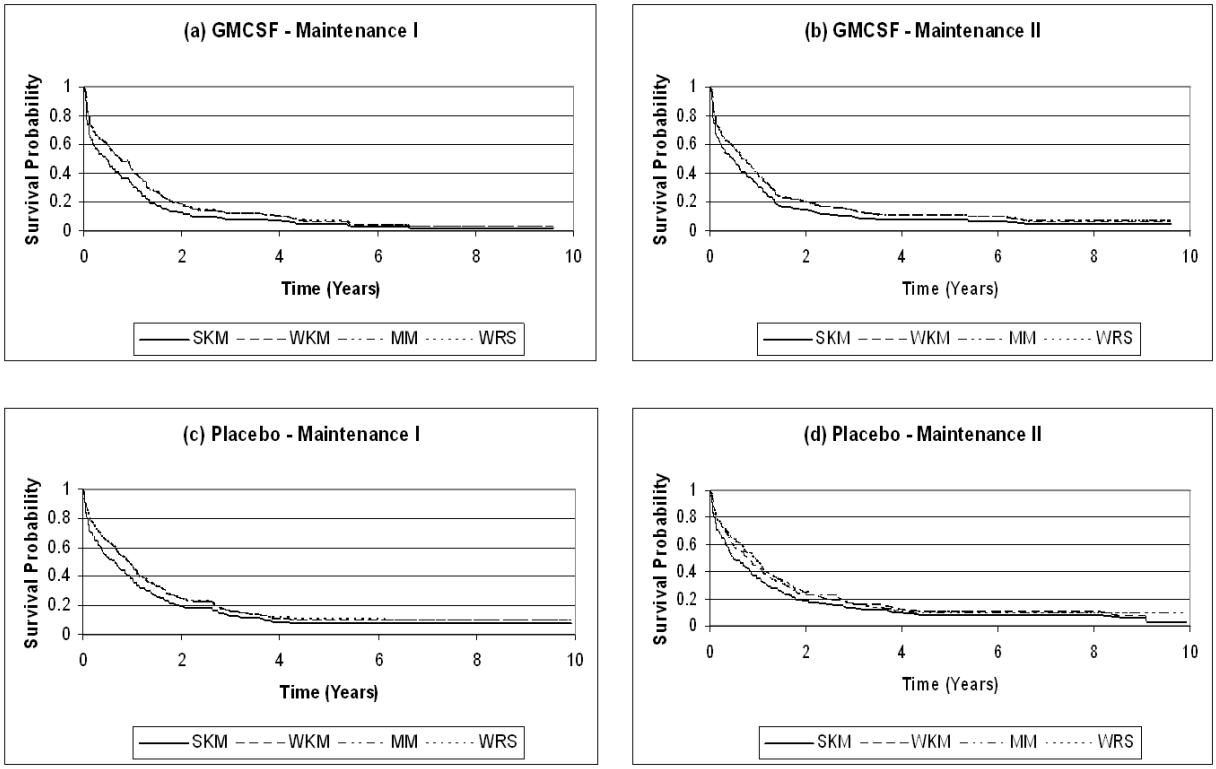

Figure 3: SKM, WKM, MM, and WRS survival estimates for four regimes in CALGB study

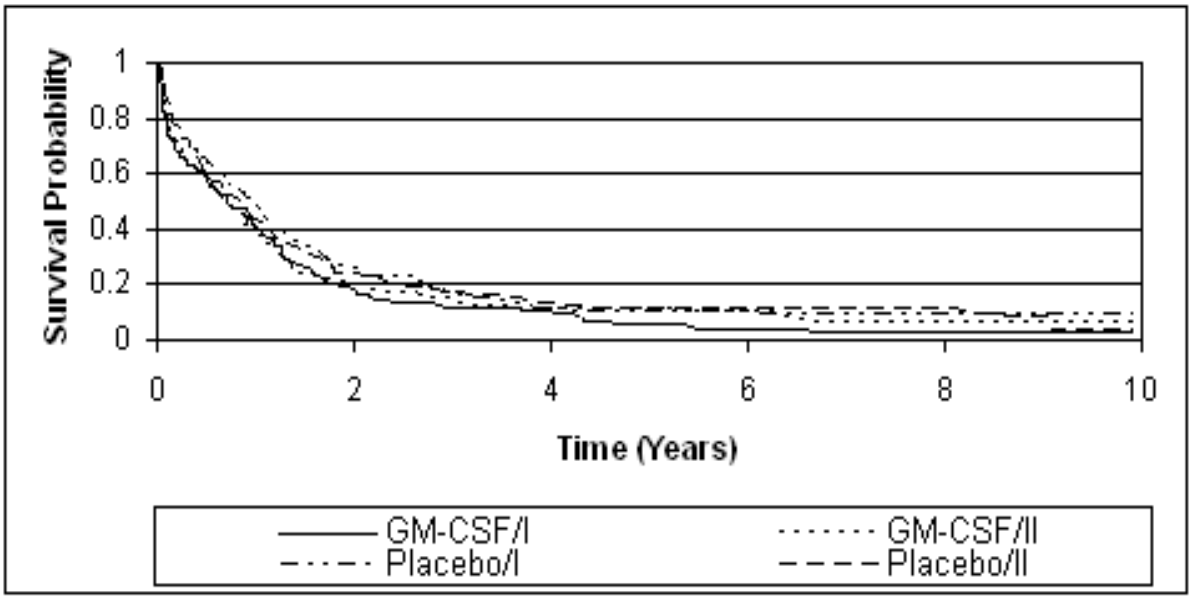

Figure 4: WKM survival estimates for four regimes in CALGB study

4.0 ASSESSING THE EFFECT OF TREATMENT REGIMES ON LONGITUDINAL OUTCOME DATA FROM SEQUENTIALLY RANDOMIZED DESIGNS

4.1 INTRODUCTION

In biomedical studies, it is common to apply multiple treatments in sequence to improve patients' quality of life. For example, the REVAMP (Research Evaluating the Value of Augmenting Medication with Psychotherapy) study [25] adopted a two-stage study design to assess the efficacy of combining pharmacotherapy and psychotherapy for the chronically depressed subjects. The study recruited a total of 808 subjects with chronic forms of major depression disorder (MDD) between 2003 and 2006. The study design is illustrated in Figure 5. At the initial stage, subjects received one of four treatments: Sertaline (SERT), Escitalopram (EcCIT), Burpropion (BUP-SR), and Venlafaxine (VLF-XR). The treatment assignment at this stage was done by REVAMP study physicians based on an algorithm which took into account the subject's treatment history. The treatment assignment was deterministic, for example, if a subject had never failed two adequate trials of Selective Serotonin Reuptake Inhibitors (SSRIs) and had no history of SERT failure in the past, this subject was assigned to the treatment with SERT. Each subject was followed for at most 12 weeks during which 24-item Hamilton Rating Scale of Depression ($HRSD_{24}$) score was collected at 2 weeks interval. During the 6 to 12 follow-up visits, if a subject's $HRSD_{24}$ score was reduced 60% or more from the study entry to a value less than 8, and the subject did not meet the diagnostic and statistical manual of mental disorders 4^{th} edition MDD criteria for two consecutive visits, the subject was considered to be a responder to the corresponding

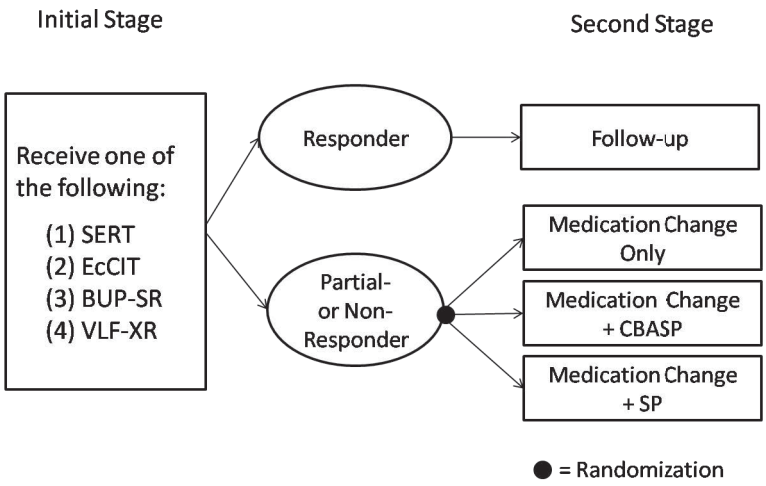

Figure 5: REVAMP study design

initial treatment. If the $HRSD_{24}$ score was only reduced less than 30%, and the subject did not meet the DSM-IV MDD criteria for two consecutive visits between week 6 to 12, the subject was considered to be a non-responder. If the subject did not meet the criteria for either a responder or a non-responder, then the subject was classified as a partial responder. At the second stage, the responders to the initial treatment moved to the follow-up stage, during which they continued to receive the same initial treatment for another 12 months with monthly follow-up visits. The partial responders and non-responders were randomly assigned to one of the three treatment options:(1) Medication change only (MC), (2) Medication change and cognitive behavioral analysis system of psychotherapy (MC/CBASP), and (3) Medication change and supportive psychotherapy (MC/SP). Details of the medication changes can be found in Trivedi [25]. The randomization rates for the three treatment options were 20%, 40%, and 40%, respectively. Similar to the initial stage, subjects were followed for 12 weeks, and the $HRSD_{24}$ score was measured repeatedly at two weeks interval.

The aims of the REVAMP study were to compare the efficacy of adding psychotherapy to a medication change versus changing medication alone (in chronic depressives with partial response or non-response to an initial antidepressant medication), and to test the efficacy of

the CBASP as an augmentation regime by comparing it to the SP. The study design allows twelve treatment regimes. In general, a treatment regime consists of an initial treatment, an intermediate response, and a second stage treatment. For the initial treatment X and the second stage treatment Y, the policy $X-Y$ can be defined as "Treat with initial treatment X, if respond continue the same treatment, otherwise switch to second stage treatment Y." For example, consider subjects treated with SERT at the initial stage. There are three possible treatment regimes these subjects could follow: (1) Treat with SERT, if respond continue SERT, otherwise change or add medication, (2) Treat with SERT, if respond continue SERT, otherwise treat with the CBASP, (3) Treat with SERT, if respond continue SERT, otherwise treat with the SP. Nine other treatment regimes can be constructed similarly with those who were treated with EcCIT, BUP-SR, and VLF-XR.

Standard methods for estimating treatment effect from longitudinal outcome data include generalized estimating equations [26, 27], generalized linear and mixed models [14, 15, 16]. The REVAMP study uses the mixed models for estimating the treatment effect for the randomized treatment groups. In our situation, the treatment regimes consist of sequences of treatments applied conditionally on intermediate response. Besides, one subject can belong to more than one regimes. For example, patients responding to SERT belongs to three different regimes, namely, SERT-MC, SERT-MC/CBASP, and SERT-MC/SP. Therefore, it is not as straightforward to estimate the effect of an regime or compare different regimes using standard longitudinal data analysis techniques. Statistical inference on treatment regimes using a summary outcome measure has been well-studied in the literature. For example, estimation of a mean response based on observational longitudinal data are proposed in Murphy, van der Laan and Robins [2] and Murphy [3]. Methods for survival outcomes were considered in Lunceford et al. [4], Wahed and Tsiatis [5, 6], Guo and Tsiatis [7], Hernan et al. [8], and Lokhnygina and Helterbrand [9]. Thall et al. [10] adapts a Bayesian approach to model the time to failure and compare two-stage adaptive treatment regimes. However, statistical methods for assessing the effect of treatment regimes on repeated measures data are not well-developed. In this article, we propose two methods for estimating treatment regime effects from longitudinal outcome data. We also investigate the use of Wald tests in comparing several treatment regimes.

In Section 4.2, we describe the notation, data structure, model, and assumptions. Section 4.3 describes the estimation procedures. Hypothesis testing for comparing the treatment regimes is described in Section 4.4. The results from simulation studies are reported in Section 4.5, followed by an application to the REVAMP study data in Section 4.6. The article is concluded with some discussions in Section 4.7.

4.2 DATA STRUCTURE AND MODELS

4.2.1 SETUP

We start with a generalized version of the REVAMP study design, where responders to initial treatments are also randomized to further treatments (possibly to maintain the response). In cases where responders are not randomized further such as the REVAMP study, we can envision a single second stage treatment for responders. Also, for simplicity, we assume that there are two treatment options at each stage. Generalization to more than two treatments will be straightforward. We depict such a design in Figure 6. Let the two initial treatments be denoted by A_1 and A_2, and the two sets of second stage treatments by B_1 and B_2 for the responders, and B_1' and B_2' for the non-responders. There are a total of eight treatment regimes in this setting, namely, $A_jB_kB_l', j, k, l = 1, 2$, where $A_jB_kB_l'$ stands for "Treat with A_j followed by B_k if respond, by B_l' otherwise." For each individual i, we can envision a number of variables described as follows. For $j, k, l = 1, 2$ and $m = 1, 2, \ldots, M$, let us define, $R_i(A_j)$ = response status if the i^{th} individual receives initial treatment A_j; $Y_{im}(A_jB_k)$ = outcome (e.g., HRSD_{24} score) measured at time t_{im} if the i^{th} individual receives B_k following a response to the initial treatment A_j; $Y_{im}(A_jB_l')$ = outcome (e.g., HRSD_{24} score) measured at time t_{im} if the ith individual receives B_l' after becoming a non-responder to the initial treatment A_j; V_i= vector of baseline covariates such as age and sex; $L_i(A_j)$= Vector of

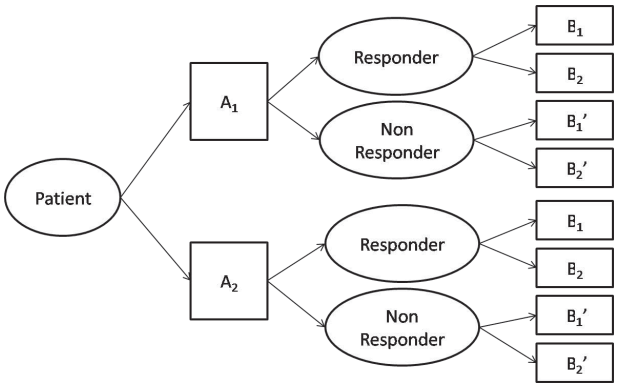

Figure 6: Example of two-stage design

variables collected during the initial treatment stage for the i^{th} individual receiving initial treatment A_j, e.g. time to initial response and minimum HRSD_{24} score observed during the initial treatment phase.

Notice that in practice not all the variables defined above could be observed for each individual. For example, if a patient actually receives A_1, then we would not be able to observe $R(A_2)$ for that patient. If a patient receives A_1, responds initially and then receives B_1, we will not be able to observe the variables $Y(A_1B_2)$, $Y(A_1B_1')$, $Y(A_1B_2')$, $Y(A_2B_1)$, $Y(A_2B_2)$, $Y(A_2B_1')$, or $Y(A_2B_2')$. These variables are referred to as counterfactuals [28]. We will use them to formulate the estimand of interest. With these notation, we can now define the outcome under the regime $A_jB_kB_l'$ as

$$Y_{im}(A_jB_kB_l') = R_i(A_j)Y_{im}(A_jB_k) + \{1 - R_i(A_j)\}Y_{im}(A_jB_l'). \tag{4.1}$$

The goal is to estimate the effect of the treatment regime $A_jB_kB_l', j, k, l = 1, 2$ on the changes in outcome Y over time adjusting for other baseline and first-stage patient characteristics.

4.2.2 THE MODEL

We postulate the model

$$E\left[Y_{im}(A_jB_kB_l')|V_i, L_i(A_j), t_{im}\right] = V_i^T\alpha(A_jB_kB_l') + L_i^T(A_j)\gamma(A_jB_kB_l') + \beta(A_jB_kB_l')t_{im} \quad (4.2)$$

to assess the effect of the treatment regime $A_jB_kB_l'$ on the changes in outcome Y over time adjusting for baseline covariate vector V_i and the vector of covariates from the initial stage $L_i(A_j)$. However, as mentioned earlier, not all patients were treated according to this regime. Therefore, the challenge would be to estimate the parameters $\theta(A_jB_kB_l') = \{\alpha(A_jB_kB_l'), \gamma(A_jB_kB_l'), \beta(A_jB_kB_l')\}$ for all $j, k, l = 1, 2$ based on the observed data. Note that the actual interest is in estimating and comparing the parameters $\beta(A_jB_kB_l'), j, k, l = 1, 2$, while treating $\{\alpha(A_jB_kB_l'), \gamma(A_jB_kB_l')\}\, j, k, l = 1, 2$ as nuisance. Also we note that in model (4.2) the effect of baseline covariate on the response Y is allowed to vary across regimes and hence the notation $\alpha(A_jB_kB_l')$. If we denote by V^* the vector of covariates formed by stacking the baseline and first stage covariates, and time, i.e.,

$$V_i^* = [V_i^T, L_i^T(A_j), t_{im}]^T,$$

model (4.2) could be simplified as

$$E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] = V_i^{*T}\theta(A_jB_kB_l'). \quad (4.3)$$

4.2.3 OBSERVED DATA

The observed data from a two-stage design (described in Figure 7) can be characterized as a set of n independent vectors

$$\{V_i, X_{ji}, L_i, R_i, R_iZ_{1i}, (1-R_i)Z_{1i}', (t_{im}, Y_{im}), m = 1, 2, \ldots, M; \}, i = 1, 2, \ldots, n,$$

where n is the total number of subjects in the sample; V_i is the baseline characteristics as defined previously; X_{ji} is the initial treatment indicator, X_{ji}=1 when the i^{th} subject was randomized to A_j, 0 otherwise; L_i is the vector of covariates observed during the initial stage,

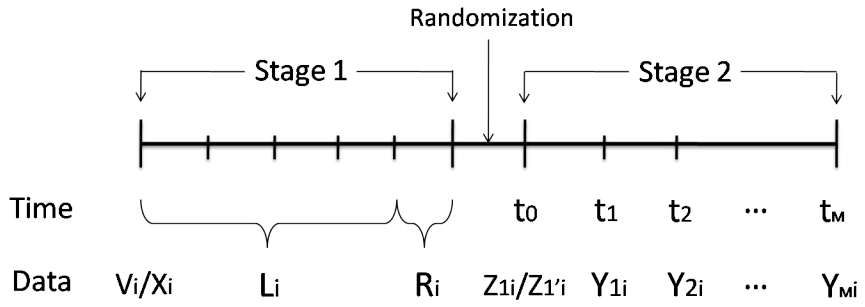

Figure 7: Structure of observed data in a typical two-stage design

Z_{1i} and Z'_{1i} are the second-stage treatment indicators for B_1 and B'_1, respectively, i.e., Z_{1i}=1 if the i^{th}subject received B_1, and Z_{1i}=0 otherwise. Similarly, Z'_{1i}=1 if the i^{th} subject received B'_1, 0 otherwise; Y_{im} is the outcome observed at time t_{im} for the subject i, $m = 1, 2, \ldots, M$. Let us define $Z_{2i} = 1 - Z_{1i}$ and $Z'_{2i} = 1 - Z'_{1i}$ so that Z_{2i} and Z'_{2i} respectively represents the indicators for B_2 and B'_2 respectively.

4.2.4 ASSUMPTIONS

As a first step toward estimation of the regime-specific parameters, counterfactual quantities defined in section 4.2.1 will be expressed in terms of observed data. We make the consistency assumption [29] that relates observed outcomes to the counterfactuals based on the actual treatment received by the individuals. Namely,

$$R_i = \sum_{j=1}^{2} X_{ji} R_i(A_j), \tag{4.4}$$

$$L_i = \sum_{j=1}^{2} X_{ji} L_i(A_j), \tag{4.5}$$

and

$$Y_{im} = \sum_{j=1}^{2} \left[X_{ji} \left\{ R_i \sum_{k=1}^{2} Z_{ki} Y_{im}(A_j B_k) + (1 - R_i) \sum_{l=1}^{2} Z'_{li} Y_{im}(A_j B'_l) \right\} \right]. \tag{4.6}$$

The consistency assumption implies that the potential outcome of a certain sequence of treatment will remain unchanged regardless of the treatment assignment mechanism. In addition, for consistent estimation of the treatment regime effects, we assume that actual treatments received at different stages are independent of counterfactuals, conditional on observed covariate history. Equivalently,

$$Pr(X_{ji} = 1 | V_i, Y_{im}(A_j B_k), Y_{im}(A_j B'_l), j, k, l = 1, 2) = Pr(X_{ji} = 1 | V_i), j = 1, 2, \tag{4.7}$$

$$\begin{aligned} Pr(Z_{ki} = 1 | X_{ji}, R_i = 1, V_i, L_i, Y_{im}(A_j B_k), Y_{im}(A_j B'_l), k, l = 1, 2) \\ = Pr(Z_{ki} = 1 | X_{ji}, R_i = 1, V_i, L_i), j = 1, 2, \end{aligned} \tag{4.8}$$

$$\begin{aligned} \text{and } Pr(Z'_{li} = 1 | X_{ji}, R_i = 0, V_i, L_i, Y_{im}(A_j B_k), Y_{im}(A_j B'_l), k, l = 1, 2) \\ = Pr(Z'_{li} = 1 | X_{ji}, R_i = 0, V_i, L_i), j = 1, 2. \end{aligned} \tag{4.9}$$

This assumption is frequently referred to as "No unmeasured confounder" [30] assumption. In the case of the REVAMP study design, (4.8) and (4.9) are automatically satisfied, since the second stage treatment is assigned through randomization. In addition, due to randomization these latter probabilities do not depend on the covariates except for the response status. Therefore, for simplicity, we will denote the probabilities in (4.8) and (4.9) by $\pi_{A_j B_k}$ and $\pi_{A_j B'_l}$ respectively.

4.3 ESTIMATION

As noted in the previous section, for fixed j, k, and l, the response for the regime $A_jB_kB_l'$, namely, $Y_{im}(A_jB_kB_l')$ is not observed for all patients. Therefore, the estimation procedure would be carried out via group-specific sub-models. Specifically, all the individuals in the sample could be identified as belonging to one of the 8 subgroups, namely, $A_jB_k, A_jB_l', j, k, l = 1, 2$, where the subgroup A_jB_k refers to those who were treated with the sequence of treatments A_j followed by B_k, and similarly for A_jB_l'. First we will express the regime-specific parameters in terms of the group-specific parameters. We set the following sub-models for group-specific responses $Y_{im}(A_jB_k)$ and $Y_{im}(A_jB_l')$:

$$E\left[Y_{im}(A_jB_k)|V_i, L_i(A_j), t_{im}\right] = V_i^T\alpha(A_jB_k) + L_i^T\gamma(A_jB_k) + \beta(A_jB_k)t_{im}, \tag{4.10}$$

and

$$E\left[Y_{im}(A_jB_l')|V_i, L_i(A_j), t_{im}\right] = V_i^T\alpha(A_jB_l') + L_i^T\gamma(A_jB_l') + \beta(A_jB_l')t_{im}. \tag{4.11}$$

Or, equivalently,

$$E\left[Y_{im}(A_jB_k)|V_i^*\right] = V_i^{*T}\theta(A_jB_k), \tag{4.12}$$

and

$$E\left[Y_{im}(A_jB_l')|V_i^*\right] = V_i^{*T}\theta(A_jB_l'), \tag{4.13}$$

where similar to the regime-specific notations for parameters, we defined group-specific parameters $\theta(A_jB_k) = \{\alpha(A_jB_k), \gamma(A_jB_k), \beta(A_jB_k)\}^T$ and $\theta(A_jB_l') = \{\alpha(A_jB_l'), \gamma(A_jB_l'), \beta(A_jB_l')\}^T$, $j, k, l = 1, 2$. We note that models (4.12) and (4.13) could be fitted by using the data from patients who were treated using the respective sequences of treatments. Thus, if we can express the regime specific parameters $\theta(A_jB_kB_l')$ in terms of group-specific parameters $\theta(A_jB_k)$ and $\theta(A_jB_l')$, then we will be able to estimate them with ease. From Equation (4.1), we can write,

$$E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] = E\left[R_i(A_j)Y_{im}(A_jB_k)|V_i^*\right] + E\left[\{1 - R_i(A_j)\}Y_{im}(A_jB_l')|V_i^*\right] \tag{4.14}$$

If we further assume that conditional on V_i^*, $R_i(A_j)$ and $Y_{im}(A_jB_k)$, and $R_i(A_j)$, and $Y_{im}(A_jB_l')$ are statistically independent, then we obtain

$$\begin{aligned} & E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] \\ &= E\left[R_i(A_j)|V_i^*\right]E\left[Y_{im}(A_jB_k)|V_i^*\right] + E\left[1-R_i(A_j)|V_i^*\right]E\left[Y_{im}(A_jB_l')|V_i^*\right]. \end{aligned} \quad (4.15)$$

Let $E(R_i(A_j)|V_i^*) = \pi_r(A_j)$ where $\pi_r(A_j)$ is the proportion of responders to the initial treatment A_j, i.e., given the initial treatment assignment, probability of response does not depend on V_i^*. Then (4.15) can be expressed as

$$\begin{aligned} & E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] \\ &= \pi_r(A_j)E\left[Y_{im}(A_jB_k)|V_i^*\right] + \{1-\pi_r(A_j)\}E\left[Y_{im}(A_jB_l')|V_i^*\right]. \end{aligned} \quad (4.16)$$

Under the model assumptions (4.10) and (4.11), equation (4.16) becomes

$$E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] = V_i^{*T}\left[\pi_r(A_j)\theta(A_jB_k) + \{1-\pi_r(A_j)\}\theta(A_jB_l')\right]. \quad (4.17)$$

By comparing (4.3) to (4.17), we can express the regime-specific parameter $\theta(A_jB_kB_l')$ as the weighted average of treatment path specific parameters as follows

$$\theta(A_jB_kB_l') = \pi_r(A_j)\theta(A_jB_k) + \{1-\pi_r(A_j)\}\theta(A_jB_l'). \quad (4.18)$$

Since the outcome is measured repeatedly over time for the same individual, to account for the correlation within individuals, one might use generalized estimating equations to fit the group-specific models or introduce random effects into these models (mixed models). Whatever way these models are fitted, once the group-specific parameters $(\theta(A_jB_k), \theta(A_jB_l'))$ are estimated along with the respective response rates, equation (4.18) could be used to obtain the regime-specific parameter estimates from the group-specific parameter estimates. Specifically,

$$\hat{\theta}(A_jB_kB_l') = \hat{\pi}_r(A_j)\hat{\theta}(A_jB_k) + \{1-\hat{\pi}_r(A_j)\}\hat{\theta}(A_jB_l'). \quad (4.19)$$

For the purpose of our analysis we have used mixed models. We accommodate random effects by adding the individual random component to the models (4.12) and (4.13). Let $H_i^T\eta_i(A_jB_k)$ and $H_i^T\eta_i(A_jB_l')$ be the random effect components for the subjects who follow a

sequence of treatments A_jB_k and $A_jB'_l$, respectively, where H_i is the vector of random effects, and η_i's are random vectors of parameters for each subject having mean 0. For example, if we choose the intercept and time as random effects, then $H_i = [1, t_{im}]^T$, $\eta_i(A_jB_k) = [\eta_{i0}(A_jB_k), \eta_{i1}(A_jB_k)]^T$, and $\eta_i(A_jB'_l) = [\eta_{i0}(A_jB'_l), \eta_{i1}(A_jB'_l)]^T$ will represent the group-specific parameters for random intercepts and slopes, respectively. In this case, the models (4.12) and (4.13) are modified slightly as follows

$$E\left[Y_{im}(A_jB_k)|V_i^*, \eta_i(A_jB_k)\right] = V_i^{*T}\theta(A_jB_k) + H_i^T\eta_i(A_jB_k), \tag{4.20}$$

and

$$E\left[Y_{im}(A_jB'_l)|V_i^*, \eta_i(A_jB'_l)\right] = V_i^{*T}\theta(A_jB'_l) + H_i^T\eta_i(A_jB'_l). \tag{4.21}$$

We assume that $\eta_i(A_jB_k)$ and $\eta_i(A_jB'_l)$ are distributed as multivariate normal with common mean $\mathbf{0}$ and variance-covariance matrices $G(A_jB_k)$ and $G(A_jB'_l)$ respectively. In the following sections, we discuss two specific methods for estimating the fixed parameters $\beta(A_jB_kB'_l), j, k, l = 1, 2$.

4.3.1 PROPOSED METHODS

We propose two methods to estimate the effect of treatment regimes on the outcome over time. In the first method, mixed model techniques are used to estimate $\beta(A_jB_k)$ and $\beta(A_jB'_l)$ in the first step and then their weighted averages are used to derive the estimates for $\beta(A_jB_kB'_l)$. We refer to this method as a two-step method. The second method uses multiple imputation approach to reconstruct observations for subjects who did not follow the regime of interest. This method involves one extra step of multiple imputation and hence will be referred to as three-step method. Both two-step and three-step estimators are described below in details.

4.3.1.1 TWO-STEP METHOD

Step 1: Estimation of treatment effects for observed treatment sequences. For each first stage treatment $A_j, j = 1, 2$, we obtain the empirical response rates

$$\hat{\pi}_r(A_j) = \frac{\sum_{i=1}^{n} X_{ji} R_i}{\sum_{i=1}^{n} X_{ji}}, j = 1, 2. \tag{4.22}$$

Next we note that under the consistency and sequential randomization assumptions (4.4)-(4.9), $Y_i(A_j B_k) = Y_i$ when $X_{ji} = 1, R_i = 1,$ and $Z_{ki} = 1$ (and, similarly for other treatment sequences). Therefore, for each of the eight observed sequences of treatments $(A_j B_k, A_j B'_l)$, $j, k, l = 1, 2$, we estimate $\beta(A_j B_k)$, $\beta(A_j B'_l)$, $j, k, l = 1, 2$ in this step using data from subjects who received respective treatment sequence. For example, for $j = k = 1$, by fitting the model (4.20) (with counterfactual Y's replaced with observed Y's) to the data from subjects who followed the $A_1 B_1$ treatment sequence, we obtain $\hat{\beta}(A_1 B_1)$. Any standard statistical procedure, such as PROC MIXED in SAS [31] or the lme function in R [32] could be used for this purpose. Note that the advantage of using such standard procedures is that the estimated variance-covariance matrices for these parameter estimates are readily available from the outputs generated by these routines. Also, model assumptions and structure of the appropriate covariance matrix G could be thoroughly examined using these routines. The residual check for normality and the covariance selection are described, for example, in Brown and Prescott [17].

Step 2: Estimation of the overall treatment regime effects. The estimates for each treatment regime effect $\hat{\beta}(A_j B_k B'_l)$ are constructed in this step. As described in (4.19), the regime-specific parameter $\hat{\beta}(A_j B_k B'_l)$ are estimated as the weighted average

$$\hat{\beta}(A_j B_k B'_l) = \hat{\pi}_r(A_j)\hat{\beta}(A_j B_k) + \{1 - \hat{\pi}_r(A_j)\}\hat{\beta}(A_j B'_l).$$

As long as the estimators $\hat{\beta}(A_j B_k)$ and $\hat{\beta}(A_j B'_l)$ are unbiased, the above estimator is approximately unbiased for the true parameter $\beta(A_j B_k B'_l)$. Approximate variance of $\hat{\beta}(A_j B_k B'_l)$ is derived as follows

$$Var\{\hat{\beta}(A_j B_k B'_l)\} \quad = \quad E[Var\{\hat{\beta}(A_j B_k B'_l)|\hat{\pi}_r(A_j)\}] + Var[E\{\hat{\beta}(A_j B_k B'_l)|\hat{\pi}_r(A_j)\}],$$

where

$$
\begin{aligned}
E[Var\{\hat{\beta}(A_jB_kB_l')|\hat{\pi}_r(A_j)\}] &= E[Var(\hat{\pi}_r(A_j)\hat{\beta}(A_jB_k) + \{1-\hat{\pi}_r(A_j)\}\hat{\beta}(A_jB_l')|\hat{\pi}_r(A_j))] \\
&= E[\hat{\pi}_r(A_j)^2 Var(\hat{\beta}(A_jB_k)|\hat{\pi}_r(A_j)) \\
&\quad +\{1-\hat{\pi}_r(A_j)\}^2 Var(\hat{\beta}(A_jB_l')|\hat{\pi}_r(A_j))] \\
&= Var(\hat{\beta}(A_jB_k))E(\hat{\pi}_r(A_j)^2) + Var(\hat{\beta}(A_jB_l'))E(\{1-\hat{\pi}_r(A_j)\}^2) \\
&= Var(\hat{\beta}(A_jB_k))[Var(\hat{\pi}_r(A_j)) + E(\hat{\pi}_r(A_j)^2)] \\
&\quad +Var(\hat{\beta}(A_jB_l'))[Var(1-\hat{\pi}_r(A_j)) + E(\{1-\hat{\pi}_r(A_j)\}^2)] \\
&= Var(\hat{\beta}(A_jB_k))[\frac{\pi_r(A_j)\{1-\pi_r(A_j)\}}{n_j} + \pi_r(A_j)^2] \\
&\quad +Var(\hat{\beta}(A_jB_l'))[\frac{\pi_r(A_j)(1-\pi_r(A_j))}{n_j} + \pi_r(A_j)^2]
\end{aligned}
$$

where $n_j = \sum_{i=1}^{n} X_{ji}$, and

$$
\begin{aligned}
Var[E(\hat{\beta}(A_jB_kB_l')|\hat{\pi}_r(A_j))] &= Var[E\{\hat{\pi}_r(A_j)\hat{\beta}(A_jB_k) + \{1-\hat{\pi}_r(A_j)\}\hat{\beta}(A_jB_l')|\hat{\pi}_r(A_j)\}] \\
&= Var[\hat{\pi}_r(A_j)\beta(A_jB_k) + \{1-\hat{\pi}_r(A_j)\}\beta(A_jB_l')] \\
&= \{\beta(A_jB_k) - \beta(A_jB_l')\}^2 Var(\hat{\pi}_r(A_j)) \\
&= \{\beta(A_jB_k) - \beta(A_jB_l')\}^2 \frac{\pi_r(A_j)(1-\pi_r(A_j))}{n_j}.
\end{aligned}
$$

Thus,

$$
\begin{aligned}
Var\{\hat{\beta}(A_jB_kB_l')\} &= Var(\hat{\beta}(A_jB_k))[\frac{\pi_r(A_j)\{1-\pi_r(A_j)\}}{n_j} + \pi_r(A_j)^2] \\
&\quad +Var(\hat{\beta}(A_jB_l'))[\frac{\pi_r(A_j)\{1-\pi_r(A_j)\}}{n_j} + \pi_r(A_j)^2] \\
&\quad +\{\beta(A_jB_k) - \beta(A_jB_l')\}^2 \frac{\pi_r(A_j)\{1-\pi_r(A_j)\}}{n_j}
\end{aligned}
$$

4.3.2 THREE-STEP METHOD

Step 1: Estimation of treatment effect for each treatment sequence. For simplicity, consider the regime $A_1B_1B_1'$. We first use Step 1 of the two-step method to obtain $\hat{\pi}_R(A_1)$, $\hat{\beta}(A_1B_1)$, $\hat{\beta}(A_1B_2)$, $\hat{\beta}(A_1B_1')$, and $\hat{\beta}(A_1B_2')$.

Step 2: Multiple imputation. Since a subject is randomized to one of the second-stage treatments, the subject's outcome for the other second-stage treatment is unobserved. For example, if a subject responds to A_1 and receives B_1, then this subject is not able to receive B_2 at the same time. Therefore, the outcome based on the B_2 are unobserved for this subject. We will treat this as a missing-data problem, and impute the outcomes *as if* the subject also received the other second-stage treatment at the same time. Since a single imputation method generates smaller standard errors in general [19], multiple imputation method is applied to reconstruct the potential outcome data for these patients (who received A_1B_2) based on their covariate history and the information borrowed from subjects who received A_1B_1. First we estimate the fixed parameters $\theta(A_1B_1)$ and variance-covariance matrix G for the corresponding random effects by fitting the model (4.20) to subjects who received A_1B_1 sequence. Then for each individual receiving the sequence A_1B_2, we use I random draws from the random effect distribution and combine it with the parameter estimate and covariate information of the A_1B_2 subjects to impute their potential outcomes $Y(A_1B_1)$. At the end of the imputation process, there will be I newly created datasets, containing the observed outcomes for the A_1B_1 subjects, and imputed outcomes for the A_1B_2 subjects.

Step 3: Estimation of the overall treatment regime effects. Because of the imputed potential outcomes in Step 2, every subject is now consistent with every regime. Therefore, we can directly estimate the overall treatment regime effects by fitting model (4.2) to these I datasets to obtain $\hat{\beta}^{(\ell)}(A_1B_1B_1'), \ell = 1, 2, \ldots, I$, and the imputed estimator for $\beta(A_1B_1B_1')$ is defined as

$$\hat{\beta}^{IMP}(A_1B_1B_1') = \frac{1}{I}\sum_{\ell=1}^{I}\hat{\beta}^{(\ell)}(A_1B_1B_1').$$

Since we adapted the multiple imputations in Step 2, we need to account for both within and between subjects variabilities. Following the formula given in Little [19], the variance of the imputed estimator can be estimated by

$$\begin{aligned} Var\left\{\hat{\beta}^{IMP}(A_1B_1B_1')\right\} &= \frac{1}{I}\sum_{\ell=1}^{I} Var\left\{\hat{\beta}^{(\ell)}(A_1B_1B_1')\right\} \\ &\quad + \frac{I+1}{I(I-1)}\sum_{\ell=1}^{I}\left\{\hat{\beta}^{(\ell)}(A_1B_1B_1') - \hat{\beta}^{IMP}(A_1B_1B_1')\right\}^2 . \quad (4.23) \end{aligned}$$

The treatment effects for the other treatment sequences are estimated in a similar manner. The variance of this estimator is expected to be larger than the variance of the two-step estimator as multiple imputations introduces further variability into the model.
than the variance of the two-step estimator as multiple imputations introduces further variability into the model.

4.4 HYPOTHESIS TESTING

Finding the best treatment regime in the two-stage randomized designs is equivalent to simultaneously testing whether one treatment regime is significantly superior to the others. Specifically, testing the following null hypothesis is our primary interest:

$$H_0 : \beta(A_1B_1B_1') = \beta(A_1B_1B_2') = \beta(A_1B_2B_1') = \beta(A_1B_2B_2')$$

Since this null hypothesis is equivalent to testing three pair-wise comparisons between $\beta(A_1B_1B_1')$ and $\beta(A_1B_1B_2')$, $\beta(A_1B_1B_1')$ and $\beta(A_1B_2B_1')$, and $\beta(A_1B_1B_1')$ and $\beta(A_1B_2B_2')$, the null hypothesis can also be expressed as

$$H_0 : A^T\beta = 0 \quad (4.24)$$

where,

$$\beta = \begin{bmatrix} \beta(A_1B_1B_1') \\ \beta(A_1B_1B_2') \\ \beta(A_1B_2B_1') \\ \beta(A_1B_2B_2') \end{bmatrix},$$

and

$$A^T = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 1 & 0 & -1 & 0 \\ 1 & 0 & 0 & -1 \end{bmatrix}.$$

The test statistics is constructed as the Wald statistic

$$\chi^2 = \hat{\beta}^T A\{A^T Cov(\hat{\beta})A\}^{-1}A^T\hat{\beta}, \tag{4.25}$$

where, $\hat{\beta}$ is the vector of parameter estimates corresponding to β and $Cov(\hat{\beta})$ is the estimated variance-covariance matrix of $\hat{\beta}$. In the previous section, we had derived the formula for the variance of $\hat{\beta}(A_jB_kB_l')$, which can be estimated by substituting unbiased estimates of the appropriate quantities. The covariance between $\hat{\beta}(A_1B_1B_1')$ and $\hat{\beta}(A_1B_2B_2')$, as well as $\hat{\beta}(A_1B_2B_1')$ and $\hat{\beta}(A_1B_1B_2')$ are set to zero since these treatment regimes are independent as they do not share any common second stage treatments. To obtain the covariances between other regime-specific coefficients, we use a method similar to the multivariate delta method [33] based on the Taylor series expansion of the estimator itself. The parameter $\beta(A_jB_kB_l')$ is treated as the function of the three unknown parameters (i.e. $\pi_r(A_j)$, $\beta(A_jB_k)$, and $\beta(A_jB_l')$), so that using Taylors series expansion, we obtain

$$\begin{aligned} &\hat{\beta}(A_jB_kB_l') \\ &= \hat{\pi}_r(A_j)\hat{\beta}(A_jB_k) + \{1-\hat{\pi}_r(A_j)\}\hat{\beta}(A_jB_l') \\ &\approx \beta(A_jB_kB_l') + \{\beta(A_jB_k) - \beta(A_jB_l')\}\{\hat{\pi}_r(A_j) - \pi_r(A_j)\} + \{\hat{\beta}(A_jB_k) - \beta(A_jB_k)\}\hat{\pi}_r(A_j) \\ &\quad +\{\hat{\beta}(A_jB_l') - \beta(A_jB_l')\}\{1-\pi_r(A_j)\}. \end{aligned}$$

Then, the covariance between $\hat{\beta}(A_1B_1B_1')$ and $\hat{\beta}(A_1B_1B_2')$ is approximated by

$$
\begin{aligned}
& cov[\hat{\beta}(A_1B_1B_1')\hat{\beta}(A_1B_1B_2')] \\
&= E[\{\hat{\beta}(A_1B_1B_1') - \beta(A_1B_1B_1')\}\{\hat{\beta}(A_1B_1B_2') - \hat{\beta}(A_1B_1B_2')\}] \\
&\approx E[(\{(\beta(A_1B_1) - \beta(A_1B_1')\}\{\hat{\pi}(A_1) - \pi_r(A_1)\} \\
&\quad +\{\hat{\beta}(A_1B_1) - \beta(A_1B_1)\}\hat{\pi}_r(A_1) + \{\hat{\beta}(A_1B_1') - \beta(A_1B_1')\}\{1 - \pi_r(A_1)\}), \\
&\quad \{(\beta(A_1B_1) - \beta(A_1B_2')\}\{\hat{\pi}_r(A_1) - \pi_r(A_1)\} + \{\hat{\beta}(A_1B_1) - \beta(A_1B_1)\}\hat{\pi}_r(A_1) \\
&\quad +\{\hat{\beta}(A_1B_2') - \beta(A_1B_2')\}\{1 - \pi_r(A_1)\})] \\
&= E[\{\beta(A_1B_1) - \beta(A_1B_1')\}\{\beta(A_1B_1) - \beta(A_1B_2')\}\{\hat{\pi}_r(A_1) - \pi_r(A_1)\}^2 \\
&= E[\{\beta(A_1B_1) - \beta(A_1B_1')\}\{\beta(A_1B_1) - \beta(A_1B_2')\}\{\hat{\pi}_r(A_1) - \pi_r(A_1)\}^2] \\
&= \{\beta(A_1B_1) - \beta(A_1B_1')\}\{\beta(A_1B_1) - \beta(A_1B_2')\}Var(\hat{\pi}_r(A_1)) \\
&= \{\beta(A_1B_1) - \beta(A_1B_1')\}\{\beta(A_1B_1) - \beta(A_1B_2')\}\left[\frac{\pi_r(A_1)\{1 - \pi_r(A_1)\}}{n_1}\right].
\end{aligned}
$$

The covariance then can be estimated by replacing the parameters with the corresponding estimates.

Under the null hypothesis, the Wald statistic (4.25) is compared to the critical values of a χ^2_3 distribution. Other linear combinations of regime-specific treatment effects may be tested in a similar manner.

4.5 SIMULATION STUDY

In order to examine the properties of the proposed estimators, we have conducted several simulation studies. We generated data by simulating a two-stage randomized study as shown in Figure 6. The number of follow-up visits during the second stage was set to four. For simplicity, we only generated data for the subjects with A_1 treatment, and therefore, we will have only four treatment regimes, namely, $A_1B_1B_1'$, $A_1B_1B_2'$, $A_1B_2B_1'$, and $A_1B_2B_2'$.

For individual i, the response status R_i is generated from a Bernoulli distribution with mean $\pi_r = 0.5$. Given the response status, the second-stage treatment indicators Z_{1i} and Z'_{1i} were generated respectively for responders and non-responders from Bernoulli distributions with $\pi_{A_1B_1} = 0.5$ and $\pi_{A_1B'_1} = 0.5$. The covariate, age, is randomly drawn from a normal distribution with mean 30, with standard deviation of 5. The initial stage outcome $y^{(1)}$ depends on R_i and it was generated from a normal distribution with a mean of 20 for the responders and 30 for the non-responders. The variance was set to 2 for both responders and non-responders. For the repeatedly measured outcomes for the subjects receiving A_jB_k, we generated the data from the following model

$$Y_{im}(A_jB_k) = \{\eta_{0i} + \beta_0(A_jB_k)\} + \{\eta_{1i} + \beta_1(A_jB_k)\}t_{im} + \alpha(A_jB_k)age_i + \gamma(A_jB_k)y_i^{(1)} + \epsilon_{im},$$

where $(\eta_{0i}, \eta_{1i})^T \sim N(\mathbf{0}, G(A_jB_k))$, $\epsilon_{im} \sim N(0, \sigma_e^2)$, and independently of η_{0i} and η_{1i}. We set $G(A_jB_k)$ as

$$G(A_jB_k) = \begin{bmatrix} \sigma_0 & \rho\sqrt{\sigma_0\sigma_1} \\ \rho\sqrt{\sigma_0\sigma_1} & \sigma_1 \end{bmatrix}.$$

Similarly, the true outcome for the sequence of treatments $A_jB'_l$ was generated using

$$Y_{im}(A_jB'_l) = \{\eta'_{0i} + \beta_0(A_jB'_l)\} + \{\eta'_{1i} + \beta_1(A_jB'_l)\}t_{im} + \alpha(A_jB'_l)age_i + \gamma(A_jB'_l)y_i^{(1)} + \epsilon'_{im},$$

where $(\eta'_{0i}, \eta'_{1i})^T \sim N(\mathbf{0}, G(A_jB'_l))$, and $\epsilon'_{im} \sim N(0, \sigma_e^{'2})$. For our simulations, we set $G(A_jB_k)$ $= G(A_jB'_l)$ and $\sigma_e^2 = \sigma_e^{'2}$. Thus our models have intercept and time as both fixed and random effects.

In simulation scenario 1, we assumed that there were clear treatment differences among four treatment sequences, while in simulation scenario 2, there was no treatment differences. In scenario 1, we choose $\beta_0(A_1B_1)$=$\beta_0(A_1B_2)$=20, $\beta_1(A_1B_1)$=-2.5, $\beta_1(A_1B_2)$=-0.1, $\beta_0(A_1B'_1)$ $= \beta_0(A_1B'_2) = 30$, $\beta_1(A_1B'_1) =$ -2.0 and $\beta_1(A_1B'_2) =$ -0.5, leading to $\beta(A_1B_1B'_1) =$ -2.25, $\beta(A_1B_1B'_2) =$ -1.50, $\beta(A_1B_2B'_1) =$ -1.05, and $\beta(A_1B_2B'_2) =$ -0.30. In scenario 2, we changed the parameters to $\beta_0(A_1B_1) = \beta_0(A_1B_2) = 20$, $\beta_0(A_1B'_1) = \beta_0(A_1B'_2) = 30$, and $\beta_1(A_1B_1)$ $= \beta_1(A_1B_2) = \beta_1(A_1B'_1) = \beta_1(A_1B'_2) = 0$, leading to no treatment effect for all regimes. The parameters for the variance-covariance matrix G were set to $\sigma_0 = 0.35$, $\sigma_1 = 0.25$, and $\rho =$ 0.001. For the variance of ϵ_{im}, σ_e^2 was set to 2. The sequence-specific age effects were set

to $\alpha(A_1B_1) = 0.1$, $\alpha(A_1B_2) = 0.2$, $\alpha(A_1B_1') = 0.15$, and $\alpha(A_1B_2') = 0.25$. Finally, we chose the effect of initial stage outcome as $\gamma(A_1B_1) = \gamma(A_1B_1')$ = -0.2, and $\gamma(A_1B_2) = \gamma(A_1B_2')$ = -0.25.

Since it is unrealistic to assume that everyone completes the study, in addition to creating two different scenarios for the treatment regime effect, the proposed methods were tested in different missing data situations [19]: (1) no missing data, (2) missing completely at random (MCAR), and (3) missing at random (MAR). For its simplicity, we selected a monotone missing pattern for both MCAR and MAR situations. Selecting the monotone missing pattern means that we assume that once a subject misses a visit, all subsequent visits are missed as well. For the MCAR situation, at first, 30% and 60% of subjects were randomly selected to have some outcome data missing. Of these, 50% were randomly selected to have missing Y_{i4}, and the remaining 50% were to have missing Y_{i3} and Y_{i4}. For the MAR situation, we also generated 30% and 60% missing data. However, in this case, the rate of missing data depended on the treatment sequences. When 30% of data are missing, 2.5% among the subjects with treatment sequences A_1B_1 or A_1B_2, 10% among the subjects with A_1B_1', and 15% among the A_1B_2' subjects have some missing data. The percentages were doubled for the 60% missing situation. Similar to the MCAR situation, among those who had missing data, 50% of them were missing Y_{i4}, and the other 50% have missing Y_{i3} and Y_{i4}. In both scenarios and all missing situations, 500 Monte-Carlo datasets were generated with two different sample sizes of 500 and 1000. Only for the complete data situation, we generated additional datasets with a sample size of 200.

For each simulated dataset, $\beta(A_jB_kB_l'), j, k, l = 1, 2$ and their standard errors were estimated using the methods described in Section 4.3. Results are presented using Monte Carlo means, standard errors, and coverage probabilities of 95% CIs. The simulation results are summarized in Tables 4 to 10.

Table 4 shows the results of scenario 1 when there was no missing data. For all sample sizes, the estimates from both two-step and three-step methods were very close to the true values with negligible biases (0.00-0.04). The variance estimators for two-stage method were consistent as seen by the agreement between the average estimated standard error and the MCSE. However, the variance estimator for the three-step method was larger than the MCSE

Table 4: **Simulation result for two- and three-step methods with no missing data.** *Monte Carlo mean, Monte Carlo standard error, standard error, and coverage rate (based on 95% C.I.) for all treatment regimes when the treatment regimes differ*

			Two-step Method			Three-step Method		
Sample Size	Treatment Regime	True Param.	MC Mean (MCSE)	SE	Coverage Rate(%)	MC Mean (MCSE)	SE	Coverage Rate(%)
200	$A_1B_1B_1'$	-2.25	-2.24(0.099)	0.096	93.0	-2.28(0.099)	0.097	93.4
	$A_1B_1B_2'$	-1.50	-1.50(0.119)	0.102	90.4	-1.54(0.120)	0.135	96.0
	$A_1B_2B_1'$	-1.05	-1.05(0.119)	0.101	91.2	-1.09(0.119)	0.108	91.0
	$A_1B_2B_2'$	-0.30	-0.30(0.095)	0.096	95.6	-0.34(0.096)	0.094	92.4
500	$A_1B_1B_1'$	-2.25	-2.25(0.062)	0.060	95.2	-2.26(0.062)	0.059	94.0
	$A_1B_1B_2'$	-1.50	-1.50(0.078)	0.064	90.2	-1.51(0.078)	0.079	95.6
	$A_1B_2B_1'$	-1.05	-1.05(0.073)	0.064	91.6	-1.06(0.073)	0.065	91.6
	$A_1B_2B_2'$	-0.30	-0.30(0.062)	0.060	94.6	-0.32(0.062)	0.057	92.2

perhaps due to the multiple imputations. For the two-step method, the coverage rate ranged between 90.2% and 95.6% while the range for the three-step method was between 91.0% and 96.0%. The results of scenario 2 when there is no missing data are reported in Table 6. Again the estimates were approximately unbiased, and the coverage rates for the two methods were similar. For both methods, increase in sample size from 200 to 500 did not affect the properties of the estimators.

Tables 7 and 8 summarize the results of scenarios 1 and 2 respectively when the missing data are completely at random. The estimates for both methods were approximately unbiased, and as expected, the percentage of missing data did not affect the estimates. Compared to the two-step method, the three-step method had slightly larger bias, probably due to the additional variability introduced through multiple imputation. The coverage rates for the three-step method were generally higher (93.6%-98.6%) than the ones for the two-step method (90.6%-95.6%) since the variance estimates were larger than the MC variances. Since the estimates from the mixed models are expected to be unbiased when the data are missing completely at random, the results are not unexpected.

Tables 9 and 10 report the results of scenario 1 and 2 when the data are missing at random. The results were very similar to those from the MCAR situation. The estimates were approximately unbiased even when 60% of the data had at least one missing assessment.

Table 5: **Simulation result for two- and three-step methods with no missing data.** *Monte Carlo mean, Monte Carlo standard error, standard error, and coverage rate (based on 95% C.I.) for all treatment regimes when there were no effects of treatment regime*

		Two-step Method			Three-step Method		
Sample Size	Treatment Regime	MC Mean (SE)	MCSE	Coverage Rate(%)	MC Mean (SE)	MCSE	Coverage Rate(%)
200	$A_1B_1B_1'$	0.00(0.095)	0.096	95.0	-0.05(0.095)	0.095	92.0
	$A_1B_1B_2'$	-0.01(0.095)	0.096	95.2	-0.05(0.096)	0.098	92.6
	$A_1B_2B_1'$	0.00(0.095)	0.095	94.4	-0.04(0.094)	0.091	91.2
	$A_1B_2B_2'$	-0.01(0.094)	0.095	95.0	-0.05(0.093)	0.094	92.8
500	$A_1B_1B_1'$	0.00(0.063)	0.060	94.8	-0.01(0.063)	0.057	92.6
	$A_1B_1B_2'$	0.01(0.058)	0.060	96.4	-0.01(0.058)	0.060	95.6
	$A_1B_2B_1'$	0.00(0.063)	0.060	93.8	-0.01(0.063)	0.055	90.2
	$A_1B_2B_2'$	0.00(0.059)	0.060	96.6	-0.01(0.059)	0.057	94.4

4.6 APPLICATION TO REVAMP DATA

The proposed methods were applied to a dataset from the REVAMP study, that motivated this research. In the REVAMP study (see section 1 for details), the initial treatment was not randomly assigned. We compare the treatment regimes that shares the same initial treatment. This will allow us, for example, to answer the question of which treatment regime results in the greatest reduction of depression scores over time, given the subject received SERT as an initial treatment. The REVAMP study provides four initial treatment options. However since the number of subjects who received BUP-SR and VLF-XR were small, we focus on estimating the effect of treatment regimes for those who received SERT only. Figure 8 illustrates the number of patients with SERT including actual treatment sequences. A total of 618 subjects received SERT, and there were three possible regimes for the subjects with SERT: (1) Treat with SERT and if responded, continue to treat with SERT, otherwise change or add medication (n=186), (2) Treat with SERT and if responded, continue to treat with SERT, otherwise treat with the CBASP (n=250), and (3) Treat with SERT and if responded, continue to treat with SERT, otherwise treat with the SP (n=259).

Figure 9 shows trajectories of first- and second-stage outcomes for six selected subjects. The vertical lines indicate the end of the initial stage. Subjects 1 and 2 show a trend of

Table 6: **Simulation result for two- and three-step methods with no missing data.** *Monte Carlo mean, Monte Carlo standard error, standard error, and coverage rate (based on 95% C.I.) for all treatment regimes when there were no effects of treatment regime*

		Two-step Method			Three-step Method		
Sample Size	Treatment Regime	MC Mean (SE)	MCSE	Coverage Rate(%)	MC Mean (SE)	MCSE	Coverage Rate(%)
200	$A_1B_1B_1'$	0.00(0.095)	0.096	95.0	-0.05(0.095)	0.095	92.0
	$A_1B_1B_2'$	-0.01(0.095)	0.096	95.2	-0.05(0.096)	0.098	92.6
	$A_1B_2B_1'$	0.00(0.095)	0.095	94.4	-0.04(0.094)	0.091	91.2
	$A_1B_2B_2'$	-0.01(0.094)	0.095	95.0	-0.05(0.093)	0.094	92.8
500	$A_1B_1B_1'$	0.00(0.063)	0.060	94.8	-0.01(0.063)	0.057	92.6
	$A_1B_1B_2'$	0.01(0.058)	0.060	96.4	-0.01(0.058)	0.060	95.6
	$A_1B_2B_1'$	0.00(0.063)	0.060	93.8	-0.01(0.063)	0.055	90.2
	$A_1B_2B_2'$	0.00(0.059)	0.060	96.6	-0.01(0.059)	0.057	94.4

Table 7: **Simulation result for two- and three-step methods with** 30% **and** 60% **MCAR data.** *Monte Carlo mean, Monte Carlo standard error, standard error, and coverage rate (based on 95% C.I.) for all treatment regimes when the treatment regimes differ*

				Two-step Method			Three-step Method		
Sample Size	Missing Rate	Treatment Regime	True Param.	MC Mean (SE)	MC SE	Coverage Rate(%)	MC Mean (SE)	MC SE	Coverage Rate(%)
500	30%	$A_1B_1B_1'$	-2.25	-2.25(0.066)	0.067	95.4	-2.27(0.066)	0.072	96.4
		$A_1B_1B_2'$	-1.50	-1.50(0.081)	0.070	90.6	-1.52(0.081)	0.091	96.8
		$A_1B_2B_1'$	-1.05	-1.05(0.077)	0.070	94.2	-1.07(0.078)	0.076	93.8
		$A_1B_2B_2'$	-0.30	-0.30(0.068)	0.066	95.2	-0.32(0.069)	0.069	93.6
	60%	$A_1B_1B_1'$	-2.25	-2.25(0.076)	0.075	94.0	-2.28(0.077)	0.100	97.2
		$A_1B_1B_2'$	-1.50	-1.50(0.092)	0.078	90.2	-1.54(0.092)	0.120	98.2
		$A_1B_2B_1'$	-1.05	-1.05(0.087)	0.078	93.0	-1.08(0.088)	0.096	97.0
		$A_1B_2B_2'$	-0.30	-0.30(0.074)	0.074	94.6	-0.34(0.075)	0.094	97.4
1000	30%	$A_1B_1B_1'$	-2.25	-2.25(0.046)	0.046	95.4	-2.26(0.054)	0.069	98.2
		$A_1B_1B_2'$	-1.50	-1.50(0.056)	0.049	90.6	-1.51(0.065)	0.085	98.6
		$A_1B_2B_1'$	-1.05	-1.05(0.055)	0.049	91.2	-1.06(0.064)	0.064	95.0
		$A_1B_2B_2'$	-0.30	-0.30(0.048)	0.046	94.0	-0.31(0.054)	0.064	97.0
	60%	$A_1B_1B_1'$	-2.25	-2.25(0.054)	0.053	95.6	-2.26(0.054)	0.069	98.2
		$A_1B_1B_2'$	-1.50	-1.50(0.064)	0.055	91.6	-1.51(0.065)	0.085	98.6
		$A_1B_2B_1'$	-1.05	-1.05(0.062)	0.055	92.2	-1.06(0.064)	0.064	95.0
		$A_1B_2B_2'$	-0.30	-0.30(0.053)	0.053	93.2	-0.31(0.054)	0.064	97.0

Table 8: **Simulation result for two- and three-step methods with** 30% **and** 60% **MCAR data.** *Monte Carlo mean, Monte Carlo standard error, standard error, and coverage rate (based on 95% C.I.) for all treatment regimes when there were no effects of treatment regime*

			Two-step Method			Three-step Method		
Sample Size	Missing Rate	Treatment Regime	MC Mean (SE)	MC SE	Coverage Rate(%)	MC Mean (SE)	MC SE	Coverage Rate(%)
500	30%	$A_1B_1B_1'$	0.00(0.070)	0.066	93.4	-0.02(0.069)	0.070	93.6
		$A_1B_1B_2'$	0.01(0.064)	0.066	97.0	-0.02(0.065)	0.073	97.0
		$A_1B_2B_1'$	0.00(0.068)	0.066	94.2	-0.02(0.068)	0.068	93.6
		$A_1B_2B_2'$	0.00(0.063)	0.066	95.0	-0.02(0.068)	0.070	96.0
	60%	$A_1B_1B_1'$	0.00(0.075)	0.075	94.2	-0.03(0.075)	0.096	97.8
		$A_1B_1B_2'$	0.00(0.072)	0.075	95.4	-0.03(0.072)	0.100	99.0
		$A_1B_2B_1'$	0.00(0.078)	0.075	94.0	-0.04(0.078)	0.093	96.2
		$A_1B_2B_2'$	0.00(0.075)	0.075	94.2	-0.04(0.075)	0.096	98.0
1000	30%	$A_1B_1B_1'$	0.00(0.047)	0.046	95.6	0.00(0.047)	0.047	95.4
		$A_1B_1B_2'$	0.00(0.046)	0.046	95.4	0.00(0.046)	0.049	96.6
		$A_1B_2B_1'$	0.00(0.046)	0.046	96.0	0.00(0.046)	0.046	95.6
		$A_1B_2B_2'$	0.00(0.048)	0.046	94.2	0.00(0.048)	0.047	95.0
	60%	$A_1B_1B_1'$	0.00(0.054)	0.053	94.6	-0.01(0.055)	0.066	98.4
		$A_1B_1B_2'$	0.00(0.053)	0.053	95.6	-0.01(0.053)	0.069	99.0
		$A_1B_2B_1'$	0.00(0.055)	0.053	94.8	-0.01(0.055)	0.063	97.8
		$A_1B_2B_2'$	0.00(0.052)	0.053	94.6	-0.01(0.053)	0.066	98.4

Table 9: **Simulation result for two- and three-step methods with** 30% **and** 60% **MAR data.** *Monte Carlo mean, Monte Carlo standard error, standard error, and coverage rate (based on 95% C.I.) for all treatment regimes when the treatment regimes differ*

				Two-step Method			Three-step Method		
Sample Size	Missing Rate	Treatment Regime	True Param.	MC Mean (SE)	MC SE	Coverage Rate(%)	MC Mean (SE)	MC SE	Coverage Rate(%)
500	30%	$A_1B_1B_1'$	-2.25	-2.25(0.069)	0.066	94.0	-2.27(0.069)	0.070	93.4
		$A_1B_1B_2'$	-1.50	-1.50(0.084)	0.071	90.6	-1.50(0.084)	0.094	96.4
		$A_1B_2B_1'$	-1.05	-1.05(0.078)	0.070	91.0	-1.08(0.079)	0.076	94.0
		$A_1B_2B_2'$	-0.30	-0.30(0.069)	0.068	96.0	-0.32(0.069)	0.074	96.8
	60%	$A_1B_1B_1'$	-2.25	-2.25(0.069)	0.071	95.4	-2.28(0.070)	0.086	97.0
		$A_1B_1B_2'$	-1.50	-1.50(0.088)	0.078	91.0	-1.56(0.089)	0.119	96.4
		$A_1B_2B_1'$	-1.05	-1.05(0.087)	0.078	91.4	-1.10(0.089)	0.098	93.0
		$A_1B_2B_2'$	-0.30	-0.30(0.083)	0.079	93.0	-0.34(0.084)	0.108	98.0
1000	30%	$A_1B_1B_1'$	-2.25	-2.25(0.047)	0.046	95.2	-2.25(0.043)	0.041	92.6
		$A_1B_1B_2'$	-1.50	-1.50(0.055)	0.050	92.4	-1.50(0.053)	0.055	96.8
		$A_1B_2B_1'$	-1.05	-1.05(0.056)	0.049	91.6	-1.05(0.053)	0.045	90.4
		$A_1B_2B_2'$	-0.30	-0.30(0.047)	0.048	94.6	-0.30(0.044)	0.040	91.6
	60%	$A_1B_1B_1'$	-2.25	-2.25(0.054)	0.053	95.6	-2.25(0.043)	0.041	92.6
		$A_1B_1B_2'$	-1.50	-1.50(0.064)	0.055	91.6	-1.50(0.053)	0.055	96.8
		$A_1B_2B_1'$	-1.05	-1.05(0.062)	0.055	92.2	-1.05(0.053)	0.045	90.4
		$A_1B_2B_2'$	-0.30	-0.30(0.053)	0.053	93.2	-0.30(0.044)	0.040	91.6

Table 10: **Simulation result for two- and three-step methods with** 30% **and** 60% **MAR data.** *Monte Carlo mean, Monte Carlo standard error, standard error, and coverage rate (based on 95% C.I.) for all treatment regimes when there were no effects of treatment regime*

			Two-step Method			Three-step Method		
Sample Size	Missing Rate	Treatment Regime	MC Mean (SE)	MC SE	Coverage Rate(%)	MC Mean (SE)	MC SE	Coverage Rate(%)
500	30%	$A_1B_1B_1'$	0.00(0.067)	0.065	95.0	-0.02(0.068)	0.068	93.8
		$A_1B_1B_2'$	0.01(0.065)	0.067	97.0	-0.01(0.066)	0.075	97.4
		$A_1B_2B_1'$	0.00(0.070)	0.067	92.8	-0.02(0.070)	0.069	92.4
		$A_1B_2B_2'$	0.00(0.065)	0.068	95.8	-0.02(0.066)	0.076	96.4
	60%	$A_1B_1B_1'$	0.01(0.072)	0.071	94.6	-0.02(0.072)	0.083	97.6
		$A_1B_1B_2'$	0.01(0.074)	0.075	95.8	-0.01(0.075)	0.098	98.8
		$A_1B_2B_1'$	0.00(0.079)	0.075	95.0	-0.03(0.079)	0.094	97.6
		$A_1B_2B_2'$	0.00(0.077)	0.079	95.2	-0.03(0.077)	0.111	99.4
1000	30%	$A_1B_1B_1'$	0.00(0.046)	0.046	95.2	0.00(0.047)	0.046	94.8
		$A_1B_1B_2'$	0.00(0.048)	0.047	94.8	0.00(0.048)	0.052	96.8
		$A_1B_2B_1'$	0.00(0.047)	0.047	95.2	0.00(0.047)	0.046	94.6
		$A_1B_2B_2'$	0.00(0.050)	0.048	93.6	0.00(0.050)	0.051	95.0
	60%	$A_1B_1B_1'$	0.00(0.050)	0.050	95.2	0.00(0.047)	0.046	94.8
		$A_1B_1B_2'$	0.00(0.053)	0.053	94.8	0.00(0.048)	0.052	96.8
		$A_1B_2B_1'$	0.00(0.053)	0.053	94.6	0.00(0.047)	0.046	94.6
		$A_1B_2B_2'$	0.00(0.056)	0.056	95.8	0.00(0.050)	0.051	95.0

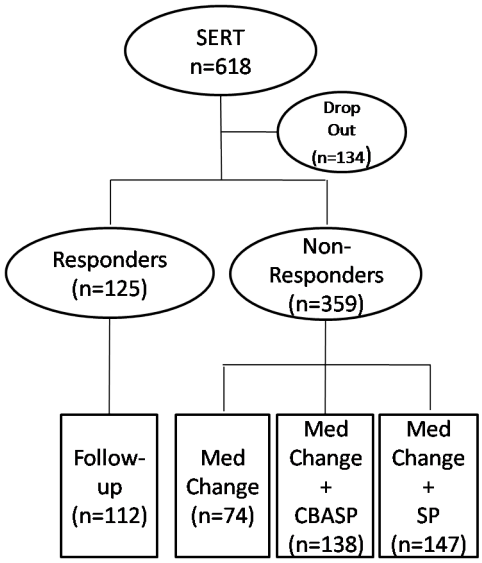

Figure 8: Patients receiving SERT as initial treatments in REVAMP design

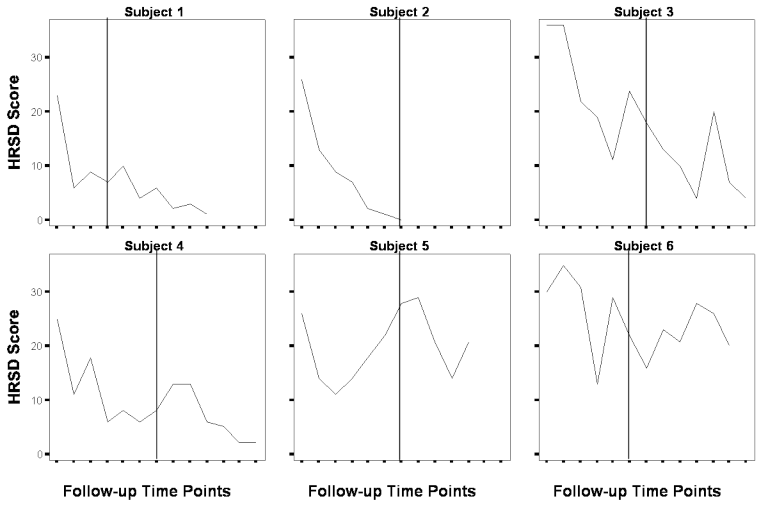

Figure 9: Outcome trend for responders, partial-responders, and non-responders. The vertical lines indicate the end of the initial stage

outcomes for the responders. Since the outcome was measured by HRSD_{24}, lower scores indicate that subjects are recovering from the MDD. For Subject 1, the initial treatment was effective so that the HRSD_{24} score was reduced significantly by the second visit, and the subject continued with the same treatment at the follow-up stage. For subject 2, the initial treatment also worked well, and this subject decided not to stay in the study for the follow-up stage. The outcome trend for the partial-responders is illustrated by Subjects 3 and 4. For these subjects, the initial treatment was not as effective as the first two subjects. They moved to the second-stage and continued to be treated with one of the second-stage treatments. Subjects 5 and 6 are non-responders. Their scores over time remained high, and at the end of the initial stage, they were randomized to one of the second stage treatments.

We analyzed the HRSD_{24} scores in the second stage using the methods described in previous sections. Since we assume that each subject join the study with varying medication history, and the effect of the same treatment may vary across subjects, we selected to fit random coefficient models with random intercept and slope. For the two-step method, in Step 1, we fit the models as in (4.20) and (4.21). We decided to include the baseline age and the HRSD_{24} score at the end of initial stage ($y^{(1)}$) as covariates so that V_i^T=$[1_i, Age_i]$, L_i^T=$y_i^{(1)}$, t_{im} is the week (treated continuous), at which m^{th} measurement is taken, and H_i^T=$[1_i, t_{im}]$ is the design matrix for random intercept and slope. Specifically, a model for those who received MC as a second-stage treatment is as follows

$$\begin{aligned} Y_{im}(MC) &= \alpha_1(MC) + \alpha_2(MC)Age_i + \gamma_3(MC)y_i^{(1)} + \beta_1(MC)t_{im} + \eta_{1i}(MC) \\ &\quad +\eta_{2i}(MC)t_{im} + \epsilon_{im}. \end{aligned} \tag{4.26}$$

Similar models were used for the other second-stage treatments CBASP/MC and SP/MC. In Step 2, as in (4.19), three overall effects for the three treatment regimes β(SERT-MC), β(SERT-CBASP/MC), and β(SERT-SP/MC) were estimated. We also used the three-step methods to estimate theses parameters.

For both methods, we have tested if there were any differences in treatment effects among treatment regimes within each initial treatment. We used a Wald Chi-square test with 2 degree of freedom. The results of the data analysis are summarized in Table 11.

Table 11: REVAMP data analysis result

Initial Trt	Method	Regime	$\beta_{time}(SE)$	Test Statistic	P-value
SERT	Two-step	SERT-MC	-0.409 (0.11)	0.172	0.9172
		SERT-CBASP/MC	-0.435 (0.08)		
		SERT-SP/MC	-0.389 (0.08)		
	Three-step	SERT-MC	-0.359 (0.09)	1.043	0.593
		SERT-CBASP/MC	-0.478 (0.09)		
		SERT-SP/MC	-0.449 (0.08)		

Among the SERT regimes, both methods showed that the SERT-CBASP/MC regime seems to be the most effective, followed by the SERT-SP/MC and the SERT-MC regimes. However, the Wald Chi-square test showed that the three regimes were not significantly different from each other.

4.7 DISCUSSION

We proposed two methods (we referred them as two- and three-step methods) to estimate the effect of treatment regimes from a sequentially randomized two stage trial when data are collected longitudinally. These methods took two different approaches. The two-step method adapted mixed model techniques to estimate the observed treatment sequence effects, and those estimates were combined to obtain the overall treatment regime effect by taking their weighted averages. For the three-step method, a multiple imputation method was used to impute outcomes for those who were not consistent with the regime of interest due to randomization. After the imputation process, the treatment regime effect was directly estimated by fitting a mixed model for each treatment regime. Both methods are simple to apply since standard statistical packages can be used to implement them. Simulation results showed that the estimates provide good coverage rates for 95% confident intervals. However,

mixed models are sensitive to normality assumption [17] as well as a missing data [19]. To account for the former, one can accomodate GEE-type peocedures in the methods described here. We investigated the issue of missing data patterns in our simulations to show that the methods proposed work well when the missing is (completely) at random. The issue of missing not at random is addressed in Chpater 5.

5.0 ASSESSING THE EFFECT OF TREATMENT REGIMES WHEN LONGITUDINAL OUTCOME DATA ARE NOT MISSING AT RANDOM

5.1 INTRODUCTION

In longitudinal clinical trials, missing data are often unavoidable. In REVAMP study (described in Chapter 4), 11% of subjects dropped out from the study during the first stage for various reasons. Some subjects stopped participating in the study since they felt the treatment was not effective, and some subjects simply moved to a different location. Examinig the subjects' dropout pattern is important since standard methods for analyzing repeatedly measured outcomes, such as generalized estimating equations (GEE), have limitations such that the data need to be missing completely at random (MCAR) or at least missing at random (MAR). When data are not missing at random (NMAR), these methods are known to produce biased results [17]. Therefore, different methods such as Pattern Mixture models [20] or Selection models [21] need to be employed. In this chapter, we propose a method to assess the effect of two-stage treatment strategies on longitudinally observed outcome data when data are NMAR.

In Section 5.2, we first review three patterns of missing data and a standard method for the analysis of NMAR data such as a random-coefficient pattern mixture model. The proposed method is described in Section 5.3. The results from simulation studies are reported in Section 5.4, followed by the discussion in Section 5.5.

5.2 MISSING DATA REVIEW

5.2.1 THREE PATTERNS OF MISSING DATA

According to Rubin [18], there are three different types of missing data mechanism: (1) Missing Completely at Random (MACAR), (2) Missing at Random (MAR), and (3) Not Missing at Random (NMAR). First let us define G as the missing data indicator vector, Y be the outcome matrix which includes observed outcome Y_{obs} and missing outcome Y_{mis}, and ϕ is the unknown parameter associated with missing data. MCAR and MAR can be expressed as

1. MCAR: f(G|Y, ϕ) = f(G|ϕ) for all Y and ϕ
2. MAR: f(G|Y, ϕ) = f(G|Y_{obs}, ϕ) for all Y_{mis} and ϕ,

In words, if missing data do not depend on the outcomes, the data are classified as MCAR. If missing data depends on Y_{obs} and ϕ, the data are considered as MAR, and if the missing data depend on Y_{mis}, the data are NMAR.

The NMAR data in a longitudinal study occur when subjects drop out from the study because of their health-related outcomes. For example, if a subject receive a treatment at baseline and if it is not effective (i.e. the outcomes continuously showed that he/she was not responding to the treatment), the subject might choose not to participate in the study any further. This type of dropout needs to be distinguished from random dropouts.

5.2.2 RANDOM-COEFFICIENT PATTERN MIXTURE MODELS

When missing data are NMAR, standard methods for analyzing continuous outcome data such as GEE or Mixed Models produce biased results [19]. For such data, the pattern mixture models [20] and the selection models [21] are the two most common methods. Since the pattern mixture models have an advantage that we do not have to specify the distribution of missing patterns, in this chapter, we focus on this approach. Since we selected to use random-

coefficient models in Section 5.3, we review random-coefficient pattern mixture models below.

The random-coefficient pattern mixture models can be fitted in three-steps: fit a random coefficient model per stratified data, find the estimate for the parameter of interest, and finally combine the estimates by multiplying with the proportion of each missing data pattern. This models can be expressed as a factorized likelihood. For i^{th} subject where $i = 1, ..n$, let Y_i be the vector of continuous outcomes, G_i is the missing data indicator, X_i is the fixed covariate design matrix, and β_i is the coefficient of random effect. The joint likelihood of Y_i, G_i and β_i can be factorized as follows

$$[Y_i, G_i, \beta_i | X_i] = [Y_i | X_i, \beta_i, G_i][\beta_i | X_i, G_i][G_i | X_i], \tag{5.1}$$

where $[Y_i|X_i, \beta_i, G_i]$ models the repeated outcomes stratified by missing data pattern, $[\beta_i|X_i, G_i]$ models the within-subject variation due to random effect, and $[G_i|X_i]$ models the proportion of subjects in each missing data pattern.

Little [20] introduces one special type of random-coefficient pattern mixture models. It is called Random-effect-dependent drop-out model, and we assume that the missing pattern depends only on X_i and β_i. In this model, the joint likelihood is simplified to

$$[Y_i, G_i, \beta_i | X_i] = [Y_i | \beta_i][\beta_i | X_i, G_i][G_i | X_i]. \tag{5.2}$$

and each component of the joint likelihood assumed to have the following distributions

$$[Y_i|\beta_i] \sim N_M\left(\begin{bmatrix} 1 & t_{i1} \\ \vdots & \vdots \\ 1 & t_{iM} \end{bmatrix} \begin{bmatrix} \beta_{i0} \\ \beta_{i1} \end{bmatrix}, \sigma_e^2 \mathbf{I} \right),$$

$$[\beta_i | X_i = x, G_i = g] \sim N_2(\beta_x^{(g)}, \Gamma),$$

and

$$[G_i | X_i = x] \sim Multinomial(\pi_x),$$

where β_i^T=(β_{i0}, β_{i1}) is the random intercept and slope, X_i is the fixed effect variable, such as an indicator for treatment group, π_x is the vector of proportions of subjects with $X = x$

within the subjects who fall in different missing patterns. Once π_x and $\beta_x^{(g)}$ are estimated, the overall treatment effect can be combined as follows

$$E(\beta|X_i = x) = \sum_{g=1}^{M} \pi_x^{(g)} \beta_x^{(g)}. \tag{5.3}$$

5.3 PROPOSED METHOD

We use the same design described in Figure 6 in Chapter 4 and follow the same notation as well. With the NMAR data, each subject has a set of observed data consist of the following n independent vectors

$$\{V_i, X_{ji}, L_i, R_i, R_i Z_{1i}, (1-R_i)Z'_{1i}, G_i, (t_{im}, Y_{im}), m = 1, 2, \ldots, M; \}, i = 1, 2, \ldots, n,$$

where n is the total number of subjects in the sample; V_i is the baseline characteristics such as age; X_i is the initial treatment indicator, X_{ji}=1 when the i^{th} subject was randomized to A_j, 0 otherwise; L_i is the vector of covariates observed during the initial stage, Z_{1i} and Z'_{1i} are the second-stage treatment indicators for B_1 and B'_1, respectively, i.e., Z_{1i}=1 if the i^{th} subject received B_1, and Z_{1i}=0 otherwise. Similarly, Z'_{1i}=1 if the i^{th} subject received B'_1, 0 otherwise; G_i is the dropout indicator, $G_i = 1$ for completers, $G_i = 2$ for the dropouts before M^{th} visit, and $G_i = 3$ for the dropouts before $(M-1)^{th}$ visit and so forth; Y_{im} is the outcome observed at time t_{im} for the subject i, $m = 1, 2, \ldots, M$. Let us define $Z_{2i} = 1 - Z_{1i}$ and $Z'_{2i} = 1 - Z'_{1i}$ so that Z_{2i} and Z'_{2i} respectively represents the indicators for B_2 and B'_2 respectively. We assume a monotone missing pattern as illustrated in Figure 10.

As in Section 4.3, estimation of the treatment regime effects are conducted separately for each treatment sequence. In addition, the data are stratified by the dropout pattern within each observed sequence of treatments in order to model the NMAR component. The same consistency assumption described in Section **??** is applied, and the goal is to estimate the overall treatment regime effects by utilizing the observed data. We propose a method to

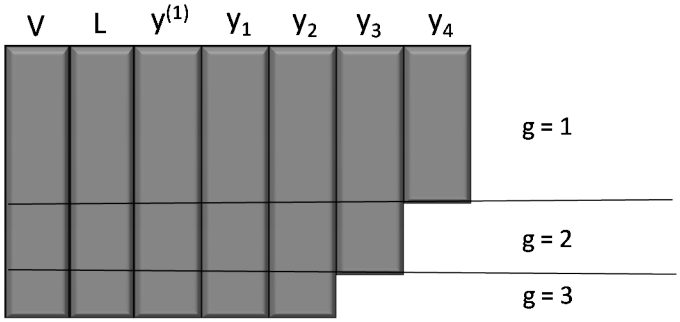

Figure 10: Monotone Missing Patterns

estimate the treatment regime effects by incorporating a pattern-mixture model for missing data. We refer to this as pattern-mixture model (PMM) method where the overall treatment regime effects $\beta(A_jB_kB_l')$ for $j,k,l=1,2$ are estimated in the following three steps.

Step 1: Estimation of treatment effects for dropout patterns per observed treatment sequence. For $g=1,2,..M$, we estimate the treatment effect per dropout pattern $\beta^{(g)}(A_jB_k)$ for responders and $\beta^{(g)}(A_jB_l')$ for non-responders. Specifically, we fit M random-coefficient models separately for the responder and non-responders each treatment sequence as follows

$$E\left[Y_{im}^{(g)}(A_jB_k)|V_i,L_i(A_j),t_{im},G_i\right]=$$
$$V_i^T\alpha^{(g)}(A_jB_k)+L_i^T\gamma^{(g)}(A_jB_k)+\beta^{(g)}(A_jB_k)t_{im}+H_i^T\eta_i^{(g)}(A_jB_k)$$

and,

$$E\left[Y_{im}^{(g)}(A_jB_l')|V_i,L_i(A_j),t_{im},G_i\right]=$$
$$V_i^T\alpha^{(g)}(A_jB_l')+L_i^T\gamma^{(g)}(A_jB_l')+\beta^{(g)}(A_jB_l')t_{im}+H_i^T\eta_i^{(g)}(A_jB_l')$$

In addition, for $g=1,2,..M$, the empirical dropout rate for observed treatment sequences $\hat{\pi}^{(g)}_{A_jB_k}$ and $\hat{\pi}^{(g)}_{A_jB_l'}$ are estimated as follows,

$$\hat{\pi}^{(g)}_{A_jB_k} = \frac{\sum_{i=1}^{n} X_{ji} R_i Z_{ki} I(G_i = g)}{\sum_{i=1}^{n} X_{ji} R_i Z_{ki}} \quad j,k = 1,2.$$

and

$$\hat{\pi}^{(g)}_{A_jB'_l} = \frac{\sum_{i=1}^{n} X_{ji}(1-R_i) Z'_{li} I(G_i = g)}{\sum_{i=1}^{n} X_{ji}(1-R_i) Z'_{li}} \quad j,l = 1,2.$$

Step 2: Estimation of treatment effects for observed treatment sequences. Drop-out pattern-specific treatment effect estimates are then combined as follows to obtain the treatment-sequence-specific estimates

$$\hat{\beta}(A_jB_k) = \sum_{g=1}^{M} \hat{\pi}^{(g)}_{A_jB_k} \hat{\beta}^{(g)}(A_jB_k) \quad j,k = 1,2.$$

and

$$\hat{\beta}(A_jB'_l) = \sum_{g=1}^{M} \hat{\pi}^{(g)}_{A_jB'_l} \hat{\beta}^{(g)}(A_jB'_l) \quad j,l = 1,2.$$

Variance of these estimates are obtained as follows

$$
\begin{aligned}
Var(\hat{\beta}(A_jB_k)) &= Var\left[\sum_{g=1}^{M}\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g)}(A_jB_k)\right] \\
&= \sum_{g=1}^{M}Var\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g)}(A_jB_k)\right] + \sum_{g\neq g'}Cov\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g)}(A_jB_k), \hat{\pi}^{(g')}_{A_jB_k}\hat{\beta}^{(g')}(A_jB_k)\right] \\
&= E\left[Var\left(\hat{\pi}^{(1)}_{A_jB_k}\hat{\beta}^{(1)}(A_jB_k)\cdots+\hat{\pi}^{(M)}_{A_jB_k}\hat{\beta}^{(M)}(A_jB_k)|\hat{\pi}^{(1)}_{A_jB_k}\cdots\hat{\pi}^{(M)}_{A_jB_k}\right)\right] \\
&+ Var\left[E\left(\hat{\pi}^{(1)}_{A_jB_k}\hat{\beta}^{(1)}(A_jB_k)\cdots+\hat{\pi}^{(M)}_{A_jB_k}\hat{\beta}^{(M)}(A_jB_k)|\hat{\pi}^{(1)}_{A_jB_k}\cdots\hat{\pi}^{(M)}_{A_jB_k}\right)\right] \\
&+ \sum_{g\neq g'}Cov\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g)}(A_jB_k), \hat{\pi}^{(g')}_{A_jB_k}\hat{\beta}^{(g')}(A_jB_k)\right] \\
&= Var(\hat{\beta}^{(1)}(A_jB_k))\left[\frac{\pi^{(1)}_{A_jB_k}(1-\pi^{(1)}_{A_jB_k})}{n_{A_jB_k}}+(\pi^{(1)}_{A_jB_k})^2\right]\cdots \\
&+ Var(\hat{\beta}^{(M)}(A_jB_k))\left[\frac{\pi^{(M)}_{A_jB_k}(1-\pi^{(M)}_{A_jB_k})}{n_{A_jB_k}}+(\pi^{(M)}_{A_jB_k})^2\right] \\
&+ \hat{\beta}^{(1)}(A_jB_k)^2\left[\frac{\pi^{(1)}_{A_jB_k}(1-\pi^{(1)}_{A_jB_k})}{n_{A_jB_k}}\right]\cdots+\hat{\beta}^{(M)}(A_jB_k)^2\left[\frac{\pi^{(M)}_{A_jB_k}(1-\pi^{(M)}_{A_jB_k})}{n_{A_jB_k}}\right] \\
&+ \sum_{g\neq g'}-\beta^{(g)}(A_jB_k)\beta^{(g')}(A_jB_k)\pi^{(g)}_{A_jB_k}\pi^{(g')}_{A_jB_k}/n_{A_jB_k} \qquad (5.4)
\end{aligned}
$$

since

$$
\begin{aligned}
& E\left[Var\left(\hat{\pi}^{(1)}_{A_jB_k}\hat{\beta}^{(1)}(A_jB_k)\cdots+\hat{\pi}^{(M)}_{A_jB_k}\hat{\beta}^{(M)}(A_jB_k)|\hat{\pi}^{(1)}_{A_jB_k},\cdots\hat{\pi}^{(M)}_{A_jB_k}\right)\right] \\
= \;& E\left[(\hat{\pi}^{(1)}_{A_jB_k})^2Var(\hat{\beta}^{(1)}(A_jB_k))\cdots+(\hat{\pi}^{(M)}_{A_jB_k})^2Var(\hat{\beta}^{(M)}(A_jB_k))|\hat{\pi}^{(1)}_{A_jB_k},\cdots\hat{\pi}^{(M)}_{A_jB_k}\right] \\
= \;& Var(\hat{\beta}^{(1)}(A_jB_k))E((\hat{\pi}^{(1)}_{A_jB_k})^2)+Var(\hat{\beta}^{(2)}(A_jB_k))E((\hat{\pi}^{(2)}_{A_jB_k})^2)\cdots+Var(\hat{\beta}^{(M)}(A_jB_k))E((\hat{\pi}^{(M)}_{A_jB_k})^2) \\
= \;& Var(\hat{\beta}^{(1)}(A_jB_k))[Var(\hat{\pi}^{(1)}_{A_jB_k})+E(\hat{\pi}^{(1)}_{A_jB_k})^2]+Var(\hat{\beta}^{(2)}(A_jB_k))[Var(\hat{\pi}^{(2)}_{A_jB_k})+E(\hat{\pi}^{(2)}_{A_jB_k})^2] \\
& \cdots+Var(\hat{\beta}^{(M)}(A_jB_k))\left[Var(\hat{\pi}^{(M)}_{A_jB_k})+E(\hat{\pi}^{(M)}_{A_jB_k})^2\right] \\
= \;& Var(\hat{\beta}^{(1)}(A_jB_k))\left[\frac{\pi^{(1)}_{A_jB_k}(1-\pi^{(1)}_{A_jB_k})}{n_{A_jB_k}}+(\pi^{(1)}_{A_jB_k})^2\right] \\
& \cdots+Var(\hat{\beta}^{(M)}(A_jB_k))\left[\frac{\pi^{(M)}_{A_jB_k}(1-\pi^{(M)}_{A_jB_k})}{n_{A_jB_k}}+(\pi^{(M)}_{A_jB_k})^2\right]
\end{aligned}
$$

and

$$
\begin{aligned}
& Var\left[E\left(\hat{\pi}^{(1)}_{A_jB_k}\hat{\beta}^{(1)}(A_jB_k)\cdots+\hat{\pi}^{(M)}_{A_jB_k}\hat{\beta}^{(M)}(A_jB_k)|\hat{\pi}^{(1)}_{A_jB_k},\cdots\hat{\pi}^{(M)}_{A_jB_k}\right)\right] \\
= \; & Var\left[\hat{\pi}^{(1)}_{A_jB_k}E(hat\beta^{(1)}(A_jB_k))\cdots+\hat{\pi}^{(M)}_{A_jB_k}E(\hat{\beta}^{(M)}(A_jB_k))|\hat{\pi}^{(1)}_{A_jB_k},\cdots\hat{\pi}^{(M)}_{A_jB_k}\right] \\
= \; & E((\hat{\beta}^{(1)}(A_jB_k))^2)Var(\hat{\pi}^{(1)}_{A_jB_k})\cdots+E((\hat{\beta}^{(M)}(A_jB_k))^2)Var(\hat{\pi}^{(M)}_{A_jB_k}) \\
= \; & (\hat{\beta}^{(1)}(A_jB_k))^2\left[\frac{\pi^{(1)}_{A_jB_k}(1-\pi^{(1)}_{A_jB_k})}{n_{A_jB_k}}\right]\cdots+(\hat{\beta}^{(M)}(A_jB_k))^2\left[\frac{\pi^{(M)}_{A_jB_k}(1-\pi^{(M)}_{A_jB_k})}{n_{A_jB_k}}\right]
\end{aligned}
$$

and

$$
\begin{aligned}
& Cov\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g)}(A_jB_k),\hat{\pi}^{(g')}_{A_jB_k}\hat{\beta}^{(g')}(A_jB_k)\right] \\
= \; & E\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g)}(A_jB_k)\hat{\pi}^{(g')}_{A_jB_k}\hat{\beta}^{(g')}(A_jB_k)\right]-E\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g')}(A_jB_k)\right]E\left[\hat{\pi}^{(g')}_{A_jB_k}\hat{\beta}^{(g')}(A_jB_k)\right] \\
= \; & E\left[E\left(\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g)}(A_jB_k)\hat{\pi}^{(g')}_{A_jB_k}\hat{\beta}^{(g')}(A_jB_k)|\hat{\pi}^{(g)}_{A_jB_k},\hat{\pi}^{(g')}_{A_jB_k}\right)\right] \\
& -E\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g)}(A_jB_k)\right]E\left[\hat{\pi}^{(g')}_{A_jB_k}\hat{\beta}^{(g')}(A_jB_k)\right] \\
= \; & E\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\pi}^{(g')}_{A_jB_k}E\left(\hat{\beta}^{(g)}(A_jB_k)\hat{\beta}^{(g')}(A_jB_k)|\hat{\pi}^{(g)}_{A_jB_k},\hat{\pi}^{(g')}_{A_jB_k}\right)\right] \\
& -E\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\beta}^{(g)}(A_jB_k)\right]E\left[\hat{\pi}^{(g')}_{A_jB_k}\hat{\beta}^{(g')}(A_jB_k)\right] \\
= \; & \beta^{(g)}(A_jB_k)\beta^{(g')}(A_jB_k)E\left[\hat{\pi}^{(g)}_{A_jB_k}\hat{\pi}^{(g')}_{A_jB_k}\right]-\pi^{(g)}_{A_jB_k}\beta^{(g)}(A_jB_k)\pi^{(g')}_{A_jB_k}\beta^{(g')}(A_jB_k) \\
= \; & \beta^{(g)}(A_jB_k)\beta^{(g')}(A_jB_k)\left[Cov(\hat{\pi}^{(g)}_{A_jB_k},\hat{\pi}^{(g')}_{A_jB_k})+E(\hat{\pi}^{(g)}_{A_jB_k})E(\hat{\pi}^{(g')}_{A_jB_k})\right] \\
& -\pi^{(g)}_{A_jB_k}\beta^{(g)}(A_jB_k)\pi^{(g')}_{A_jB_k}\beta^{(g')}(A_jB_k) \\
= \; & \beta^{(g)}(A_jB_k)\beta^{(g')}(A_jB_k)Cov(\hat{\pi}^{(g)}_{A_jB_k},\hat{\pi}^{(g')}_{A_jB_k})+\pi^{(g)}_{A_jB_k}\beta^{(g)}(A_jB_k)\pi^{(g')}_{A_jB_k}\beta^{(g')}(A_jB_k) \\
& -\pi^{(g)}_{A_jB_k}\beta^{(g)}(A_jB_k)\pi^{(g')}_{A_jB_k}\beta^{(g')}(A_jB_k) \\
= \; & -\beta^{(g)}(A_jB_k)\beta^{(g')}(A_jB_k)\pi^{(g)}_{A_jB_k}\pi^{(g')}_{A_jB_k}/n_{A_jB_k}
\end{aligned}
$$

The variance of $\hat{\beta}(A_jB'_l)$ is estimated in a similar manner.

Step 3: Estimation of the overall treatment regime effects. Finally, the estimation of the treatment effect per treatment regime are combined as follows

$$\hat{\beta}(A_jB_kB'_l)=\hat{\pi}_r\hat{\beta}(A_jB_k)+(1-\hat{\pi}_r)\hat{\beta}(A_jB'_l)\quad j,k,l=1,2.$$

where the empirical response rate are estimated as

$$\hat{\pi}_r(A_j) = \frac{\sum_{i=1}^{n} X_{ji} R_i}{\sum_{i=1}^{n} X_{ji}}, j = 1, 2. \tag{5.5}$$

The variance of $\hat{\beta}(A_j B_k B_l')$ is estimated exactly the same way as the two-step method described in Chapter 4.

5.4 SIMULATION STUDY

We conducted several simulation studies to examine the performance of the pattern-mixture model in estimating regime effects in the presence of non-ignorable missing data. As described in Chapter 4, we generated data to simulate a two-stage randomized study as shown in Figure 6. The outcomes are generated from a multivariate normal distribution, and the number of follow-up visits during the second stage is set to four to mimic the REVAMP study. Again similar to the previous chapter, since the subjects who were randomized to A_1 and A_2 are independent, we only generated data for the subjects with A_1 treatment, and therefore, we will have only four treatment regimes, namely, $A_1 B_1 B_1'$, $A_1 B_1 B_2'$, $A_1 B_2 B_1'$, and $A_1 B_2 B_2'$.

Following the definition of NMAR described in Section 5.2, in order to generate NMAR data, we need to allow the distribution of missing data to depend on the missing outcome itself. Therefore, we first create the following models to obtain the probability of missing Y_3 and/or Y_4

$$P(G = 1|age, Y_4) = \frac{exp[\phi_1 * age + \phi_2 * Y_4]}{1 + exp[\phi_1 * age + \phi_2 * Y_4]},$$

and similarly, we fit a model for the missing Y_3,

$$P(G = 2|age, Y_3) = \frac{exp[\phi_1 * age + \phi_3 * Y_3]}{1 + exp[\phi_1 * age + \phi_3 * Y_3]}.$$

Based on the probabilities, the missing data indicator M_1 and M_2 are drawn from a Bernoulli distribution with probability of success $P(G = 1|age, Y_4)$ and $P(G = 2|age, Y_3)$, respectively.

Then the dropout indicator G_i is created: $G_i = 1$ if $M_1 = 0$ and $M_2 = 0$, $G_i = 2$ if $M_1 = 1$ and $M_2 = 0$, and $G_i = 3$ if $M_1 = 1$ and $M_2 = 1$. Approximately 40% and 60% of NMAR data are generated by setting ϕ_1 = -0.09, and $\phi_2 = \phi_3 = 0.08$ for 40% missing data, and ϕ_1 = -0.08, $\phi_2 = \phi_3 = 0.08$ for 60% missing data.

Similar to the simulation studies in Chapter 4, we have tested the proposed method in two different scenarios. In simulation scenario 1, we assumed that there were clear treatment differences among four treatment sequences, while in simulation scenario 2, there was no treatment differences. The specification of true parameters are exactly the same as in Chapter 4; therefore, we set $\beta(A_1B_1B_1') =$ -2.25, $\beta(A_1B_1B_2') =$ -1.50, $\beta(A_1B_2B_1') =$ -1.05, and $\beta(A_1B_2B_2') =$ -0.30. for scenario 1, and these four parameters are set to 0 for the second scenario.

Table 12 shows the results of scenario 1 and 2 when the data are NMAR. The PMM estimator is compared with the two-step estimator proposed in Chapter 4. One of the assumptions for using the two-step method is that the missing data have to be at least missing at random. Here we examine the performance of the method if the assumption was violated. The simulation study showed that the bias for the PMM method is generally smaller than the one for the two-step method. The relative bias for two-step method ranges from 2% to s high as 17% whereas the same for PMM method ranges from 0.7% to 7%. The coverage rate for the PMM method is generally higher compared to the Two-step method. For the first scenario, the coverage rates for the PMM method range between 88.0% and 99.2%, while the rates for the two-step method range between 80.4% and 92.6%. For the scenario 2, the difference is not very obvious because the treatment effects are set to 0. This means that the effect of NMAR is smaller compared to the scenario 1. Overall, the PMM estimator is approximately asymptotically unbiased, and showed an improvement over the two-step method applied for the NMAR data.

Table 12: **Simulation result for two-step and PMM methods with** 40% **and** 60% **NMAR data.** *Monte Carlo mean, Monte Carlo standard error, standard error, and coverage rate (based on 95% C.I.) for all treatment regimes when the treatment regimes differ and when there were no effects of treatment regime*

			Two-step Method			PMM Method		
Missing Rate	Treatment Regime	True Param.	MC Mean (SE)	MC SE	Coverage Rate(%)	MC Mean (SE)	MC SE	Coverage Rate(%)
40%	$A_1B_1B_1'$	-2.25	-2.27(0.045)	0.045	92.6	-2.26(0.048)	0.061	98.0
	$A_1B_1B_2'$	-1.50	-1.53(0.056)	0.048	85.2	-1.15(0.059)	0.058	93.0
	$A_1B_2B_1'$	-1.05	-1.08(0.056)	0.048	85.2	-1.07(0.059)	0.067	96.8
	$A_1B_2B_2'$	-0.30	-0.34(0.051)	0.047	82.0	-0.32(0.054)	0.047	89.0
60%	$A_1B_1B_1'$	-2.25	-2.28(0.045)	0.046	92.6	-2.26(0.050)	0.065	99.2
	$A_1B_1B_2'$	-1.50	-1.53(0.055)	0.049	84.0	-1.51(0.062)	0.060	94.2
	$A_1B_2B_1'$	-1.05	-1.09(0.055)	0.049	83.4	-1.07(0.064)	0.070	95.4
	$A_1B_2B_2'$	-0.30	-0.35(0.048)	0.048	80.4	-0.32(0.056)	0.050	88.0
40%	$A_1B_1B_1'$	0.00	-0.04(0.047)	0.047	89.2	-0.01(0.054)	0.050	93.2
	$A_1B_1B_2'$	0.00	-0.04(0.047)	0.047	88.4	-0.01(0.055)	0.051	92.8
	$A_1B_2B_1'$	0.00	-0.04(0.046)	0.047	88.2	-0.01(0.055)	0.046	87.8
	$A_1B_2B_2'$	0.00	-0.04(0.047)	0.047	87.8	-0.01(0.056)	0.047	88.0
60%	$A_1B_1B_1'$	0.00	-0.05(0.048)	0.048	84.6	-0.02(0.058)	0.053	92.8
	$A_1B_1B_2'$	0.00	-0.05(0.049)	0.048	83.8	-0.02(0.059)	0.054	92.2
	$A_1B_2B_1'$	0.00	-0.05(0.048)	0.048	84.4	-0.02(0.060)	0.049	87.4
	$A_1B_2B_2'$	0.00	-0.05(0.049)	0.049	83.8	-0.02(0.060)	0.050	86.8

5.5 CONCLUSION

In this chapter, we used pattern-mixture model (PMM) in conjunction with the two-step and three-step methods described in earlier chapters to assess the effect of two-stage treatment regimes on longitudinally observed outcome data when data are not missing at random but monotone. The PMM method stratifies the data according observed treatment sequence by the dropout pattern (monotonicity). Simulation studies were conducted to examine how the PMM method performed in large sample properties, and also to compare the results to those from the two-step method proposed in Chapter 4. The simulation result showed that the PMM method provides improved estimates over the two-step method in terms of the relative bias and the 95% coverage rate when there are monotone missing data and the missing data mechanism depends on the missing outcome itself.

One limitation of this method is, similar to any stratified data analysis, the sample size needs to be sufficiently large within each strata. When there are only a few subjects falls in the stratified group, either the estimation of the parameter of interest may not be possible, or might produce biased result.

6.0 CONCLUSION

Adaptive treatment regimes are sets of rules that govern treatment assignment in a time-varying course of treatment based on observed covariates and intermediate responses. Such regimes are very common in biomedical studies of cancer, depression and AIDS since they provide patient-specific overall plan for treatment. Statistical inference for treatment regimes using a summary outcome measure such as time-to-event and mean response has been well-studied in the literature. However, statistical methods for assessing the effect of treatment strategies on repeated measures data are not well-developed. In this thesis, we worked on two types of outcomes arising from a two-stage sequentially randomization design, namely, survival and longitudinal data.

First, for the time-to-event data, we adapted an inverse-probability weighting approach to generalize the standard Kaplan-Meier estimates in two-stage randomized setting. The proposed method was compared with the two existing methods (i.e. the marginal mean model based estimator and the weighted risk set estimator) using simulation studies. Our simulation studies showed that the proposed weighted Kaplan-Meier method was asymptotically unbiased, and performed very similar to the two existing methods. The advantage of the proposed method is that it is quite simple to use, particularly the variance estimator for this method is expressed explicitly in a much simplified form compared to the other two estimators. Next, for the longitudinal data, we introduced three methods to assess the effect of treatment regimes. We proposed two methods (i.e. two- and three-step methods), which took two different approaches to estimate the treatment regime effects. The two-step method adapted mixed model techniques to estimate the observed treatment sequence effects, and then combined those estimates to obtain the overall treatment regime effect by taking their weighted averages. For the three-step method, a multiple imputation method

was used to impute outcomes for those who were not consistent with the regime of interest. Since everyone was consistent with every regime after the imputation process, the treatment regime effect was directly estimated by fitting a mixed model for each treatment regime. The simulation studies showed that both methods produce approximately unbiased results and provide uniform coverage rates for 95% confidence intervals when the data are either complete, missing completely at random, or missing at random. When the data are not missing at random (NMAR) however, these methods may produce biased results. To overcome this limitation, we applied pattern-mixture model approach (PMM method) to assess the treatment regime effects when the data are NMAR but monotone. The pattern-mixture model approach was used in conjunction with the two-step method. First, the data were stratified by the missing data pattern within each group of observed treatment sequence. Next, for each stratified data, the parameter of interest was estimated, and the treatment sequence effects were estimated by taking the weighted averages. Finally the overall treatment regime effects were estimated by combining the estimated treatment sequence effects with the empirical missing data response rate. The simulation studies were conducted to examine the performance of the PMM method, and the results were compared to those obtained using the two-step method (assuming that the data was complete). The results showed that the PMM method had minimal bias, and showed a great improvement over the two-step method in terms of bias and coverage probabilities.

Assessing the effect of treatment strategies on longitudinally observed outcome data is important in identifying effective treatment strategies for treating chronic diseases such as AIDS, depression and cancer. Proposed statistical methods provide useful tools for unbiased estimation of the effects of treatment strategies from sequentially randomized (two-stage) designs. Availability of these methods will help advance the research in AIDS, cancer, depression, hepatitis and other disease areas.

BIBLIOGRAPHY

[1] R M. Stone, D T. Berg, S L. George, R K. Dodge, P A. Paciucci, P. Schulman, E J. Lee, J O. Moore, B L. Powell, and C A. Schiffer. Granulocytemacrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukimia. *The New England Journal of Medicine*, 332:1671–1677, 1995.

[2] S A. Murphy, M J. Van Der Laan, and J M. Robins. Marginal mean models for dynamic regimes. *Journal of American Statistical Association*, 96:1410–1423, 2001.

[3] S.A. Murphy. Optimal dynamic treatment regimes (with discussion). *Journal of Royal Statistical society*, 65:331–336, 2003.

[4] J K. Lunceford, M. Davidian, and A A. Tsiatis. Estimation of survival distributions of treatment policies in two-stage randomization designs in clinical trials. *Biometrics*, 58:48–57, 2002.

[5] A S. Wahed and A A. Tsiatis. Optimal estimator for the survival distribution and related quantities for treatment policies in two-stage randomization designs in clinical trials. *Biometrics*, 60(1):124–133, 2004.

[6] A S. Wahed and A A. Tsiatis. Semi-parametric efficient estimation of the survival distribution for treatment policies in two-stage randomization designs in clinical trials with censored data. *Biometrika*, 93:147–161, 2006.

[7] X. Guo and A A. Tsiatis. A weighted risk set estimator for survival distributions in two-stage randomization designs with censored survival data. *The International Journal of Biostatistics*, 1:00–00, 2005.

[8] M A. Hernan and J M. Robins. Estimating causal effects from epidemiological data. *J Epidemiol Community Health*, 60(7):578–86, 2006.

[9] Y. Lokhnygina and J D. Helterbrand. Cox regression methods for two-stage randomization design. *Biometrics*, 63:422–428, 2007.

[10] P F. Thall, L H. Wooten, C J. Logothetis, and N M. Tannir R .Milikan. Baysesian and frequentest two-stage treatment strategies based on sequential failure times subject to interval centering. *Statistics in Medicine*, 26:4687–4702, 2007.

[11] E L. Kaplan and P. Meier. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*, 53:457–481, 1958.

[12] M. Greenwood. The natural duration of cancer. reports on public health and medical subjects. *London: Her Majesty's Stationery Office*, 33:1–26, 1926.

[13] O O. Aalen. Nonparametric inference for a family of counting processes. *Annals of Statistics*, 6:701–726, 1978.

[14] N M. Laird and J H. Ware. Random effects models for longitudinal data. *Biometrics*, 38:963–974, 1982.

[15] N T. Longford. *Random Coefficients Models*. Oxford University Press, Oxford, 1993.

[16] H. Goldstein. *Multilevel Statistical Models (third edition)*. Edward Arnold, London, 2003.

[17] H. Brown and R. Prescott. *Applied Mixed Models in Medicine*. John Wiley & Sons, Inc., England, 2006.

[18] D B. Rubin. Inference and missing data (with discussion). *Biometrika*, 63:581–592, 1976.

[19] RJ A. Little and D B. Rubin. *Statistical Analysis with Missing Data*. John Wiley & Sons, Inc., New Jersey, 2002.

[20] RJ A. Little. Modeling the drop-out mechanism in repeated-measures studies. *Journal of American Statistical Association*, 90:1112–1121, 1995.

[21] J. Heckman. The common structure of statistical models of truncation, sample selection and limited dependable variables, and a simple estimator for such models. *Annals of Economic and Social Mesurement*, 5:475–492, 1976.

[22] PW. Lavori and R. Dawson. A design of for testing clinical strategies: biased individually tailored within-subject randomization. *Journal of the Royal Statistical society*, 163:29–38, 2000.

[23] J M. Robins, A. Rotnitzky, and L P. Zhao. Estimation of regression coefficients when some regressors are not always observed. *Journal of the American Statistical Association*, 89:846–866, 1994.

[24] J. Xie and C. Liu. Adjusted kaplan-meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Statistics in Medicine*, 24:3089–3110, 2005.

[25] M H. Trivedi, J H. Kocsis, M E. Thase, D W. Morris, S R. Wisniewski, A C. Leon, A J. Gelenberg, D N. Klein, G. Niederehe, A F. Schatzberg, P T. Ninan, and M B. Keller.

Revamp - research evaluating the value of augmenting medication with psychotherapy: Rationale and design. *Psychopharmacology Bulletin*, 41:5–7, 2008.

[26] K Y. Liang and S L. Zeger. Longitudinal data analysis using generalized linear models. *Biometrika*, 73:13–22, 1986.

[27] S L. Zeger and K Y. Liang. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*, 42:121–130, 1986.

[28] P W. Holland. Statistics and causal inference. *Journal of the American Statistical Association*, 81:945–960, 1986.

[29] H. Ko, J W. Hogan, and Mayer K H. Mayer. Estimating causal treatment effects from longitudinal hiv natural history studies using marginal structural models. *Biometrics*, 59(1):152–62, 2003.

[30] J M. Robins. *Causal Inference from complex longitudinal data. In Latent Variable Modeling and Applications to Causality, M Berkane (ed)*. Springer-Verlag, New York, 1997.

[31] R C. Littell, G A. Milliken, W W. Stroup, and R D. Wolfinger. *SAS System for Mixed Models*. SAS Institute., Cary, NC, 1996.

[32] J C. Pinheiro and D M. Bates. *Mixed-Effect Models in S and S-plus*. Springer-Verlag, New York, 1994.

[33] G W. Oehlert. A note on the delta method. *The American Statistician*, 46:27–29, 1992.