Journal of Statistical Research *ISSN 0256 - 422 X*
2012, Vol. 46, No. 2, pp. 233-254

ASSESSING THE EFFECT OF TREATMENT REGIMES ON LONGITUDINAL OUTCOME DATA: APPLICATION TO REVAMP STUDY OF DEPRESSION

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SUMMARY

Depression studies frequently adopt two-stage designs to examine the efficacy of augmenting pharmacotherapy with psychotherapy. Initially subjects receive one of the several treatments; if they respond, they continue the same treatment; however, if they fail to respond, they move to the next stage and are randomized to other treatment options. Outcomes such as 24-item Hamilton Rating Scale of Depression (HRSD_{24}) scores are then collected repeatedly to monitor the progress of the subject. The goal is to assess the effect of treatment regimes (consisting of initial treatment, initial response and the second stage treatment combinations) on HRSD_{24} profile. Statistical inference for assessing treatment regimes using a summary outcome measure such as mean response has been well-studied in the literature. Statistical methods for assessing the effect of treatment strategies on repeated measures data focused mainly on estimating equations. In this article, we propose two methods based on mixed models and multiple imputations to assess the effect of treatment regimes on the longitudinal HRSD_{24} scores. Methods are compared through simulation studies and through an application to a depression study. The simulation studies showed that the estimates from both methods are approximately unbiased, and provide good coverage rates for 95% confidence intervals.

Keywords and phrases: Adaptive Treatment Regimes, Longitudinal Data Analysis, Mixed Models

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 (Trivedi *et al.*, 2008) adopted a two-stage study design to assess the efficacy of combining pharmacotherapy and psychotherapy for the chronically depressed subjects.

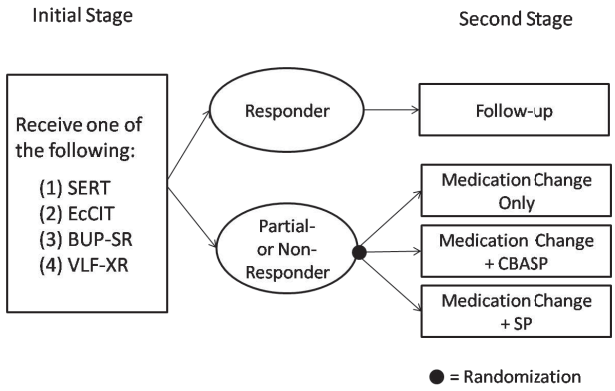

Figure 1: REVAMP study design.

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 1.

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 a 24-item Hamilton Rating Scale of Depression (HRSD_{24}) score was collected at two week 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 initial treatment. If the HRSD_{24} score was only reduced less than 30%, and the subject did not meet, for two consecutive visits, the MDD criteria from the diagnostic and statistical manual of mental disorders (DSM-IV), 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 *et al.* (2008). 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 week intervals.

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, and conditional on an intermediate response, 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 (Liang and Zeger, 1986; Zeger and Liang, 1986), generalized linear and mixed models (Goldstein, 2003; Laird and Ware, 1982; Longford, 1993). 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 regime. 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 a 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. Methods for survival outcomes were considered in Lunceford, Davidian, and Tsiatis (2002), Wahed and Tsiatis (2004, 2006), Guo and Tsiatis (2005), Hernan and Robins (2006), and Lokhnygina and Helterbrand (2007). Thall *et al.* (2007) adopts a Bayesian approach to model the time to failure and compare two-stage adaptive treatment regimes. Statistical methods for assessing the effect of treatment strategies on repeated measures data focused mainly on estimating equations. For example, estimation of a mean response based on observational longitudinal data were proposed in Murphy, Van Der Laan, and Robins (2001) and Murphy (2003). 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 2, we describe the notation, data structure, model, and assumptions. Section 3 describes the estimation procedures. Hypothesis testing for comparing the treatment regimes is described in Section 4. The results from simulation studies are reported in Section 5, followed by an application to the REVAMP study data in Section 6. The article is concluded with some discussions in Section 7.

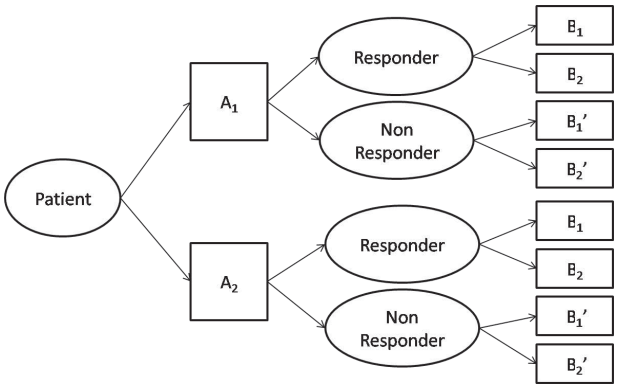

Figure 2: Example of two-stage design.

2 Data Structure and Models

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. We depict such a design in Figure 2. 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. Generalization to more than two treatments will be straightforward.

With this set-up, 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' otherwise". The goal is to compare these eight regimes based on the rate of decline during stage two of the treatment. For each individual i, we define the following counterfactual variables (Holland, 1986). For $j, k, l = 1, 2$ and $m = 1, 2, \ldots, M$, the variable $R_i(A_j)$ defines the response status had the i^{th} individual received initial treatment A_j; $Y_{im}(A_jB_k)$ denotes the outcome (e.g., HRSD_{24} score) measured at time t_{im} had the i^{th} individual received B_k following a response to the initial treatment A_j; similarly, $Y_{im}(A_jB_l')$ denotes the outcome measured at time t_{im} had the ith individual received B_l' after becoming a non-responder to the initial treatment A_j; V_i denotes the vector of baseline covariates such as age, sex, and variables collected during the initial stage of treatment such as time to initial response and minimum HRSD_{24} score observed during the initial treatment phase.

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 also referred to as counterfactuals (Holland, 1986). However, 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

$$Y_{im}(A_jB_kB_l') = R_i(A_j)Y_{im}(A_jB_k) + \{1 - R_i(A_j)\}Y_{im}(A_jB_l'). \tag{2.1}$$

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 during the second stage adjusting for other baseline and first-stage patient characteristics.

2.2 The model

We postulate the model

$$E\left[Y_{im}(A_jB_kB_l')|V_i, t_{im}\right] = V_i^T\alpha(A_jB_kB_l') + \beta(A_jB_kB_l')t_{im} \tag{2.2}$$

to assess the effect of the treatment regime $A_jB_kB_l'$ on the changes in outcome Y over time adjusting for baseline and initial stage covariate vector V_i. However, as mentioned earlier, not all patients were treated according to this regime. Therefore, the challenge would be to estimate the parameters $\theta(A_jB_kB_l') = \{\alpha(A_jB_kB_l'), \beta(A_jB_kB_l')\}$ 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 $\alpha(A_jB_kB_l'), j, k, l = 1, 2$ as nuisance. Also we note that in model (2.2) 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., $V_i^* = [V_i^T, t_{im}]^T$, model (2.2) could be simplified as

$$E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] = {V_i^*}^T\theta(A_jB_kB_l'). \tag{2.3}$$

2.3 Observed data

The observed data from a two-stage design (described in Figure 3) can be characterized as a set of n independent vectors

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

where n is the total number of subjects in the sample; V_i is the baseline and initial stage 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; 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.

2.4 Assumptions

As a first step toward estimation of the regime-specific parameters, counterfactual quantities defined in section 2.1 will be expressed in terms of observed data. We make the consistency assumption

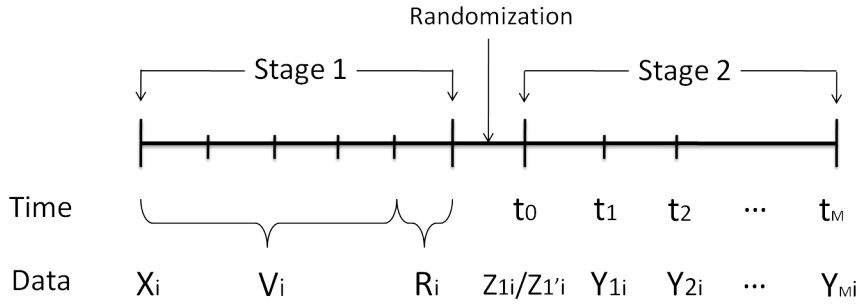

Figure 3: Structure of observed data in a typical two-stage design.

(Ko, Hogan, and Mayer, 2003) that relates observed outcomes to the counterfactuals based on the actual treatment received by the individuals, namely,

$$R_i = \sum_{j=1}^{2} X_{ji} R_i(A_j), \tag{2.4}$$

and

$$Y_{im} = \sum_{j=1}^{2} \left[X_{ji} \left\{ R_i \sum_{k=1}^{2} Z_{ki} Y_{im}(A_j B_k) + (1 - R_i) \sum_{l=1}^{2} Z'_{li} Y_{im}(A_j B'_l) \right\} \right]. \tag{2.5}$$

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 future counterfactuals, conditional on observed covariate history. Equivalently,

$$\begin{aligned} Pr(X_{ji} = 1 | V_i, Y_{im}(A_j B_k), Y_{im}(A_j B'_l), j, k, l = 1, 2) \\ = Pr(X_{ji} = 1 | V_i), j = 1, 2, \end{aligned} \tag{2.6}$$

$$\begin{aligned} Pr(Z_{ki} = 1 | X_{ji}, R_i = 1, V_i, Y_{im}(A_j B_k), Y_{im}(A_j B'_l), k, l = 1, 2) \\ = Pr(Z_{ki} = 1 | X_{ji}, R_i = 1, V_i), j = 1, 2, \end{aligned} \tag{2.7}$$

$$\begin{aligned} \text{and } Pr(Z'_{li} = 1 | X_{ji}, R_i = 0, V_i, Y_{im}(A_j B_k), Y_{im}(A_j B'_l), k, l = 1, 2) \\ = Pr(Z'_{li} = 1 | X_{ji}, R_i = 0, V_i), j = 1, 2. \end{aligned} \tag{2.8}$$

This assumption is frequently referred to as "No unmeasured confounder" (Robins, 1997) assumption. In the case of the REVAMP study design, (2.7) and (2.8) 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 (2.7) and (2.8) by $\pi_{A_j B_k}$ and $\pi_{A_j B'_l}$ respectively.

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 $Y_{im}(A_jB_l')$:

$$E\left[Y_{im}(A_jB_k)|V_i, t_{im}\right] = V_i^T\alpha(A_jB_k) + \beta(A_jB_k)t_{im}, \tag{3.1}$$

and

$$E\left[Y_{im}(A_jB_l')|V_i, t_{im}\right] = V_i^T\alpha(A_jB_l') + \beta(A_jB_l')t_{im}. \tag{3.2}$$

Or, equivalently,

$$E\left[Y_{im}(A_jB_k)|V_i^*\right] = {V_i^*}^T\theta(A_jB_k), \tag{3.3}$$

and

$$E\left[Y_{im}(A_jB_l')|V_i^*\right] = {V_i^*}^T\theta(A_jB_l'), \tag{3.4}$$

where similar to the regime-specific notations for parameters, we have defined group-specific parameters $\theta(A_jB_k) = \{\alpha(A_jB_k), \beta(A_jB_k)\}^T$ and $\theta(A_jB_l') = \{\alpha(A_jB_l'), \beta(A_jB_l')\}^T$, $j, k, l = 1, 2$. We note that models (3.3) and (3.4) 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 (2.1), we can write,

$$\begin{aligned} E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] = {} & E\left[R_i(A_j)Y_{im}(A_jB_k)|V_i^*\right] + \\ & E\left[\{1 - R_i(A_j)\}Y_{im}(A_jB_l')|V_i^*\right]. \end{aligned} \tag{3.5}$$

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

$$\begin{aligned} E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] = {} & E\left[R_i(A_j)|V_i^*\right]E\left[Y_{im}(A_jB_k)|V_i^*\right] \\ & + E\left[1 - R_i(A_j)|V_i^*\right]E\left[Y_{im}(A_jB_l')|V_i^*\right]. \end{aligned} \tag{3.6}$$

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 (3.6) can be expressed as

$$\begin{aligned} E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] = {} & \pi_r(A_j)E\left[Y_{im}(A_jB_k)|V_i^*\right] \\ & + \{1 - \pi_r(A_j)\}E\left[Y_{im}(A_jB_l')|V_i^*\right]. \end{aligned} \tag{3.7}$$

Under the model assumptions (3.1) and (3.2), equation (3.7) becomes

$$E\left[Y_{im}(A_jB_kB_l')|V_i^*\right] = V_i^{*T}[\pi_r(A_j)\theta(A_jB_k) + \{1-\pi_r(A_j)\}\theta(A_jB_l')]. \tag{3.8}$$

By comparing (2.3) to (3.8), we can express the regime-specific parameter $\theta(A_jB_kB_l')$ as the weighted average of treatment path specific parameters as follows

$$\theta(A_jB_kB_l') = \pi_r(A_j)\theta(A_jB_k) + \{1-\pi_r(A_j)\}\theta(A_jB_l'). \tag{3.9}$$

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 (3.9) could be used to obtain the regime-specific parameter estimates from the group-specific parameter estimates. Specifically,

$$\hat{\theta}(A_jB_kB_l') = \hat{\pi}_r(A_j)\hat{\theta}(A_jB_k) + \{1-\hat{\pi}_r(A_j)\}\hat{\theta}(A_jB_l'). \tag{3.10}$$

For the purpose of our analysis we have used mixed models. We accommodate random effects by adding the individual random component to the models (3.3) and (3.4). 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 (3.3) and (3.4) are modified slightly as follows

$$E\left[Y_{im}(A_jB_k)|V_i^*, \eta_i(A_jB_k)\right] = V_i^{*T}\theta(A_jB_k) + H_i^T\eta_i(A_jB_k), \tag{3.11}$$

and

$$E\left[Y_{im}(A_jB_l')|V_i^*, \eta_i(A_jB_l')\right] = V_i^{*T}\theta(A_jB_l') + H_i^T\eta_i(A_jB_l'). \tag{3.12}$$

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 $\beta(A_jB_kB_l'), j, k, l = 1, 2$.

3.1 Methods of Estimation

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.

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

$$\hat{\pi}_r(A_j) = \frac{\sum_{i=1}^n X_{ji} R_i}{\sum_{i=1}^n X_{ji}}, j = 1, 2. \tag{3.13}$$

Next we note that under the consistency and sequential randomization assumptions (2.4)-(2.8), $Y_i(A_j B_k) = Y_i$ 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 (3.11) (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 (Littell *et al.*, 1996) or the *lme* function in R (Pinheiro and Bates, 1994) 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 (2006).

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 (3.10), 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

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

More detailed calculation can be found in Appendix A.

3.1.2 Three-step Method

Step 1: Estimation of treatment effect for each treatment sequence. For simplicity, consider the regime $A_1 B_1 B_1'$. We first use Step 1 of the two-step method to obtain $\hat{\pi}_R(A_1)$, $\hat{\beta}(A_1 B_1)$, $\hat{\beta}(A_1 B_2)$, $\hat{\beta}(A_1 B_1')$, and $\hat{\beta}(A_1 B_2')$.

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 (Little and Rubin, 2002), 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 (3.11) 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 (2.2) 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 (Little, 2002), the variance of the imputed estimator can be estimated by

$$Var\left\{\hat{\beta}^{IMP}(A_1B_1B_1')\right\} = \frac{1}{I}\sum_{\ell=1}^{I} Var\left\{\hat{\beta}^{(\ell)}(A_1B_1B_1')\right\} + \frac{I+1}{I(I-1)}\sum_{\ell=1}^{I}\left\{\hat{\beta}^{(\ell)}(A_1B_1B_1') - \hat{\beta}^{IMP}(A_1B_1B_1')\right\}^2. \quad (3.14)$$

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.

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

$$H_0 : A^T\beta = 0, \tag{4.1}$$

where

$$\beta = \begin{bmatrix} \beta(A_1B_1B_1') \\ \beta(A_1B_1B_2') \\ \beta(A_1B_2B_1') \\ \beta(A_1B_2B_2') \end{bmatrix} \quad \text{and} \quad A^T = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 1 & 0 & -1 & 0 \\ 1 & 0 & 0 & -1 \end{bmatrix}.$$

The test statistics is constructed as the Wald statistic

$$\chi^2 = \hat{\beta}^T A\{A^T Cov(\hat{\beta})A\}^{-1}A^T\hat{\beta}, \tag{4.2}$$

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 (Oehlert, 1992) 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

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

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

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

More detailed calculation is in Appendix B. The covariance then can be estimated by replacing the parameters with the corresponding estimates.

Under the null hypothesis, the Wald statistic (4.2) 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.

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 2. The number of follow-up visits during the second stage was set to four. For simplicity, we only generated data for the subjects with treatment A_1, 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 π_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

$$\begin{aligned} Y_{im}(A_jB_k) = \{\eta_{0i} + \beta_0(A_jB_k)\} + \{\eta_{1i} + \beta_1(A_jB_k)\}t_{im} + \alpha_1(A_jB_k)age_i \\ + \alpha_2(A_jB_k)y_i^{(1)} + \epsilon_{im}, \end{aligned} \tag{5.1}$$

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

$$\begin{aligned} Y_{im}(A_jB_l') = \{\eta_{0i}' + \beta_0(A_jB_l')\} + \{\eta_{1i}' + \beta_1(A_jB_l')\}t_{im} + \alpha_1(A_jB_l')age_i \\ + \alpha_2(A_jB_l')y_i^{(1)} + \epsilon_{im}', \end{aligned} \tag{5.2}$$

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 $\alpha_1(A_1B_1)$ = 0.1, $\alpha_1(A_1B_2)$ = 0.2, $\alpha_1(A_1B_1')$ = 0.15, and $\alpha_1(A_1B_2')$ = 0.25. Finally, we chose the effect of initial stage outcome as $\alpha_2(A_1B_1)$ = $\alpha_2(A_1B_1')$ = -0.2, and $\alpha_2(A_1B_2)$ = $\alpha_2(A_1B_2')$ = -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 two different missing data situations: (1) no missing data, and (2) missing at random (MAR). For its simplicity, we selected a monotone missing pattern for the MAR situation. Selecting the monotone missing pattern means that we assume that once a subject misses a visit, all subsequent visits are missed as well. We generated 30% and 60% missing data. The rate of missing data depended on the treatment sequences; therefore, 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. Among those who had missing data, 50% of them were missing Y_{i4}, and the other 50% have missing Y_{i3} and Y_{i4}. For the MAR situation, 500 Monte-Carlo datasets were generated with two different sample sizes of 500 and 1000 and for the complete data situation, 500 datasets were generated with sample sizes of 200 and 500.

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 3. Results are presented using Monte Carlo means, standard errors, and coverage probabilities of 95% CIs. The simulation results are summarized in Tables 1 to 4.

Table 1 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 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 2. 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 3 and 4 report the results of scenario 1 and 2 when the data are missing at random. The estimates were unbiased even when 60% of the data had at least one missing assessment. 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 were similar between the two- and three-step methods.

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

Table 1: **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

Table 2: **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

BUP-SR and VLF-XR were small, we focus on estimating the effect of treatment regimes for those who received SERT only. 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 (SERT-SERT-MC; n=186), (2) Treat with SERT and if responded, continue to treat with SERT, otherwise treat with the CBASP (SERT-SERT-MC/CBASP; n=250), and (3) Treat with SERT and if responded, continue to treat with SERT, otherwise treat with the SP (SERT-SERT-MC/SP; n=259).

Figure 4 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 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 (3.11) and (3.12). 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=[$1_i, Age_i, y_i^{(1)}$], 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

$$\begin{aligned} Y_{im}(MC) = \alpha_1(MC) + \alpha_2(MC)Age_i + \alpha_3(MC)y_i^{(1)} + \beta_1(MC)t_{im} \\ + \eta_{1i}(MC) + \eta_{2i}(MC)t_{im} + \epsilon_{im}. \end{aligned} \tag{6.1}$$

Similar models were used for the other second-stage treatments MC/CBASP and MC/SP. In Step 2, as in (3.10), three overall effects for the three treatment regimes β(SERT-SERT-MC), β(SERT-SERT-MC/CBASP), and β(SERT-SERT-MC/SP) 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 5.

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

Table 3: **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 4: **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

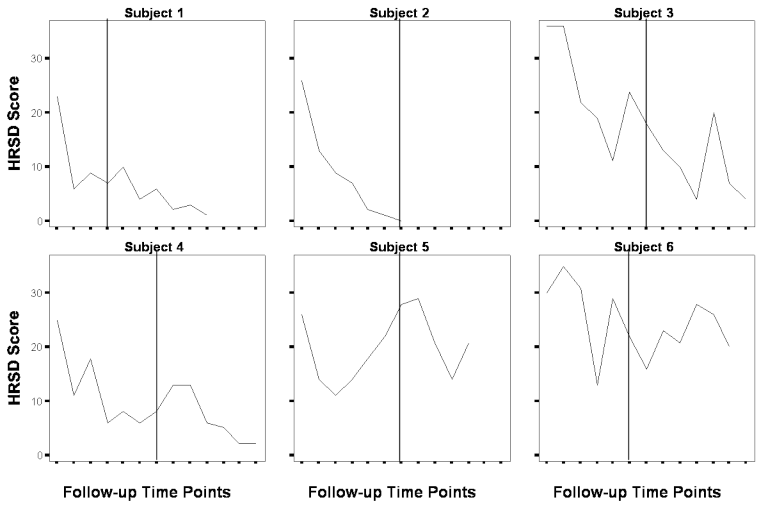

Figure 4: Outcome trend for responders, partial-responders, and non-responders. The vertical lines indicate the end of the initial stage.

Table 5: REVAMP data analysis result.

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

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% confidence intervals. However, mixed models are sensitive to normality assumption (Brown and Prescott, 2006) as well as a missing data (Little, 2002). To account for the former, one can accommodate GEE-type procedures 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 at random. The issue of missing not at random in this situation remains a topic for our future research.

A Variance Estimation of Treatment Effect

Approximate variance of $\hat{\beta}(A_jB_kB_l')$ is derived as follows

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

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

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

Thus,

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

B Covariance Estimation Between Two Treatment Effects

Using Taylors series expansion, we obtain

$$\begin{aligned} & cov[\hat{\beta}(A_1 B_1 B_1'), \hat{\beta}(A_1 B_1 B_2')] \\ &= E[\{\hat{\beta}(A_1 B_1 B_1') - \beta(A_1 B_1 B_1')\}\{\hat{\beta}(A_1 B_1 B_2') - \beta(A_1 B_1 B_2')\}] \\ &\approx E[(\{(\beta(A_1 B_1) - \beta(A_1 B_1')\}\{\hat{\pi}(A_1) - \pi_r(A_1)\} \\ &\quad + \{\hat{\beta}(A_1 B_1) - \beta(A_1 B_1)\}\hat{\pi}_r(A_1) + \{\hat{\beta}(A_1 B_1') - \beta(A_1 B_1')\}\{1-\pi_r(A_1)\}), \\ &\quad \{(\beta(A_1 B_1) - \beta(A_1 B_2')\}\{\hat{\pi}_r(A_1) - \pi_r(A_1)\} + \{\hat{\beta}(A_1 B_1) - \beta(A_1 B_1)\}\hat{\pi}_r(A_1) \\ &\quad + \{\hat{\beta}(A_1 B_2') - \beta(A_1 B_2')\}\{1-\pi_r(A_1)\})] \\ &= E[\{\beta(A_1 B_1) - \beta(A_1 B_1')\}\{\beta(A_1 B_1) - \beta(A_1 B_2')\}\{\hat{\pi}_r(A_1) - \pi_r(A_1)\}^2 \\ &= E[\{\beta(A_1 B_1) - \beta(A_1 B_1')\}\{\beta(A_1 B_1) - \beta(A_1 B_2')\}\{\hat{\pi}_r(A_1) - \pi_r(A_1)\}^2] \\ &= \{\beta(A_1 B_1) - \beta(A_1 B_1')\}\{\beta(A_1 B_1) - \beta(A_1 B_2')\}Var(\hat{\pi}_r(A_1)) \\ &= \{\beta(A_1 B_1) - \beta(A_1 B_1')\}\{\beta(A_1 B_1) - \beta(A_1 B_2')\}\left[\frac{\pi_r(A_1)\{1-\pi_r(A_1)\}}{n_1}\right]. \end{aligned}$$

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