Robust analyses for longitudinal clinical trials with missing and non-normal continuous outcomes

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Abstract

Missing data is unavoidable in longitudinal clinical trials, and outcomes are not always normally distributed. In the presence of outliers or heavy-tailed distributions, the conventional multiple imputation with the mixed model with repeated measures analysis of the average treatment effect (ATE) based on the multivariate normal assumption may produce bias and power loss. Control-based imputation (CBI) is an approach for evaluating the treatment effect under the assumption that participants in both the test and control groups with missing outcome data have a similar outcome profile as those with an identical history in the control group. We develop a general robust framework to handle non-normal outcomes under CBI without imposing any parametric modeling assumptions. Under the proposed framework, sequential weighted robust regressions are applied to protect the constructed imputation model against non-normality in both the covariates and the response variables. Accompanied by the subsequent mean imputation and robust model analysis, the resulting ATE estimator has good theoretical properties in terms of consistency and asymptotic normality. Moreover, our proposed method guarantees the analysis model robustness of the ATE estimation, in the sense that its asymptotic results remain intact even when the analysis model is misspecified. The superiority of the proposed robust method is demonstrated by comprehensive simulation studies and an AIDS clinical trial data application.

keywords: Longitudinal clinical trial; missing data; multiple imputation; robust regression; sensitivity analysis.
1 Introduction

1.1 Missing data in clinical trials

Analysis of longitudinal clinical trials often presents difficulties as inevitably some participants do not complete the study, thereby creating missing outcome data. Additionally, some outcome data among participants who complete the study may not be of interest on account of intercurrent events such as initiation of rescue therapy prior to the analysis time point. With the primary interest focusing on evaluating the treatment effect in longitudinal clinical trials, the approach to handling missingness plays an essential role and has gained substantial attention from the US Food and Drug Administration (FDA) and National Research Council (Little et al., 2012). The ICH E9(R1) addendum provides a detailed framework of defining estimands to target the major clinical question in a population-level summary with the consideration of intercurrent events that may cause additional missingness (ICH, 2021).

The missing at random (MAR; Rubin, 1976) mechanism is often invoked in analyses that seek to evaluate the treatment efficacy. However, MAR is unverifiable and may not be practical in some clinical trials. Further, if the response at the primary time point is of interest regardless of whether participants have complied with the test or comparator treatments through the primary time point (corresponding to a ‘treatment policy’ intercurrent event strategy), an analysis based on the MAR assumption would not be appropriate, because such an analysis would assume that responses in those who drop out would follow the same trajectory as responses in those who remain in treatment. A more plausible assumption would be that the treatment effect may quickly fade away, leading to a missing not at random (MNAR) assumption that responses among those who fail to complete treatments in both treatment groups behave similarly to the responses among those in the control group with identical historical covariates. Drawn on the idea of the zero-dose model in Little and Yau (1996), Carpenter et al. (2013) refer to this scenario as the control-based imputation (CBI). Since the CBI represents a deviation from MAR, it is widely used in sensitivity analyses to explore the robustness of the study results against the untestable MAR assumption (e.g., Carpenter et al., 2013; Cro et al., 2016). Furthermore, an increasing number of clinical studies have applied this approach to primary analyses (Tan et al., 2021). Throughout the paper, we focus on jump-to-reference (J2R) as one favorable scenario of the CBI used in the FDA statistical review and evaluation reports (e.g., US Food and Drug Administration, 2016), which assumes that the missing outcomes in the treatment group will have the same outcome mean profile as those with identical historical information in the
control group. Our goal is to assess the average treatment effect (ATE) under J2R.

1.2 Multiple imputation

Multiple imputation (MI; [Rubin, 2004]) followed by a mixed-model with repeated measures (MMRM) analysis acts as a standard approach to analyze longitudinal clinical trial data under J2R. The main idea of MI applied in longitudinal trials is to use MMRM to impute the missing components and then conduct full-data analysis on each imputed dataset. The simple implementation and high flexibility of MI underlie the recommendation of this approach by the FDA and National Research Council ([Little et al., 2012]).

However, this approach relies heavily on the parametric modeling assumptions in the construction of both the imputation and the analysis model, where a normal distribution is typically assumed. In reality, the distribution of the outcomes may suffer from extreme outliers or a heavy tail, which contradicts the normality assumption. A motivating CD4 count dataset in Section 2 further addresses that a simple transformation such as the log transformation sometimes cannot fix the non-normality issue ([Mehrotra et al., 2012]). In the presence of outliers or heavy tails, applying the methods that rely on the normal distribution may produce bias and power loss. To tackle the issue in longitudinal clinical trials under MAR, [Mogg and Mehrotra, 2007] and [Mehrotra et al., 2012] suggest substituting the conventional analysis of covariance model in the full-data analysis step of MI with the rank-based regression ([Jaeckel, 1972]) or Huber robust regression ([Huber et al., 1973]) to down-weight the impact of non-normal response values. When the missingness mechanism is MNAR, a gap exists in the extension of the robust method to handle the MNAR-related scenarios.

1.3 Our contribution: a robust framework

We develop a general robust framework to evaluate the ATE for non-normal longitudinal outcomes with missingness under the scenario where missing response data in both the test and reference groups are assumed to follow the same trajectory as the complete data in the reference group. We propose applying robust regression in conjunction with mean imputation to relax the parametric modeling assumption required by MI in both the imputation and analysis stages. Inspired by the sequential linear regression model involved in many longitudinal studies, where the current outcomes are regressed recursively on the historical information ([Tang, 2017]), we replace the least squares (LS) estimator with the estimator obtained by minimizing the robust loss function such as the Huber loss, the absolute loss ([Huber, 2004]), and the ε-insensitive loss ([Smola and Schölkopf, 2004]), to mitigate the impact of non-normality in the response variable. While the robust regression lacks
the protection against outliers in the covariates (Chang et al., 2018), a weighted sequential robust regression model is put forward using the idea in Carroll and Pederson (1993) to down-weight the influential covariates by a robust Mahalanobis distance. Followed by mean imputation and a robust analysis step, the estimator from our proposed method has solid theoretical guarantees in terms of consistency and asymptotic normality.

Rosenblum and Van Der Laan (2009) establish a test robustness result for randomized clinical trials with complete data; i.e., for a wide range of analysis models, testing the existence of the non-zero ATE has an asymptotically correct type-1 error even under model misspecification. However, they focus only on the LS model estimators when no ATE exists; and the property remains unclear when the model is estimated via the robust loss function under any arbitrary ATE value. To uncover the ambiguity, we extend the test robustness property to our proposed method for ATE estimation in the context of missing data. We formally show that the ATE estimator obtained from the various non-LS loss functions, including the Huber loss, the absolute loss, and the $\epsilon$-insensitive loss is analysis model-robust, in the sense that its asymptotic properties remain the same even when the analysis model is incorrectly specified. Although the paper mainly focuses on the J2R scenario, the established method and the desired theoretical properties are extendable to robust estimators under other MNAR-related conditions.

The rest of the paper is organized as follows. Section 2 addresses a real-data example to motivate the demand for the robust method. Section 3 introduces notations, assumptions under J2R, and an overview of the existing methods to handle missingness along with their drawbacks in the presence of non-normal data. Section 4 presents our proposed robust method and its detailed implementation steps. Section 5 provides the asymptotic results of the ATE estimator and discusses the analysis model robustness property. Section 6 conducts comprehensive simulation studies to validate the proposed method. Section 7 returns to the motivating example to illustrate the performance of the robust method in practice. Section 8 draws the conclusion.

2 A motivating application

Study 193A conducted by the AIDS Clinical Trial Group compares the effects of dual or triple combinations of the HIV-1 reverse transcriptase inhibitors (Henry et al., 1998). The data consists of the longitudinal outcomes of the CD4 count data at baseline and during the first 40 weeks of follow-up, with the fully-observed baseline covariates as age and gender. In the trial, the participants are randomly assigned among the four treatments regarding dual or triple therapies. We focus on
Figure 1: Spaghetti plots of the log-transformed CD4 count data separated by the two treatments.

the treatment comparison between arm 1 (zidovudine alternating monthly with 400 mg didanosine) and arm 2 (zidovudine plus 400mg of didanosine plus 400mg of nevirapine). As arm 1 involves fewer combinations of inhibitors than arm 2, we view it as the reference group. Among individuals in these two arms, we delete the ones with missing baseline CD4 counts, partition the time into discrete intervals \((0, 12], (12, 20], (20, 28], (28, 36]\) and \((36, 40]\), and create a dataset with a monotone missingness pattern. Since the original CD4 counts are highly skewed, we conduct a log transformation to get the transformed CD4 counts as \(\log(\text{CD4} + 1)\) and use them as the outcomes of interest. Figure 1 presents the spaghetti plots of the transformed CD4 counts. Although there are no outstanding outliers, severe missingness is evident in the data, with only 34 of 320 participants in arm 1 and 46 of 330 participants in arm 2 completing the trial. The high dropout rates in this data reflect a typical missing data issue in longitudinal clinical trials, leading to the demand of conducting imputation for the missing components to prevent the substantial information loss if we focus on only the complete data.

We check the normality of the data by fitting sequential linear regressions on the current outcomes against all historical information and examining the conditional residuals at each visit point for model diagnosis. An assessment of the normality of the responses via the Shapiro-Wilk test and the normal QQ plots are presented in Figure 2. Each normality test indicates a violation of the normal assumption, and the normal QQ plots reveal that the CD4 counts remain heavy-tailed even after
the log transformation. Under this circumstance, potentially biased and inefficient treatment effect estimates may occur when applying the conventional MI along with the MMRM analysis. It motivates the development of a robust method to assess the treatment effect precisely under non-normality.

3 Basic setup

Consider a longitudinal clinical trial with $n$ participants and $t$ follow-up visits. Let $A_i$ be the binary treatment without loss of generality, $X_i$ be the $p$-dimensional fully-observed baseline covariates including the intercept term with a full-column rank, $Y_{is}$ be the continuous outcome of interest at visit $s$, where $i = 1, \cdots, n$, and $s = 1, \cdots, t$. In longitudinal clinical trials, participants are randomly assigned to different treatment groups with non-zero probabilities. When missingness is involved, denote the observed indicator at visit $s$ as $R_{is}$, where $R_{is} = 1$ if $Y_{is}$ is observed and $R_{is} = 0$ otherwise. We assume a monotone missingness pattern throughout the paper, i.e., if the missingness begins at visit $s$, we have $R_{is'} = 1$ for $s' < s$ and $R_{is'} = 0$ for $s' \geq s$. Denote $H_{is} = (X_i^T, Y_{i1}, \cdots, Y_{is})^T$
as the history up to visit \( s \), with \( H_{i0} = X_i \). Since the outliers in the baseline covariates can be identified and removed by data inspection before further analysis, throughout we assume that no outliers exist in the baseline covariates. However, outliers may exist in the longitudinal outcomes due to data-collection error in the long period of study.

In most longitudinal clinical trials with continuous outcomes, the endpoint of interest is the mean difference of the outcomes at the last visit point between the two treatments. We utilize the pattern-mixture model (PMM; Little, 1993) framework to express the ATE as a weighted average over the missing patterns, i.e.,

\[
\tau = \mathbb{E}(Y_{it} \mid A_i = 1) - \mathbb{E}(Y_{it} \mid A_i = 0) = \sum_{s=1}^{t+1} \mathbb{E}(Y_{it} \mid R_{is-1} = 1, R_{is} = 0, A_i = a) \mathbb{P}(R_{is-1} = 1, R_{is} = 0 \mid A_i = a)
\]

if we let \( R_{i0} = 1 \) and \( R_{it+1} = 0 \) for each individual. The assumed condition regarding the missing components is formed for the identification of the pattern-specific expectation \( \mathbb{E}(Y_{it} \mid R_{is-1} = 1, R_{is} = 0, A_i = a) \). We describe one scenario based on the CBI model proposed by Carpenter et al. (2013) for illustration.

### 3.1 Jump-to-reference imputation model

The CBI model (Carpenter et al., 2013) provides a scenario to model missingness in longitudinal clinical trials. We focus on one specific CBI model as J2R, whose plausibility reveals if the investigators believe that participants who discontinue the treatment have the same outcome mean performance as the ones in the control group with the same covariates. The following assumptions illustrate the J2R imputation model for the ATE identification.

**Assumption 1 (Partial ignorability of missingness)** \( R_{is} \perp Y_{is'} \mid (H_{is-1}, A_i = 0) \) for \( s' \geq s \).

Assumption 1 characterizes the MNAR missing mechanism under J2R. The conventional MAR assumption is only required for the missing data in the control group. We do not impose any missing assumptions in the treatment group.

**Assumption 2 (J2R outcome mean model)** For individuals who receive treatment \( a \) with historical information \( H_{is-1} \) and drop out at visit \( s \),

\[
\mathbb{E}(Y_{it} \mid H_{is-1}, R_{is-1} = 1, R_{is} = 0, A_i = a) = \mathbb{E}(Y_{it} \mid H_{is-1}, A_i = 0).
\]

Assumption 2 offers a strategy to model the conditional mean of the missing component under J2R. Given the same historical information, the outcome mean will “jump” to the same conditional mean in the control group no matter the prior treatment. Combining with Assumption 1, the conditional expectation \( \mathbb{E}(Y_{it} \mid H_{is-1}, A_i = 0) = \mathbb{E}\{ \cdots \mathbb{E}(Y_{it} \mid H_{it-1}, R_{it} = 1, A_i = 0) \cdots \mid H_{is-1}, R_{is} = 0 \} \) can be written as...
$1, A_i = 0$} is identified through a series of sequential regressions on the current outcome against the available historical information.

Throughout the paper, we assume a linear relationship between the outcomes and the historical covariates in the J2R imputation model for simplicity. Extensions to nonlinear relationships are manageable, if the sequential regressions of the observed data are fitted in backward order, i.e., we start from the available data at the last visit point and use the predicted value as the outcome to regress on the previous history recursively to construct the imputation model. The elaboration of the sequential fitting procedure is provided in Section S2 in the supplementary material.

### 3.2 Overview of the existing methods and the drawbacks

MI proposed by [Rubin (2004)](#) provides a fully parametric approach to handle missingness under MNAR. Normality is often assumed for its simplicity and robustness against moderate model misspecification in the implementation of MI ([Mehrotra et al., 2012](#)). One common MI procedure in longitudinal clinical trials under J2R is summarized in the following steps:

**Step 1.** For the control group, fit the sequential regression for the observed data at each visit point against the available history. Denote the estimated model parameter as $\hat{\theta}_{s-1}$ for $s = 1, \ldots, t$.

**Step 2.** Impute missing data sequentially to form $M$ imputed datasets: For individuals who have missing values at visit $s$, impute $Y_{is}^{(m)}$ from the conditional distribution $f(Y_{is} \mid H_{is-1}^{s(m)}, A_i = 0; \hat{\theta}_{s-1})$ estimated in Step 1, where $H_{is-1}^{s(m)} = (X_i^T, Y_{i1}^{s(m)}, \ldots, Y_{is-1}^{s(m)})^T$ and $Y_{is}^{s(m)} = R_i Y_{is} + (1 - R_i) Y_{is}^{(m)}$ for $m = 1, \ldots, M$.

**Step 3.** For each imputed dataset, perform the complete data analysis by fitting the imputed outcomes at the last visit point on a working analysis model. Denote $\hat{\tau}^{(m)}$ as the ATE estimator of the $m$th imputed dataset.

**Step 4.** Combine the estimation results from $M$ imputed datasets and obtain the MI estimator as

$$\hat{\tau}_{\text{MI}} = M^{-1} \sum_{m=1}^M \hat{\tau}^{(m)},$$

with the variance estimator by Rubin’s rule as

$$\hat{\Psi}(\hat{\tau}_{\text{MI}}) = \frac{1}{M} \sum_{m=1}^M \hat{\Psi}(\hat{\tau}^{(m)}) + \left(1 + \frac{1}{M}\right) B_M,$$

where $B_M = (M - 1)^{-1} \sum_{m=1}^M (\hat{\tau}^{(m)} - \hat{\tau}_{\text{MI}})^2$ is the between-imputation variance.

Traditionally, the imputation model in Step 1 and the analysis model in Step 3 are obtained from the MMRM analysis, where we assume an underlying normal distribution for both the observed...
and the imputed data. However, as illustrated in the motivating CD4 count dataset in Section 2, normality may be violated, leading to a biased estimate of the target ATE parameter. With the consideration of non-normality, Mogg and Mehrotra (2007) and Mehrotra et al. (2012) modify the analysis model in Step 3 by replacing the LS estimator with the estimator obtained from the robust loss function.

One drawback of MI is that it is fully parametric. The consistency of the MI estimator relies heavily on the correct specification of the imputation distribution, i.e., the conditional distribution given the observed data, which is often assumed to be normal. When a severe deviation from the assumed imputation distribution is detected in the data, the estimation may not be reliable. The possible misspecification of the imputation distribution also exists in the “robust” approaches proposed by Mogg and Mehrotra (2007) and Mehrotra et al. (2012), where the imputation model still depends on the normality assumption as required by MI. Moreover, the MI estimator is not efficient in general. The inefficiency becomes more serious when it comes to interval estimation. The variance estimation using Rubin’s combining rule may produce an inconsistent variance estimate even when the imputation and analysis models are the same correctly specified models (Wang and Robins, 1998; Robins and Wang, 2000). Under the MNAR assumption, the overestimation issue raised from Rubin’s variance estimator is more pronounced (e.g., Lu, 2014; Liu and Pang, 2016; Yang and Kim, 2016; Guan and Yang, 2019; Yang et al., 2021; Liu et al., 2022). One can resort to the bootstrap variance estimation to obtain a consistent variance estimator, which however exaggerates the computational cost.

The unsatisfying performance of MI under non-normality motivates us to develop a robust approach to accommodate the possible model misspecification resulting from outliers or heavy-tailed errors without the reliance on parametric models. In the following sections, a weighted robust regression model in conjunction with mean imputation is proposed to overcome the issues in MI.

4 Proposed robust method

We propose a mean imputation procedure based on robust regression in both the imputation and the analysis models to obtain valid inferences under J2R when the data suffers from a heavy tail or extreme outliers. To relax the strong parametric modeling assumption required by MI, mean imputation is preferred. Mehrotra et al. (2012) shed light on the possibility of incorporating the robust regression in the analysis step of MI to handle non-normality. Based on this idea, we further suggest using the sequential robust regression model in the imputation step to protect against deviations
from normality for the observed data.

Throughout this section, we focus on the robust estimators obtained from minimizing the robust loss functions such as the Huber loss, the absolute loss \cite{Huber2004}, and the \(\varepsilon\)-insensitive loss \cite{Smola2004} to account for the impact of outliers or heavy-tailed data. To obtain a valid mean-type estimator, a symmetric error distribution assumption is imposed whenever a robust regression is applied.

Motivated by the sequential linear regression model under normality, where we regress the current outcomes on the historical information at each visit point to produce the sequential inferences, we develop a sequential robust regression procedure for the observed data to obtain valid inferences that are less likely to be influenced by non-normality. For the longitudinal data with a monotone missingness pattern, a robust regression is fitted on the observed data at each visit point, incorporating the observed historical information. Specifically, for the available data at visit \(s\) for \(s = 1, \cdots, t\), the imputation model parameter estimate \(\hat{\alpha}_{s-1}\) minimizes the loss function

\[
\sum_{i=1}^{n} (1 - A_i) R_{is} \rho(Y_{is} - H_{is}^{T} \alpha_{s-1}).
\]

Here, \(\rho(x)\) is the robust loss function. For example, the Huber loss function is defined as \(\rho(x) = 0.5x^2 I(|x| < l) + \{l|x| - 0.5l^2\} I(|x| \geq l)\), where the constant \(l > 0\) controls the influence of the non-normal data points and \(I(\cdot)\) is an indicator function \cite{Huber1973}. When \(l \to \infty\), the Huber-type robust estimator is equivalent to the conventional LS estimator. We also provide the definitions of the absolute loss and the \(\varepsilon\)-insensitive loss in Section S1.1 in the supplementary material.

Remark 1 (Tuning constant \(l\) in the Huber loss function) The tuning constant \(l\) in the Huber loss function mitigates the impact of extreme values and heavy-tailed errors in the data. \cite{Kelly1992} argues the existence of trade-offs between the bias and variance in the selection of the tuning constant. A small value of \(l\) provides more protections against non-normal values, yet suffers from the loss of efficiency if the data is indeed normal. In practice, a common recommendation of the tuning constant is \(l = 1.345\sigma\), where \(\sigma\) is the standard deviation of the errors \cite{Fox2002}. We use the Huber loss function with this tuning parameter to get the robust estimators throughout the simulation studies and real data application.

While the estimator from the robust loss function provides protection against extreme outliers in the response variables, it is not robust against outliers in the covariates \cite{Chang2018}, leading to an imprecise estimation and a loss of efficiency. In longitudinal data with the use of sequential
regressions, the issue becomes more profound, where the outcome is treated both as the response variable in the current regression and as the covariate in the subsequent regression. To deal with the outliers in the covariates, we utilize the idea in Carroll and Pederson (1993) to down-weight the high leverage point in the covariates via a robust Mahalanobis distance. Specifically, for a \( p \)-dimensional covariate \( X \), we calculate the robust Mahalanobis distance as
\[
d = (X - \mu)^T V^{-1} (X - \mu),
\]
where \( \mu \) is a robust estimate of the center and \( V \) is a robust estimate of the covariance matrix. The trisquared redescending function is applied to form the assigned weights as
\[
w(u; \nu) = u \left\{ 1 - \left( \frac{u}{\nu} \right)^2 \right\}^3 \mathbb{I}(|u| \leq \nu),
\]
where \( u = (d/\nu)^{1/2} \) and \( \nu \) is a tuning parameter to control the down-weight level. Therefore, in the sequential weighted robust regression model, the robust estimate \( \hat{\alpha}_{s-1}^w \minimizes the weighted loss
\[
\sum_{i=1}^{n} (1 - A_i) R_{i,s} w(H_{i,s-1}; \nu_{s-1}) \rho(Y_i - H_{i,s-1}^T \hat{\alpha}_{s-1}).
\]
(1)

Remark 2 (Tuning constants in the trisquared redescending function) When selecting the tuning parameter, Carroll and Pederson (1993) used a fixed constant \( \nu = 8 \) to illustrate a specific down-weight behavior for cross-sectional studies. In longitudinal clinical trials involving multiple weighted sequential regressions, the tuning parameter \( \nu_{s-1} \) can be selected via cross-validation at each visit point, for \( s = 1, \cdots, t \). The main idea is to conduct a \( K \)-fold cross-validation for the observed data at each visit point and determine the optimal tuning parameter \( \nu_{s-1} \) which minimizes the squared errors. Specifically, we first partition the observed data at visit \( s \) into \( K \) parts denoted as \( P_1, \cdots, P_K \). The part \( P_j \) is then left for the test, and the remaining \((K - 1)\) folds are utilized to learn the robust estimator \( \hat{\alpha}_{s-1,j}^w \), for \( j = 1, \cdots, K \). The optimal \( \nu_{s-1} \) minimizes the cross-validation sum of the squared errors
\[
\sum_{j=1}^{K} \sum_{i \in P_j} (Y_i - H_{i,s-1}^T \hat{\alpha}_{s-1,j})^2.
\]

After obtaining the robust estimates of the imputation model parameters, we impute the missing components by their conditional outcome means sequentially based on Assumptions [1] and [2] and construct the imputed data \( Y_{i,s}^* = R_{i,s} Y_i + (1 - R_{i,s}) H_{i,s-1}^T \hat{\alpha}_{s-1}^w \), where \( H_{i,s-1}^w = (X_i^T, Y_{i1}^*, \cdots, Y_{is-1}^*)^T \). Complete data analysis is then conducted on the imputed data, where we again minimize the robust loss function to mitigate the impact of outliers in the response variable. Note that since we assume that there are no outliers in the baseline covariates, assigning the weights to the loss function becomes unnecessary. Consider a general form of the working model in the analysis step as
\[
\mu(A, X | \gamma) = Ag(X; \gamma^{(0)}) + h(X; \gamma^{(1)}),
\]
(2)
where \( g(X; \gamma^{(0)}) \) and \( h(X; \gamma^{(1)}) \) are integrable functions bounded on compact sets, and \( \gamma = (\gamma^{(0)T}, \gamma^{(1)T})^T \). The robust estimator \( \hat{\gamma} = (\hat{\gamma}^{(0)T}, \hat{\gamma}^{(1)T})^T \) can be found by minimizing the loss
\[
\sum_{i=1}^{n} \rho \{ Y^*_i - \mu(A_i, X_i | \gamma) \},
\]
and the resulting ATE estimator \( \hat{\tau} \) is estimated by the mean differences between the two groups as
\[
\hat{\tau} = n^{-1} \sum_{i=1}^{n} g(X_i; \hat{\gamma}^{(0)}).
\]

The modeling form (2) is commonly satisfied in randomized trials when constructing the working model for analysis. For example, the standard analysis model without the interaction term between the treatment and the baseline covariates as \( \mu(A, X | \gamma) = \gamma^{(0)}A + \gamma^{(1)T}X \) gratifies this form when \( g(X; \gamma^{(0)}) = \gamma^{(0)} \) and \( h(X; \gamma^{(1)}) = \gamma^{(1)T}X \); a similar logic applies to the interaction model \( \mu(A, X | \gamma) = \gamma^{(0)}TA X + \gamma^{(1)T}X \). As we will elaborate in the next section, the ATE estimator \( \hat{\tau} \) is analysis model-robust, in the sense that its asymptotic results stay intact regardless of the specification of the analysis model. The implementation of the proposed mean imputation-based robust method is as follows.

Step 1. For the observed data in the control group, fit the sequential weighted robust regression at each visit point and get the sequential model parameter estimates \( \hat{\alpha}_s^{w} \) by minimizing the weighted loss (1) for \( s = 1, \ldots, t \).

Step 2. Impute missing data sequentially by the conditional outcome mean according to Assumptions 1 and 2 and obtain the imputed data \( Y^*_i = R_{is}Y_i + (1-R_{is})H_{is-1}^{T}\hat{\alpha}_s^{w} \), where \( H_{is-1} = (X_i^T, Y_i^*, \ldots, Y_{is-1}^*)^T \) for \( s = 1, \ldots, t \).

Step 3. Set up an appropriate working model \( \mu(A, X | \gamma) \) in the form (2), perform the complete data analysis and get the ATE estimator \( \hat{\tau} \) by minimizing the loss function (3).

The good theoretical properties of the ATE estimator along with a linearization-based variance estimator are provided in the next section.

5 Theoretical properties and analysis model robustness

We present the asymptotic theory of the ATE estimator in terms of consistency and asymptotic normality along with a variance estimator based on three robust loss functions as the Huber loss, the absolute loss, and the \( \varepsilon \)-insensitive loss. To illustrate the theorems in a straightforward way, we introduce additional notations. Denote \( \varphi(H_{is}, \alpha_{s-1}) = (1-A_i)R_{is}w(H_{is-1}; \nu_{s-1}) \psi(Y_{is} - H_{is-1}^{T}\alpha_{s-1})H_{is-1} \)
as the function derived from minimizing the weighted loss function \([1]\) in the imputation model, where \(\psi(x) = \partial \rho(x) / \partial x\) is the derivative of the robust loss function, and \(\alpha_{s-1,0}\) as the true parameter such that \(\mathbb{E}\{\varphi(H_{is}, \alpha_{s-1}) \mid H_{is-1}\} = 0\). Let \(\hat{\alpha}^w = (\hat{\alpha}_0^w, \cdots, \hat{\alpha}_{t-1}^w)^T\) be the combination of the model estimators from \(t\) sequential regression models in the imputation, and \(\alpha_0 = (\alpha_{0,0}^T, \cdots, \alpha_{t-1,0}^T)^T\) be the corresponding true model parameters. In terms of the components in the analysis model, denote \(\varphi_a(Z_i, \gamma) = \psi \{Y_{it}^* - \mu(A_i, X_i \mid \gamma)\} \partial \mu(A_i, X_i \mid \gamma) / \partial \gamma^T\), where \(Z_i^* = (A_i, X_i^T, Y_{it}^*)^T\) represents the imputed data in the model, \(\gamma_0\) is the true parameter such that \(\mathbb{E}\{\varphi_a(Z_i, \gamma)\} = 0\), and \(\tau_0\) is the true ATE such that \(\tau_0 = \mathbb{E}(Y_{it} \mid A = 1) - \mathbb{E}(Y_{it} \mid A = 0)\). Suppose \(\gamma^{(1)}\) is a \(d_0\)-dimensional vector, and \(\gamma^{(1)}\) is a \(d_1\)-dimensional vector.

**Theorem 1** Under the regularity conditions listed in Section S1.1 in the supplementary material, the ATE estimator \(\hat{\tau} \overset{d}{\rightarrow} \tau_0\) as the sample size \(n \rightarrow \infty\), for \(s = 1, \cdots, t\).

**Theorem 2** Under the regularity conditions listed in Section S1.2 in the supplementary material, as the sample size \(n \rightarrow \infty\),

\[
\sqrt{n}(\hat{\tau} - \tau_0) \overset{d}{\rightarrow} \mathcal{N}(0, \mathbb{V}\{V_{\gamma,i}(\alpha_0, \gamma_0)\})
\]

where \(V_{\gamma,i}(\alpha_0, \gamma_0) = \left\{\partial g(X_i; \gamma^{(0)}) / \partial \gamma^T\right\} c^T V_{\gamma,i}(\alpha_0, \gamma_0),
\]

\(V_{\gamma,i}(\alpha_0, \gamma_0) = D^{-1}_\varphi \left[ \varphi_a \{Z_i^*(\beta_i), \gamma_0\} + \sum_{s=1}^{t} \mathbb{E} \left\{ R_{s-1}(1 - R_s) \frac{\partial \mu(A, X \mid \gamma_0) \partial \psi(e) }{\partial e} H_{is-1}^T \right\} U_{t,s-1,i}(\alpha_0) \right],
\]

\(U_{t,s-1,i}(\alpha_0) = (I_{p+s-2}, \alpha_{s-1,0}) U_{t,s,i}(\alpha_0) + (0_{p+s-2}, 1) \beta_{t,s} q(H_{is}, \alpha_{s-1,0})\) for \(s < t\), \(U_{t,t-1,i}(\alpha_0) = q(H_{it}, \alpha_{t-1,0})\, and \(q(H_{is}, \alpha_{s-1,0}) = [-\mathbb{E}\{\varphi(H_{is}, \alpha_{s-1,0})H_{is-1}^T \mid H_{is-1}\} / \partial \alpha_{s-1}^T]^{-1} \varphi(H_{is}, \alpha_{s-1,0})\). Here, \(c^T = (I_{d_0}, 0_{d_0 \times d_1})\) is a matrix where \(I_{d_0}\) is a \((d_0 \times d_0)\)-dimensional identity matrix and \(0_{d_0 \times d_1}\) is a \((d_0 \times d_1)\)-dimensional zero matrix, \(0_{p+s-2}\) is a \((p + s - 2)\)-dimensional zero vector, \(D_\varphi = \partial \mathbb{E}\{\varphi_a \{Z_i^*(\beta_i), \gamma_0\}\} / \partial \gamma^T\) where \(Z_i^*(\beta_i) = (A_i, X_i^T, Y_{it}^*(\beta_i))^T\) and \(Y_{it}^*(\beta_i)\) refers to the imputed value \(Y_{it}^*\) based on the true imputation parameters \(\beta_i = (\beta_{t,0}^T, \cdots, \beta_{t,t-1}^T)^T\) which satisfy

\[
\begin{cases}
\beta_{t,t-1} = \alpha_{t-1,0} & \text{if } s = t, \\
\beta_{t,s-1} = (I_{p+s-2}, \alpha_{s-1,0})(I_{p+s-1}, \alpha_{s,0}) \cdots (I_{p+t-3}, \alpha_{t-2,0}) \alpha_{t-1,0} & \text{if } s < t,
\end{cases}
\]

and \(e_i = Y_{it}^*(\beta_i) - \mu(A_i, X_i \mid \gamma_0)\).

The asymptotic variance in Theorem 2 motivates us to obtain a linearization-based variance
estimator by plugging in the estimated values as
\[
\hat{V}(\hat{\tau}) = \frac{1}{n^2} \sum_{i=1}^{n} \{ V_{\tau,i}(\hat{\alpha}^w, \hat{\gamma}) - \bar{V}_{\tau,i}(\hat{\alpha}^w, \hat{\gamma}) \}^2,
\]
where \( \bar{V}_{\tau,i}(\hat{\alpha}^w, \hat{\gamma}) = n^{-1} \sum_{i=1}^{n} V_{\tau,i}(\hat{\alpha}^w, \hat{\gamma}) \), \( V_{\tau,i}(\hat{\alpha}^w, \hat{\gamma}) = \{ \partial g(X_i; \hat{\gamma}^{(0)}) / \partial \gamma^T \} c^T V_{\gamma,i}(\hat{\alpha}^w, \hat{\gamma}) \),

\[
V_{\gamma,i}(\hat{\alpha}^w, \hat{\gamma}) = D^{-1} \left[ \varphi_a(Z_i^*, \hat{\gamma}) + \sum_{s=1}^{t} \left\{ \frac{1}{n} \sum_{i=1}^{n} R_{isa-1}(1 - R_{iss}) \frac{\partial \mu(A_i, X_i | \hat{\gamma})}{\partial \gamma^T} \frac{\partial \psi(\hat{e}_i)}{\partial e_i} H_{isa-1}^T \right\} U_{t,s-1,i}(\hat{\alpha}^w) \right],
\]
\[
U_{t,s-1,i}(\hat{\alpha}^w) = (I_{p+s-2}, \hat{\alpha}^w_{s-1}) U_{t,s,i}(\hat{\alpha}^w) + (0_{p+s-2}, 1) \hat{\beta}_{t,s} q(H_{is}, \hat{\alpha}^w_{s-1}) \text{ for } s < t, U_{t,t-1,i}(\hat{\alpha}^w) = q(H_{it}, \hat{\alpha}^w_{t-1}),
\]
and \( q(H_{is}, \hat{\alpha}^w_{s-1}) = \left[ -n^{-1} \sum_{i=1}^{n} \{ \partial \varphi(H_{is}, \hat{\alpha}^w_{s-1}) / \partial \alpha_{T_{s-1}}^T \} H_{isa-1}^T \right]^{-1} \varphi(H_{is}, \hat{\alpha}^w_{s-1}) \). Also, \( \hat{e}_i = Y_i^* - \mu(A_i, X_i | \hat{\gamma}) \), \( \hat{D} = n^{-1} \sum_{i=1}^{n} \partial \varphi_a(Z_i^*, \hat{\gamma}) / \partial \gamma^T \), and

\[
\frac{\hat{\beta}_{t,m-1} = \hat{\alpha}^w_{m-1}}{\hat{\beta}_{t,s} = (I_{p+s-2}, \hat{\alpha}^w_{s-1})(I_{p+s-1}, \hat{\alpha}^w_{s}) \cdots (I_{p+t-3}, \hat{\alpha}^w_{t-2}) \hat{\alpha}^w_{t-1}} \text{ if } s < t,
\]
for \( s = 1, \ldots, t \). Since the ATE estimator is asymptotically linear, we can also use bootstrap to obtain a replication-based variance estimator.

We consider a specific working model as the interaction model for analysis and present the asymptotic theories of the ATE estimator in Section S1.3 in the supplementary material. The interaction model is one of the most common models in the clinical trials suggested in ICH (2021), which is also used in the simulation studies and real data application in the paper.

Theorems 1 and 2 extend the test robustness (Rosenblum and Van Der Laan, 2009) to the analysis model robustness in two aspects. First, the robustness expands its plausibility from the hypothesis test to the ATE estimation. Second, the robust estimator obtained from minimizing the loss function further broadens the types of the model estimator used in the analysis model. The resulting ATE estimator via the robust loss remains consistent and has the identical asymptotic normality even when the analysis model is misspecified.

6 Simulations

We conduct simulation studies to validate the finite-sample performance of the proposed robust method. Consider a longitudinal clinical trial with two treatment groups and five visits. Set the sample size for each group as 500 and generate the data separately for each treatment. The baseline covariates \( X \in \mathbb{R}^2 \) are a combination of a continuous variable generated from the standard normal
distribution and a binary variable generated from a Bernoulli distribution with the success probability of 0.3. The longitudinal outcomes are generated in a sequential manner, regressing on the historical information separately for each group based on some specific distributions. The group-specific data generating parameters are given in Section S3.1 in the supplementary material.

The missingness mechanism is set to be MAR with a monotone missingness pattern. For the visit point \( s \), if \( R_{is'-1} = 0 \), then \( R_{is'} = 0 \) for \( s' = s, \cdots, t \); otherwise, let \( R_{is} \mid (H_{is-1}, A_i = a) \sim \text{Bernoulli} \{\pi_s(a, H_{is-1})\} \). We model the observed probability \( \pi_s(a, H_{is-1}) \) at visit \( s > 1 \) as a function of the observed information as \( \text{logit} \{\pi_s(a, H_{is-1})\} = \phi_{1a} + \phi_{2a} Y_{is-1} \), where \( \phi_{1a} \) and \( \phi_{2a} \) are the tuning parameters for the observed probabilities. The parameters are tuned to achieve the observed probability around 0.8 in each group.

We select the Huber loss function to obtain robust estimators for its prevalence. Table 1(a) summarizes the three methods we aim to compare in the simulation studies. We apply distinct estimation approaches for each method in the imputation and analysis models, along with different imputation methods, where MI stands for the conventional method used in longitudinal clinical trials and Robust stands for our proposed method. LSE can be viewed as a transition from the conventional MI method to the proposed robust method. In terms of the variance estimation, Rubin’s and bootstrap methods are compared for the MI estimator while the linearization-based and bootstrap variance estimates are compared for the mean imputation estimators.

The simulation results are based on 10,000 Monte Carlo (MC) simulations under \( H_0 : \tau = 0 \) and 1000 MC simulations under one specific alternative hypothesis \( H_1 : \tau = \tau_0 \), with the number of bootstrap replicates \( B = 100 \) and the imputation size \( M = 10 \) for MI. The tuning parameter of Huber robust regression is \( l = 1.345\sigma \), and the tuning parameters of the sequential weighted robust models are \( \nu_{s-1} = 10 \) for \( s = 1, \cdots, 5 \). The imputation size \( M \) and the tuning parameters \( \nu_{s-1} \) do not have a strong impact on the inferences (results are not shown). We assess the estimators using the point estimate (Point est), the MC variance (True var), the variance estimate (Var est), the relative bias of the variance estimate computed by \( \frac{\mathbb{E}\{\hat{V}(\hat{\tau})\} - \mathbb{V}(\hat{\tau})}{\mathbb{V}(\hat{\tau})} \), the coverage rate of 95% confidence interval (CI), the type-1 error under \( H_0 \), the power under \( H_1 \), and the root mean squared error (RMSE). We choose the 95% Wald-type CI estimated by \( (\hat{\tau} - 1.96\hat{\nu}^{1/2}(\hat{\tau}), \hat{\tau} + 1.96\hat{\nu}^{1/2}(\hat{\tau})) \).

### 6.1 Data with extreme outliers

We first focus on the settings when the outcomes are generated sequentially from the normal distribution with or without severe outliers. To produce the outliers in the longitudinal outcomes, we randomly select 10 individuals from the top 30 completers with the highest outcomes at the last visit.
point per group and multiply the original values by three for all post-baseline outcomes. We also consider adding extreme values only to one specific group and present the results in Section S3.2 in the supplementary material.

Table 1(b) and the first two rows of Figure 3 illustrate the simulation results of the original data and the data with extreme outliers under the normal distribution. Without the presence of outliers, all methods produce unbiased point estimates. The robust method is slightly less efficient compared to MI and LSE, as it has a larger MC variance and a smaller power. For MI, Rubin’s variance estimate is conservative and inefficient, causing the coverage rate to be far away from the empirical value and the power to be smaller, which matches the observations detected in previous literature regarding J2R in longitudinal clinical trials (e.g., Liu and Pang, 2016; Liu et al., 2022). However, using bootstrap can fix the overestimation issue and produce a reasonable coverage rate and power. When outliers exist, only the robust method produces an unbiased point estimate, a well-controlled type-1 error under $H_0$, and a satisfying coverage rate under $H_1$ with a smaller RMSE.

6.2 Data from a heavy-tailed distribution

To assess the performance of the estimator from our proposed robust method in heavy-tailed distributions, we generate the longitudinal outcomes sequentially from a t-distribution with the degrees of freedom as 5 in time order. The detailed setup of the data-generating process is also given in Section S3.1 in the supplementary material.

Table 1(c) and the last row of Figure 3 show the simulation results. All the methods result in unbiased point estimates. The robust method produces the ATE estimator with the smallest MC variance, indicating the superiority of Huber robust regression under a heavy-tailed distribution. The linearization-based variance estimates behave similarly to the bootstrap variance estimates for the two mean imputation-based methods, with comparable coverage rates and powers.

The overall simulation results indicate a recommendation of the proposed robust approach with the linearization-based variance estimation to obtain unbiased point estimates and save computation time. The advocated method works well in terms of consistency, well-controlled type-1 errors, higher powers under $H_1$, and smaller RMSEs. Even under the normality assumption, our proposed method has comparable performance as the conventional MI method, with only a slight loss in the power. When encountering a heavy-tailed distribution or extreme outliers, the proposed method outperforms with more reasonable coverage rates and higher powers. Similar interpretations apply to the simulation results under $H_0$ given in Section S3.2 in the supplementary material.
Table 1: Summary of the simulation methods and results.

(a) Different estimation and imputation approach in the four methods used for comparison.

| Method | Imputation model | Imputation method | Analysis model |
|--------|-----------------|------------------|---------------|
| MI     | LS              | MI               | LS            |
| LSE    | Weighted Huber regression | Mean imputation | LS            |
| Robust | Weighted Huber regression | Mean imputation | Huber regression |

(b) Simulation results under the normal distributions without or with extreme outliers. Here the true value $\tau = 71.18\%$.

| Case       | Method | Point est ($\times 10^{-2}$) | True var ($\times 10^{-2}$) | Var est ($\times 10^{-2}$) | Relative bias (%) | Coverage rate (%) | Power (%) | RMSE ($\times 10^{-2}$) |
|------------|--------|-----------------------------|-----------------------------|---------------------------|------------------|-----------------|-----------|------------------|
| No outliers| MI     | 70.89                       | 3.02                        | 5.35                      | 3.22             | 77.00           | 6.39      | 98.90            |
|            | LSE    | 70.93                       | 3.03                        | 3.25                      | 3.15             | 7.14            | 4.04      | 95.40            |
|            | Robust | 70.09                       | 3.26                        | 3.41                      | 3.38             | 4.75            | 3.73      | 95.00            |
| Outliers   | MI     | 77.42                       | 3.92                        | 12.42                     | 8.97             | 216.36          | 128.51    | 99.70            |
|            | LSE    | 74.02                       | 4.18                        | 6.18                      | 5.94             | 47.85           | 42.18     | 98.30            |
|            | Robust | 72.34                       | 3.44                        | 3.53                      | 3.49             | 2.75            | 1.40      | 95.00            |
| in both    | MI     | 70.54                       | 3.00                        | 5.35                      | 3.16             | 78.07           | 5.27      | 99.30            |
|            | LSE    | 70.42                       | 2.90                        | 3.21                      | 3.06             | 10.49           | 5.43      | 96.30            |
|            | Robust | 69.81                       | 2.72                        | 2.90                      | 2.81             | 6.38            | 3.11      | 94.90            |

$\hat{V}_1$ denotes the variance estimate obtained by Rubin’s rule in MI and linearization in mean imputation-based methods; $\hat{V}_{\text{Boot}}$ denotes the bootstrap variance estimates.

(c) Simulation results under the t-distribution. Here the true value $\tau = 68.09\%$.

| Method | Point est ($\times 10^{-2}$) | True var ($\times 10^{-2}$) | Var est ($\times 10^{-2}$) | Relative bias (%) | Coverage rate (%) | Power (%) | RMSE ($\times 10^{-2}$) |
|--------|-----------------------------|-----------------------------|---------------------------|------------------|-----------------|-----------|------------------|
| MI     | 70.42                       | 3.00                        | 5.35                      | 3.16             | 78.07           | 5.27      | 99.30            |
| LSE    | 70.54                       | 2.90                        | 3.21                      | 3.06             | 10.49           | 5.43      | 96.30            |
| Robust | 69.81                       | 2.72                        | 2.90                      | 2.81             | 6.38            | 3.11      | 94.90            |

$\hat{V}_1$ denotes the variance estimate obtained by Rubin’s rule in MI and linearization in mean imputation-based methods; $\hat{V}_{\text{Boot}}$ denotes the bootstrap variance estimates.
Figure 3: Plot for the simulation results under different distributions.

Type-1 error comparison under normal and H0: $\tau = 0$

Power comparison under normal and H1: $\tau = 0.7118$

Type-1 error comparison under normal with outliers and H0: $\tau = 0$

Power comparison under normal with outliers and H1: $\tau = 0.7118$

Type-1 error comparison under t-distribution and H0: $\tau = 0$

Power comparison under t-distribution and H1: $\tau = 0.6809$

Var type: Rubin, Linearization, Bootstrap
7 Estimating effects of HIV-1 reverse transcriptase inhibitors

We now apply our proposed robust method to the motivating example introduced in Section 2. The primary goal is to assess the ATE between the two arms at the study endpoint under the J2R condition. The results of the normality test and the symmetry test proposed by Miao et al. (2006) in Figure 2 indicate that the data are symmetrically distributed without severe outliers, yet suffer from a heavy tail that deviates from normality. MI, mean imputation with LS estimators, and the proposed robust method using the Huber loss function are compared with respect to the point estimation, the variance estimation based on Rubin’s variance estimator or the linearization-based variance estimator, Wald-type 95% CI and CI length. For MI, the imputation size is $M = 100$. The tuning parameters for the weights in the robust method are selected via cross-validation, with the procedure described in Section S4 in the supplementary material.

Table 2 shows the analysis results of the group means and the ATE under J2R. MI uses the sequential linear regressions estimated by the LS estimators for the imputation model, resulting in different point estimates compared to other mean imputation-based methods, where the imputation model is obtained via robust regressions. Using LS or Huber loss in the analysis model also has a slight difference in the estimation because of the heavy tail. While the conventional MI method may contaminate the inference when the data deviates from the normal distribution, the proposed robust method preserves an unbiased estimate and a narrower CI, which coincides with the conclusions drawn from the simulation studies. All the implemented methods show a statistically significant treatment effect under J2R, uncovering the superiority of triple therapies.

| Variable  | Method | Point est     | 95% CI       | CI length |
|-----------|--------|---------------|--------------|-----------|
| Mean arm 1 | MI     | -0.68         | (-0.84, -0.53) | 0.31      |
|           | LSE    | -0.54         | (-0.67, -0.42) | 0.25      |
|           | Robust | -0.53         | (-0.64, -0.41) | 0.23      |
| Mean arm 2 | MI     | -0.39         | (-0.55, -0.24) | 0.31      |
|           | LSE    | -0.23         | (-0.35, -0.11) | 0.24      |
|           | Robust | -0.27         | (-0.38, -0.16) | 0.22      |
| Difference| MI     | 0.29          | (0.07, 0.51)  | 0.44      |
|           | LSE    | 0.31          | (0.20, 0.41)  | 0.21      |
|           | Robust | 0.26          | (0.16, 0.35)  | 0.19      |
8 Conclusion

The non-normality issue frequently occurs in longitudinal clinical trials due to extreme outliers or heavy-tailed errors. With growing attention to evaluating the treatment effect with an MNAR missingness mechanism, we establish a robust method with the weighted robust regression and mean imputation under J2R for the longitudinal data, without the reliance on parametric models. The weighted robust regression provides double-layer protection against non-normality in both the covariates and the response variable, therefore ensuring a valid imputation model estimator. Mean imputation and the subsequent robust analysis model further guarantee a valid ATE estimator with good theoretical properties. The proposed method also enjoys the analysis model robustness property, in the sense that the consistency and asymptotic normality of the ATE estimator are satisfied even when the analysis model is incorrectly specified.

The symmetry error distribution, which is an essential assumption in the robust regression using the robust loss, must be satisfied in order to obtain a grounded inference for the ATE. It may not always be the case in practice. When encountering skewed distributions with asymmetric noises, biases and imprecisions may be detected in our proposed robust method. Takeuchi et al. (2002) provide a novel robust regression method motivated by data mining to handle asymmetric tails and obtain reasonable mean-type estimators. The extension of the proposed robust method may be plausible by replacing the robust regression with their proposed regression model.

While we focus solely on a monotone missingness pattern throughout the development of the robust method, intermittent missingness is also ubiquitous in longitudinal clinical trials. To handle intermittent missing data with a non-ignorable missingness mechanism when the outcomes are non-normal, Elashoff et al. (2012) suggest incorporating the Huber loss function in the pseudo-log-likelihood expression to obtain robust inferences. It is possible to extend our proposed robust method using their idea. We leave it as a future working direction.

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Supplementary material

The supplementary material contains the proofs and more technical details.
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Supplementary material for "Robust analyses for longitudinal clinical trials with missing and non-normal continuous outcomes" by Liu et al.

The supplementary material contains technical details, additional simulations, and real-data application results. Section S1 gives the regularity conditions and the proof of the model-robust ATE estimator obtained from the proposed robust method in terms of consistency and asymptotic normality, and provides an example of the working model for illustration and extensions to other robust loss functions. Section S2 provides the sequential regression procedure. Section S3 shows additional simulation results when the data is incorporated from outliers or different data-generating distributions. Section S4 adds additional notes on the real data.

S1 Asymptotic results for the ATE estimator

In this section, we present the asymptotic properties of the ATE estimator \( \hat{\tau} \) obtained from the proposed robust method in terms of consistency and asymptotic normality. To begin with, we explore the asymptotic properties of \( \hat{\alpha}_s \) based on the observed data at visit \( s \) in the control group that minimizes the weighted loss function (1) in the main text. Since the Huber loss is strongly convex, minimizing the loss function is equivalent to find the root of the first derivative

\[
\sum_{i=1}^{n} (1 - A_i) R_{is} w(H_{is}^{-1}; \nu_{s-1}) \psi(Y_{is} - H_{is}^{T} \alpha_{s-1}) H_{is-1} = 0.
\]

We give the consistency result for the robust estimator \( \hat{\alpha}_s \) in the following lemma.

Lemma S1 Assume the following regularity conditions:

C1. There exists a unique \( \alpha_{s-1,0} \) lying in the interior of the Euclidean parameter space \( \Theta \), such that the distribution of the observed regression errors \( (Y_s - H_{s-1}^{T} \alpha_{s-1,0}) \) is symmetric around 0.

C2. \( \mathbb{E} \{ \psi(Y_s - H_{s-1}^{T} \alpha_{s-1}) \mid H_{s-1} \} \) is dominated by an integrable function \( g(H_{s-1}) \) for all \( H_{s-1} \subset \mathbb{R}^{p+s-1} \) and \( \alpha_{s-1} \) with respect to the conditional distribution function \( f(Y_s \mid H_{s-1}, \alpha_{s-1}) \).

Then, the estimator \( \hat{\alpha}_s \) \( \xrightarrow{p} \alpha_{s-1,0} \) as the sample size \( n \to \infty \), for \( s = 1, \ldots, t \).

Proof: Note that by the definition of Huber function, \( \psi(Y_s - H_{s-1}^{T} \alpha_{s-1}) \) is a continuous function for \( \alpha_{s-1} \) and a measurable function for \( H_s \). By the regularity condition C2, it satisfies the conditions for
Theorem 2 in Jennrich (1969). Thus

\[ \psi(Y_s - H_{s-1}^T \alpha_{s-1}) \xrightarrow{a.s.} E\{\psi(Y_s - H_{s-1}^T \alpha_{s-1}) \mid H_{s-1}\} \] uniformly for all \( \alpha_{s-1} \in \Theta \).

In the weighted sequential robust regression, at sth visit point, the true value \( \beta_{s-1,0} \) is the unique solution such that \( E\{(1 - A)R_s w(H_{s-1}; \nu_{s-1})\psi(Y_s - H_{s-1}^T \alpha_{s-1})H_{s-1} \mid H_{s-1}\} = 0 \) since it is a randomized trial and by Assumption 1,

\[
E\{(1 - A)R_s w(H_{s-1}; \nu_{s-1})\psi(Y_s - H_{s-1}^T \alpha_{s-1})H_{s-1} \mid H_{s-1}\}
= E(1 - A)E(R_s \mid H_{s-1})E\{w(H_{s-1}; \nu_{s-1})\psi(Y_s - H_{s-1}^T \alpha_{s-1})H_{s-1} \mid H_{s-1}\}
= E(1 - A)E(R_s \mid H_{s-1})E\{\psi(Y_s - H_{s-1}^T \alpha_{s-1}) \mid H_{s-1}\}w(H_{s-1}; \nu_{s-1})H_{s-1}.
\]

By the regularity condition C1, \((Y_s - H_{s-1}^T \alpha_{s-1,0})\) is symmetric around 0 indicates that \( E\{\psi(Y_s - H_{s-1}^T \alpha_{s-1}) \mid H_{s-1}\} = 0 \). Based on the regularity conditions C1 and C2, we apply Theorem 7.1 in Boos and Stefanski (2013) and get \( \hat{\alpha}_{s-1}^w \xrightarrow{P} \alpha_{s-1,0} \), for \( s = 1, \cdots, t \).

After obtaining the imputation model estimate \( \hat{\alpha}_{s-1}^w \) for each visit point, we conduct sequential mean imputation to the missing components and get \( Y_s^* = R_s Y_s + (1 - R_s)H_{s-1}^* \hat{\alpha}_{s-1}^w \), where \( H_{s-1}^* = (X_s^T, Y_1^*, \cdots, Y_{s-1}^*)^T \) for \( s = 1, \cdots, t \). Denote the true imputation model parameter needed for imputing the outcome at visit \( t \) when the individual drops out at visit \( s \) as \( \beta_{t,s-1} \), such that \( E(Y_t \mid H_{s-1}, R_s = 1, R_0 = 0, A = a) = H_{s-1}^T \beta_{t,s-1} \) for \( t \geq s \). The following lemma characterizes the relationship between \( \beta_{t,s-1} \) and the sequential imputation model parameters \( \alpha_{s-1,0}, \cdots, \alpha_{t-1} \).

**Lemma S2** Under the regularity conditions C1 and C2, the parameter \( \beta_{t,s-1} \) in formula (S2) relates to the sequential imputation model parameters \( \alpha_{s-1,0}, \cdots, \alpha_{t-1,0} \) in the following way:

\[
\beta_{t,t-1} = \alpha_{t-1,0} \quad \text{if} \ s = t, \tag{S1}
\]

\[
\beta_{t,s-1} = (I_{p+s-2}, \alpha_{s-1,0}) (I_{p+s-1}, \alpha_{s,0}) \cdots (I_{p+t-3}, \alpha_{t-2,0}) \alpha_{t-1,0} \quad \text{if} \ s < t.
\]

**Proof**: The regularity condition C1 implies that the distribution of the errors \((Y_s - H_{s-1}^T \alpha_{s-1,0})\) is symmetric, we have \( E(Y_s \mid H_{s-1}) = H_{s-1}^T \alpha_{s-1,0} \) for \( s = 1, \cdots, t \). If the individual in group \( a \) drops out at visit \( t \), the missing value at visit \( t \) is imputed by

\[
H_{t-1}^T \beta_{t,t-1} = E(Y_t \mid H_{t-1}, R_{t-1} = 1, R_t = 0, A = a)
= E(Y_t \mid H_{t-1}, A = 0; \alpha_{t-1,0}) \quad \text{(By Assumption 2)}
\]

S2
\[ = H_{t-1}^T \alpha_{t-1,0} \text{ (By C1).} \]

if using the true imputation model parameter.

We then prove formula [S1] by induction. Suppose the result holds for the individual who drops out at visit \( s \), i.e., we impute the value at the last visit point by \( \mathbb{E}(Y_t \mid H_{s-1}, A = 0) = H_{s-1}^T \beta_{t,s-1} \).

Then for the one in group \( a \) who drops out at visit \( s-1 \), the missing outcome at visit \( s \) is imputed by

\[
H_{s-2}^T \beta_{t,s-2} = \mathbb{E}(Y_t \mid H_{s-2}, R_{s-2} = 1, R_{s-1} = 0, A = a)
\]

\[ = \mathbb{E}(Y_t \mid H_{s-2}, A = 0) \text{ (By Assumption 2)} \]

\[ = \mathbb{E}\{\mathbb{E}(Y_t \mid H_{s-1}, A = 0) \mid H_{s-2}, A = 0\} \]

\[ = \mathbb{E}(H_{s-1}^T \beta_{t,s-1} \mid H_{s-2}, A = 0) \]

\[ = (H_{s-2}^T, \mathbb{E}(Y_{s-1} \mid H_{s-2}, A = 0))^T \beta_{t,s-1} \]

\[ = H_{s-2}^T (\mathbf{I}_{p+s-2}, \alpha_{s-2,0}) \beta_{t,s-1}. \]

Then we have

\[ \beta_{t,s-2} = (\mathbf{I}_{p+s-2}, \alpha_{s-2,0}) \beta_{t,s-1} \]

\[ = (\mathbf{I}_{p+s-2}, \alpha_{s-2,0}) (\mathbf{I}_{p+s-2}, \alpha_{s-1,0})(\mathbf{I}_{p+s-1}, \alpha_{s,0}) \cdots (\mathbf{I}_{p+t-3}, \alpha_{t-2,0})\alpha_{t-1,0}, \]

which completes the proof. \( \square \)

Lemma [S2] suggests an estimator of \( \beta_{t,s-1} \) by plugging in the sequential imputation model parameter estimates \( \hat{\alpha}_{s-1}^w, \ldots, \hat{\alpha}_{t-1}^w \) in formula [S1]. Set \( R_0 = 1 \), we can rewrite the imputed value \( Y_t^* \) at the last visit point based on the observed history, the dropout pattern, and the estimated imputation model parameters as

\[ Y_t^* = R_t Y_t + \sum_{s=1}^{t} R_{s-1} (1 - R_s) H_{s-1}^T \hat{\beta}_{t,s-1}, \quad \text{(S2)} \]

where \( \hat{\beta}_{t,s-1} \) is the estimate of \( \beta_{t,s-1} \). We proceed to prove the consistency of the ATE estimator \( \hat{\tau} \).

### S1.1 Proof of Theorem 1

To illustrate the dependence of the imputed value \( Y_t^* \) with the imputed parameter estimates \( \hat{\beta}_t := (\hat{\beta}_{t,0}, \ldots, \hat{\beta}_{t,t-1})^T \), we rewrite \( Y_t^* \) as \( Y_t^*(\hat{\beta}_t) \) and \( Z^* \) as \( Z^*(\hat{\beta}_t) \). Denote \( \beta_t := (\beta_{t,0}, \ldots, \beta_{t,t-1})^T \) as the true value.
We do not assume the correct model form for the analysis model, instead, we give a wide range of models of the form (2) in the main text. When a symmetric error distribution is imposed, we write the model as

\[ Y^*_t(\hat{\beta}_t) = \mu(A, X \mid \gamma_0) + \varepsilon, \]

\[ = (A - \pi)g(X; \gamma_0^0) + \tilde{h}(X) + \varepsilon \]  

(S3)

where \( \varepsilon \) is the error term and is symmetric around 0, and \( \tilde{h}(X) = \pi g(X; \gamma_0^0) + h(X; \gamma_0^1) \). Under the symmetric error assumption, \( \gamma_0^0 \) satisfies that \( \mathbb{E} \{ g(X; \gamma_0^0) \} = \mathbb{E}(Y_t \mid A = 1) - \mathbb{E}(Y_t \mid A = 0) = \tau_0 \).

The robust estimator \( \hat{\gamma} = (\hat{\gamma}^0, \hat{\gamma}^1)^T \) is obtained from

\[ (\hat{\gamma}^0, \hat{\gamma}^1) = \arg \min \frac{1}{n} \sum_{i=1}^{n} \rho \left\{ Y^*_i(\hat{\beta}_t) - \mu(A, X \mid \gamma) \right\}. \]

We now want to show that \( \hat{\gamma}^0 \) obtained from the robust loss function satisfies that \( \hat{\tau} = \sum_{i=1}^{n} g(X_i; \hat{\gamma}^0) \overset{p}{\to} \tau_0 \). Before restating Theorem 1 in the main text with technical details, we first give the definitions of the two robust loss functions as the absolute loss and the \( \varepsilon \)-insensitive loss. The absolute loss function is defined as \( \rho_a(x) = |x| \). The \( \varepsilon \)-insensitive loss is defined as \( L_{\varepsilon}(x) = \max\{ |x| - \varepsilon, 0 \} \), where the constant \( \varepsilon > 0 \) provides a tolerance margin where no penalties are given (Smola and Schölkopf, 2004).

**Theorem S1**  Under the regularity conditions C1 and C2, and assume the following regularity conditions hold for \( a = 0, 1 \):

C3. Given the baseline covariates, the error term is conditionally independent with the treatment variable, i.e., \( \varepsilon \perp A \mid X \).

C4. For any \( \zeta \), the term \( K_1 := \tilde{h}(X) + \varepsilon_i - \tilde{h}(X; \zeta) \) has an expectation and a finite second moment, i.e., \( \mathbb{E}[K_1] < \infty \) and \( \mathbb{E}(K_1^2) < \infty \), where \( \tilde{h}(X) = \pi g(X; \gamma_0^0) + h(X) \), \( \tilde{h}(X; \zeta) \) is a parametric model of \( \tilde{h}(X) \), and \( \gamma_0^0 \) is the unique solution such that \( \mathbb{E} \{ g(X; \gamma_0^0) \} = \tau_0 \).

C5. For any \( \gamma^0 \), the term \( K_2 := (A - \pi) \{ g(X; \gamma^0) - g(X; \gamma_0^0) \} \) has an expectation and a finite second moment, i.e., \( \mathbb{E}[K_2] < \infty \) and \( \mathbb{E}(K_2^2) < \infty \).

C6. For any \( f_j(X) \), \( \mathbb{P} \{ X : g(X; \gamma^0) - g(X; \gamma_0^0) \neq 0 \} > 0 \), for \( \forall \gamma^0 \neq 0 \).

C7. The error term \( \varepsilon \mid X = x \) has a non-zero density function.
C8. The function $G_2(\zeta) := \mathbb{E}[\rho(K_1)]$ has a unique global minimizer $\zeta^*$. 

Then, the ATE estimator $\hat{\tau} \xrightarrow{P} \tau_0$ as the sample size $n \to \infty$, for $s = 1, \cdots, t$.

Proof: We begin the proof by rewriting the working model (2). Note that

$$
\mu(A, X \mid \gamma) = Ag(X; \gamma^{(0)}) + h(X; \gamma^{(1)})
$$

$$
= (A - \pi) g(X; \gamma^{(0)}) + \pi g(X; \gamma^{(0)}) + h(X; \gamma^{(1)})
$$

$$
= (A - \pi) g(X; \gamma^{(0)}) + \tilde{h}(X; \zeta),
$$

(S4)

where $\tilde{h}(X; \zeta) = \pi g(X; \gamma^{(0)}) + h(X; \gamma^{(1)})$ and $\zeta$ combines the parameters $\gamma^{(0)}$ and $\gamma^{(1)}$. We are interested in estimating $g(X; \gamma^{(0)})$, as it is the only part that connects with the ATE estimation. We want to prove that $\hat{\gamma}^{(0)}$ obtained from minimizing the Huber loss function satisfies that $\hat{\gamma}^{(0)} \xrightarrow{P} \gamma_0^{(0)}$, regardless of the model specification.

By Lemmas [S1] and [S2] we have $\hat{\beta}_t \xrightarrow{P} \beta_t$. Follow the similar proof in Lemma [S1] by continuous mapping theorem, we have $Y_t^*(\hat{\beta}_t) = Y_t^*(\beta_t) + o_P(1) = (A - \pi) g(X; \gamma_0^{(0)}) + \tilde{h}(X) + \varepsilon + o_P(1)$. Therefore, minimizing the loss function $n^{-1} \sum_{i=1}^n \rho \{ Y_i(\hat{\beta}_t) - \mu(A_i, X_i \mid \gamma) \}$ is asymptotically equivalent to minimizing $n^{-1} \sum_{i=1}^n \rho \{ Y_i(\beta_t) - \mu(A_i, X_i \mid \gamma) \}$.

We then follow the proof in Xiao et al. (2019) to verify the consistency of the estimator under $H_0$ using the Huber loss function, the absolute loss function, or the $\varepsilon$-insensitive loss.

(i) For the Huber loss, denote $L_n(\gamma^{(0)}, \zeta) = \sum_{i=1}^n \rho \{ Y_i(\hat{\beta}_t) - \mu(A_i, X_i \mid \gamma) \}$, where $\rho(x) = 0.5x^2 I(|x| < l) + \{l|x| - 0.5l^2\} I(|x| \geq l)$. Then the estimator based on the Huber loss is

$$
(\hat{\gamma}^{(0)}, \hat{\zeta}) = \text{argmin} L_n(\gamma^{(0)}, \zeta)
$$

$$
= \text{argmin} \left\{ L_n(\gamma^{(0)}, \zeta) - L_n(\gamma_0^{(0)}, \zeta) \right\} + \left\{ L_n(\gamma_0^{(0)}, \zeta) - L_n(\gamma_0^{(0)}, \zeta') \right\},
$$

(S5)

where $\zeta'$ is a fixed value. We examine the two terms in the objective function (S5) separately.

For the first term in the function (S5), $L_n(\gamma^{(0)}, \zeta) - L_n(\gamma_0^{(0)}, \zeta)$

$$
= \frac{1}{n} \sum_{i=1}^n \rho \left[ \tilde{h}(X) + \varepsilon_i - \tilde{h}(X; \zeta) - (A - \pi) \left\{ g(X; \gamma^{(0)}) - g(X; \gamma_0^{(0)}) \right\} \right]
$$

$$
- \rho \left[ \tilde{h}(X) + \varepsilon_i - \tilde{h}(X; \zeta) - (A - \pi) \left\{ g(X; \gamma^{(0)}) - g(X; \gamma_0^{(0)}) \right\} \right]
$$

$$
: = \frac{1}{n} \sum_{i=1}^n d_{i1}.
$$
The regularity conditions C4 and C5 allow us to apply the weak law of large number (WLLN) to $L_n(\gamma(0), \zeta) - L_n(\gamma_0(0), \zeta)$, since

$$|d_{i1}| \leq \frac{1}{2} (K_1 - K_2)^2 - l|K_1| + \frac{1}{2}l^2$$

$$= \frac{1}{2} (K_1 - l)^2 + |K_2||K_2 - 2K_1|$$

has a finite expectation. Thus, by WLLN, $L_n(\gamma(0), \zeta) - L_n(\gamma_0(0), \zeta) \xrightarrow{p} \mathbb{E}(D_1) = G_1(\gamma(0), \zeta)$, where $D_1 = \rho(K_1 - K_2) - \rho(K_1)$. We claim that $G_1(\gamma(0), \zeta) \geq 0$ and reaches 0 if and only if $\gamma(0) = \gamma_0(0)$.

First, note that $G_1(\gamma_0(0), \zeta) = \rho(K_1) - \rho(K_1) = 0$. We proceed to prove that $G_1(\gamma(0), \zeta) > 0$ for $\forall \gamma(0) \neq \gamma_0(0)$ and consider the following four cases:

(a) If $K_1 > l$, we have

$$D_1 = \rho(K_1 - K_2) - \rho(K_1) \geq l(K_1 - K_2) - \frac{1}{2}l^2 - \left(lK_1 - \frac{1}{2}l^2\right) = -lK_2.$$

(b) If $K_1 < -l$, repeat the step in 1 and we can get $D_1 \geq lK_2$.

(c) If $K_1 \in [-l, l]$ and $K_1 - K_2 \in [-l, l]$, then

$$D_1 = \frac{1}{2}(K_1 - K_2)^2 - \frac{1}{2}K_1^2 = -K_1K_2 + \frac{1}{2}K_1^2.$$

(d) If $K_1 \in [-l, l]$ and $K_1 - K_2 \notin [-l, l]$, then

$$D_1 = l|K_1 - K_2| - \frac{1}{2}l^2 - \frac{1}{2}K_1^2$$

$$= \frac{1}{2}(K_1 - K_2)^2 - \frac{1}{2}|K_1 - K_2|^2 - \frac{1}{2}K_1^2$$

$$\geq \frac{1}{2}(K_1 - K_2)^2 - \frac{1}{2}K_2^2 - \frac{1}{2}K_1^2 = -K_1K_2.$$

The inequality holds since by triangle inequality, $0 < |K_1 - K_2| - l \leq K_1 + |K_2| - l \leq |K_2|$.

Incorporating the four cases together and taking expectations, we have

$$G_1(\gamma(0), \zeta) \geq \mathbb{E}\{ -lK_2 \mathbb{I}(K_1 > l) \} + \mathbb{E}\{ lK_2 \mathbb{I}(K_1 < -l) \}$$

$$+ \mathbb{E}\left\{ \left( -K_1K_2 + \frac{1}{2}K_1^2 \right) \mathbb{I}(K_1 \in [-l, l]) \mathbb{I}(K_1 - K_2 \in [-l, l]) \right\}$$

$$+ \mathbb{E}\{ -K_1K_2 \mathbb{I}(K_1 \in [-l, l]) \mathbb{I}(K_1 - K_2 \notin [-l, l]) \}$$
Note that by the regularity condition C3, \( \mathbb{P}(A) = \pi \), and \( A \parallel X \) (randomized trial), we have

\[
\mathbb{E} \{ -lK_2 \mathbb{I}(K_1 > l) \} = -l \mathbb{E} \left[ \mathbb{E}(K_2 \mid X) \mathbb{E} \{ \mathbb{I}(K_1 > l) \mid X \} \right] = -l \mathbb{E} \left[ \mathbb{E}(A - \pi) \left\{ g(X; \gamma^*(0)) - g(X; \gamma_0^*(0)) \right\} \mid X \right] \mathbb{E} \{ \mathbb{I}(K_1 > l) \mid X \} = 0.
\]

Similarly, we have \( \mathbb{E} \{ lK_2 \mathbb{I}(K_1 < l) \} = \mathbb{E} \{ -K_1K_2 \mathbb{I}(K_1 \in [-l, l]) \} = 0 \). Therefore,

\[
G_1(\gamma^*(0), \zeta) \geq \mathbb{E} \left\{ \frac{1}{2} K_2^2 \mathbb{I}(K_1 \in [-l, l]) \mathbb{I}(K_1 - K_2 \in [-l, l]) \right\}.
\]

By the regularity conditions C6 and C7, we know that \( G_1(\gamma^*(0), \zeta) > 0 \) for \( \forall \gamma \neq \gamma_0^*(0) \).

For the second term in the function (S5), denote \( L_n(\gamma_0^*(0), \zeta) - L_n(\gamma_0^*(0), \zeta') = n^{-1} \sum_{i=1}^n d_2 \). By the regularity condition C4, WLLN is applied, and we have \( L_n(\gamma_0^*(0), \zeta) - L_n(\gamma_0^*(0), \zeta') \xrightarrow{p} \mathbb{E}(D_2) = G_2(\zeta) \).

The results for the first term combined with the regularity condition C8 implies that \( (\gamma_0^*(0), \zeta^*) \) is the unique minimizer of \( G_1(\gamma^*(0), \zeta) + G_2(\zeta) \). Since the Huber loss function is strongly convex, by the argmax continuous mapping theorem, we have \( \hat{\gamma}^*(0) \xrightarrow{p} \gamma_0^*(0) \). By continuous mapping theorem, \( \hat{\gamma} = n^{-1} \sum_{i=1}^n g(X_i; \gamma^*(0)) \xrightarrow{p} \mathbb{E} \{ g(X_i; \gamma^*(0)) \} = \gamma_0^* \).

(ii) For the absolute loss, denote \( L_{a,n}(\gamma^*(0), \zeta) = n^{-1} \sum_{i=1}^n \rho_a \{ Y_i - \mu(A, X \mid \gamma) \} \), where \( \rho_a(x) = |x| \) is the absolute loss. Then the estimator based on \( \rho_a(x) \) is

\[
(\hat{\gamma}^*(0), \hat{\zeta}) = \arg\min L_{a,n}(\gamma^*(0), \zeta)
\]

\[
= \arg\min \left\{ L_{a,n}(\gamma^*(0), \zeta) - L_{a,n}(\gamma_0^*(0), \zeta) \right\} + \left\{ L_{a,n}(\gamma_0^*(0), \zeta) - L_{a,n}(\gamma_0^*(0), \zeta') \right\}, \quad (S6)
\]

where \( \zeta' \) is a fixed value. We again examine the two terms in the objective function (S6) separately.

For the first term in the function (S6), \( L_{a,n}(\gamma^*(0), \zeta) - L_{a,n}(\gamma_0^*(0), \zeta) \)

\[
= \frac{1}{n} \sum_{i=1}^n \left( \rho_a \left[ \tilde{h}(X) + \varepsilon_i - \tilde{h}(X; \zeta) - (A - \pi) \left\{ g(X; \gamma^*(0)) - g(X; \gamma_0^*(0)) \right\} \right] 
- \rho_a \left[ \tilde{h}(X) + \varepsilon_i - \tilde{h}(X; \zeta) - (A - \pi) \left\{ g(X; \gamma^*(0)) - g(X; \gamma_0^*(0)) \right\} \right] \right)
\]
The regularity conditions C4 and C5 allow us to apply WLLN to \( L_{a,n}(\gamma(0),\zeta) - L_{a,n}(\gamma_0(0),\zeta) \), since
\[
|d_{i1}| \leq |K_1 - K_2| + |K_1| \leq 2|K_1| + |K_2| 
\]
has a finite expectation. Thus, by WLLN, \( L_{a,n}(\gamma(0),\zeta) - L_{a,n}(\gamma_0(0),\zeta) \xrightarrow{p} E(D_1) = G_1(\gamma(0),\zeta) \), where \( D_1 = \rho_a(K_1 - K_2) - \rho_a(K_1) \).

First, note that \( G_1(\gamma_0(0),\zeta) = \rho_a(K_1) - \rho_a(K_1) = 0 \). We proceed to prove that \( G_1(\gamma(0),\zeta) > 0 \) for \( \forall \gamma(0) \neq \gamma_0(0) \) and consider the following two cases:

(a) If \( K_1 \geq 0 \), we have \( D_1 = |K_1 - K_2| - |K_1| \geq K_1 - K_2 - K_1 = -K_2 \).

(b) If \( K_1 < 0 \), we have \( D_1 = |K_1 - K_2| - |K_1| \geq K_2 - K_1 + K_1 = K_2 \).

Incorporating the four cases together and taking expectations, we have \( G_1(\gamma(0),\zeta) \geq E\{ -K_2 I(K_1 \geq 0) \} + E\{ K_2 I(K_1 < 0) \} \). Follow the same proof, we have \( E\{ -K_2 I(K_1 \geq 0) \} = E\{ K_2 I(K_1 < 0) \} = 0 \).

By the regularity conditions C6 and C7, we know that \( G_1(\gamma(0),\eta) > 0 \) for \( \forall \gamma(0) \neq \gamma_0(0) \). The remaining proof follows similar steps the proof for the Huber loss.

(iii) For the \( \varepsilon \)-insensitive loss, denote \( L_{\varepsilon,n}(\gamma(0),\zeta) = n^{-1} \sum_{i=1}^{n} L_{\varepsilon} \{ Y_i - \mu(A, X | \gamma) \} \), where \( L_{\varepsilon}(x) = \max \{|x| - \varepsilon, 0\} \) is the \( \varepsilon \)-insensitive loss. Then the estimator based on \( L_{\varepsilon}(x) \) is

\[
(\hat{\gamma}(0), \hat{\zeta}) = \arg\min_{\gamma(0), \zeta} L_{\varepsilon,n}(\gamma(0), \zeta)
\]

\[
= \arg\min \left\{ L_{\varepsilon,n}(\gamma(0), \zeta) - L_{\varepsilon,n}(\gamma_0(0), \zeta) \right\} + \left\{ L_{\varepsilon,n}(\gamma_0(0), \zeta) - L_{\varepsilon,n}(\gamma_0(0), \zeta') \right\}, \tag{S7}
\]

where \( \zeta' \) is a fixed value. We again examine the two terms in the objective function \( (S7) \) separately.

For the first term in the function \( (S7) \), \( L_{\varepsilon,n}(\gamma(0), \zeta) - L_{\varepsilon,n}(\gamma_0(0), \zeta) \)

\[
= \frac{1}{n} \sum_{i=1}^{n} \left( L_{\varepsilon} \left[ \tilde{h}(X) + \varepsilon_i - \tilde{h}(X; \zeta) - (A - \pi) \left\{ g(X; \gamma(0)) - g(X; \gamma_0(0)) \right\} \right] - L_{\varepsilon} \left[ \tilde{h}(X) + \varepsilon_i - \tilde{h}(X; \zeta) - (A - \pi) \left\{ g(X; \gamma(0)) - g(X; \gamma_0(0)) \right\} \right] \right)
\]

\[
:= \frac{1}{n} \sum_{i=1}^{n} d_{i1}
\]

The regularity conditions C4 and C5 allow us to apply WLLN to \( L_{\varepsilon,n}(\gamma(0), \zeta) - L_{\varepsilon,n}(\gamma_0(0), \zeta) \), since
\[
|d_{i1}| \leq |K_1 - K_2| + \varepsilon + |K_1| + \varepsilon \leq 2|K_1| + |K_2| + 2\varepsilon 
\]
has a finite expectation. Thus, by WLLN, \( L_{\varepsilon,n}(\gamma(0), \zeta) - L_{\varepsilon,n}(\gamma_0(0), \zeta) \xrightarrow{p} E(D_1) = G_1(\gamma(0), \zeta) \), where \( D_1 = L_{\varepsilon}(K_1 - K_2) - L_{\varepsilon}(K_1) \).
First, note that \( G_1(\gamma_0, \zeta) = \mathcal{L}_\varepsilon(K_1) - \mathcal{L}_\varepsilon(K_1) = 0 \). We proceed to prove that \( G_1(\gamma_0, \zeta) > 0 \) for \( \forall \gamma_0 \neq \gamma_0^0 \) and consider the following two cases:

(a) If \( K_1 \geq \varepsilon \), we have \( D_1 = \max (|K_1 - K_2| - \varepsilon, 0) - K_1 + \varepsilon \geq |K_1 - K_2| - |K_1| \geq K_1 - K_2 - K_1 = -K_2 \).

(b) If \( K_1 \leq -\varepsilon \), we have \( D_1 = \max (|K_1 - K_2| - \varepsilon, 0) + K_1 + \varepsilon \geq |K_1 - K_2| - |K_1| \geq K_2 - K_1 + K_1 = K_2 \).

(c) If \( |K_1| < \varepsilon \), we have \( D_1 = \max (|K_1 - K_2| - \varepsilon, 0) - 0 \geq 0 \).

Incorporating the four cases together and taking expectations, we have \( G_1(\gamma_0, \zeta) \geq \mathbb{E} \{ -K_2 \mathbb{I}(K_1 \geq \varepsilon) \} + \mathbb{E} \{ K_2 \mathbb{I}(K_1 \leq -\varepsilon) \} \). Follow the same proof, we have \( \mathbb{E} \{ -K_2 \mathbb{I}(K_1 \geq \varepsilon) \} = \mathbb{E} \{ K_2 \mathbb{I}(K_1 \leq \varepsilon) \} = 0 \).

By the regularity conditions C6 and C7, we know that \( G_1(\gamma_0, \zeta) > 0 \) for \( \forall \gamma_0 \neq \gamma_0^0 \). The remaining proof follows similar steps the proof for the Huber loss. \( \square \)

### S1.2 Proof of Theorem 2

To explore the asymptotic normality of the estimator \( \hat{\tau} \), we first focus on the asymptotic normality of \( \hat{\alpha}_{s-1}^w \) for \( s = 1, \ldots, t \). Denote \( \varphi(H_s, \alpha_{s-1}) := (1 - A)R_s w(H_{s-1}; \rho_{s-1}) \psi(Y_s - H_{s-1}^T \alpha_{s-1})H_{s-1} \), where \( \psi(x) = \frac{\partial \rho(x)}{\partial x} \) is the derivative of the robust loss function. Therefore, \( \hat{\alpha}_{s-1}^w \) is the solution to the estimating equations \( \sum_{s=1}^n \varphi(H_{is}, \alpha_{s-1}) = 0 \).

**Lemma S3** Assume the regularity conditions C1 and C2 and the following conditions:

C9. The partial derivative \( \mathbb{E} \{ \varphi(Y_s - H_{s-1}^T \alpha_{s-1}) \mid H_{s-1} \} \) with respect to \( \alpha_{s-1} \) exists and is continuous around \( \alpha_{s-1,0} \) almost everywhere. The second derivative of \( \mathbb{E} \{ \varphi(Y_s - H_{s-1}^T \alpha_{s-1}) \mid H_{s-1} \} \) with respect to \( \alpha_{s-1} \) is continuous and dominated by some integrable functions;

C10. The partial derivative of \( \mathbb{E} \{ \varphi(H_s, \alpha_{s-1}) \mid H_{s-1} \} \) with respect to \( \alpha_{s-1} \) is nonsingular.

C11. The variance \( \forall \{ q(H_s, \alpha_{s-1,0}) \} \) is finite, where

\[
q(H_s, \alpha_{s-1,0}) = \left[ -\frac{\partial \mathbb{E} \{ \varphi(H_{is}, \alpha_{s-1,0})H_{is-1}^T \mid H_{is-1} \} }{\partial \alpha_{s-1}^T} \right]^{-1} \varphi(H_s, \alpha_{s-1,0}).
\]

Then, for \( s = 1, \ldots, t \), as the sample size \( n \to \infty \),

\[
\sqrt{n}(\hat{\alpha}_{s-1}^w - \alpha_{s-1,0}) \xrightarrow{d} \mathcal{N}(0, \mathbb{V} \{ q(H_s, \alpha_{s-1,0}) \} ).
\]
Lemma S4 Assume the regularity conditions C1–C11 and the following conditions:

C12. The variance \( \mathbb{V}\{U_{t,s-1,i}(\alpha_0)\} \) is finite, where \( U_{t,s-1,i}(\alpha) \) is the linearization form produced by \( \hat{\beta}_{t,s-1} \), i.e., \( \hat{\beta}_{t,s-1} - \beta_{t,s-1} = n^{-1} \sum_{i=1}^{n} U_{t,s-1,i}(\alpha_0) + o_P(n^{-1/2}) \). Specifically, \( U_{t,s,i}(\alpha_0) = (I_{p+s-2}, \alpha_{s-1,0}) U_{t,s+1,i}(\alpha_0) + (0^T_{p+s-2}, 1) \beta_{t,s} q(H_{is}, \alpha_{s-1,0}) \) and \( U_{t,t-1,i}(\alpha_0) = q(H_{it}, \alpha_{t-1,0}) \).

Then, as the sample size \( n \to \infty \), for \( s = 1, \ldots, t \),

\[
\sqrt{n}(\hat{\beta}_{t,s-1} - \beta_{t,s-1}) \overset{d}{\to} \mathcal{N}\left(0, \mathbb{V}\{U_{t,s-1,i}(\alpha_0)\}\right).
\]

Proof: Lemma S2 indicates that \( \hat{\beta}_{t,t-1} = \hat{\alpha}_{t-1}^w \), thus \( \hat{\beta}_{t,t-1} \) shares the same linearization form as \( \hat{\alpha}_{t-1}^w \), i.e.,

\[
\hat{\beta}_{t,t-1} - \beta_{t,t-1} = \frac{1}{n} \sum_{i=1}^{n} q(H_{it}, \alpha_{t-1,0}) + o_P(n^{-1/2})
= \frac{1}{n} \sum_{i=1}^{n} U_{t,t-1,i}(\alpha_0) + o_P(n^{-1/2}).
\]

For the individuals who drop out at visit \( t-1 \), the corresponding imputation parameter estimate \( \hat{\beta}_{t,t-2} \) can be expressed as

\[
\hat{\beta}_{t,t-2} = (I_{p+t-3}, \hat{\alpha}_{t-2,0}) \hat{\alpha}_{t-1}^w
\]
\begin{equation}
= (\mathbf{I}_{p+t-3}, \hat{\alpha}_{t-2,0}^w) \hat{\beta}_{t,t-1}
= (\mathbf{I}_{p+t-3}, \mathbf{0}^T_{p+t-3}) \hat{\beta}_{t,t-1} + \hat{\alpha}_{t-2}^w (\mathbf{0}^T_{p+t-3}, 1) \hat{\beta}_{t,t-1}. \tag{S8}
\end{equation}

The linearization form of the first term in formula (S8) can be obtained directly via delta-method as

\[(\mathbf{I}_{p+t-3}, \mathbf{0}^T_{p+t-3}) \hat{\beta}_{t,t-1} - (\mathbf{I}_{p+t-3}, \mathbf{0}^T_{p+t-3}) \beta_{t,t-1} = \frac{1}{n} \sum_{i=1}^{n} (\mathbf{I}_{p+t-3}, \mathbf{0}^T_{p+t-3}) q(H_{it}, \alpha_{t-1,0}) + o_p(n^{-1/2}).\]

For the second term, let \(g_{t-2}(\alpha_{t-2}, \beta_{t,t-1}) := \alpha_{t-2} (\mathbf{0}^T_{p+t-3}, 1) \beta_{t,t-1}.1\) we have \(\nabla g_{t-2}(\alpha_{t-2,0}, \beta_{t,t-1}) = \{(\mathbf{0}^T_{p+t-3}, 1) \beta_{t,t-1}, \alpha_{t-2,0} (\mathbf{0}^T_{p+t-3}, 1)\}^T\). Under the regularity condition C9 by Theorem 5.27 in Boos and Stefanski (2013), we have

\[g_{t-2}(\hat{\alpha}_{t-2}^w, \hat{\beta}_{t,t-1}) - g_{t-2}(\alpha_{t-2,0}, \beta_{t,t-1}) = \frac{1}{n} \sum_{i=1}^{n} \nabla g_{t-2}(\alpha_{t-2,0}, \beta_{t,t-1}) \left( \begin{array}{c} q(H_{it-1}, \alpha_{t-2,0}) \\ U_{t,t-1,i}(\alpha_0) \end{array} \right) + o_p(n^{-1/2})\]

\[= \frac{1}{n} \sum_{i=1}^{n} (\mathbf{0}^T_{p+t-3}, 1) \beta_{t,t-1} q(H_{it-1}, \alpha_{t-2,0}) + \alpha_{t-2,0} (\mathbf{0}^T_{p+t-3}, 1) U_{t,t-1,i}(\alpha_0) + o_p(n^{-1/2}).\]

Combine the two terms together, we have

\[\hat{\beta}_{t,t-2} - \beta_{t,t-2} = \frac{1}{n} \sum_{i=1}^{n} (\mathbf{0}^T_{p+t-3}, 1) \beta_{t,t-1} q(H_{it-1}, \alpha_{t-2,0}) + \{ (\mathbf{I}_{p+t-3}, \mathbf{0}^T_{p+t-3}) + \alpha_{t-2,0} (\mathbf{0}^T_{p+t-3}, 1)\} U_{t,t-1,i}(\alpha_0) + o_p(n^{-1/2})\]

\[= \frac{1}{n} \sum_{i=1}^{n} (\mathbf{I}_{p+t-3}, \alpha_{t-2,0}) U_{t,t-1,i}(\alpha_0) + (\mathbf{0}^T_{p+t-3}, 1) \beta_{t,t-1} q(H_{it-1}, \alpha_{t-2,0}) + o_p(n^{-1/2})\]

\[= \frac{1}{n} \sum_{i=1}^{n} \left( I_{p+t-3}, \alpha_{t-2,0} \right) U_{t,t-1,i}(\alpha_0) + o_p(n^{-1/2}),\]

which matches the result in the lemma when \(s = t - 2\).

We then prove the lemma by induction. Suppose the result holds for the individual who drops out at visit \(s + 1\), i.e.,

\[\hat{\beta}_{t,s} - \beta_{t,s} = \frac{1}{n} \sum_{i=1}^{n} U_{t,s,i}(\alpha_0) + o_p(n^{-1/2})\]

\[= \frac{1}{n} \sum_{i=1}^{n} (\mathbf{I}_{p+s-1}, \alpha_{s,0}) U_{t,s,i}(\alpha_0) + (\mathbf{0}^T_{p+s-1}, 1) \beta_{t,s+1} q(H_{is+1}, \alpha_{s,0}) + o_p(n^{-1/2}).\]
Then for individuals in group $a$ who drop out at visit $s$, the corresponding imputation parameter estimate $\hat{\beta}_{t,s-1}$ can be expressed as

$$\hat{\beta}_{t,s-1} = (I_{p+s-2}, \hat{\alpha}_{s-1,0}) \hat{\beta}_{t,s}$$

$$= (I_{p+s-2}, 0^T_{p+s-2}) \hat{\beta}_{t,s} + \hat{\alpha}_{s-1,0} (0^T_{p+s-2}, 1) \hat{\beta}_{t,s}. \quad (S9)$$

Similarly, the linearization form of the first term in formula (S9) can be obtained directly via delta-method as

$$(I_{p+s-2}, 0^T_{p+s-2}) \hat{\beta}_{t,s} - (I_{p+s-2}, 0^T_{p+s-2}) \beta_{t,s} = \frac{1}{n} \sum_{i=1}^{n} (I_{p+s-2}, 0^T_{p+s-2}) U_{t,s,i}(\alpha_0) + o_p(n^{-1/2}).$$

For the second term, let $g_{s-1}(\alpha_{s-1}, \beta_{t,s}) := \alpha_{s-1} (0^T_{p+s-2}, 1) \beta_{t,s}$. Then we have $\nabla g_{s-1}|_{(\alpha_{s-1,0}, \beta_{t,s})} = \{(0^T_{p+s-2}, 1) \beta_{t,s}, \alpha_{s-1,0} (0^T_{p+s-2}, 1)\}^T$. Under the regularity condition C9, we have

$$g_{s-1}(\hat{\alpha}_{s-1}, \hat{\beta}_{t,s}) - g_{t-2}(\alpha_{s-1,0}, \beta_{t,s}) = \frac{1}{n} \sum_{i=1}^{n} \nabla g_{s-1}|_{(\alpha_{s-1,0}, \beta_{t,s})} \left( q(H_{is}, \alpha_{s-1,0}) \right) + o_p(n^{-1/2})$$

$$= \frac{1}{n} \sum_{i=1}^{n} (0^T_{p+s-2}, 1) \beta_{t,s} q(H_{is}, \alpha_{s-1,0})$$

$$+ \alpha_{s-1,0} (0^T_{p+s-2}, 1) U_{t,s,i}(\alpha_0) + o_p(n^{-1/2}).$$

Combine the two terms, the linearization form of $\hat{\beta}_{t,s-1}$ is

$$\hat{\beta}_{t,s-1} - \beta_{t,s-1} = \frac{1}{n} \sum_{i=1}^{n} (0^T_{p+s-2}, 1) \beta_{t,s} q(H_{is}, \alpha_{s-1,0})$$

$$+ \{(I_{p+s-2}, 0^T_{p+s-2}) + \alpha_{s-1,0} (0^T_{p+s-2}, 1)\} U_{t,s,i}(\alpha_0) + o_p(n^{-1/2})$$

$$= \frac{1}{n} \sum_{i=1}^{n} (I_{p+s-2}, \alpha_{s-1,0}) U_{t,s,i}(\alpha_0) + (0^T_{p+s-2}, 1) \beta_{t,s} q(H_{is}, \alpha_{s-1,0}) + o_p(n^{-1/2})$$

$$= \frac{1}{n} \sum_{i=1}^{n} U_{t,s-1,i}(\alpha_0) + o_p(n^{-1/2}).$$

Apply the central limit theorem based on the regularity condition C12 and we complete the proof.

We restate Theorem 2 in the main text below with technical details.

**Theorem S2** Under the regularity conditions C1–C12, and assume the following regularity condi-
C13. The partial derivatives \( \varphi_a \{ Z^*(\beta_t), \gamma \} \) with respect to \( \gamma \) and \( \beta_t \) exist and are continuous around \( \gamma_0 \) and \( \beta_t \) almost everywhere. The second derivatives of \( \varphi_a \{ Z^*(\beta_t), \gamma \} \) with respect to \( \gamma_0 \) and \( \beta_t \) are continuous and dominated by some integrable functions.

C14. The partial derivative of \( \mathbb{E} [\varphi_a \{ Z^*(\beta_t), \gamma \}] \) with respect to \( \gamma \) at \( \gamma = \gamma_0 \), i.e., \( D_{\varphi} = \partial \mathbb{E} \left[ \varphi_a \{ Z^*(\beta_t), \gamma_0 \} \right] / \partial T \), is nonsingular.

C15. The partial derivative \( g(X, \gamma^{(0)}) \) with respect to \( \gamma^{(0)} \) exists and is continuous around \( \gamma^{(0)}_0 \) almost everywhere. The second derivative of \( g(X, \gamma^{(0)}) \) with respect to \( \gamma^{(0)}_0 \) is continuous and dominated by some integrable functions.

C16. The variance \( \mathbb{V} \{ V_{\tau,i}(\alpha_0, \gamma_0) \} \) is finite, where \( V_{\tau,i}(\alpha_0, \gamma_0) = \left\{ \partial g(X_i; \gamma^{(0)}_0) / \partial T \right\} c^T V_{\tau,i}(\alpha_0, \gamma_0) \),

\[
V_{\tau,i}(\alpha_0, \gamma_0) = D_{\varphi}^{-1} \left[ \varphi_a \{ Z^*_i(\beta_t), \gamma_0 \} + \sum_{s=1}^{t} \mathbb{E} \left\{ R_{s-1}(1 - R_s) \frac{\partial \mu(A,X \mid \gamma_0)}{\partial T} \frac{\partial \psi(c)}{\partial e} H_{s-1}^T \right\} U_{t,s-1,i}(\alpha_0) \right],
\]

\( e_i = Y_{it}^*(\beta_t) - \mu(A,X \mid \gamma_0) \), and \( c^T = (I_{d_0}, 0_{d_0 \times d_1}) \). Here, \( I_{d_0} \) is a \((d_0 \times d_0)\)-dimensional identity matrix, \( 0_{d_0 \times d_1} \) is a \((d_0 \times d_1)\)-dimensional zero matrix.

Then, as the sample size \( n \to \infty \),

\[
\sqrt{n}(\hat{\gamma} - \gamma_0) \xrightarrow{d} \mathcal{N}(0, \mathbb{V} \{ V_{\tau,i}(\alpha_0, \gamma_0) \}).
\]

**Proof:** Consider a Taylor expansion of the function \( \sum_{i=1}^{n} \varphi_a \{ Z^*_i(\hat{\beta}_t), \gamma \} \) with respect to \( \gamma \) around \( \gamma_0 \), under the regularity conditions C13 and C14, we have the linearization form of \( \hat{\gamma} \) as

\[
\hat{\gamma} - \gamma_0 = \frac{1}{n} \sum_{i=1}^{n} \left[ -\frac{1}{n} \sum_{i=1}^{n} \frac{\partial \varphi_a \{ Z^*_i(\hat{\beta}_t), \gamma_0 \}}{\partial T} \right]^{-1} \varphi_a \{ Z^*_i(\hat{\beta}_t), \gamma_0 \} - o_p(n^{-1/2})
\]

\[
= \left( -\frac{\partial \mathbb{E} [\varphi_a \{ Z(\beta_t), \gamma_0 \}]}{\partial T} \right)^{-1} \frac{1}{n} \sum_{i=1}^{n} \varphi_a \{ Z^*_i(\hat{\beta}_t), \gamma_0 \} + o_p(n^{-1/2})
\]

\[
= D_{\varphi}^{-1} \frac{1}{n} \sum_{i=1}^{n} \varphi_a \{ Z^*_i(\hat{\beta}_t), \gamma_0 \} + o_p(n^{-1/2}).
\]

Therefore,

\[
\sqrt{n}(\hat{\gamma} - \gamma_0) = D_{\varphi}^{-1} n^{-1/2} \sum_{i=1}^{n} \varphi_a \{ Z^*_i(\hat{\beta}_t), \gamma_0 \} + o_p(1)
\]
\[= D^{-1}_\varphi \left[ n^{-1/2} \sum_{i=1}^{n} \varphi_a \{ Z_i^* (\beta_t), \gamma_0 \} \right. \]

\[+ \left. n^{-1/2} \sum_{i=1}^{n} \varphi_a \left\{ Z_i^* (\hat{\beta}_t), \gamma_0 \right\} - n^{-1/2} \sum_{i=1}^{n} \varphi_a \{ Z_i^* (\beta_t), \gamma_0 \} \right] + o_p(1). \quad (S10)\]

The first term in formula (S10) is the sum of i.i.d. components with \( \mathbb{E} [\varphi_a \{ Z_i^* (\beta_t), \gamma_0 \}] = 0 \). Then by the central limit theorem, the first term converges to a normal distribution with the mean 0 and the variance \( \mathbb{V} [\varphi_a \{ Z_i^* (\beta_t), \gamma_0 \}] \).

For the term \( n^{-1/2} \sum_{i=1}^{n} \varphi_a \{ Z_i^* (\beta_t), \gamma_0 \} \) in formula (S10), consider a Taylor expansion of \( n^{-1} \sum_{i=1}^{n} \varphi_a \{ Z_i^* (\hat{\beta}_t), \gamma_0 \} \) with respect to \( \hat{\beta}_t \) around \( \beta_t \), again by the regularity conditions C13 and C14, we have

\[ \frac{1}{n} \sum_{i=1}^{n} \varphi_a \left\{ Z_i^* (\hat{\beta}_t), \gamma_0 \right\} = \frac{1}{n} \sum_{i=1}^{n} \varphi_a \{ Z_i^* (\beta_t), \gamma_0 \} + \frac{1}{n} \sum_{i=1}^{n} \frac{\partial \varphi_a \{ Z_i^* (\beta_t), \gamma_0 \}}{\partial \beta_t} (\hat{\beta}_t - \beta_t) + o_p(n^{-1/2}) \]

\[= \frac{1}{n} \sum_{i=1}^{n} \varphi_a \{ Z_i^* (\beta_t), \gamma_0 \} + \frac{\partial \mathbb{E} [\varphi_a \{ Z_i^* (\beta_t), \gamma_0 \}]}{\partial \beta_t} (\hat{\beta}_t - \beta_t) + o_p(n^{-1/2}). \]

Note that

\[ \frac{\partial \mathbb{E} [\varphi_a \{ Z_i^* (\beta_t), \gamma_0 \}]}{\partial \beta_t} = \left( \frac{\partial \mathbb{E} [\varphi_a \{ Z_i^* (\beta_t), \gamma_0 \}]}{\partial \beta_t^1, \gamma_0}, \ldots, \frac{\partial \mathbb{E} [\varphi_a \{ Z_i^* (\beta_t), \gamma_0 \}]}{\partial \beta_t^T, \gamma_0} \right). \]

From formula (S2), each component of the derivative \( \frac{\partial \mathbb{E} [\varphi_a \{ Z_i^* (\beta_t), \gamma_0 \}]}{\partial \beta_t^T, \gamma_0} \) can be obtained by the Chain Rule as

\[ \frac{\partial \mathbb{E} [\varphi_a \{ Z_i^* (\beta_t), \gamma_0 \}]}{\partial \beta_t^T, \gamma_0} = \mathbb{E} \left\{ R_{s-1} (1 - R_s) \frac{\partial \mu (A, X \mid \gamma_0)}{\partial \gamma^T} \frac{\partial \psi(e)}{\partial e} H_{s-1}^T \right\}, \]

for \( s = 1, \cdots, t \). Then we can apply the linearization form stated in Lemma S4 under the regularity condition C13 by Theorem 5.27 in Boos and Stefanski (2013), we have

\[ n^{-1} \sum_{i=1}^{n} \varphi_a \left\{ Z_i^* (\hat{\beta}_t), \gamma_0 \right\} - n^{-1} \sum_{i=1}^{n} \varphi_a \left\{ Z_i^* (\beta_t), \gamma_0 \right\} \]

\[= \frac{1}{n} \sum_{i=1}^{n} \sum_{s=1}^{t} \mathbb{E} \left\{ R_{s-1} (1 - R_s) \frac{\partial \mu (A, X \mid \gamma_0)}{\partial \gamma^T} \frac{\partial \psi(e)}{\partial e} H_{s-1}^T \right\} U_{t,s-1,i}(\alpha_0) + o_p(n^{-1/2}). \]

Therefore, equation (S10) can be further expressed as

\[\sqrt{n}(\hat{\gamma} - \gamma_0) = n^{-1/2} \sum_{i=1}^{n} D^{-1}_\varphi \left[ \varphi_a \{ Z_i^* (\beta_t), \gamma_0 \} + \sum_{s=1}^{t} \mathbb{E} \left\{ R_{s-1} (1 - R_s) \frac{\partial \mu (A, X \mid \gamma_0)}{\partial \gamma^T} \frac{\partial \psi(e)}{\partial e} H_{s-1}^T \right\} U_{t,s-1,i}(\alpha_0) \right]\]
By the regularity condition C15, the ATE estimator \( \hat{\tau} = n^{-1} \sum_{i=1}^{n} g(X_i; \hat{\gamma}(0)) \) can be linearized as
\[
\hat{\tau} - \tau_0 = \frac{1}{n} \sum_{i=1}^{n} \frac{\partial g(X_i; \hat{\gamma}(0))}{\partial \gamma} (\hat{\gamma}(0) - \gamma(0)) + o_P(1).
\]

By the regularity condition C16 and apply the central limit theorem, we complete the proof. \( \square \)

**S1.3 An example: using the interaction model for the ATE estimation**

The working model in the form of (2) in the main text covers a wide range of analysis models in practice. We give an example of using the interaction model for analysis, i.e., fit the regression model with the interaction between the treatment variable and the baseline covariates for the imputed data, as it is one of the most common models in the clinical trials suggested in ICH (2021).

**Example 1** When using an interaction model in the analysis step, the working model can be written as \( \mu(A, X | \gamma) = AX^T \gamma^{(0)} - X^T \gamma^{(1)} \), and the ATE estimator \( \hat{\tau} \) can then be obtained by solving the estimating equations
\[
\sum_{i=1}^{n} \left( \psi(Y_{it}^* - A_iX_i^T \gamma^{(0)} - X_i^T \gamma^{(1)})(A_iX_i^T, X_i^T) \right) = 0.
\]

Denote \( V_i = \langle A_iX_i^T, X_i^T \rangle \) and \( \gamma_0 = (\gamma^{(0)}_0, \gamma^{(1)}_0)^T \) such that \( \mathbb{E}\{ \psi(Y_{it}^* - A_iX_i^T \gamma^{(0)} - X_i^T \gamma^{(1)}) \} = 0 \). Applying Theorems 1 and 2, the estimator \( \hat{\tau} \xrightarrow{p} \tau_0 \) and \( \sqrt{n}(\hat{\tau} - \tau_0) \xrightarrow{d} \)
\[ \mathcal{N}(0, \nabla \{V_{\tau,i}(\alpha_0, \gamma_0, \mu_X)\}) \], where \( V_{\tau,i}(\alpha_0, \gamma_0, \mu_X) = (X_i - \mu_X)^T \gamma_0^{(0)} + \mu_X^T V_{\gamma(0),i}(\alpha_0, \gamma_0), \)

\[ V_{\gamma(0),i}(\alpha_0, \gamma_0) = c^T D^{-1}_\varphi \left[ \psi(e_i)V_i + \sum_{s=1}^{t} \mathbb{E} \left\{ R_{is-1} (1 - R_{is}) V_i \frac{\partial \psi(e_i)}{\partial e_i} H_{is-1}^T U_{t,s-1,i}(\alpha_0) \right\} \right], \]

\[ U_{t,s-1,i}(\alpha_0) = (I_{p+s-2}, \alpha_{s-1,0}) U_{t,s,i}(\alpha_0) + (0^T_{p+s-2}, 1) \beta_{t,s} q(H_{is}, \alpha_{s-1,0}), U_{t,t-1,i}(\alpha_0) = q(H_{it}, \alpha_{t-1,0}), \]

and

\[ q(H_{is}, \alpha_{s-1,0}) = \left( -\frac{\partial \mathbb{E} \{ \varphi(H_{is}, \alpha_{s-1,0}) H_{is-1}^T | H_{is-1} \} }{\partial \alpha_{s-1}} \right)^{-1} \varphi(H_{is}, \alpha_{s-1,0}). \]

Here, \( c = (I_p, 0_{p \times p}) \), where \( I_p \) is a \((p \times p)\)-dimensional identity matrix, \( 0_{p \times p} \) is a \((p \times p)\)-dimensional zero matrix, \( e_i = Y_i^T (\hat{\beta}_t) - V_i^T \gamma^*, D_\varphi = \partial \mathbb{E} \{ \psi(e_i)V_i \} / \partial \gamma^T \), and

\[
\begin{cases}
\beta_{t,t-1} = \alpha_{t-1,0} & \text{if } s = t, \\
\beta_{t,s-1} = (I_{p+s-2}, \alpha_{s-1,0})(I_{p+s-1}, \alpha_{s,0}) \cdots (I_{p+t-3}, \alpha_{t-2,0}) \alpha_{t-1,0} & \text{if } s < t,
\end{cases}
\]

for \( s = 1, \ldots, t. \)

The asymptotic variance in Example 1 motivates us to obtain a linearization-based variance estimator by plugging in the estimated values as

\[ \hat{V}(\hat{\tau}) = \frac{1}{n^2} \sum_{i=1}^{n} \left\{ V_{\tau,i}(\hat{\alpha}_w, \hat{\gamma}, \hat{\mu}_X) - \bar{V}_\tau(\hat{\alpha}_w, \hat{\gamma}, \hat{\mu}_X) \right\}^2, \]

where \( \bar{V}_\tau(\hat{\alpha}_w, \hat{\gamma}, \hat{\mu}_X) = n^{-1} \sum_{i=1}^{n} V_{\tau,i}(\hat{\alpha}_w, \hat{\gamma}, \hat{\mu}_X), V_{\tau,i}(\hat{\alpha}_w, \hat{\gamma}, \hat{\mu}_X) = (X_i - \hat{\mu}_X)^T \gamma(0) + \hat{\mu}_X^T V_{\gamma(0),i}(\hat{\alpha}_w, \hat{\gamma}), \)

\[ V_{\gamma(0),i}(\hat{\alpha}_w, \hat{\gamma}) = c^T D^{-1}_\varphi \psi(e_i)V_i + \sum_{s=1}^{t} \left\{ \frac{1}{n} \sum_{i=1}^{n} R_{is-1} (1 - R_{is}) V_i \frac{\partial \psi(e_i)}{\partial e_i} H_{is-1}^T U_{t,s-1,i}(\hat{\alpha}_w) \right\} \]

\[ U_{t,s-1,i}(\hat{\alpha}_w) = (I_{p+s-2}, \hat{\alpha}_{s-1,1}) U_{t,s,i}(\hat{\alpha}_w) + (0^T_{p+s-2}, 1) \hat{\beta}_{t,s} \hat{q}(H_{is}, \hat{\alpha}_{s-1,1}), U_{t,t-1,i}(\hat{\alpha}_w) = \hat{q}(H_{it}, \hat{\alpha}_{t-1,1}), \]

and

\[ \hat{q}(H_{is}, \hat{\alpha}_{s-1,1}) = \left( \frac{1}{n} \sum_{i=1}^{n} \frac{\partial \varphi(H_{is}, \hat{\alpha}_{s-1,1})}{\partial \alpha_{s-1}} H_{is-1}^T \right)^{-1} \varphi(H_{is}, \hat{\alpha}_{s-1,1}). \]

Also, \( \hat{e}_i = Y_i^* - V_i^T \hat{\gamma}, \hat{D}_\varphi = n^{-1} \sum_{i=1}^{n} \partial \psi(e_i)V_i / \partial \gamma^T \), and

\[
\begin{cases}
\hat{\beta}_{t,t-1} = \hat{\alpha}_{t-1} & \text{if } s = t, \\
\hat{\beta}_{t,s-1} = (I_{p+s-2}, \hat{\alpha}_{s-1,1})(I_{p+s-1}, \hat{\alpha}_s) \cdots (I_{p+t-3}, \hat{\alpha}_{t-2,1}) \hat{\alpha}_{t-1} & \text{if } s < t,
\end{cases}
\]
for $s = 1, \cdots, t$. In practice, $\hat{\mu}_X$ is estimated by the overall mean of the baseline covariates. We can also use the nonparametric bootstrap to obtain a replication-based variance estimator. In the simulation studies and real data application, we use the interaction model for analysis.

## S2 Illustration of the sequential regression procedure

### S2.1 Sequential linear regression

In the main text, the sequential linear regression is mentioned multiple times in Sections 2, 3, and 4, under the assumed scenario where the current outcomes and the historical covariates have a linear relationship. Since the imputation model under J2R focuses on the control group, we fit the current observed outcomes $Y_s$ in the control group against the historical information $H_{s-1}$ via a linear model to get the model parameter estimator $\hat{\alpha}_{s-1}$ by solving the estimating equations

$$
\sum_{i=1}^{n}(1 - A_i)R_{is}H_{is-1}(Y_{is} - H_{is-1}^T\alpha_{s-1}) = 0.
$$

Our proposed weighted sequential robust regression model, whose robust loss function is of the form (1), is motivated by this sequential linear regression model.

### S2.2 Extension to general sequential regression

In Section 3 in the main text, we mentioned a possible extension to the nonlinear relationship between the current outcomes and the historical covariates for the ATE identification. We now provide some insights into it. The key for the ATE identification under the PMM framework is to form the assumption of the pattern-specific expectation $E(Y_{it} \mid R_{is-1} = 1, R_{is} = 0, A_i = a)$, which can be identified via the iterated expectations $E(Y_{it} \mid H_{is-1}, A_i = 0) = E\{\cdots E(Y_{it} \mid H_{it-1}, R_{it} = 1, A_i = 0) \cdots \mid H_{is-1}, R_{is} = 1, A_i = 0\}$ based on Assumptions 1 and 2 under J2R. If a nonlinear relationship is suspected, we can consider adding nonlinear terms in the parametric models or turn to flexible models such as semiparametric models or machine learning models for model fitting. One natural way to estimate the iterated expectation $E(Y_{it} \mid H_{is-1}, A_i = 0)$ is to fit the sequential regressions (via flexible models or parametric models with nonlinear terms) in backward order. We again focus on the control group and give the detailed implementation steps as follows.

**Step 1.** For the participants who are fully observed, i.e., with the observed indicator $R_{it} = 1$, fit the regression model on $Y_{it}$ against the history $H_{it-1}$. Use the fitted model to predict the outcomes for those who are observed until $(t - 1)$th visit time. Denote the predicted outcomes as $\hat{E}(Y_{it} \mid H_{it-1}, R_{it} = 1, A_i = 0)$.

**Step 2.** For the participants who are observed until $(t - 1)$th visit, fit the regression model on the predicted outcomes $\hat{E}(Y_{it} \mid H_{it-1}, R_{it} = 1, A_i = 0)$ obtained in Step 1 against the history $H_{it-2}$.
Use the fitted model to predict the outcomes for those who are observed until \((t - 2)\)th visit time. Denote the predicted outcomes as \(\hat{E}\{\hat{E}(Y_{it} \mid H_{it-1}, R_{it} = 1, A_i = 0) \mid H_{it-2}, R_{it-1} = 1, A_i = 0}\).

**Step 3.** Follow the similar procedure \((t - s - 2)\) times by fitting the regression model in backward order. Obtain the predicted outcomes \(\hat{E}(Y_{it} \mid H_{is-1}, A_i = 0)\) at last.

### S3 Additional notes on the simulation studies

#### S3.1 Simulation setting

In the simulation studies, the sample size is 500 for each group. The baseline covariates \(X = (X_1, X_2)^T\) are generated independently by \(X_1 \sim \mathcal{N}(0, 1)\) and \(X_2 \sim \text{Bernoulli}(0.3)\). The longitudinal outcomes are generated sequentially:

(a) at \(t = 1\), generate \(Y_1 = 0.5 + X_1 - 0.2X_2 + \varepsilon_1\) for both groups;

(b) at \(t = 2\), generate

\[
\begin{cases}
Y_2 = 0.4 + 0.14X_1 + 0.52X_2 + 0.01Y_1 + \varepsilon_2 & \text{if } A = 0; \\
Y_2 = 1.79 + 0.35X_1 - 0.05X_2 + 0.33Y_1 + \varepsilon_2 & \text{if } A = 1;
\end{cases}
\]

(c) at \(t = 3\), generate

\[
\begin{cases}
Y_3 = 0.77 + 0.02X_1 + 0.06X_2 + 0.71Y_1 + 0.84Y_2 + \varepsilon_3 & \text{if } A = 0; \\
Y_3 = 2.52 + 1.16X_1 - 0.51X_2 - 1.53Y_1 + 0.46Y_2 + \varepsilon_3 & \text{if } A = 1;
\end{cases}
\]

(d) at \(t = 4\), generate

\[
\begin{cases}
Y_4 = 1.44 - 0.45X_1 - 0.24X_2 - 0.50Y_1 - 0.39Y_2 + 0.53Y_3 + \varepsilon_4 & \text{if } A = 0; \\
Y_4 = 2.72 - 0.46X_1 - 0.06X_2 + 0.91Y_1 + 0.19Y_2 + 0.70Y_3 + \varepsilon_4 & \text{if } A = 1;
\end{cases}
\]

(e) at \(t = 5\), generate

\[
\begin{cases}
Y_5 = 4.37 - 0.84X_1 - 0.31X_2 + 0.01Y_1 + 0.35Y_2 - 0.32Y_3 + 0.81Y_4 + \varepsilon_5 & \text{if } A = 0; \\
Y_5 = 4.21 - 0.02X_1 - 1.26X_2 + 0.24Y_1 - 0.18Y_2 + 0.65Y_3 + 0.13Y_4 + \varepsilon_5 & \text{if } A = 1;
\end{cases}
\]
where \( \varepsilon_k \) is from a distribution with mean 0 and standard deviation \( \sigma_k \), and \( \sigma = (\sigma_1, \cdots, \sigma_5)^T = (2.0, 1.8, 2.0, 2.1, 2.2)^T \). For the missing mechanisms, we set \( \phi_{11} = -3.5, \phi_{12} = -3.6, \phi_{21} = \phi_{22} = 0.2 \). The tuning parameter in the weighted robust regression is set as 10. We also try to use cross-validation to obtain the tuning parameters, which leads to very similar results. Therefore, to save computation time, the tuning parameter is fixed in the MC simulation as \( q_{s-1} = 10 \) for \( s = 1, \cdots, 5 \).

We consider two cases with the existence of extreme outliers or a heavy-tailed distribution as follows.

(a) Data with/without extreme outliers: The error terms are generated by \( \varepsilon_k \sim N(0, \sigma_k^2) \) to form the multivariate normal distribution (MVN). To create the outliers, we randomly select 10 individuals from the 30 completers with the maximum outcomes at the last visit point per group and multiply the original values by three for all post-baseline outcomes.

(b) Data from a heavy-tailed distribution: We choose a common heavy-tailed distribution as t distribution. The error terms are generated by \( \varepsilon_k \sim (3/5)^{1/2} \sigma_k t_5 \) to get the same variation as the normal distribution, where \( t_5 \) is the standard t-distribution with the degrees of freedom as 5.

### S3.2 Additional simulation results

For the data with/without extreme outliers, apart from Table 1(b) in the main text, we consider two more cases to incorporate the outliers only in one specific group, with the same approach to generate the outliers as presented in the main text. We again compare all the methods in terms of point and variance estimation, type-1 error, power, and RMSE.

Similar to the interpretation from Table 1 in the main text, Table S1 validates the superiority of the proposed robust method, as it shows unbiased point estimates, well-controlled type-1 errors under \( H_0 \), and high powers under \( H_1 \).

Table S1: Simulation results under the normal distribution with extreme points at all post-baseline visit points. Here the true value \( \tau = 71.18\% \).

| Case        | Method | Point est (\( \times 10^{-2} \)) | True var (\( \times 10^{-2} \)) | Var est (\( \times 10^{-2} \)) | Relative bias (%) | Coverage rate (%) | Power (%) | RMSE (\( \times 10^{-2} \)) |
|-------------|--------|----------------------------------|----------------------------------|-------------------------------|-------------------|-----------------|-----------|---------------------------|
| Outliers    | MI     | 43.07 4.29                        | 13.10 6.23                       | V̂_1  V̂_{boot}               | 98.00  84.80      | 8.80  40.80     | 34.90    |
|               | LSE    | 51.44 3.66                        | 4.71 4.39                       | V̂_1  V̂_{boot}               | 88.70  86.90      | 68.60  70.70    | 27.48    |
|               | Robust | 74.86 3.44                        | 3.54 3.48                       | V̂_1  V̂_{boot}               | 94.80  93.90      | 98.10  97.80    | 18.91    |
| Outliers    | MI     | 116.55 3.43                       | 8.29 6.40                       | 141.36 86.31                 | 74.40  58.80      | 100.00 100.00   | 49.00    |
|               | LSE    | 94.11 3.63                        | 4.73 4.69                       | 30.24 28.98                  | 84.90  86.20      | 99.70  99.70    | 29.82    |
|               | Robust | 67.71 3.28                        | 3.41 3.38                       | 3.94 3.04                    | 94.50  93.70      | 95.40  96.00    | 18.44    |
We also conduct the simulations under $H_0$ for each case. Under $H_0$, we choose the same sequential regression coefficients for both the control group and the treatment group. In addition, the tuning parameter in the missing mechanism model is set as $\phi_{11} = \phi_{12} = -3.5$ and $\phi_{21} = \phi_{22} = 0.2$. To achieve the accuracy of 0.01, we choose the Monte Carlo sample size as 10,000.

Table S2 presents the simulation results under MVN and $H_0$ without or with extreme outliers. Although the point estimates seem to be unbiased when outliers exist (since we generate the outliers in the same way for both groups, the bias for each group cancels off), the type-1 error is extremely far away from the empirical value, suggesting huge variabilities for the MI and LSE methods. The proposed robust method outperforms as we observe a well-controlled type-1 error, satisfying point and variance estimation results. The first two rows of Figure 3 in the main text visualizes the simulation results.

Table S2: Simulation results under the normal distribution and $H_0$ without or with extreme outliers. Here the true value $\tau = 0$.

| Case          | Method | Point est ($\times 10^{-2}$) | True var ($\times 10^{-2}$) | Var est ($\times 10^{-2}$) | Relative bias (%) | Type-1 error (%) | RMSE ($\times 10^{-2}$) |
|---------------|--------|------------------------------|-----------------------------|-----------------------------|-------------------|-----------------|------------------------|
| No outliers   | MI     | 0.02                         | 2.76                        | 3.73                        | 2.75              | 35.35           | -0.23                  | 2.12 5.17 16.60         |
|               | LSE    | 0.03                         | 2.72                        | 2.71                        | 2.71              | -0.25           | -0.21                  | 4.86 5.16 16.49         |
|               | Robust | -0.94                        | 2.94                        | 2.89                        | 2.96              | -1.50           | 0.73                   | 4.96 5.06 17.17         |
| Outliers      | MI     | 0.13                         | 3.61                        | 11.55                       | 8.77              | 219.61          | 142.52                 | 0.07 0.36 19.01         |
| in both groups| LSE    | 0.01                         | 3.90                        | 5.49                        | 5.53              | 40.92           | 41.93                  | 1.89 2.17 19.74         |
|               | Robust | -1.05                        | 3.03                        | 2.90                        | 3.00              | -4.36           | -1.05                  | 5.26 5.29 17.45         |

Table S3 presents the simulation results under MVT and $H_0$. Although all the methods have unbiased point estimates, the proposed robust method is more efficient as the MC variance and RMSE are small. The last row of Figure 3 also visualizes the simulation results.

Table S3: Simulation results under the t-distribution and $H_0$. Here the true value $\tau = 0$.

| Method | Point est ($\times 10^{-2}$) | True var ($\times 10^{-2}$) | Var est ($\times 10^{-2}$) | Relative bias (%) | Type-1 error (%) | RMSE ($\times 10^{-2}$) |
|--------|------------------------------|-----------------------------|-----------------------------|-------------------|-----------------|------------------------|
| MI     | -0.14                        | 2.78                        | 3.75                        | 2.76              | 34.87           | -0.77                  | 2.33 5.35 16.68         |
| LSE    | -0.13                        | 2.76                        | 2.73                        | 2.73              | -1.05           | -0.95                  | 5.09 5.39 16.60         |
| Robust | -1.05                        | 2.46                        | 2.41                        | 2.47              | -2.18           | 0.52                   | 5.38 5.47 15.72         |
The repeated CD4 count data is available at https://content.sph.harvard.edu/fitzmaur/ala/cd4.txt. It keeps track of the longitudinal CD4 counts during the first 40 weeks of the clinical trial. Since the original CD4 counts are highly skewed, we conduct a log transformation to get the transformed CD4 count as log(CD4 + 1) and use it as the outcome of interest. As the longitudinal outcomes are collected at 8-week intervals, we factorize the continuous-time variable into the intervals (0, 12], (12, 20], (20, 28], (28, 36] and (36, 40]. To ensure that only one outcome is involved in a time interval for each individual, only the outcome that is nearest to week 8k in the kth visit interval is preserved for k = 1, · · · , 5. Since our proposed method is only valid for a monotone missingness pattern, we delete the observations after the first occurrence of missingness for each individual to create a monotone missingness dataset and use it for further analysis. The fully-observed baseline covariates consist of age, gender, and the baseline log CD4 counts. The created data suffers from severe missingness. In arm 1, only 34 participants complete the study, while 94 drop out before week 12, 52 drop out before week 20, 47 drop out before week 28, 17 drop out before week 36, and 76 drop out before week 40; in arm 2, only 46 participants complete the study, while 94 drop out before week 12, 48 drop out before week 20, 51 drop out before week 28, 20 drop out before week 36, and 71 drop out before week 40.

We first conduct a scrutiny of the data to check the existence of extreme outliers and/or a violation of normality. Figure 1 in the main text presents the spaghetti plots of the repeated CD4 counts separated by each treatment. From the figure, there are no outstanding outliers in the data. Arm 2 has a higher average of the CD4 counts than arm 1.

Then we check for normality by fitting sequential linear regressions on the current outcomes against all historical information in arm 1 and examining the conditional residuals at each visit point for model diagnosis. Figure 2 in the main text presents the QQ normal plots for the conditional residuals. Note that we only focus on the data in arm 1 since the imputation model under J2R relies solely on the data in the reference group. From the figure, heavier tails are detected at each visit point beyond the confidence region. We further conduct the Shapiro-Wilk normality test for the conditional residuals. All the tests return p-values that are much smaller than 0.05, therefore we reject the null hypothesis and conclude that the data does not follow a normal distribution. Moreover, we conduct a symmetry test proposed by Miao et al. (2006) on the conditional residuals. All the resulting p-values are larger than 0.05 and suggests that the residuals are symmetric around 0, which allows us to obtain valid inferences of the ATE via the proposed robust methods. All the test results
are presented in Figure 2 at visit $s$ for $s = 1, \cdots, 5$.

In the implementation of the weighted robust method, the tuning parameters in formula (1) are selected via cross-validation. Specifically, to mitigate the impact of outliers that are existed in the covariates in the imputation model, we first conduct the cross-validation to select the tuning parameter at each visit point in the sequential robust regression that returns the smallest MSE, then insert the chosen tuning parameters in the imputation model and further select the tuning parameter for the analysis model in each group by cross-validation. The resulting tuning parameters for the imputation model are $(20, 19.5, 17.5, 15, 8)$. The choice of tuning parameters is not sensitive to the final estimation.