A Comparison of Estimand and Estimation Strategies for Clinical Trials in Early Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a chronic, degenerative neurological disorder. PD cannot be prevented, slowed, or cured as of today but highly effective symptomatic treatments are available. We consider relevant estimands and treatment effect estimators for randomized trials of a novel treatment which aims to slow down disease progression versus placebo in early, untreated PD. A commonly used endpoint in PD trials is the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which is longitudinally assessed at scheduled visits. The most important intercurrent events (ICEs) which affect the interpretation of the MDS-UPDRS are study treatment discontinuation and initiation of symptomatic treatment. Different estimand strategies are discussed; Hypothetical or treatment policy strategies, respectively, for different types of ICEs seem most appropriate in this context. Several estimators based on multiple imputation which target these estimands are proposed and compared in terms of bias, mean-squared error, and power in a simulation study. The investigated estimators include methods based on a missing-at-random (MAR) assumption, with and without the inclusion of time-varying ICE-indicators, as well as reference-based imputation methods. Simulation parameters are motivated by data analyses of a cohort study from the Parkinson's Progression Markers Initiative (PPMI).

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1. Introduction

Parkinson's disease (PD) is a chronic, degenerative neurological disorder characterized by movement problems such as rigidity, slowness, and tremor. More than 6 million individuals worldwide are affected by PD. At this time, no cure or disease-modifying therapy for PD exists. Levodopa preparations are the most widely prescribed treatments for PD. Levodopa is a highly effective symptomatic treatment for motor symptoms but it is not disease-modifying (Verschuur et al. 2019). Moreover, over time, individuals require more frequent and higher levodopa doses and eventually lose their long-duration response to dopaminergic medication, and their short-duration response decreases. Other commonly used initial symptomatic treatments for PD include dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors (Armstrong and Okun 2020).

The most commonly used assessment scale in clinical trials of PD is the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al. 2008). The MDS-UPDRS is a multimodal scale assessing both impairment and disability. It consists of four subscales (Parts I–IV). Part I (13 items) measures non-motor experiences of daily living, Part II (13 items) assesses motor experiences of daily living, Part III (18 items with some items applying to multiple body parts resulting in 33 answers total) measures the motor signs of PD and Part IV (4 items) measures the motor complications, dyskinesias and motor fluctuations. Part IV is typically only assessed after a patient has started dopaminergic treatment. Each question is rated between 0 and 4, where 0 = Normal, 1 = Slight, 2 = Mild, 3 = Moderate, 4 = Severe.

For the following, we assume that a double-blind, randomized trial comparing a new and potentially disease modifying intervention treatment versus placebo is to be conducted in early, untreated PD. The primary endpoint is the change from baseline to a fixed time point (e.g., at 12 months) in the MDS-UPDRS sum of Parts I+II+III score (called “MDS-UPDRS score” in the sequel for simplicity). The outcome assessments are assumed to be scheduled at regular intervals (e.g., every two months).

The aim of this article is to critically appraise several possible choices for the primary estimand in this setting, to propose treatment effect estimators which are aligned with these estimands, and to explore them in a simulation study. The article is structured as follows: Section 2 reviews the estimands framework and proposes three relevant estimands for our setting. Section 3 discusses corresponding treatment effect estimators. In Section 4, the proposed estimands and estimators are compared in a simulation study. The simulation parameters are motivated...
by data analyses of a cohort study from the Parkinson’s Progression Markers Initiative (PPMI) (Marek et al. 2011) which are reported in the supplementary Appendix. We conclude with a discussion of our findings and potential alternative estimands.

2. Estimands Framework and Definition of Investigated Estimands

The “ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials” presents a structured framework to link trial objectives to a precise description of the targeted principles for clinical trials” presents a structured framework to analysis in clinical trials to the guideline on statistical prin-

The ICH E9 (R1) addendum explicitly allows that different strategies are applied to different ICEs and we consider three estimands. First, a pure hypothetical estimand which applies a hypothetical strategy to both study treatment discontinuation and initiation of symptomatic therapy. This envisions a hypothetical scenario where all patients fully adhere to the randomized study drug and symptomatic treatment is not available. It is acknowledged that the clinical relevance of such a hypothetical scenario is unclear. For example, it is the responsibility of the investigator based on benefit/risk considerations to withdraw a patient from study treatment in case the well-being of the patient might otherwise be compromised, and symptomatic medications must be made available for ethical reasons. However, a hypothetical estimand may still be relevant for phase 2 proof-of-concept trials. Second, we consider a mixed estimand which applies a treatment policy strategy to study treatment discontinuation and a hypothetical strategy to initiation of symptomatic therapy. This envisions a scenario where treatment discontinuations do occur and their impact on the outcome is of interest but where patients would not initiate symptomatic treatments (or, at least, defer symptomatic treatment until the end of follow-up). Third, we consider a pure treatment policy strategy where a treatment policy strategy is applied to both ICEs. An estimand which uses a hypothetical strategy for study treatment discontinuation and a treatment policy strategy for initiation of symptomatic treatment was not investigated because it was considered to be less clinically relevant and more artificial than the mixed estimand. All proposed estimands are summarized in Table 1.

To illustrate the targeted estimands in the early PD setting, we assume that the intervention treatment slows down the rate of decline as assessed by the MDS-UPDRS score in the long term but, unlike the symptomatic treatment, it does not have a rapid and potent short-term effect on symptoms. This is visualized in Figure 1 which shows stylized MDS-UPDRS trajectories for two dummy subjects assuming that they had either been assigned to placebo or to intervention treatment, respectively. The first subject, represented by a solid black line, does not experience any ICEs and would have had a better outcome (represented by a more shallow slope) if assigned to alternative strategies are revisited in the discussion section. For the treatment policy strategy, the treatment effect in the presence of the ICEs is targeted and analyses include all observed outcomes regardless whether the subject had an ICE or not. In order to estimate a treatment effect under a treatment policy strategy without strong assumptions, it is critical that all patients are followed up to obtain their outcome assessments also after the ICE. For the hypothetical strategy, a scenario is envisaged in which the ICE would not occur. Under this strategy, compatible outcome values after the ICE are not directly observable and handled using models for missing data.

Table 1. Proposed estimands and corresponding strategies for the two ICEs.

| ICE                        | Study treatment discontinuation | Initiation of symptomatic treatment |
|----------------------------|---------------------------------|-------------------------------------|
| Hypothetical estimand      | Hypothetical strategy            | Hypothetical strategy               |
| Mixed estimand             | Treatment policy strategy        | Hypothetical strategy               |
| Treatment policy estimand  | Treatment policy strategy        | Treatment policy strategy           |

For the purpose of the primary analysis, we consider treatment policy and hypothetical strategies to be most suitable to address the two ICEs of randomized treatment discontinuation and initiation of symptomatic treatment, respectively.
the intervention. The second subject, represented by a solid gray line, would have discontinued randomized study treatment and subsequently initiated symptomatic treatment regardless of the assigned treatment group. If assigned to the placebo group, the subject’s trajectory may be unaffected by study treatment discontinuation. However, initiation of symptomatic treatment may be associated with a rapid improvement in the MDS-UPDRS score. If assigned to the intervention group, the rate of disease progression may be slower initially but then revert to the placebo slope after treatment discontinuation. The second subject may also initiate symptomatic treatment in the intervention treatment group after their worsening in the MDS-UPDRS score from baseline exceeded six points and, again, they may subsequently experience a rapid improvement. The solid lines in Figure 1 correspond to the values relevant for the treatment policy estimand. In contrast, the dashed lines represent the relevant values for the mixed estimand which envisions a scenario without symptomatic treatment. It is important to note that, as shown in Figure 1, the pure treatment policy estimand favors patients who initiate symptomatic treatment. Indeed, the observed change in the MDS-UPDRS score at 12 months, which is relevant for the treatment policy estimand would assign a larger (i.e., worse) outcome to the first subject, represented by a black line, than to the second subject, represented by a gray line. However, it could be argued that the first subject has a more favorable outcome than the second subject. Thus, the pure treatment policy estimand may implicitly rank patients in a counter-intuitive way in the presence of potent symptomatic treatment.

3. Missing Data Assumptions and Estimators

3.1. Missing Data Assumptions and Multiple Imputation Methods

It is critical to align the treatment effect estimator with the targeted estimand (Mallinckrodt et al. 2020). In addition, the definition of a treatment effect estimator requires an appropriate handling of missing data in line with plausible missing data assumptions. Missing data may occur due to missed assessments or study withdrawal. In our analyses, we do not distinguish between missing data due to missed assessments and missing data after study withdrawal, that is, we consider study withdrawal to be ignorable. PD patients are fully aware of their disease and therefore interested in receiving the best possible care also after discontinuing study treatment. Therefore, we anticipate that in a carefully designed and executed study, the extent of missed assessments and study withdrawals will be relatively low. However, outcomes under a hypothetical strategy are not directly observable and any observed post-ICE outcomes are consequently ignored and treated as missing data under this strategy.

For the implementation of the estimators, we consider three different missing data assumptions:

- **Basic MAR**: Missing outcome data is similar to observed data from patients in the same treatment group with the same baseline characteristics and the same observed outcomes. More formally, this assumes that data are missing at random (MAR) after accounting for the randomized treatment group, baseline characteristics, and observed outcomes.

- **MNAR (Reference-based missingness)**: Until study treatment discontinuation, missing outcome data is similar to observed data from patients in the same treatment group with the same baseline characteristics who did not discontinue study treatment. After study treatment discontinuation, missing data is similar to observed data from patients in the placebo arm with similar baseline characteristics who did not discontinue study treatment. This assumes that treatment discontinuation does not impact outcomes in the placebo group but that patients randomized to the intervention treatment behave similarly to placebo group patients after discontinuation.

- **Time-dependent MAR**: Missing outcome data is similar to observed data from patients in the same treatment group...
with the same baseline characteristics who have the same ICE status at the relevant outcome visit. More formally, this assumes that data is MAR after accounting for the randomized treatment group, baseline characteristics, time-varying ICE indicators, and observed outcomes.

As in Polverejan and Dragalin (2020), we use multiple imputation (MI) methods for treatment effect estimation because this provides a flexible framework for imputing under different missingness mechanisms and different imputation techniques for different categories of subjects. We focus on conventional Bayesian MI as described in Little and Rubin (2002) and Carpenter, Roger, and Kenward (2013) which creates multiply imputed datasets based on Bayesian posterior draws of imputation parameters and combines treatment effect estimates and variances across imputed datasets using Rubin’s rules. A relevant alternative approach which is not explored here is to create imputations based on maximum likelihood estimates of imputation parameters and to use resampling techniques for inference (von Hippel and Bartlett 2021; Wolbers et al. 2022).

In our context, Bayesian MI consists of the following steps. First, a Bayesian imputation model is fitted which is a multivariate normal Bayesian mixed model for repeated measures (MMRM) of the outcomes depending on the randomized treatment group, the visit, visit-by-treatment interactions, and appropriate baseline covariates. Frequently, a common unstructured covariance matrix is assumed for both treatment groups. For models assuming time-dependent MAR, additional time-varying covariates are included in the imputation model. If post-discontinuation outcomes are available in the dataset, MI under a reference-based missingness assumption is implemented by excluding post-discontinuation outcomes from the imputation model fit but keeping them in the subsequent imputation and analysis steps as described in Wolbers et al. (2022). Second, for each posterior parameter draw from the imputation model, an imputed dataset is generated. This proceeds by randomly imputing missing data conditional on the patient’s baseline characteristics and observed outcomes, and the patient’s marginal mean and covariance matrix predicted by the parameters from the imputation model. Under a reference-based missingness assumption, the marginal imputation mean appropriately combines mean trajectories from the assigned arm and the placebo arm after discontinuation as described in Carpenter, Roger, and Kenward (2013, sec 4). Third, each imputed dataset is analyzed. As imputed datasets are complete, the analysis step may consist of fitting a simple ANCOVA model to the change in the MDS-UPDRS score from baseline to a fixed time point (e.g., at 12 months) with the treatment group as the main covariate and adjustment for the baseline MDS-UPDRS score and other important baseline covariates. Finally, inferences are pooled across multiple imputed dataset using Rubin’s rules. For a more technical and complete discussions of Bayesian MI methods we refer to Little and Rubin (2002) and Carpenter, Roger, and Kenward (2013).

3.2. Estimators for the Hypothetical Estimand

For the hypothetical estimand, any outcomes collected after treatment discontinuation or initiation of symptomatic treatment are not of interest and considered as missing for the purpose of treatment effect estimation. That is, multiple imputation will be applied to all data after an ICE addressed using a hypothetical strategy regardless whether they are “truly missing” or not. The basic MAR assumption is often a good starting point for implementing a hypothetical strategy (Mallinckrodt et al. 2020) and can be implemented as described in the previous section. In the sequel, we refer to this estimator as \( \text{MAR(hypothetical)} \). The basic MAR assumption is expected to provide a “best” expected treatment effect, one that is not majorly affected by ICEs. However, it is not implausible that the occurrence of intercurrent events identifies subjects who would have had worse outcomes than others even if (counter to fact) they had been kept on study treatment and symptomatic treatment was not available. Thus, in practice, imputations under a missing not at random (MNAR) assumptions such as reference-based imputations are also relevant for estimating hypothetical estimands (Mallinckrodt et al. 2020). Of note, in this setting, the MI-based estimator is asymptotically equivalent to the popular MMRM model (Mallinckrodt et al. 2008; Siddiqui 2011).

3.3. Estimators for the Mixed Estimand

The mixed estimand applies a treatment policy strategy to study treatment discontinuation and a hypothetical strategy to symptomatic treatment initiation. Therefore, outcomes collected after symptomatic treatment initiation are not of interest and considered as missing for the purpose of treatment effect estimation. In contrast, outcomes collected after study treatment discontinuation but prior to symptomatic treatment are compatible with the treatment policy strategy and will be included in the analysis.

A patient may experience both study treatment discontinuation and symptomatic treatment initiation in either order. A complication for the estimator of the mixed estimand arises for patients who initiate symptomatic treatment prior to study treatment discontinuation. The reason is that for these patients it is unknown whether and when they would have subsequently discontinued study treatment in the (hypothetical) absence of symptomatic treatment discontinuation. For our estimators, we assume for simplicity reasons that the likelihood of study treatment discontinuation does not depend on whether the patient previously initiated symptomatic medication or not, that is, we base estimation on the observed ICEs of treatment discontinuation. Without such an assumption, estimation would be even more involved and require modeling or imputing the ICE study treatment discontinuation in the absence of observed symptomatic treatment initiations. As only few patients are expected to experience multiple ICEs in a trial, we believe that such a simplification is justifiable.

Four different estimators for the mixed estimands will be explored in the simulation study and are described below: one estimator assuming basic MAR, one estimator assuming reference-based missingness, and two estimators assuming time-dependent MAR.

The estimator based on a basic MAR assumption is referred to as \( \text{MAR(mixed)} \) in the sequel. Importantly, imputations based on the basic MAR assumption do not account for the effect of treatment discontinuation whereas, typically, patients who discontinue active treatment would be expected to benefit less (or
not at all) from the randomized treatment. Moreover, missing data is much more likely to occur after treatment discontinuation. In practice, this implies that the imputation model which is based on observed data is dominated by on-treatment outcomes and, consequently, imputations after treatment discontinuation may be over-optimistic.

Reference-based imputation models were introduced by Carpenter, Roger, and Kenward (2013) to formalize the idea of imputing missing data after treatment discontinuation in both arms based on the control arm. A popular reference-based imputation method is copy-increments in reference (CIR) which will be used for the estimator CIR(mixed). In the placebo control arm, CIR assumes no impact of treatment discontinuation whereas in the active arm, it assumes that a patient's post-discontinuation mean increments are equal to those from the placebo arm. Informally, this means that the treatment benefit accrued up to discontinuation is retained but that there is no additional residual benefit after discontinuation which may be considered a relatively conservative imputation strategy for an intervention which aims to slow down disease progression. For the mixed estimand, the CIR assumption was applied to impute all missing data after study treatment discontinuation. Such missing data may occur due to missed assessments, study withdrawal, or structural missingness after symptomatic treatment initiation.

Estimators based on a time-dependent MAR assumption have been proposed by Guizzaro et al. (2021). Rather than building separate imputation models for pre- and post-discontinuation data, we assume that discontinuation only affects a patient’s mean trajectory and that this can be modeled by including appropriate time-varying covariates. In principle, the effect of treatment discontinuation on outcomes may depend on both the timing of the discontinuation and the time between the discontinuation and the visit at which the outcome value is to be imputed, but in practice more parsimonious models with fewer degrees of freedom are required. Specifically, we model the effect of treatment discontinuation either by including treatment arm specific binary time-varying post-discontinuation indicators (estimator TV1-MAR(mixed)) or time-varying variables which are set equal to 0 up to the treatment discontinuation and to the time from treatment discontinuation at subsequent visits (estimator TV2-MAR(mixed)). The former model assumes that the effect of treatment discontinuation is a constant shift in outcomes whereas the latter implies a change in the slope of outcome trajectories. The latter may be more plausible for a disease-modifying treatment in early PD given that changes in MDS-UPDRS scores over time are approximately linear in untreated patients as shown in the supplementary materials.

3.4. Estimators for the Treatment Policy Estimand

All measured outcomes before or after any ICE are relevant for a pure treatment policy estimand and are therefore included in the analysis. If no missed outcome assessments or study withdrawals occur then no imputation would be necessary for the treatment policy estimand. In the presence of missing data, we investigate three different estimators: a simple estimator based on the basic MAR assumption (MAR(treatment policy)) and two estimators which include time-varying covariates (TV3-MAR(treatment policy) and TV4-MAR(treatment policy)). The two estimators under a time-dependent MAR assumption use the same time-varying covariates to model post-discontinuation data as described for the mixed estimand. In addition, both models include treatment group specific binary time-varying indicators of initiation of symptomatic treatment.

All examined estimators are summarized in Table 2.

4. Simulation Study

4.1. Data Simulation

Parameters for modeling MDS-UPDRS trajectories in the control group, initiations of symptomatic treatment, and the effect of symptomatic treatment on MDS-UPDRS trajectories were motivated by detailed data analyses of the Parkinson’s Progression Markers Initiative (PPMI) database. Longitudinal changes in the MDS-UPDRS score and other clinical and biological measures were published by Simuni et al. (2018). Analyses which are targeted to our simulations and use a more recent cutoff of the PPMI database are summarized in the supplementary materials. Horvath and colleagues estimated clinically meaningful within-patient changes in MDS-UPDRS scores using anchor-based analyses and determined thresholds of 2–3 points for

| Table 2. Proposed estimators and imputation strategies for all estimands. |
|---------------------------------------------|
| **Imputation strategy** |  |
| MAR (hypothetical) | Impute based on baseline characteristics and assigned treatment group. |
| MAR (mixed) | Impute based on baseline characteristics and assigned treatment group. |
| CIR (mixed) | As for MAR (hypothetical) prior to study treatment discontinuation, according to increments in control group after discontinuation. |
| TV1-MAR (mixed) | Impute based on baseline characteristics, assigned treatment group, and a time-varying binary "post treatment discontinuation" indicator. |
| TV2-MAR (mixed) | Impute based on baseline characteristics, assigned treatment group, and a time-varying "time since treatment discontinuation" variable. |
| MAR (treatment policy) | Impute based on baseline characteristics and assigned treatment group. |
| TV3-MAR (treatment policy) | As for TV1-MAR but include also a time-varying binary "on symptomatic treatment" indicator. |
| TV4-MAR (treatment policy) | As for TV2-MAR but include also a time-varying binary "on symptomatic treatment" indicator. |

*Estimators for the hypothetical estimand include only pre-ICE data.

*Estimators for the mixed estimand include only data before symptomatic treatment initiation.

*Estimators for the treatment policy estimand include all observed outcome data.
the MDS-UPDRS part I and II scores and 3–5 points for the MDS-UPDRS part III score, respectively (Horvath et al. 2015, 2017). Acknowledging that a new treatment may not affect all MDS-UPDRS parts equally, we chose a target treatment effect of $-4$ points ($+6$ points/year on intervention vs. $+10$ points/year on placebo) for the hypothetical estimand in our simulations. In order to pressure test the different estimators, we simulated study treatment discontinuation rates and study drop-out rates that are at the upper range of what might be expected in an actual trial in early PD.

Specifically, the simulation study generated hypothetical 1:1 randomized trials with the following parameters:

- The sample size was varied from 75 to 300 patients per group in increments of 25 patients.
- The treatment duration of the trials was 12 months with bimonthly visit from randomization until 12 months.
- The mean trajectory of the MDS-UPDRS score in the placebo group in the absence of ICEs increased linearly by 10 points from 30 points at baseline to 40 points at 12 months.
- The mean trajectory of the MDS-UPDRS score in the intervention group in the absence of ICEs increased linearly by 6 points from 30 points at baseline to 36 points at 12 months.
- The covariance structure of the baseline and follow-up values in both groups was implied by a random intercept and slope model with a standard deviation of 10 for the intercept and of 5 (per year) for the slope, and a correlation of 0.5. In addition, an independent residual error with standard deviation 6 was added to each assessment. This implies marginal standard deviations ranging from 11.7 at baseline to 14.5 at the 12 month visit in both groups.
- The probability of study treatment discontinuation after each visit was set to 2% for the placebo group (implying an overall discontinuation probability of 11.4% before the 12 month visit) and to 3% after each visit for the intervention group (overall 16.7%). A slightly higher discontinuation rate in the treatment arm is plausible in settings where treatment discontinuations are primarily due to safety and tolerability issues and not due to lack of efficacy.
- Study treatment discontinuations were simulated to have no impact on MDS-UPDRS trajectories in the placebo group. For the intervention group, it was assumed that the fixed slope increased to the placebo group slope after discontinuation.
- Patients who discontinued study treatment had a 50% probability of withdrawing from the study leading to missing outcome data from the time of discontinuation onward.
- The probability of initiation of symptomatic treatment after each visit was simulated independently of study treatment discontinuation. In line with analyses of the PPMI database reported in the supplementary materials, the probability was dependent on the observed MDS-UPDRS score with an 1.5-fold higher odds for each +10 points increase. That is, if the MDS-UPDRS score at a visit differed by 10 points between two subjects, then the subject with the higher score had a 1.5-fold higher odds of initiating symptomatic treatment at that visit. Moreover, a lower probability of symptomatic treatment initiation was chosen for earlier visits. Specifically, for a patient with an MDS-UPDRS score of 30 at a visit, the probability was 0% to discontinue after the baseline visit, 2.5% after the month 2 and 4 visits, and 7.5% after subsequent visits. This implies that the overall probability of symptomatic treatment initiation during the 12 month study was 33% in the placebo group and 30% in the intervention group.
- Initiation of symptomatic treatment was associated with an immediate improvement in the MDS-UPDRS score according to a rescaled beta-distribution with parameters $\alpha = 2$, $\beta = 1.5$ and range from $-25$ to 0 points. This implies a median drop by $-10.34$ points (inter-quartile range $-15.14$ to $-5.97$ points). Moreover, the fixed slope after initiation of symptomatic treatment was set to 0. It is worth remarking that an almost flat slope was estimated from the PPMI data by considering only the first 12 months of follow-up (see the supplementary materials for details). This does not assume that patients won't have a worsening of the disease later in time.

The targeted treatment effects by the three estimands, that is, the simulation truth, was determined by simulating a large trial with $n = 3,000,000$ subjects per treatment group and were $-4.00$ points ($+6.00$ vs. $+10.00$) for the hypothetical estimand, $-3.60$ points ($+6.40$ vs. $+10.00$) for the mixed estimand, and $-2.85$ points ($+2.36$ vs. $+5.21$) for the treatment policy estimand. Marginal mean trajectories in both treatment groups corresponding to these estimands are shown in Figure 2 and illustrate the pronounced impact of symptomatic treatment initiations on the treatment policy estimand.

### 4.2. Implementation of Estimators and other Simulation Study Parameters

Estimators were implemented as described in Section 3. Specifically, we used Bayesian multiple imputation (with $M = 100$ random imputations per dataset) and Rubin’s rules for pooling inferences across multiple imputed datasets. The imputation model had the mean change from baseline in the MDS-UPDRS score as the outcome, the treatment group, the (categorical) visit, treatment-by-visit interactions, the baseline MDS-UPDRS score, and baseline MDS-UPDRS score-by-visit interactions as covariates, and assumed a common unstructured covariance matrix in both groups. For estimators involving time-varying covariates, these covariates (as well as treatment by time-varying covariate interaction terms) were additionally included in the imputation model. The analysis model was an ANCOVA model with the mean change from baseline in the MDS-UPDRS score at 12 months as the outcome, the treatment assignment as the main covariate, and adjustment for the baseline MDS-UPDRS score. For each scenario and estimator, results were averaged over 10,000 simulated datasets. Reported performance measures are the bias and mean-squared error for each treatment effect estimator and the power of the associated significance test of the null hypothesis of a treatment effect of 0 at a two-sided significance level of 5%.

### 4.3. Simulation Results

The performance of all estimators for the three estimands is summarized in Table 3. Only the results for the scenarios with a
Hypothetical estimand
Mixed estimand
Treatment–policy estimand

![Graph showing MDS-UPDRS total score change from baseline (higher values worse)](image)

**Figure 2.** Marginal mean MDS-UPDRS trajectories for the intervention (gray lines) and placebo (black lines) groups in the simulation study relevant to the hypothetical, mixed, and treatment policy estimands, respectively. The targeted treatment effect (“simulation truth”) at 12 months is −4.00 points for the hypothetical estimand, −3.60 for the mixed estimand, and −2.85 for the treatment policy estimand.

### Table 3. Performance of all estimators for the three estimands for a sample size of 300 patients per treatment group based on 10,000 simulated datasets.

| Estimator                  | Targeted effect (‘truth’) | Estimate Mean | Bias   | RMSE | Mean SE |
|----------------------------|---------------------------|---------------|--------|------|--------|
| MAR (hypothetical)         | −4.00                     | −3.99         | 0.01   | 0.95 | 0.95   |
| MAR (mixed)                | −3.60                     | −3.77         | −0.18  | 0.94 | 0.92   |
| CIR (mixed)                | −3.60                     | −3.59         | 0.01   | 0.86 | 0.91   |
| TV1-MAR (mixed)            | −3.60                     | −3.68         | −0.08  | 0.94 | 0.93   |
| TV2-MAR (mixed)            | −3.60                     | −3.59         | 0.01   | 0.94 | 0.94   |
| MAR (treatment policy)     | −2.85                     | −2.97         | −0.12  | 0.97 | 0.98   |
| TV1-MAR (treatment policy) | −2.85                     | −2.89         | −0.04  | 0.97 | 0.98   |
| TV2-MAR (treatment policy) | −2.85                     | −2.81         | 0.04   | 0.98 | 0.99   |

**RMSE** = empirical root mean-squared error of estimates, mean **SE** = mean of the standard errors associated with the 10,000 treatment effect estimates.

The simulated power of the estimators for all investigated sample sizes is presented in Figure 3.

For the hypothetical estimand, the basic MAR estimator based only on pre-ICEs data had negligible empirical bias. It was also associated with the largest study power compared to all other estimators. Compared to the CIR estimator for the mixed estimand and estimator TV4-MAR with time-varying covariates for the treatment policy estimand, the two estimators with lowest bias for these two estimands, its power was 66% compared to 62% and 37%, respectively, for a sample size of 100 patients per group, and 99% compared to 98% and 81% for a sample size of 300.

For the mixed estimand, the estimator based on CIR imputation and estimator TV2-MAR based on a time-varying covariate representing the time from treatment discontinuation had negligible bias. Estimator TV1-MAR which included a time-varying indicator of treatment discontinuation slightly overestimated the magnitude of the treatment effect. This bias is due to a misspecification of the time-varying effect of treatment discontinuation on outcomes compared to the simulation parameters. The basic MAR estimator more substantially overestimated the magnitude of the treatment effect because the imputation did not take into account treatment discontinuations. The RMSE was comparable for all MAR-based estimators but substantially lower for the CIR-based estimator. This is well known and occurs because reference-based imputations in the intervention group borrow information from the control group which induces a positive correlation between the two groups and a corresponding reduction in the frequentist variance of the treatment effect contrast (Seaman, White, and Leacy 2014; Wolbers et al. 2022). This variance reduction is not properly captured by Rubin’s rules which explains why the average standard error of the treatment effect estimates is only slightly reduced compared to the basic MAR estimator (Bartlett 2021). Estimators with time-varying covariates had slightly elevated average standard errors. In terms of power, the basic MAR estimator had the highest power, followed by the CIR-based estimator, and estimators TV1-MAR and TV2-MAR based on a time-dependent MAR assumption. The corresponding power estimates were 64%, 62%, 60%, and 57% for a sample size of 100 and 91%, 91%, 89%, and 86% for a sample size of 200 patients per group. The slightly larger power for the basic MAR estimator over the CIR-based estimator is likely an artifact of the anti-conservative bias of the basic MAR estimator.

For the treatment policy estimand, the basic MAR estimator based on all observed data had the largest bias and overestimated the magnitude of the treatment effect. The estimators based on a time-dependent MAR assumption reduced the bias...
by a factor of three but still had a small bias because the specified time-varying indicator variable representing the impact of symptomatic treatment on the outcome was not fully compatible with the simulated effect. The targeted treatment effect of the treatment policy estimand was substantially smaller than for the other estimands and the variability of the estimators (represented by the mean standard error) was substantially larger because of the increased variability in the longitudinal data caused by the symptomatic treatment. Consequently, a larger sample size of 300 patients per group was required until all estimators were associated with a study power above 80% (86% for the basic MAR estimator, 84% for estimator TV3-MAR, and 81% for estimator TV4-MAR).

A last remark regarding the number of failures to obtain a valid treatment effect estimate based on MI. Our Bayesian MI implementation relied on an initial frequentist MMRM fit of the base imputation model with an unstructured covariance matrix to inform the starting values and the prior distribution for the Bayesian imputation model. This is in accordance with the SAS implementation of reference-based imputation by the Drug Information Association Scientific Working Group on Estimands and Missing Data (Roger 2021). If the initial MMRM model failed to converge, then no treatment effect estimator could be determined for a simulation run and it was consequently omitted from all summaries reported above. For all estimators without time-varying covariates, convergence failures were extremely rare and the maximum number of failures observed for any estimator and sample size was 0.06% (6/10,000). For estimators TV1-MAR and TV2-MAR, we observed 2.50% (250/10,000) and 2.49% (249/10,000) failures for a sample size of 75 patients per group, respectively, and 0.73% (73/10,000) failures for both estimators for a sample size of 100 per group. For larger sample sizes, the number of failures for these estimators never exceeded 0.20% (20/10,000). For estimators TV3-MAR and TV4-MAR, we observed 1.44% (144/10,000) and 1.46% (146/10,000) failures for a sample size of 75 patients per group, respectively, and 0.29% (29/10,000) failures for both estimators for a sample size of 100 per group. For larger sample sizes, the number of failures for these estimators never exceeded 0.12% (12/10,000). The larger proportion of failures of estimators involving time-varying covariates occurs because they fail if no data is available to inform the regression parameter of the time-varying covariates. Our simulation set-up implies that the probability that a randomly chosen patient discontinues study medication and has at least one observed post-discontinuation outcome prior to symptomatic treatment initiation is 4.98% in the control group and 7.36% in the intervention group. For simulated dataset with a sample size of 75 patients per group, this implies a probability of 2.48% that no post-discontinuation outcomes prior to symptomatic treatment initiation are included in at least one of the treatment groups. The probability of 2.48% is almost identical to the reported proportion of failures for the estimators TV1-MAR and TV2-MAR of the mixed estimand for this sample size.

5. Discussion
We proposed three different estimands and corresponding treatment effect estimators for an intervention treatment which aims to slow down disease progression in early PD and compared them in a realistic simulation study. A key challenge in this setting is that a substantial proportion of patients may initiate potent symptomatic treatment which could mask the effect of an intervention with significant long-term benefits but less potency for short-term symptom relief. None of the three estimands is uniformly superior to the others. The treatment effect of the hypothetical estimand is relatively straightforward to estimate using a standard MMRM model or multiple imputation under a basic MAR assumption. The hypothetical estimand was also associated with the highest power in our simulation study. However, the clinical relevance of the hypothetical estimand is not clear because in clinical practice, treatment discontinuations due to adverse events or lack of efficacy may occur and symptomatic treatments may also be mandated for some subjects. Therefore, we believe that the hypothetical estimand is primarily relevant to signal-seeking and dose-finding trials. The mixed estimand corresponds to a somewhat more realistic scenario where treatment discontinuations are possible but symptomatic treatments are not allowed (or, more pragmatically, would be deferred until the end of the one year follow-up). For treatments
in Alzheimer’s disease dementia, the guidance document by the European Medicines Agency states that “an appropriate target of estimation could be based on a hypothetical scenario in which the new concomitant medication or modifications in the dose of concomitant medications had not been introduced” (Committee for Medicinal Products for Human Use (CHMP) 2018). Thus, a hypothetical strategy for symptomatic treatment initiation might also be acceptable to regulators in early PD. The treatment policy estimand is closest to the traditional intention-to-treat principle but implicitly favors patients who initiate symptomatic medications. It is also associated with a substantially attenuated treatment effect and larger variability. A consequence of this is that trials powered for the treatment policy estimand would require substantially larger sample sizes than the other estimands \( n \approx 300 \) patients per group compared to \( n \approx 175 \) for the mixed and \( n \approx 150 \) for the hypothetical estimand, respectively, for \( >80\% \) power in our simulation study. In our simulation study, the probability of symptomatic treatment initiation during the 12 month study was \( 33\% \) in the placebo group and \( 30\% \) in the intervention group, that is, it was only marginally higher in the placebo group. If the difference in the rate of symptomatic treatment initiations between treatment groups was substantially larger, for example, due to a very large intervention effect, then this could, at worst, completely mask a relevant treatment effect for the treatment policy estimand.

The discussed missing data assumptions and estimators illustrate the complexity of handling multiple ICEs which may occur in either order and may be addressed by different strategies. For the mixed and the treatment policy estimand, a basic MAR assumption for missing data is no longer tenable and the associated estimators had the largest (and anti-conservative) bias. Alternatives based on reference-based imputation or MAR imputation based on models which include time-varying covariates eliminated the bias or reduced it substantially. For a treatment which aims to slow down disease progression, the reference-based CIR assumption is quite plausible and relatively conservative. The associated treatment effect estimator was unbiased and had slightly larger power than imputations with time-varying covariates for the mixed estimand in our simulation study. Of note, the power gain of the CIR estimator is expected to be even larger if inference was based on frequentist valid standard errors rather than the conventional Rubin’s rules (Seaman, White, and Leacy 2014; Bartlett 2021; Wolbers et al. 2022). A disadvantage of reference-based imputation methods is that imputations are not informed by retrieved post-discontinuation data. If post-discontinuation data is frequently collected, then models including time-varying covariates are a less assumption-dependent alternative (Guizzaro et al. 2021). In our simulation study, these methods were successful at reducing bias and had acceptable power despite a relatively large simulated study drop-out rate of \( 50\% \) after treatment discontinuation. However, these methods are also no panacea because they rely on realistic models for post-discontinuation outcomes.

We tried to make the simulation study as realistic as possible but any simulation study of this complexity has limitations. Study treatment discontinuations were simulated as independent of MDS-UPDRS scores and it could be that the bias of the basic MAR estimator for the mixed estimand would be even larger if this independence assumption did not hold. Moreover, we simulated post-discontinuation trajectories according to a CIR assumption which naturally favors the CIR-based estimator. Finally, the time-varying MAR assumption held for all our simulations and all investigated estimators may be biased under more complex not missing at random scenarios. In practice, any estimator relies on missing data assumptions and it is important to pressure test the impact of these assumptions via suitable sensitivity analyses. As an example, the MAR assumption for the hypothetical estimand would be violated if longitudinal assessments other than the MDS-UPDRS score existed which affected both the occurrence of the ICEs and also subsequent MDS-UPDRS scores. A further complication occurs if all patients whose MDS-UPDRS score exceeded a certain threshold deterministically discontinued study treatment or initiated symptomatic treatment. This would lead to a violation of the so-called positivity assumption. As a consequence, methods based on MMRM or MI are still feasible, but the validity of their estimates relies on extrapolation beyond the data (Parra, Daniel, and Bartlett 2021). The positivity assumption is unlikely to be violated in the early PD setting. Specifically, analysis of the PPMI cohort reported in the supplementary Appendix demonstrates that while the probability of symptomatic treatment initiation depends on the MDS-UPDRS score, the association is far from deterministic. However, it remains plausible that patients who experience an ICE may have had worse outcomes than predicted by MAR if the ICE could have been prevented. One possibility to stress-test the impact of the MAR assumption on treatment effect estimates and inference are sensitivity analyses which apply a \( \delta \)-adjustment to MAR-imputed data prior to the analysis to reflect the anticipated magnitude of this worsening (Cro et al. 2020).

Alternative strategies for dealing with the ICE of symptomatic treatment initiation may also be considered. Darken et al. (2020) proposed a so-called "attributable estimand" which would handle the ICE with a composite strategy. In practice, this can be implemented by imputing suitably unfavorable outcomes for patients with the ICE. However, it is difficult to justify the exact penalty that can be considered as “suitably unfavorable.” The principal stratification strategy would determine treatment effects in the subgroup of patients who would not have initiated symptomatic treatment regardless of the assigned treatment group (Bornkamp et al. 2021). Effects in principal strata can only be estimated under assumptions that cannot be tested empirically and the clinical relevance of such an estimand is less clear. Finally, a while on treatment strategy could be applied and the last outcome value prior to symptomatic treatment initiation rather than the outcome value at a fixed time point could be used in the analysis. Again, the clinical relevance of such a strategy is less clear. Therefore, we believe that these alternative strategies are usually better suited for exploratory and sensitivity analyses than for a primary analysis.

Another possibility is to change the endpoint and the outcome measure altogether. For disease-modifying treatments, a slope model which assumes a linear progression rate has been proposed as an alternative to the MMRM model. A comparison of slopes between treatment groups is typically more powerful than a comparisons of changes at a fixed time point but it also relies on stronger assumptions (Chen et al. 2018). As another possibility, a time-to-event endpoint such as the time to an
increase in the MDS-UPDRS score by a pre-determined threshold could be defined. Many patients may reach this endpoint prior to the initiation of symptomatic treatment hence, limiting its impact. It would be interesting to compare such alternative approaches to the endpoints discussed in this article. Finally, the time to initiation of symptomatic could also be considered as an endpoint. Our analyses of the PPMI data showed a clear association between higher MDS-UPDRS scores and the likelihood of symptomatic treatment initiation. However, the association was far from deterministic and it seems likely that subjective factors such as doctor and patient preferences also affect the timing of symptomatic treatment initiation.

A general limitation of clinical trials with a limited follow-up duration of 12–24 months and the proposed MDS-UPDRS-based estimands is that they can only demonstrate a relatively short-term delay or slowing of disease progression. As stated in the guideline on clinical investigation of medicinal products in the treatment of PD by the European Medicines Agency, this does not imply that a new agent is also a disease modifier. The latter would require the additional demonstration of an effect on the underlying pathophysiology of the disease by for example, biochemical markers or neuroimaging measures (Committee for Medicinal Products for Human Use (CHMP) 2012). Moreover, long-term follow-up of patients after the primary endpoint assessment is desirable.

In conclusion, we discussed the complexity of defining suitable estimands and estimators in early PD and suggested three estimands and corresponding treatment effect estimators. Estimators based on reference-based imputation or imputation models which included time-varying covariates improved upon standard MI or MMRM analyses which had substantially larger bias. More research and regulatory guidance is needed to establish consensus endpoints and estimands for developing novel treatments in early PD.

6. Software Implementation

R code for the reported simulation study has been uploaded to github and can be found at github.com/sociale/Simulation_PDestimands_manuscript. The implementation of all multiple imputation estimators is based on the R package “rbmi” (Reference Based Multiple Imputation) which is described in Gower-Page, Noci, and Wolbers (2022) and available from cran.r-project.org/web/packages/rbmi/.

Supplementary Materials

The supplementary materials describe data analyses of a cohort study from the Parkinson’s Progression Markers Initiative (PPMI) (Marek et al. 2011) which informed the simulation study.

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Data Availability Statement

Data for the supplementary analyses which informed the simulation study were obtained from the Parkinson’s Progression Markers Initiative (PPMI) (www.ppmi-info.org/, download of data on 30 Nov 2020). Qualified researchers may obtain access to the full breadth of individual-level PPMI data via www.ppmi-info.org/access-data-specimens/download-data.

Disclosure statement

The authors report that there are no competing interests to declare.

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References

Armstrong, M. J., and Okun, M. S. (2020), “Diagnosis and Treatment of Parkinson Disease: A Review,” JAMA, 323, 548–560. [491]
Bartlett, J. W. (2021), “Reference-based Multiple Imputation—What is the Right Variance and How to Estimate it,” Statistics in Biopharmaceutical Research, DOI: 10.1080/19466351.2021.1983455. [497,499]
Bornkamp, B., Rufibach, K., Lin, J., Liu, Y., Mehrotra, D. V., Roychoudhury, S., Schmidli, H., Shentu, Y., and Wolbers, M. (2021), “Principal Stratum Strategy: Potential Role in Drug Development,” Pharmaceutical Statistics, 20, 737–751. [499]
Carpenter, J. R., Roger, J. H., and Kenward, M. G. (2013), “Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation,” Journal of Biopharmaceutical Statistics, 23, 1352–1371. [494,495]
Chen, Y.-F., Ni, X., Fleisher, A. S., Zhou, W., Aisen, P., and Mohs, R. (2018), “A Simulation Study Comparing Slope Model with Mixed-Model Repeated Measure to Assess Cognitive Data in Clinical Trials of Alzheimer’s Disease,” Alzheimer’s & Dementia: Translational Research & Clinical Interventions, 4, 46–53. [499]
Committee for Medicinal Products for Human Use (CHMP) (2012), “Guideline on Clinical Investigation of Medicinal Products in the Treatment of Parkinson’s Disease (revision 2 – adopted guideline),” available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-parkinsons-disease-en-0.pdf. [500]
——— (2018), “Guideline on the Clinical Investigation of Medicines for the Treatment of Alzheimer’s Disease (revision 2 – adopted guideline),” available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicines-treatment-alzheimers-disease-revision-2_en.pdf. [499]
Cro, S., Morris, T. P., Kenward, M. G., and Carpenter, J. R. (2020), “Sensitivity Analysis for Clinical Trials with Missing Continuous Outcome Data using Controlled Multiple Imputation: A Practical Guide,” Statistics in Medicine, 39, 2815–2842. [499]
Darken, P., Nyberg, J., Ballal, S., and Wright, D. (2020), “The Attributable Estimand: A New Approach to Account for Intercurrent Events,” Pharmaceutical Statistics, 19, 626–635. [499]
Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., and Dubois, B. (2008), “Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results,” Movement Disorders: Official Journal of the Movement Disorder Society, 23, 2129–2170. [491]
Gower-Page, C., Noci, A., and Wolbers, M. (2022), “rbmi: A R package for standard and reference-based multiple imputation methods,” Journal of Open Source Software, 7, 4251. [500]
Guizzaro, L., Pétavy, F., Ristl, R., and Gallo, C. (2021), “The Use of a Variable Representing Compliance Improves Accuracy of Estimation of the Effect of Treatment Allocation Regardless of Discontinuation in Trials with Incomplete Follow-up,” *Statistics in Biopharmaceutical Research*, 13, 119–127. [495,499]

Horvath, K., Aschermann, Z., Acs, P., Deli, G., Janszky, J., Komoly, S., Balázs, É., Takács, K., Karádi, K., and Kovács, N. (2015), “Minimal Clinically Important Difference on the Motor Examination Part of MDS-UPDRS,” *Parkinsonism & Related Disorders*, 21, 1421–1426. [496]

Horvath, K., Aschermann, Z., Marton, K., Makkos, A., Mark, H., Janszky, J., Komoly, S., Karádi, K., and Kovács, N. (2017), “Minimal Clinically Important Differences for the Experiences of Daily Living Parts of Movement Disorder Society—Sponsored Unified Parkinson’s Disease Rating Scale,” *Movement Disorders*, 32, 789–793. [496]

ICH E9 working group (2019), “ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials,” available at [https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf](https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf). [492]

Little, R. J. A., and Rubin, D. B. (2002), *Statistical Analysis with Missing Data* (2nd ed.), New York: Wiley. [494]

Mallinckrodt, C. H., Bell, J., Liu, G., Ratitch, B., O’Kelly, M., Lipkovich, I., Singh, P., Xu, L., and Molenberghs, G. (2020), “Aligning Estimators with Estimands in Clinical Trials: Putting the ich e9 (r1) Guidelines into Practice,” *Therapeutic Innovation & Regulatory Science*, 54, 353–364. [493,494]

Mallinckrodt, C. H., Lane, P. W., Schnell, D., Peng, Y., and Mancuso, J. P. (2008), “Recommendations for the Primary Analysis of Continuous Endpoints in Longitudinal Clinical Trials,” *Drug Information Journal*, 42, 303–319. [494]

Marek, K., Jennings, D., Lasch, S., Siderowf, A., Tanner, C., Simuni, T., Coffey, C., Kieburtz, K., Flagg, E., Chowdhury, S., and Poewe, W. “The Parkinson Progression Marker Initiative (PPMI),” *Progress in Neurobiology*, 95, 629–635. [492,500]

Parra, C. O., Daniel, R. M., and Bartlett, J. W. (2021), “Hypothetical Estimands in Clinical Trials: A Unification of Causal Inference and Missing Data Methods,” available at [https://arxiv.org/abs/2107.04392](https://arxiv.org/abs/2107.04392). [499]

Polverejan, E., and Dragalin, V. (2020), “Aligning Treatment Policy Estimands and Estimators—A Simulation Study in Alzheimer’s Disease,” *Statistics in Biopharmaceutical Research*, 12, 142–154. [494]

Roger, J. (2021), “Reference-based MI via Multivariate Normal RM (the “five macros” and miwithd),” available at [https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data](https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data). [498]

Seaman, S. R., White, I. R., and Leacy, F. P. (2014), “Comment on ‘Analysis of Longitudinal Trials with Protocol Deviations: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation,’ by Carpenter, Roger, and Kenward,” *Journal of Biopharmaceutical Statistics*, 24, 1358–1362. [497,499]

Siddiqui, O. (2011), “MMRM versus MI in Dealing with Missing Data—A Comparison based on 25 NDA Data Sets,” *Journal of Biopharmaceutical Statistics*, 21, 423–436. [494]

Simuni, T., Siderowf, A., Lasch, S., Coffey, C. S., Caspell-Garcia, C., Jennings, D., Tanner, C. M., Trojanowski, J. Q., Shaw, L. M., Seibyl, J., and Schuff, N. “Longitudinal Change of Clinical and Biological Measures in Early Parkinson’s Disease: Parkinson’s Progression Markers Initiative Cohort,” *Movement Disorders*, 33, 771–782. [495]

Verschuur, C. V. M., Suwijn, S. R., Boel, J. A., Post, B., Bloem, B. R., van Hilten, J. J., van Laar, T., Tissingh, G., Munts, A. G., Deuschl, G., and Lang, A. E. (2019), “Randomized Delayed-Start Trial of Levodopa in Parkinson’s Disease,” *New England Journal of Medicine*, 380, 315–324. [491]

von Hippel, P. T., and Bartlett, J. W. (2021), “Maximum Likelihood Multiple Imputation: Faster Imputations and Consistent Standard Errors Without Posterior Draws,” *Statistical Science*, 36, 400–420. [494]

Wolbers, M., Noci, A., Delmar, P., Gower-Page, C., Yiu, S., and Bartlett, J. W. (2022), “Standard and Reference-based Conditional Mean Imputation,” *Pharmaceutical Statistics*. DOI: 10.1002/pst.2234. [494,497,499]