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Estimand-Aligned Multiple Imputation Strategies in CNS Trials with Complex Intercurrent Events

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ABSTRACT

Multiple imputation (MI) is a robust approach for handling missing data in sensitivity analyses, especially when evaluating different intercurrent event (ICE) strategies. In this context, ICE 1 and ICE 2 represent distinct assumptions about post-ICE outcomes, such as treatment discontinuation or rescue medication use. MI enables the generation of plausible values under each ICE scenario, preserving statistical integrity while exploring the impact of varying assumptions. The challenge lies in aligning imputation models with the estimand framework, ensuring that each ICE strategy reflects clinically meaningful interpretations. By implementing tailored imputation models for ICE 1 and ICE 2, analysts can assess the robustness of primary results and quantify uncertainty due to missingness. This approach supports regulatory expectations for transparency and comprehensive sensitivity analysis, ultimately strengthening the credibility of treatment effect estimates in submissions.

INTRODUCTION

A structured, estimand-aligned multiple imputation (MI) strategy was implemented to handle missing endpoint data arising from intercurrent events (ICEs). The approach was designed to (1) distinguish between different types of missing data, (2) apply assumptions appropriate to each approach, and (3) ensure transparency and traceability in accordance with ICH E9(R1) guidance.

The imputation process consisted of five sequential steps.

Step 1: Derivation of Intercurrent Event Indicators

ICE flags were derived based on predefined clinical criteria to classify subjects according to the type of treatment discontinuation. Subjects were categorized into mutually exclusive ICE groups to support estimand-specific handling of post-ICE data.

- **ICE-1:** Subjects who discontinued study treatment due to adverse events or lack of efficacy
- **ICE-2:** Subjects who discontinued study treatment for reasons other than those defined under ICE-1

These classifications were used to drive the imputation strategy applied to post-ICE endpoint values.

Step 2: Imputation of Intermittent Missing Data (MAR Assumption)

Intermittent (non-monotone) missing endpoint values that were not attributable to intercurrent events were assumed to be Missing At Random (MAR). These values were imputed using a Markov Chain Monte Carlo (MCMC) method, adjusting for baseline covariates and relevant prognostic factors.

This step was performed to convert the dataset into a monotone missing data structure, enabling the use of monotone imputation methods for post-ICE missingness in subsequent steps.

Specifically, the MCMC-based imputation was implemented as a preprocessing step to resolve intermittent missingness while preserving dropout-related missing data, thereby creating a monotone missing data pattern required for downstream monotone regression and controlled imputation approaches. A total of 1000 imputed datasets were generated using different random seeds to show imputation uncertainty along with subgrouping to avoid higher correlation which stabilizes the covariance matrix.

```
PROC MI data = mcmc_in out = mcmc_out nimpute = 1000 seed = 2024;
 MCMC impute=monotone;
 BY <Treatment> <Additional Variables>;
 VAR <Other Covariates>;
 RUN;
```

Step 3: Handling of ICE-1 (Control-Based Imputation, MNAR Assumption)

For subjects classified as ICE-1, all endpoint values collected after the occurrence of the intercurrent event were set to missing, regardless of whether observations were available. This was done to ensure alignment with the estimand definition.

Post-ICE missing values for ICE-1 subjects were then imputed using a control-based multiple imputation approach implemented under a controlled Missing Not At Random (MNAR) framework. This strategy reflects the assumption that, following treatment discontinuation due to adverse events or lack of efficacy, subjects would behave similarly to those in the reference (control) group.

The control-based strategy was operationalized by estimating imputation model parameters using reference arm observations only, consistent with a pattern-mixture formulation of controlled MNAR imputation.

```
proc mi data=ice1_in out=ice1_out nimpute=1 seed=2024;
 by _Imputation_;
 class <Any Categorical Covariates>;
 monotone reg(/details);
 var <Covariates>;
 mnar model<Visits to be analyzed in MMRM>/ modelobs= (<Treatment>='1'));
 run;
```

Step 4: Handling of ICE-2 (Treatment Policy Strategy)

For subjects classified as ICE-2, missing endpoint data were imputed under a treatment policy strategy. Under this assumption, outcomes following treatment discontinuation are considered reflective of the treatment effect, and therefore imputation was performed using standard monotone regression methods under a MAR framework.

This approach preserves post-ICE data behavior consistent with the treatment policy estimand.

```
PROC MI data=DATA_ICE2_IN out=DATA_ICE2_OUT nimpute=1 seed=2024;
 CLASS <Any Categorical Covariates>;
 MONOTONE REG;
 VAR <Covariates>;
 BY IMPUTATION_;
 RUN;
```

Step 5: Final Analysis and Statistical Inference

The primary efficacy analysis was performed on the multiple imputed datasets generated across all imputation steps and intercurrent event categories. Analysis-ready datasets were constructed for each imputation replicate, preserving the multiple imputation structure.

Within each imputed dataset, the primary endpoint was analyzed using a Mixed Model for Repeated Measures (MMRM), including fixed effects for treatment, visit, and treatment-by-visit interaction, with baseline endpoint value

included as a covariate. An unstructured covariance matrix was used to model within-subject correlations, and statistical inference was based on Kenward–Roger degrees of freedom.

```
proc mixed data = mixed_in;
 by _imputation_ ;
     class <Any Categorical Covariates>;
     model <Endpoint> = <Covariates> / ddfm = kr;
     repeated <Visit>/ type=un subject= <Subject ID>;
     lsmeans <Treatment>*<Visit> / pdiff cl alpha=.05;
     lsmestimate <Treatment>*<Visit>
          "Drug_vs_Placebo_Week_X"   [x, x x] [x, x x],
          "Drug_vs_Placebo_Week_X"   [x, x x] [x, x x],
          "Drug_vs_Placebo_Week_X"   [x, x x] [x, x x],
          "Drug_vs_Placebo_Week_X"   [x, x x] [x, x x],
          "Drug_vs_Placebo_Week_X"   [x, x x] [x, x x]
          / cl;
     ods output lsmeans=lsmeans lsmestimates=lsmestimates;
 run;
```

Treatment effect estimates and associated standard errors obtained from the MMRM analyses were subsequently combined across imputations using Rubin's rules, as implemented via PROC MIANALYZE, to derive overall point estimates, confidence intervals, and p-values that appropriately reflect uncertainty due to missing data.

```
proc mianalyze parms=lsmeans;
 by <Visit> <Treatment>;
 modeleffects <Treatment>*<Visit>;
 ods output ParameterEstimates=lsmeans_params;
 run;
```

Methodological Considerations

This stepwise imputation framework explicitly separates intermittent missingness from post-intercurrent event missingness and applies distinct assumptions aligned with the estimand framework. By implementing MAR-based imputation for intermittent missing data and estimand specific controlled imputation for post-ICE data, this approach enhances transparency, interpretability, and regulatory acceptability of missing data handling.

During implementation of the MCMC based imputation, warnings related to covariance matrix singularity were observed, indicating numerical instability in the initial model specification (see Appendix A).

Programming challenges faced while performing analysis

During implementation of the MCMC-based multiple imputation step, model convergence warnings were observed, indicating singularity in the estimated covariance matrix. Such warnings typically arise when linear dependencies or near perfect correlations exist among covariates, or when limited variability is present within subsets of the data used for model estimation.

To address this issue, the set of covariates included in the MCMC imputation model was simplified to retain clinically relevant and prognostically important variables while excluding redundant or highly correlated covariates. This refinement improved numerical stability of the estimation process and ensured successful convergence of the MCMC algorithm without altering the underlying imputation assumptions.

This pragmatic adjustment reflects common best practice in multiple imputation implementations and supports robust and reproducible estimation while maintaining alignment with the estimand framework.

Explicit ADaM derivations were added to align with the statistical analysis plan. This allows for traceability from the planned analysis documentation to the program code.

CONCLUSION

This work demonstrates a structured, estimand-aligned multiple imputation approach for handling missing data arising from intercurrent events. By separating intermittent missingness from post-intercurrent event missingness and applying tailored imputation strategies, the proposed framework improves transparency, traceability, and regulatory acceptability. The stepwise implementation provides a practical blueprint for translating estimand concepts into reproducible analysis workflows using standard statistical tools.

Appendix A: MCMC Diagnostics and Convergence Assessment

The following SAS® log excerpt illustrates the covariance matrix singularity warning encountered during the initial MCMC based multiple imputation step, prior to covariate simplification. The warning occurred due to the higher linear dependency and correlation between the analyzable columns.

```
NOTE: Writing HTML Body file: sashtml5.htm
WARNING: A covariance matrix computed in the EM process is singular. The linearly dependent variables
         for the observed data are excluded from the likelihood function. This may result in an
         unexpected change in the likelihood between iterations prior to the final convergence.
NOTE: The EM algorithm (MLE) converges in 22 iterations.
```

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