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Application of Tipping Point Analysis in Clinical Trials using the Multiple Imputation Procedure in SAS

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ABSTRACT

In phase 3 clinical studies, tipping point analysis has been increasingly requested by regulatory agencies as a sensitivity analysis under missing not at random (MNAR) assumption to assess the robustness of the primary analysis results. One way to implement the tipping point analysis is using the SAS procedure PROC MI, which includes two steps: step one is to impute missing data using multiple imputation (MI) under missing at random (MAR) assumption, and step two uses the MNAR statement to adjust the MI imputed values by a pre-specified set of shift parameters for each treatment group independently. The tipping points are outcomes where the significance of treatment effect is just reversed.

In practice, the actual shifts to the MI imputed values are not always exactly the same as the shift parameters specified in the MNAR statement. We summarize our experience with this issue and potential pitfalls in implementing the tipping point analysis using PROC MI and propose alternative options such that the expected shift can be achieved.

For continuous endpoints, a commonly used imputation method is fully conditional specifications (FCS) which assumes the existence of a joint distribution for all variables (e.g., response across visits). Due to the iterative nature of the FCS method, the final shift may deviate from the specified shift values. A method of sequential FCS is proposed to guarantee the shift values are as expected and exact for continuous endpoint at the target visit, and to make sure a variable at any visit can only be affected by previous visits. For binary endpoints utilizing logistic regression for the imputation model, the shift parameters are not directly applied on the probability scale, but rather are applied on the logit scale. While a constant shift is applied on the logit scale, the shift on the probability scale is no longer constant due to the non-linearity of the logit link function, and the resulting average shift in response rate at the population level cannot be predetermined. Therefore, the exact shift based on the response rate for binary outcomes cannot be achieved by the MNAR statement in PROC MI for tipping point analysis. Alternative option is proposed, such as MI through a direct binary sampling approach.

1. INTRODUCTION

Missing data occur inevitably in almost all clinical trials. Reasons for missingness may vary, such as patients could be lost to follow up during the trial or withdraw consent. Ongoing patients may also have missing measurements due to logistical reasons while staying in the trial. Missing data impose challenges to the intention-to-treat (ITT) analysis of the clinical trials. Ignoring patients with missing data can be inefficient at best but more often can lead to biased interpretability of the outcomes. All statistical models/methods for handling missing data are based on certain assumptions about missing data that are untestable or unverifiable. Several modern statistical methods attempt to reduce the bias from missing data based on the missing data mechanisms. The definition of the missing data mechanisms is coined by Rubin and Little [1], which is the keystone for the missing data field and forms the theoretical framework. Basically, three mechanisms are defined: Missing Completely At Random (MCAR) assumes that the missingness of an observation does not depend on either observed or unobserved measurements; Missing At Random (MAR) assumes that the missingness of an observation depends only on observed measurements; and Missing Not At Random (MNAR) assumes that the missingness of an observation depends on unobserved measurements.

In clinical trials there have been increased feedback/attention from regulatory authorities in the pre-specification of missing data handling methods that allow different assumptions on missing mechanism. MAR is a commonly used assumption for the primary efficacy analyses in clinical trials. In general, likelihood-based approaches and multiple imputation (MI) based approaches are suggested for the primary efficacy analysis and are valid under MAR. For continuous data, linear mixed-effects model for repeated measurements (MMRM) is usually used; for categorical data or count data, generalized linear mixed-effects model (GLMM) may be considered. GLMM and Generalized Estimating Equation (GEE) are included in the CHMP missing data guidance (2010) and FDA sponsored National Research Council report on the prevention and treatment of missing data in clinical trials (2010) as viable approaches under MAR assumption. MI method [2] can be an alternative option for both continuous and categorical data.

Since the missing data mechanism is unknown and MNAR cannot be completely ruled out, regulatory agencies often request sensitivity analyses under the MNAR assumption for handling missing data to evaluate the robustness of the primary analysis results. Tipping point analysis is a popular sensitivity analysis under MNAR by finding the “point(s)” where the *p*-value is tipped to be insignificant under varying assumptions for the missing outcomes for the different treatment groups independently. The goal of tipping point analysis is to explore the plausibility of missing data assumptions under which the conclusion change, i.e. under which there is no longer evidence of a treatment effect. The outcomes from a tipping point analysis provide clinical reviewers information to help determine if these outcomes are implausibly unfavorable. Yan et al. [3] proposed tipping point analysis based on summary statistics. In their methods, mean of missing outcomes is imputed by mean of observed outcomes and adjusted by pre-specified values for continuous variables and response rate of missing outcomes is adjusted at population level. Since the data were not imputed at patient level, analytic models adjusting for covariates cannot be fitted. In this article, we focus on conducting tipping point analysis using the MI method for both continuous and binary endpoints. The MI procedure appropriately accounts for the imputation uncertainty and allows more flexible models to impute missing values based on observed data. Tipping point analysis can be implemented using SAS PROC MI with the MNAR statement and typically includes two steps: step one is to impute missing data using MI under MAR, and step two uses the MNAR statement to adjust the MI imputed values by a pre-specified set of shift parameters for each treatment group independently. For continuous endpoints, the MNAR statement can be used in conjunction with either the MONOTONE or FCS statements. For binary endpoints, the MNAR statement can also be implemented, though it is challenging to achieve pre-specified shift on the probability scale for the missing outcomes. Alternative

approaches can be considered for binary endpoints, such as MI through a direct Bernoulli sampling approach without using PROC MI. This article provides detailed discussion on the application of tipping point analyses for both continuous and binary endpoints using SAS.

The rest of the paper is organized as follows. In section 2, we describe a simulated dataset that is used to illustrate the methods in this article. In section 3, we present the analysis methods and example SAS code for continuous variables. In section 4, we present the analysis methods and example SAS code for binary variables. We discuss our findings and recommendations in the last section 5.

2. SIMULATED DATASET

A simulated dataset is utilized to facilitate the demonstration of tipping point analyses application using SAS. The dataset is set up with two treatment groups: active vs. control, with a sample size of 200 subjects per group, and a total of 6 visits for each subject. Visit 1 is the baseline visit and Visit 6 is the target visit where the endpoint is tested for treatment difference between the two groups. The continuous outcome is generated with mean=17 for the control group vs. mean=13 for the active group at the target visit. The binary outcome is generated by dichotomizing the continuous outcome, with a response rate of 17% for the control group vs. 30% for the active group at the target visit. The simulated dataset assumes MAR with 20% of missing data for both groups at the target visit. Without loss of generality, the missing data has monotone missing pattern.

The simulated dataset is used to demonstrate the proposed methods for tipping point analysis for continuous endpoint in section 3 and for binary endpoint in section 4. The simulation details are described in the Appendix.

3. TIPPING POINT ANALYSIS FOR CONTINUOUS ENDPOINTS

3.1 ANALYSIS STEPS AND GENERAL CONSIDERATIONS

The steps for conducting tipping point analysis using PROC MI for continuous endpoints are described below:

Step 1: Impute missing data under MAR using PROC MI to form M complete datasets. M can vary, usually takes 20-50. In our example, we use M=30.

Step 2: Pre-specify the set of shift parameters K_1 for active group and K_2 for control group. For given constants $k_1 \in K_1$ and $k_2 \in K_2$, adjust the imputed values by k_1 and k_2 for each group respectively using the MNAR statement in PROC MI.

Step 3: Under each pair of pre-specified shift parameters (k_1, k_2), conduct pre-specified statistical analysis for each of the M complete datasets and integrate the results across M datasets by Rubin's rule using PROC MIANALYZE.

As noted in above step 2, we allow a set of different K_1 and K_2 to conduct a two-dimensional tipping point analysis such that the assumptions about missing outcomes on the two treatment groups can vary independently and include scenarios where dropouts on active group have worse outcomes than dropouts on control group. The shift parameters in K_1 and K_2 will be set in incremental sequences to

explore the space of possible missing assumptions systematically and comprehensively. The shift of the means is usually in the direction to reduce the treatment effect until the point where the *p*-value is tipped to be insignificant. For example, if higher values of the outcome mean better treatment effect, K_1 can be set as a decreasing sequence of negative values to allow the mean of the missing outcomes in the active group to be increasingly worse. Similarly, K_2 can be set as an increasing sequence of positive values to allow the mean of the missing outcomes in the control group to be increasingly better. See an example of K_1 and K_2 in Table 1.1.

The MNAR statement in PROC MI can only be used with either the MONOTONE or FCS statement. An important point to note is that, when the multiple imputation is realized through an iterative procedure, the imputed values that are adjusted by the MNAR statement in one iteration can be used to impute values for subsequent variables (in the order specified in the VAR statement) in the next iteration. This nature of the iterative procedure may cause the final shift in the imputed values to deviate from the pre-specified shift parameters. To demonstrate how to get the exact shift in the imputed dataset as specified, we propose two approaches using SAS PROC MI in section 3.2 and 3.3 respectively.

3.2 USING SAS PROC MI MONOTONE OPTION

In this section, we illustrate the use of the MNAR statement in SAS PROC MI along with the MONOTONE option based on the simulated dataset described in section 2. By default, when the MONOTONE statement is applied, missing values are imputed sequentially for the variables in the order specified in the VAR statement. Missing values in each variable are imputed by regressing upon all previous variables in the VAR statement. The visit of interest in this example is visit 6 and the MNAR statement adjusts the imputed values in visit 6 for the 2 treatment groups respectively. Visit 6 outcome is specified as the last variable in VAR statement and therefore is the last variable to be imputed. Since no other imputation are dependent upon visit 6 outcome, the adjusted values by the MNAR statement will not be used to impute missing values for other visits. Therefore, the adjustment applied to visit 6 imputed outcomes in the final datasets will equal exactly the pre-specified shift parameter k_1 for the active group and k_2 for the control group.

Please note, the MONOTONE statement only works when the dataset has a monotone missing pattern. Our example dataset was simulated with a monotone missing pattern. If a dataset has intermittent missing data, an additional step is needed to fill in the intermittent missing data to obtain a dataset with only monotone missing pattern before implementing MI using the MONOTONE option. One option is to use the MCMC statement in PROC MI to fill in the intermittent missing data and transform the data into monotone missing pattern.

The following SAS code illustrates the use of the MNAR statement along with the MONOTONE statement. Y_j *(j=1,…, 6)* is the simulated continuous outcome at each visit *j,* and Y_6 is the outcome of the target visit.

```
PROC MI DATA=indata out=outdata  NIMPUTE=30 SEED=12345;

CLASS group;

BY group;

MONOTONE REG;
```

```
VAR Y1 Y2 Y3 Y4 Y5 Y6;

MNAR ADJUST (Y6 / SHIFT=k1 ADJUSTOBS=(group='Active'));

MNAR ADJUST (Y6 / SHIFT=k2 ADJUSTOBS=(group='Control'));

RUN;
```

3.3 USING SAS PROC MI FCS OPTION

In this section, we utilize the same dataset described in section 2 to illustrate how to conduct tipping point analysis using the MNAR statement together with the FCS option. The fully conditional specifications (FCS) assume the existence of a joint distribution for all variables included in the imputation model. When the FCS REG statement is specified, the default regression model for each variable is to impute the missing values using all other variables. For example, if the response outcome at different visits is all specified in the VAR statement, the missing values at a given visit are imputed using the data from all other visits, including later visits. In addition, the FCS imputation is based on an iterative algorithm, thus the imputed and adjusted values could be used to impute missing values for applicable variables in the next iteration step. Due to these two reasons, the actual shift in the final dataset deviates from the pre-specified shifts k_1 and k_2, as illustrated in Table 1.1. In this example, the MNAR adjusted visit 6 values were used to impute missing values at other visits, and then the imputed values at other visits in return impacts the imputation of visit 6 values through iterations. To avoid this issue, we can bypass the default FCS REG model by using separate FCS REG statements to specify the appropriate regression model to be used for each visit. More importantly, the MNAR adjusted target visit variable, i.e. visit 6 outcome in our example, should not be used to impute any other variables. In other words, visit 6 should not be specified as an independent variable in the regression model (i.e. put on the right of the equations) in any of the FCS REG statements. In this way, the adjusted visit 6 outcome will not affect other variables and in return the adjusted visit 6 outcomes will not get impacted through the iterations, so that the shifts in the final datasets will be exactly the same as specified. To better align with the nature of longitudinal data, it is reasonable to write the FCS statements sequentially, such that the response at a particular visit only depends on data collected at prior visits and not later visits. This allows the exact shift to be achieved using the sequential FCS statements.

Please note, if baseline variables are used in the imputation model, it is necessary to make sure that there are no missing values for any baseline variables. If there are missing values for any of the baseline variables, including baseline response variable and other baseline covariates, FCS REG statements should be explicitly specified to impute the missing values in the baseline variables. If FCS REG statements are not specified for baseline variables that need imputation, by default, all the variables present in the VAR statement will be used to impute the missing baseline variables, and thus the target outcome variable (i.e. visit 6 in the example) will be implicitly used to impute the missing baseline values, which, as mentioned above, will lead to shifts in the final datasets that deviate from the pre-specified shifted values.

The following SAS code uses the default FCS REG statement without specifying the regression model for each visit outcome. The resulting shifts in Table 1.1 show the discrepancy between the actual shifts and the pre-defined shifts, demonstrating that the default FCS statement cannot achieve exact shift as expected.

```
PROC MI DATA=indata out=outdata  NIMPUTE=30 SEED=12345;

CLASS group;

BY group;

FCS REG;

VAR Y1 Y2 Y3 Y4 Y5 Y6;

MNAR ADJUST (Y6 / SHIFT=k1 ADJUSTOBS=(group='Active'));

MNAR ADJUST (Y6 / SHIFT=k2 ADJUSTOBS=(group='Control'));

RUN;
```

Table 1.1 Pre-defined Shifts and Actual Shifts using Default FCS Statement

Active Group		Control Group	
Specified shift: k1	Actual shift*	Specified shift: k2	Actual shift*
-5	-6.8	1	1.4
-4	-5.5	2	2.8
-3	-4.1	3	4.2
-2	-2.8	4	5.6
-1	-1.4	5	7.0

*Actual shift is the average difference between the imputed values under MNAR vs MAR for all imputed records across 30 datasets.

The following SAS code illustrates the recommended sequential FCS approach by specifying the regression model for each outcome using separate FCS REG statements. In this example, visit 6 outcome (Y6) is the target visit endpoint to be shifted in the MNAR statement, so Y6 should not be used as a predictor variable in any of the FCS REG statements. Table 1.2 shows that exact shift is achieved using the recommended sequential FCS approach implemented using the following SAS code.

```
PROC MI DATA=indata out=outdata  NIMPUTE=30 SEED=12345;

CLASS group;

BY group;

VAR Y1 Y2 Y3 Y4 Y5 Y6;

/* There are no missing data in Y1 and Y2 in this example, so the FCS REG statements start with Y3 */

FCS REG (Y3= Y1 Y2 );

FCS REG (Y4= Y1 Y2 Y3);

FCS REG (Y5= Y1 Y2 Y3 Y4);
```

```
FCS REG (Y6= Y1 Y2 Y3 Y4 Y5);

MNAR ADJUST (Y6 / SHIFT=k1 ADJUSTOBS=(group='Active'));

MNAR ADJUST (Y6 / SHIFT=k2 ADJUSTOBS=(group='Control'));

RUN;
```

Table 1.2 Pre-defined Shifts and Actual Shifts using Proposed Sequential FCS Statements

Active Group		Control Group	
Specified shift: k1	Actual shift*	Specified shift: k2	Actual shift*
-5	-5	1	1
-4	-4	2	2
-3	-3	3	3
-2	-2	4	4
-1	-1	5	5

*Actual shift is the average difference between the imputed values under MNAR vs MAR for all imputed records across 30 datasets.

Please note in our example, there are no missing data in Y1 and Y2. If there are missing data in Y1 or Y2, they can either be imputed using other methods prior to applying PROC MI or by specifying the regression model using separate FCS REG statements (e.g. based on other potential covariates not showing in the simulated dataset). Otherwise, by default, the missing values in Y1 or Y2 will be implicitly imputed using all the variables defined in the VAR statement. As mentioned earlier, in this case the adjusted imputed Y6 will be used to impute the missing values in Y1 or Y2, and these imputed Y1 or Y2 values will then be used to impute Y6 missing data through the iterations, resulting in a deviation in the pre-specified shift in the end.

4. TIPPING POINT ANALYSIS FOR BINARY ENDPOINTS

4.1 GENERAL PRINCIPLE AND CONSIDERATIONS

For binary endpoints, tipping point analysis can be conducted without using MI, by enumerating the response rate of the missing data systematically from 0% to 100% in a stepwise manner. For example, let M_1 be the number of subjects missing outcome in the active group, and let M_2 be the number of subjects missing outcome in the control group; let X_1 be the number of subjects imputed as responders out of the M_1 subjects with missing outcome in the active group – the rest are imputed as non-responders. X_1 can take values from 0 to M_1. Similarly define X_2, with values from 0 to M_2. Given each pair of (X_1, X_2), we can obtain the *p-value* for the treatment comparison of active group versus control group using the combined observed data and imputed data for each treatment group. If one pair of parameters are found to just reverse the study conclusion, in terms of *p-value* larger than 0.05 (the original *p*-value <= 0.05), then this set of parameters are called the tipping point. This method was also demonstrated in Yan et al. [3]. This method is a two-dimensional procedure that varies response rates on each group independently and it includes scenarios where dropouts on active group have worse outcomes than dropouts on control group. However, since the assumed response rate is at the population level without patient level imputation, the analysis models cannot adjust for covariates except under the extreme cases, for

instance, the “worst” scenario, where the missing outcomes are assumed to be all non-responders in the active group and all responders in the control group. One feedback from regulatory agency for the above method is that it does not account for imputation uncertainty and is not recommended by the regulatory agency; instead, MI approach is recommended to conduct the tipping point analysis for binary outcomes.

4.2 MNAR STATEMENT WITH MONOTONE OR FCS STATEMENT CANNOT ACHIEVE EXACT SHIFT

The tipping point analysis methods for continuous endpoints using PROC MI with the MNAR statement (as discussed in sections 3.2 and 3.3) can be directly extended to binary endpoints. However, the shift parameter k is applied on the logit scale, rather than directly on the probability scale. Let p_0 be the response rate in the missing population under MAR, where $p_0 = \frac{e^{\hat{\alpha}+x\hat{\beta}}}{e^{\hat{\alpha}+x\hat{\beta}}+1}$ according to the imputation model. Let p be the response rate in the missing population under MNAR, with shift k, where $p = \frac{e^{\hat{\alpha}+x\hat{\beta}+k}}{e^{\hat{\alpha}+x\hat{\beta}+k}+1}$. In order to obtain a predetermined p, one needs to first calculate k by the following formula in order to use the MNAR statement:

$$\text{k} = \log\left(\frac{p}{1-p}\right) - \log\left(\frac{p_0}{1-p_0}\right). \quad (1)$$

On the other hand, when a constant shift (k) is applied on the logit scale, the shift on the probability scale is no longer constant due to the non-linearity of the logistic link function as shown in equation (2), where Z denotes the binary outcome. Therefore, the resulting average shift in the response rate at the population level cannot be exactly specified. As a result, the pre-determined response rate from 0% to 100% in the missing population cannot be achieved by the specified parameter k via the MNAR statement in PROC MI. This is demonstrated using the simulated dataset described in section 2. When the same sequential FCS specification model as used for continuous endpoints was applied to the binary outcomes, Table 2 shows that the actual response rates in the final datasets are different from the pre-specified response rates.

$$\Pr(Z = 1|X) = \frac{e^{\hat{\alpha}+x\hat{\beta}+k}}{e^{\hat{\alpha}+x\hat{\beta}+k}+1} \quad (2)$$

Table 2 Pre-defined Response Rates in the Missing Population and Actually Imputed Response Rates using Sequential FCS

Active Group (observed response rate 29.0%)		Control Group (observed response rate 18.5%)	
Designed response rate %: p1	Actual Imputed response rate %	Designed response rate %: p2	Actual Imputed response rate %
0	0	0	0
20	23	20	20
40	38	40	33
60	54	60	49
80	74	80	68
100	100	100	100

4.3 DIRECT BERNOULLI SAMPLING AND EXAMPLE SAS CODE

Given the limitation discussed with using the MNAR statement for binary outcomes, we propose a direct Bernoulli sampling approach for conducting tipping point analysis for binary endpoints to achieve the following goals:

- Conduct a two-dimensional analysis to allow assumed response rate to vary on each group independently and include scenarios where dropouts on active group have worse outcomes than dropouts on control group.
- Systematically assume a full range of possible response rates in the missing population to change from 0% to 100% in a stepwise manner.
- Account for imputation uncertainty through obtaining multiple datasets from Bernoulli sampling.

Assume p_1 and p_2 are the response rates in the missing population for the active group and the control group respectively, with $0 \leq p_1 \leq 100\%$, $0 \leq p_2 \leq 100\%$. For each pair of given p_1 and p_2, we assign responder or non-responder status to each patient with missing outcome in each group using direct sampling from Bernoulli distribution. Such sampling will be repeated to generate M datasets. M can vary and usually takes 20-50. Same as in the continuous example, we use M=30 in our example for binary endpoint illustration. For each given p_1 and p_2, the pre-specified statistical analysis (e.g., logistic regression) can be implemented for each imputed datasets and the analysis results can be integrated through PROC MIANALYZE. The analysis results will be obtained for all combinations of (p_1, p_2). The same example as described in section 4.2 is used to illustrate this method. As shown in Table 3, the direct Bernoulli sampling method produces actual response rates that are very close to the designed response rate with reasonably small sampling variability.

The following SAS code demonstrates the implementation of the direct Bernoulli sampling in SAS.

```
%do imp=1 %to 30;
        %let seed=%sysevalf(&seed+1);
        DATA outmis; set indata;
        &Z6= input(&Z6,1.);
        if &group="Active" then do;
        if &Z6=. then &Z6=ranbin(&seed.,1,&p1.);
        end;
        else if &group="Control" then do;
        if &Z6=. then &Z6=ranbin(&seed.,1,&p2.);
        end;
        Imputation=&nimp.;
%end;
```

Table 3 Pre-Defined Response Rates in the Missing Population and the Actually Imputed Response Rates using Direct Bernoulli Sampling

Active Group (observed response rate 29.0%)		Control Group (observed response rate 18.5%)	
Designed response rate (%): p1	Actual Imputed response rate %	Designed response rate (%): p2	Actual Imputed response rate %
0	0	0	0
20	20.0	20	19.8
40	40.0	40	40.0
60	60.1	60	60.0
80	79.6	80	80.0
100	100	100	100

5. DISCUSSION

In this article, we present different approaches to conduct tipping point analysis using MI method in SAS for both continuous and binary endpoints. We noted that exact shifts as specified in the MNAR statement are not always achieved, depending on how the imputation model is specified in PROC MI. Alternative solutions are proposed and discussed in this article for continuous and binary outcomes respectively.

To achieve exact shift for continuous endpoints, we propose using the MNAR statement along with the MONOTONE statement or with sequential FCS statements. By default, the MONOTONE statement imputes the missing values sequentially for the variables in the order specified in the VAR statement, and therefore achieves the exact shift. If the dataset has intermittent missing data, in order to use the MONOTONE statement, the intermittent missing data needs to be filled in first to obtain a dataset with only monotone missing pattern. The PROC MI MCMC statement is an option to fill in the intermittent missing data. Since the MCMC option requires multivariate normal assumption, categorical variables cannot be directly used in the imputation model. One remedy is to create dummy variables for categorical variables in the imputation model when MCMC statement is used. When using the MNAR statement along with the FCS option, the exact shift can only be achieved using the proposed sequential FCS where the MNAR adjusted target visit variable should not be used to impute missing data in any other variable. Note that any variable with missing data that does not have an imputation model explicitly specified by an FCS REG statement will by default be imputed using all other variables in the VAR statement (which includes the target visit variable), which will lead to a deviation from the pre-specified shift; therefore, a good rule of thumb is to double check that all variables in the VAR statement are properly accounted for, including baseline variables.

In practice, convergency issues may arise when using the FCS statement; the “augment” option in the FCS statement may help resolve convergency issues. In addition, if MI analysis under MAR will be presented together with the tipping point analysis, to ensure the consistency and comparability between MI results under MAR and tipping point analysis (MI analysis under MNAR) results, the specifications for the two analysis models should be the same including the random seed, the covariates, and the order of the covariates in each FCS REG statement.

For binary outcomes, the MNAR statement cannot achieve pre-specified response rate exactly since the shift parameter in MNAR statement was applied on the logit scale. Alternatively, a direct Bernoulli sampling method is proposed to achieve the prespecified response rates for the missing population for conducting tipping point analysis for binary endpoints.

In conclusion, the tipping point analyses are becoming increasingly popular as a sensitivity analysis in clinical trials to address potential MNAR assumption for missing data. We discussed practical applications of the tipping point analyses using MI in SAS and proposed modelling approaches to achieve the desired MNAR assumptions as specified for both continuous and binary outcomes.

DISCLOSURE

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APPENDIX

The simulated dataset used in the tipping point analysis in the article is described in this appendix. In the simulated dataset, the longitudinal data for both continuous and binary outcomes are generated by the following steps: (1) simulate complete longitudinal data of the continuous outcome, (2) simulate dropouts, and (3) dichotomize the observed continuous outcomes to generate binary outcomes, as described in more details below.

Step (1): Simulate complete longitudinal continuous outcomes.

The longitudinal continuous outcome is simulated from a multivariate normal distribution. The two treatment groups are assumed to have different mean profiles but the same variance-covariance matrix. The mean vectors for the two groups from visit 1- 6 are:

μ_{trt} = (20, 19, 18, 15, 15, 13)

μ_{pbo} = (20, 20, 19, 19, 18, 17)

The 6x6 correlation matrix is

$$\begin{pmatrix} 1 & 0.7 & 0.6 & 0.5 & 0.4 & 0.3 \\ 0.7 & 1 & 0.7 & 0.6 & 0.5 & 0.4 \\ 0.6 & 0.7 & 1 & 0.7 & 0.6 & 0.5 \\ 0.5 & 0.6 & 0.7 & 1 & 0.7 & 0.6 \\ 0.4 & 0.5 & 0.6 & 0.7 & 1 & 0.7 \\ 0.3 & 0.4 & 0.5 & 0.6 & 0.7 & 1 \end{pmatrix}$$

Heterogeneous Toeplitz variance-covariance structure is used to model correlation between individual subject's outcomes, where the correlation decreases as the visits are further apart.

The standard deviation of the multivariate normal distribution is assumed to be heterogeneous across visits:(7.75, 8.37, 8.94, 9.22, 9.49, 9.49).

Step (2): Simulate dropouts

After obtaining the complete data, we simulate the observed data under a monotone missing pattern. The probability of missing M_j at timepoint j, $j > 2$ and up to visit 6, follows a logistic model. The models and corresponding parameters are set as the following:

$$\mathrm{Log}\left(\frac{M_j}{1-M_j}\right) = -110 - 6 * Group + 2 * Y_{j-1} + 2 * Y_{j-2}$$

Where Group is the treatment indicator: active vs control; Y_{j-1} is the continuous outcome at previous visit. We use Z_j to denote the binary outcomes in our example at visit *j,* where *j=1,2,…,6*. The model depends on the treatment group and the continuous outcome from the previous two visits. Then a random Bernoulli variable is generated to determine if the subject dropped out or not. This process is repeated for each patient from the third visit until the patient dropped out or until the end of the study. Observed data are obtained by removing all data at and after the dropout visit.

Step (3): Dichotomize to get longitudinal binary data

After the observed longitudinal continuous data are generated, the continuous outcomes are dichotomized into binary response data, by defining a "response" as a score $Y_j \leq 8$.