

Introduction

Missing data is a common issue to every study that introduces the elements of bias and invalidates the conclusions. The most common method to handle missing data is the method of multiple imputation under MAR assumption. However, the MAR assumption may not always be clinically probable. That is why it is good practice to perform the sensitivity analysis, based on MNAR assumption, that allow to evaluate the robustness of the results to the deviations from the MAR assumption.

Objective

Perform primary efficacy analysis of laboratory parameter by using Multiple Imputation under MAR assumption.
Use Pattern Mixture Models and Tipping Point Analysis involving Multiple Imputation under MNAR assumption to examine the robustness of the primary analysis results.

Missing data mechanism		
MCAR	MAR	MCAR
the probability of being missing is the same for all cases	the probability of being missing is the same only within groups defined by the observed data	the missing values of a variable are related to the values of that variable itself

Pattern Mixture Model	Tipping Point Analysis
the imputed missing data for patients from active treatment have outcomes similar to patients from control treatment.	the imputed missing data for patients from active treatment have outcomes worse than otherwise similar patients from active treatment by a particular value, called shift

SUBJID	TRT01P	AGEGR1	TYPE	week0	week1	week2	week3	week4
001	Placebo	12-17 Years	2	x	x	x	.	.
002	Active	>= 18 Years	1	x	x	.	x	x
003	Active	6-11 Years	1	x	.	x	x	.
004	Active	>= 18 Years	2	x	x	x	x	.
005	Placebo	>= 18 Years	1	x	.	x	x	x
006	Placebo	>= 18 Years	1	x	x	.	x	x
007	Placebo	12-17 Years	1	x	x	.	x	x

Primary analysis under MAR	Active	Placebo
LS Mean (SE)	-744.6 (177.11)	390.4 (262.82)
95 % CI	(-1091.9, -397.2)	(-125.2, 906.0)
LS Mean difference A vs B (SE)	-1134.9 (243.23)	x
95 % CI	(-1611.8, -658.1)	x
P-value	<0.0001	

Pattern Mixture Model (PMM)	Active	Placebo
LS Mean (SE)	-590.42 (189.13)	323.85 (270.65)
95 % CI	(-961.35, -219.49)	(-206.75, 854.44)
LS Mean difference A vs B (SE)	-914.26 (258.73)	x
95 % CI	(-1421.44, -407.09)	x
P-value	0.0004	

Conclusion

A pattern-mixture model with control-based pattern imputation assumes the pessimistic scenario, that effect of the drug is leveled out after the drop-out. This sensitivity analysis performed on the clinical trial data proved the results of the primary analysis and showed the effectiveness of the active drug compared to the placebo.
The tipping point method as another approach used in sensitivity analysis proceeds from the assumption that the true mean of observed data and drop-outs differ by a given value (called shift value). The implementation of this method showed that if the assumption that the mean value of dropout is greater than for observed values for more than 196, then the result of the primary analysis is questionable.

