



AS02: Reassure your assumptions using sensitivity analysis

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Reassure your assumptions using sensitivity analysis

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Introduction

Sensitivity Analysis



The potential purposes of sensitivity analysis

- Impact of outliers
- Impact of protocol deviations in random clinical trials
- **Impact of missing data**
- Impact of different definitions of outcomes
- Impact of distributional assumptions

Missing data impact

Missing data can jeopardize the credibility of the study conclusions especially if their volume is large. While unbiased estimates of treatment effects can be obtained from trials without missing data, it is no longer possible when some patient data is missing. The main problem is that conclusions about treatment effects are based on untestable assumptions about the nature of the mechanism by which the missing data is generated. This is because any method of statistical analysis requires an untestable assumption about the distribution of the missing data.

Pattern-Mixture Models

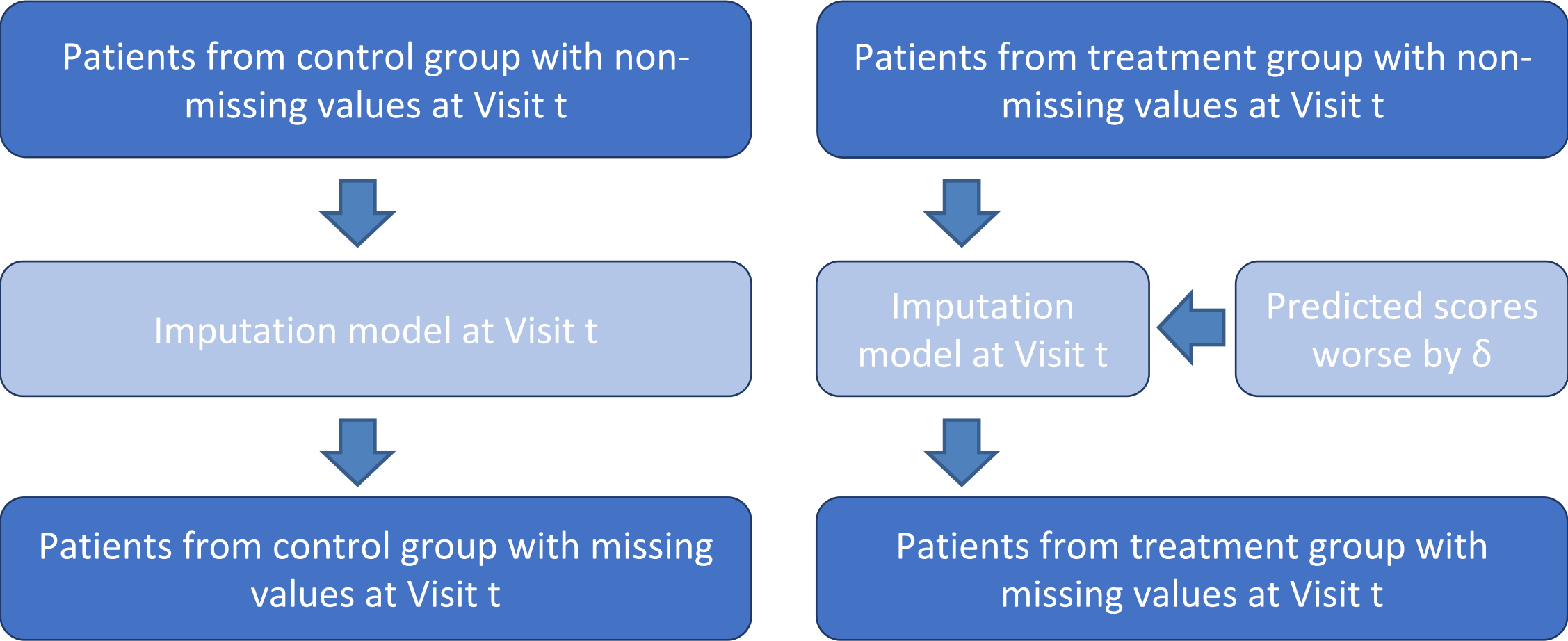
- Delta-adjusting pattern imputation with varying δ
- Control-based pattern imputation

Delta-adjusting pattern imputation (DPI)

An alternative approach to sensitivity analysis in the context of MI is the delta-adjustment method, which was proposed by Rubin (1987) within the pattern-mixture modelling framework, where the MAR imputed values are modified to reflect an assumed MNAR mechanism.

Assumptions of DPI model:

- Subjects from the experimental treatment arm who discontinue at a given time-point would have their unobserved efficacy score worse by δ compared to the observed efficacy score of subjects that continue to the next time point
- Subjects who discontinue from the control arm would exhibit the same evolution of the disease as control subjects that stay in the study
- Sensitivity analysis can be performed for a range of δ to find a “tipping point” – value of δ at which study conclusions change

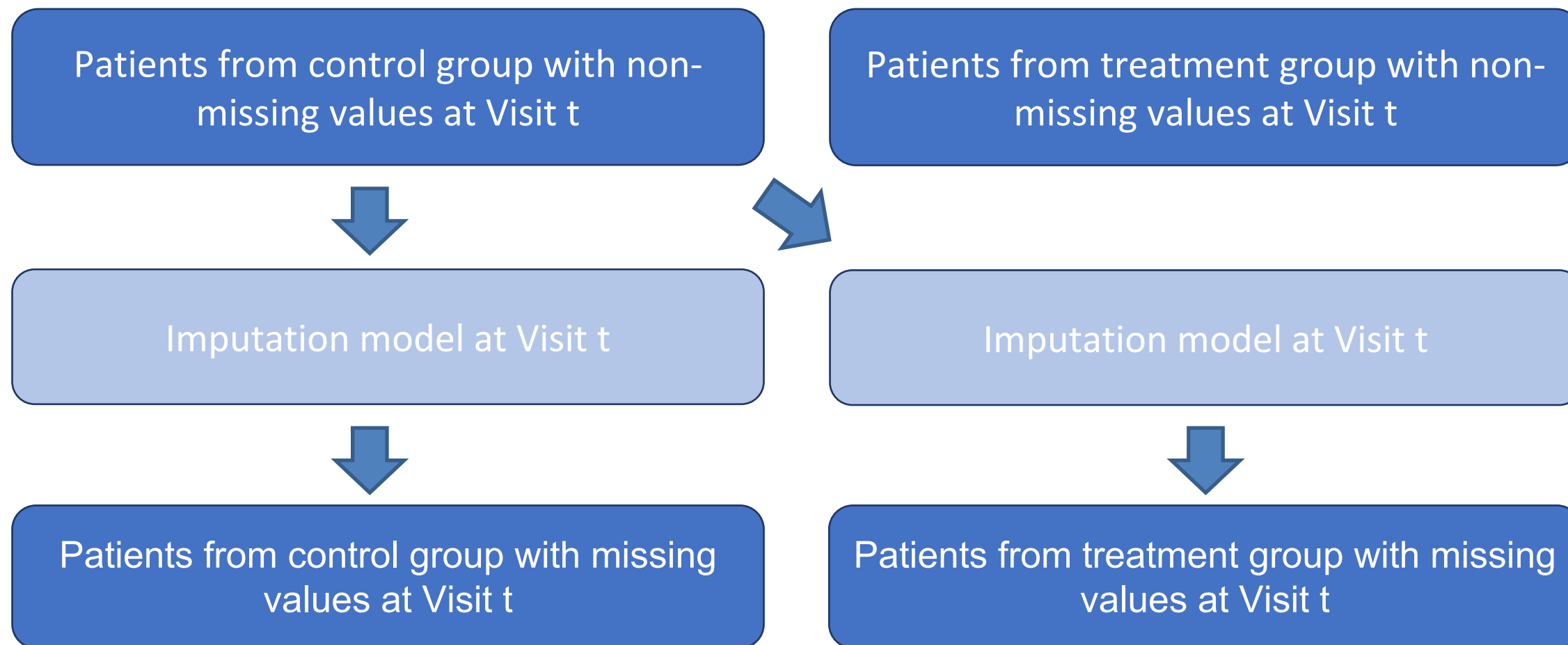


Control-based pattern imputation (CBPI)

Control-based imputation has become attractive for handling missing data in randomized trials (Carpenter et al. (2013)). It is assumed that the distribution of missing data after dropout for subjects in the test drug group is similar to the distribution in the control group.

Assumptions of CBPI model:

- After withdrawal from the study, subjects from the experimental treatment arm will exhibit the same future evolution of the disease as subjects on the control arm
- Subjects who discontinue from the control arm would exhibit the same evolution of the disease as control subjects that stay in the study





Standard MI Implementation



Multiple Imputations (MI)

Introduced by Rubin (1976, 1987) for missing data in surveys

Main features of standard MI:

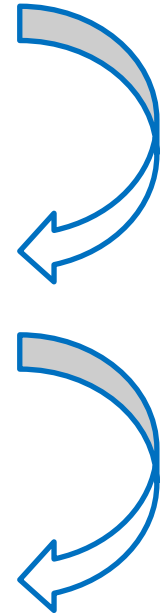
- Imputed values are randomly drawn from a distribution estimated based on non-missing data (imputation model)
- Missing values are replaced with multiple “plausible” values - multiple imputed datasets are produced
- Each imputed dataset is analyzed separately, and then the results are combined taking into account uncertainty (variability) of different imputations

Multiple imputation steps

The missing data are filled in **m** times to generate **m** complete data sets

The **m** complete data sets are analyzed by using standard procedures

The results from the **m** complete data sets are combined for the inference



SUBJID	TRTN	TRT	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8
1001	1	Treatment A	xx	xx	xx	xx	o	o
1002	2	Treatment B	xx	xx	xx	xx	xx	xx
1003	1	Treatment A	xx	xx	xx	o	xx	xx
1004	2	Treatment B	xx	xx	xx	xx	xx	o
1005	1	Treatment A	xx	xx	xx	xx	o	xx
1006	2	Treatment B	xx	xx	xx	o	o	o

Primary endpoint: change from baseline in sleep quality (daily values on a scale from 1 to 10, averaged) at Week 8.

Primary analysis: ANCOVA with the baseline as a covariate (the most commonly used covariate).

```
/*examine missing patterns*/
proc mi data = inds_tr nimpute = 0;
    var vis1 - vis6;
run;
```

Missing Data Patterns														
Group	vis1	vis2	vis3	vis4	vis5	vis6	Freq	Percent	Group Means					
									vis1	vis2	vis3	vis4	vis5	vis6
1	X	X	X	X	X	X	208	41.60	5.7026	5.5309	5.8842	5.6370	5.3875	5.5118
2	X	X	X	X	X	.	76	15.20	5.1693	5.5971	5.3539	5.8382	5.4301	.
3	X	X	X	X	.	X	54	10.18	4.9444	5.5851	5.6327	5.5462	.	5.8983
4	X	X	X	X	.	.	19	3.80	4.9978	6.3463	4.7500	5.0431	.	.



```
/*partial imputation to get monotone missing pattern*/  
proc mi data = inds_tr out = data_mono nimpute = 5;  
    var vis1 - vis6;  
    mcmc impute = monotone chain = multiple;  
    by trtn;  
run;  
  
/*perform multiple imputation of the remaining data*/  
proc mi data = data_mono out = mono_imp_reg nimpute = 1;  
    by _Imputation_;  
    var trtn vis1 - vis6;  
    class trtn;  
    monotone regression;  
run;
```



```
/*ANCOVA for each imputed dataset*/
proc mixed data = mono_imp_reg;
  class trtn;
  model chg_6 = trtn vis1 / solution;
  lsmeans trtn / diff = control('1') cl;
  ods output diffs = lsdiffs lsmeans = lsm solutionf = parms;
  by _Imputation_; /*perform analysis in each imputed dataset*/
run;

/*combining estimates with PROC MIANALYZE*/
proc mianalyze parms(classvar = full) = parms;
  class trtn;
  modeleffects Intercept trtn vis1;
  ods output ParameterEstimates = combined_parms;
run;
```





Sensitivity Analysis Implementation



```
/*perform multiple imputation*/  
proc mi data = data_mono out = mono_d1_imp1 nimpute = 1 seed =  
1113;  
    by _Imputation_;  
    var trtn vis1 vis2;  
    class trtn;  
  
    monotone reg(/details);  
run;  
  
/*Manipulate the output dataset from PROC MI to add delta to the  
value imputed at Week 1 for patients in the study drug arm*/  
data mono_d1_imp1_upd;  
    set mono_d1_imp1;  
    /* $\delta$  equal 1*/  
    if flag = "Y" and trtn = 2 then vis2 = min(vis2 + 1, 10);  
run;
```





```
/*Prepare an input dataset for the call to PROC MI: all control patients and
study drug patients with missing values at Week 1*/
data data_mono_imp data_mono_noimp;
    set data_mono;

    if trtn = 2 and ^missing(vis2) then output data_mono_noimp;
    else output data_mono_imp;
run;

proc mi data = data_mono_imp out = cbpi_1_ nimpute = 1 seed = 1123;
    by _Imputation_;
    var vis1 - vis2;      /* Treatment arm is not included as model effect*/
    monotone reg(vis2);
run;

/*Put back all patients together*/
data cbpi_1;
    set data_mono_noimp cbpi_1_;
run;
```



Tipping Point Analysis

In a tipping point analysis, missing data are imputed over a range of possible scenarios for the treatment effect. This is done in order to identify the scenario or 'tipping point' where the treatment effect in subjects with missing data overturns the significant treatment effect obtained in the MCAR or MAR analysis.

Tipping point analysis steps

- Perform a sequence of analyses assuming progressively worse values for discontinued subjects. Each time magnitude of the adjustment parameter should be increased
- Find a “tipping point” – assumptions under which the result is no longer significant
- Apply clinical judgment about the plausibility of the assumptions underlying the tipping point

Scenario	Details	Conclusion
Study conclusions change from favorable to unfavorable at $\delta = 5$	All discontinued subjects in the treatment arm would need to have sleep quality total score worse by 5 (out of 10) points compared to completers to lose statistical significance	Not a plausible assumption – primary analysis results can be considered robust
Study conclusions change from favorable to unfavorable at $\delta = 1$	All discontinued subjects in the treatment arm would need to have sleep quality total score worse by 1 (out of 10) point compared to completers to lose statistical significance	A plausible assumption – primary analysis results may be questionable



Statistic	Results											
	Standard MI			DPI ($\delta = 1$)			DPI ($\delta = 2$)			CBPI		
P-value	0.0187			0.0256			0.0283			0.0233		
LSM	Est	LCL	UCL	Est	LCL	UCL	Est	LCL	UCL	Est	LCL	UCL
Trt A	-0.19	-0.55	0.16	-0.16	-0.53	0.21	-0.14	-0.50	0.22	-0.18	-0.55	0.20
Trt B	0.40	0.06	0.73	0.41	0.07	0.76	0.42	0.08	0.76	0.31	-0.02	0.63
LS Diffs	Est	LCL	UCL	Est	LCL	UCL	Est	LCL	UCL	Est	LCL	UCL
	0.59	0.10	1.08	0.57	0.07	1.08	0.55	0.06	1.05	0.48	-0.01	0.97

P-value - P-value for the overall treatment effect

LSM - Combined LS Means estimates of change from baseline in Sleep Quality for each treatment group

LS Diffs - Combined LSM estimates of difference between Treatment A and Treatment B in the change from baseline in Sleep Quality



Conclusion



Advantages of Sensitivity Analysis

- Better decision making
- More reliable predictions
- Highlights areas for improvement
- Provides a higher level of credibility





THANK YOU

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