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How sensitive is your analysis? A case study on addressing it at ADaM level.

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ABSTRACT

Sensitivity analyses determine how the different values of an independent variable impact a particular dependent variable under a given set of conditions. Sensitivity analyses are becoming an integral component of Phase III clinical trials, as demonstrated by the latest draft (June 2017) of the Addendum on “Estimands and Sensitivity Analysis” to be incorporated into ICH’s "E9 Statistical Principles for Clinical Trials". These analyses help to explore the impact of missing data, and deviations by statistical models on trial results.

The following is an instance of how the potential bias is addressed by sensitivity analysis. In the case of inclusion of objective progression events without documentation of lesion measurements, the sensitivity analysis would consider only objective progression with documentation and deaths as progression free survival events while backdating objective progression events to the previous complete assessment in the event of missing or incomplete assessments.

The above examples and other sensitivity analyses sometimes involve the creation of data points (by Last Observation Carried Forward (LOCF), Worst Observation Carried Forward (WOCF)) at visits in the Analysis Data Model (ADaM) data sets, which do not exist in the SDTM data sets (e.g., when the visit was skipped or not performed). In this paper, we would like to present how the needs of each sensitivity analysis are addressed, sometimes by creation of new records that do not exist using Trial Visits (TV) data set in Response (ADRS) and Patient Related Outcomes (PRO) related ADaM data sets.

INTRODUCTION

In randomized blinded clinical trials, sponsors are required to specify the analyses and choose one of them as the primary analysis, as a part of the Statistical Analysis Plan (SAP) and protocol, long before they have access to the outcome data. This preplanning of analyses addresses the potential for bias and helps reduce disputes between sponsors and the Food and Drug Administration (FDA) on the interpretation of results. However, the assumptions made by these pre-specified analyses at best, use the statistical information derived from similar trials and is unverifiable at the beginning of the trial; and there exists a possibility that it may end up being unsupported by the actual data after the unblinding process is complete.

Sensitivity analysis (SA) helps to address the above issue by investigating whether the results of important analyses are sensitive or robust enough to handle the violations of the assumptions, by performing analyses targeting a specific clinical question under contrasting assumptions. In brief, SA addresses the “what if the key inputs or assumptions are changed” type of question. Consistency between the results of primary analysis and those of sensitivity analysis may thus strengthen the credibility of the findings. FDA and the European Medicines Association (EMEA), which offer guidance on Statistical Principles for Clinical Trials, also state, “It is important to evaluate the robustness of the results and primary conclusions of the trial.” Robustness refers to “the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis” (CDER & CBER, 2017)

As a part of sensitivity analysis, some “What if” scenarios involve using projected data to substitute for missing data, e.g., Last Observation Carried Forward (LOCF) is one of the commonly used approach to consider the data point of a previous time point in case a the time point of interest is missing the data point. It is often challenging to incorporate projected data while following FDA mandated traceability driven study data standards using the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and CDISC Analysis Data Model (ADaM). The objective of this paper is to provide an overview of different sensitivity analyses used in clinical trials, and using a case study to show

how to approach sensitivity analyses involving missing data in particular, while adhering to the SDTM and ADaM implementation guidelines.

TYPES OF SENSISTIVITY ANALYSIS

In this section, we describe scenarios that may require sensitivity analyses, and how one could use sensitivity analyses to ascertain the robustness of the findings of randomized clinical trials. This is not an exhaustive list, but rather illustrates some common situations where sensitivity analyses might be useful to consider (Thabane, et al., 2013) (Morris, Kahan, & White, 2014); also example sensitivity scenarios are summarized in Table 1.

OUTLIERS:

Outliers are numerically distant from the rest of the data and are usually exceptional cases in a sample. The issue with outliers is that they may drastically change the mean and thus influencing any estimation of intervention effect derived from the mean. A box-plot would give a visual confirmation of the outliers and performing a sensitivity analysis with and without the outliers would assess the impact of the outliers, on the primary outcome.

PROTOCOL DEVIATIONS:

During the clinical trials, some of the participants may not follow the pre-allocated treatment regime or might miss some of the scheduled treatment visits. Other types of protocol deviations include switching between intervention and control arms, non-implementation of intervention as prescribed (e.g., dose delays or reduction).

Usually in randomized clinical trials, the primary analysis uses an intention-to-treat (ITT) principle, i.e., assessment of the participants according to the arm they are initially randomized to, irrespective of whether they actually received the treatment or completed the treatment. Following two types of sensitivity analyses assess the impact of the protocol deviations on results:

1. Per-protocol (PP) analysis: in which participants who violate the protocol are excluded from the analysis

2. As-treated (AT) analysis: in which participants are analyzed according to the treatment they actually received.

In summary, ITT provides the “real life” scenario, in which some participants do not comply, while the PP analysis illustrates the ideal scenario in which all participants comply, and is more likely to show an effect.

CLUSTERING:

In the same trial, sponsors may recruit participants from multiple sites or countries. Each of these centers will constitute a cluster. These clusters can also be patients treated by the same physician, physicians in the same hospital, etc. Patients within a cluster often have some degree of homogeneity as compared to patients who belong to different clusters. Therefore, in order to account for the similarities within clusters one can include the following two forms of sensitivity analyses into the analytic plans:

1. Analysis with and without taking clustering into account: comparing the analysis that ignores clustering (i.e., assumes that the data are independent) to another, where the primary method of analysis is chosen to account for clustering.

2. Analysis that compares several methods of accounting for clustering.

MISSING DATA:

Almost every research study has some missing data. Mostly the data is missing due to:

- Non-response in surveys due to lack of interest, lack of time, nonsensical responses, and coding errors in data entry/transfer.
- Due to loss to follow up, dropouts, non-adherence to protocol, missing doses, and data entry errors.

Missing data can be classified as Missing Completely At Random (MCAR), and Missing Not At Random (MNAR). Consider the following example trial where a novel cancer treatment is compared to the standard of care in which participants are followed at 2, 4, 6 and 8 months. If the participant misses the follow up at 6th and 8th months and these are unrelated to the outcome of interest, which is mortality in this case, then this missing data is MCAR. The reasons such as a clinical staff being on leave or equipment failure are often unrelated to the outcome of interest. However, in the case above, if the participant missed the 6th month, as he was too ill to come to the center or 8th month appointment, as he was dead. Then, the missing data is MNAR and related to the outcome of interest. Ignoring missing data in a MNAR scenario most certainly leads to biased parameter estimates.

It is often tough to obtain the reason for missing data and hence in general, any missing data can have implications on the reliability of the research findings. There are two main approaches to handle missing data:

1. Ignore the missing data, and use complete case analysis

2. Impute the missing data, using either single or composite imputation techniques.

Imputation is one of the commonly used approaches to handle missing data. Examples of single imputation methods include mean imputation, regression technique, last observation carried forward (LOCF), and Worst observation carried forward (WOCF); and composite methods, which uses a combination of the above methods to impute missing values. There are also some statistical approaches to deal with missing data, without imputation. For example, linear mixed models are used in studies with continuous outcomes, for analyzing outcomes measured repeatedly over time. Generalized estimating equations [GEE] and random-effects generalized linear mixed models [GLMM] are usually used for categorical responses. It is important to note that in these models, it is assumed that the data is missing at random.

Scenario	**Sensitivity Analysis Options**
Outliers	• Assess outliers by a boxplot • Perform analyses with and without outliers
Protocol Deviations	Perform • Intention-to-treat analysis (as primary analysis) • As-treated analysis • Per-protocol analysis
Clustering	• Compare the analysis that ignores clustering with one primary method and multi-center trials chosen to account for clustering • Compare the analysis that ignores clustering with several methods of accounting for clustering
Missing Data	• Analyze only complete cases • Impute the missing data using single or composite imputation methods and redo the analysis

Table 1. Examples of some scenarios for sensitivity analysis in clinical trials.

INCORPORATING SENSITIVITY ANALYSIS IN ADAM DATA SETS

As a part of the clinical trial, the data is often collected into a clinical database. As mandated by the FDA's study data standards, this collected data must be converted into standard data tables, for analysis and submission purposes. The SDTM defines the way in which individual observations from a clinical study are compiled. The underlying concept is that each piece of data can be uniquely identified based on corresponding information (e.g., patient ID, date, time, study, study visit, procedure, measurement unit, etc.). Thus, each row contains one piece of data and many columns of identifying information, making it comprehensive and consistent across studies. The data in SDTM are broken into multiple "domains" such as demographics (DM), subject visits (SV), concomitant medications (CM), exposure (EX), adverse events (AE), ECG results (EG), laboratory results (LB), and vital signs (VS).

Analysis data sets are created to enable the statistical and scientific analysis of the study results. The analysis data model (ADaM) specifies the fundamental principles and standards to ensure that there is clear lineage from data collection to analysis i.e., traceability. The ADaM data sets are the "authoritative source for all data derivations used in statistical analyses." For example, if change from baseline in body weight was the primary efficacy variable, the SDTM would contain each body weight measurements. An ADaM data set would include the derived change from baseline body weight for each time point to be included in the statistical analysis, as shown in Figure 1 . In simple terms, SDTM data sets are "raw" data and ADaM data sets are the analysis data sets.

SDTM (VS Domain)

STUDYID	DOMAIN	USUBJID	VISIT	VSSEQ	VSTESTCD	VSORRES	VSORRESU
XYZ	VS	XYZ-001-001	BASELINE	1	WEIGHT	90.5	kg
XYZ	VS	XYZ-001-001	VISIT 1	2	WEIGHT	100.5	kg
XYZ	VS	XYZ-001-001	VISIT 2	3	WEIGHT	110.5	kg

A subject's weight at different visits is captured in separate rows with some repeating identifying information under the following columns:
STUDYID,DOMAIN,USUBJID,VSTESTCD.

ADaM (ADVS Dataset)

USUBJID	AVISIT	ASEQ	PARAM	AVAL	BASE	CHG
XYZ-001-001	BASELINE	1	Weight (Kg)	90.5	90.5	0
XYZ-001-001	VISIT 1	2	Weight (Kg)	100.5	90.5	10
XYZ-001-001	VISIT 2	3	Weight (Kg)	110.5	90.5	20

The subject's change from baseline is captured in a ADaM dataset, which is a derivative of the above captured SDTM data, illustrating the traceability using the columns AVAL, BASE and CHG.

Figure 1. An example of data capture at the SDTM and ADaM level.

CLUSTERING, OUTLIERS AND PROTOCOL DEVIATIONS:

The structure of the ADaM Data sets makes it easy to address the requirements of most of the sensitivity analysis. The Figure 2 below shows an example study XYZ and how each variable serves the need of each type of sensitivity analysis. For instance, the sensitivity analysis associated with clustering requires identification of data points by the cluster. In the example below, the cluster is the clinical site and the SITEID variable provides the identifying information.

For the sensitivity analysis involving the protocol deviations, the ITTFL and PPROTFL flag variables help to differentiate the subjects across the Intent-to-treat, and the per protocol populations. In this study, the outliers are defined to have a weight greater than twice the baseline weight. The CHG (Change) variable shows the change from baseline and the CRIT1FL variable flags the row with an outlier, based on the CHG value.

ADVS Dataset

USUBJID	SITEID	ITTFL	PPROTFL	AVISIT	ASEQ	PARAM	AVAL	BASE	CHG	CRIT1	CRIT1FL
XYZ-001-001	001	Y	Y	BASELINE	1	Weight (Kg)	90.5	90.5	0		
XYZ-001-001	001	Y	Y	VISIT 1	2	Weight (Kg)	100.5	90.5	10	OUTLIER:CHG >2* BASELINE	N
XYZ-001-001	001	Y	Y	VISIT 2	3	Weight (Kg)	110.5	90.5	20	OUTLIER:CHG >2* BASELINE	N
XYZ-002-002	002	Y	N	BASELINE	1	Weight (Kg)	50.5	50.5	0		
XYZ-002-002	002	Y	N	VISIT 1	2	Weight (Kg)	60.5	50.5	10	OUTLIER:CHG >2* BASELINE	N
XYZ-002-002	002	Y	N	VISIT 2	3	Weight (Kg)	120.5	50.5	70	OUTLIER:CHG >2* BASELINE	Y

ITTFL=Intent-To-Treat Population Flag , **PPROTFL**=Per-Protocol Population Flag

CRIT1=Analysis Criterion 1, **CRIT1FL**=Criterion 1 Evaluation Result Flag

Figure 2. An example data set showing the variables used for the sensitivity analysis involving clusters, outliers, and protocol deviations.

MISSING DATA:

Illustrating the missing data using the ADaM guidelines is a little complicated, as the very principle of ADaM is to maintain the traceability to SDTM data, and the missing data populated by imputation at ADaM does not exist at the SDTM level. Let us consider an example study ONC, which is a randomized double-blinded oncology study with Progression Free Survival (PFS) as the primary endpoint (Bhattacharya, Fyfe, Gray, & Sargent, 2009). This study involves some missing data where the subject missed two consecutive pre-specified scans at visit 2 and 3 respectively. A sensitivity analysis has been proposed to explore the impact of these missed scans by the following methodology. If a subject misses two or more consecutive missed scans, then the date of last radiologic tumor assessment prior to the missed visits or the date of randomization in the absence of a post-baseline radiographic tumor assessment prior to missed visits, is used for censoring. The complexity in this sensitivity analysis is how to depict the missed scans in the data set, which are not captured in the raw data, as they never happened.

As shown in Figure 3, we approach this problem using the Trial visits (TV) and the Response (RS) SDTM data sets. The TV data set has the list of all the scheduled visits and the VISITDY variable in this data set has the proposed day on which the scheduled visit is supposed to happen, as outlined in the protocol. We merge this TV data set at the subject level with the RS data set, which originally contains only VISIT 1 and VISIT 4 associated rows, as the subject is missing the VISIT 2 and VISIT 3. After merging with TV and ADaM related transformation, we will have the missed visits 2 and 3 generated in the ADRS data set. Please note that the VISITDY of TV is analogous with the AWLO variable of ADRS. The AVALC value for the VISIT 2 and 3 is set as “Missed”, and it would also have the ADT, and ADY missing as these visits never happened.

As the missed visits, VISIT 2 and 3 are consecutive, we derive a row with AVISIT “Visit prior to consecutive miss scans” having the values of VISIT, ADT, ADY and AVALC carried over from the

previous non-missing visit, VISIT 1. The DTYPE for the derived record will be “LOCF”, and the ADT of this row is used for censoring this subject instead of the considering the “PD” or “Progressive Disease” at VISIT 4 as an event. The reason is to conservatively go with a last known assessment before the consecutive missed scans, as there lies a chance that the subject could have progressed during the consecutive missed scans.

TV Dataset

STUDYID	DOMAIN	USUBJID	VISIT	VISITDY	VISITNUM	TVSTRL
ONC	TV	ONC-001-001	BASELINE	0	1	Start of Screen Epoch
ONC	TV	ONC-001-001	VISIT 1	267	2	9 Months (+/- 1 week) after the start of the Treatment Epoch
ONC	TV	ONC-001-001	VISIT 2	320	3	12 Months (+/- 1 week) after the start of the Treatment Epoch
ONC	TV	ONC-001-001	VISIT 3	411	4	15 Months (+/- 1 week) after the start of the Treatment Epoch
ONC	TV	ONC-001-001	VISIT 4	502	5	18 Months (+/- 1 week) after the start of the Treatment Epoch

RS Dataset

STUDYID	DOMAIN	USUBJID	VISIT	RSSEQ	RSTEST	RSORRES	RSDTC
ONC	RS	ONC-001-001	VISIT 1	1	Overall Response	SD	23May2014
ONC	RS	ONC-001-001	VISIT 4	2	Overall Response	PD	02Mar2015

ADRS Dataset

USUBJID	VISIT	AVISIT	ADT	ADY	AWLO	AWTARGET	AWHI	AVALC	DTYPE
ONC-001-001	VISIT 1	VISIT 1	23May2014	269	267	274	319	SD	
ONC-001-001	VISIT 2	VISIT 2			320	365	410	Missed	EXTRAP
ONC-001-001	VISIT 3	VISIT 3			411	456	501	Missed	EXTRAP
ONC-001-001	VISIT 1	Visit prior to consecutive miss scans	23May2014	269				SD	LOCF
ONC-001-001	VISIT 4	VISIT 4	02Mar2015	552	502	547	592	PD	

ADY= Analysis Day, **AWLO**= Analysis Window Beginning Time point , **AWTARGET**=Analysis Window Target,
AWHI=Analysis Window Ending Timepoint , **DTYPE**=Derivation Type, **EXTRAP**=Extrapolation, **LOCF**= Last Observation Carried Forward

Figure 3. Projecting the missing data in the ADRS data set adhering to ADaM guidelines.

CONCLUSION

Sensitivity analysis is no longer a good to have analysis, but has now become an integral part of the clinical trial’s overall analysis, as per the evolving guidance documents under preparation at the FDA. In addition, as the implementation of the SDTM and ADaM standards is being made mandatory for the new trials, there is a need to utilize the robustness of the ADaM guidelines to encompass all the analyses of a clinical trial and to make the derivations transparent without losing the traceability, and also easily understandable to the reviewers. In this paper, we have showcased some of the cases and we conclude by suggesting to embrace the ADaM guidelines to fullest extent, with the changing guidelines, for a successful submission.

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