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How to understand the basic requirements of AE analysis and build up an AE data flow that fits the analysis purpose

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ABSTRACT

Adverse Event analysis is an essential and common part of a clinical trial. AE analysis can be either straightforward or very tricky depending on different study designs. It's important for a statistical programmer to understand the data flow of AE in a clinical trial, which will help us to generate reporting outputs correctly.

In this paper, we will focus on understanding the basic requirements of AE analysis and how we build up an AE data flow to fit the analysis purpose, especially for AE with severity grade change.

INTRODUCTION

Protocol and SAP are the most important documents for a Statistical programmer to understand the study, from which you will find the details of all scheduled activities including important definitions, rules for data collection and complex derivation methods, and the way of presenting our analysis interest. Understanding these documents, we will have a big picture of what will be analyzed, and how will we manipulate the data in order to fit our final report.

GRAB INFORMATION FROM PROTOCOL AND SAP

Adverse Event (AE), which is a very common but also indispensable part in a study of clinical trial.

There's a lot of useful information available in protocol and Statistical Analysis Plan (SAP), for instance:

- AE/SAE definition and collection period
    - What is an adverse event, and when and how will we collect those AEs, especially for complex study design, there may be multiple study periods of interest. You may also want to pay attention to how to follow up AEs, usually study will stop collecting data after a study subject reaches the end of the study visit, but some studies may mention that those AEs not resolved at end of study (EOS) will be followed as long as the outcome is medically indicated.

- What information will be collected for AE/SAE
    - Common AE information includes but is not limited to AE verbatim, timing information, seriousness, severity, action taken regarding Investigational Product (IP), and causality.
    - We need to pay attention to severity, which is not equal to seriousness. For example, for a mild stroke, the severity is "mild", but it's definitely a serious AE.
    - Some studies may show an interest in analyzing AEs with severity changes, which is very tricky because you must get familiar with how will we collect the degree changes information so that you can plan how to create the data structure which supports the following analysis.

- Imputation rules for missing AE dates
  - Detailed rules for handling partial AE start or end dates. It's critical for the derivations that use the imputed dates.

    Typically, we will implement a conservative method for partial dates imputation.

    <u>Start date:</u>

    - If the day is unknown, then:
      - If the month and year match month and year of treatment exposure start dates, then impute the day the same as the exposure start date, ex. below table row 1; otherwise, assign the first day of the month, ex. below table row 2.
    - If the month is unknown, then:
      - If the year matches the year of treatment exposure start dates, then impute the month and day the same as the exposure start date, ex. below table row 3; otherwise, assign 'January 01, ex. below table row 4.
    - If the year is unknown, then the date will not be imputed.

TRTA	EXSTDTC	ROW	AESTDTC	ASTDT	ASTDTF
A	2016-04-03	1	2016-04	2016-04-03	D
		2	2016-05	2016-05-01	D
		3	2016	2016-04-03	M
		4	2017	2017-01-01	M

    <u>End date:</u>

    - If the day is unknown, then:
      - If the month and year match month and year of treatment exposure end dates, then impute the day the same as the exposure end date, ex. below table row 1; otherwise, assign the last day of the month, ex. below table row 2.
    - If the month is unknown, then:
      - If the year matches the year of treatment exposure end dates, then impute the month and day the same as the exposure end date, ex. below table row 3; otherwise, assign 'December 31', ex. below table row 4.
    - If the year is unknown, then the date will not be imputed. Treat it as ongoing.

TRTA	EXENDTC	ROW	AEENDTC	AENDT	AENDTF
A	2016-04-03	1	2016-04	2016-04-03	D
		2	2016-05	2016-05-31	D
		3	2016	2016-04-03	M
		4	2017	2017-12-31	M

Generally speaking, this conservative method is straightforward, but things can be tricky for a crossover study design.

TRTA	EXSTDTC	ROW	AESTDTC	ASTDT	ASTDTF
A	2016-04-03	1	2016-05	?	?
B	2016-05-16				

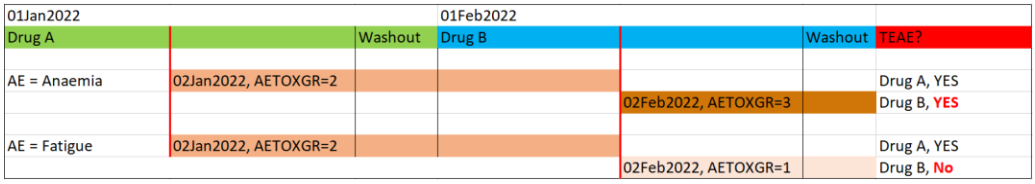
For the situation shown above, we are not sure whether this AE happened during treatment A period or treatment B period. For a concervative way, we need to impute this partial date for both treatment arms.

TRTA	EXSTDTC	ROW	AESTDTC	ASTDT	ASTDTF
A	2016-04-03	1	2016-05	2016-05-01	D
B	2016-05-16		2016-05	2016-05-16	D

So we will get two records in ADaM.ADAE shown above, and partial AE end date will follow the same rule for records derivation.

- Rules for TEAE
  - It's important to understand the definition of Treatment Emergent AE (TEAE), whether you are only defining TEAE as those AEs will happen on or after treatment or also considering those happened before treatment but get worsened afterward.

    For example, If we have a trial including two treatments each followed by a washout period. As shown below, Fatigue occurred after taking Drug A, and the toxicity grade decreased from 2 to 1 at Drug B period. Without worsening toxicity, fatigue is a TEAE during Drug A period, not Drug B. While anaemia occurred after taking Drug A and get worsen after switching to Drug B, so the anaemia is considered a TEAE for both Drug A and B.

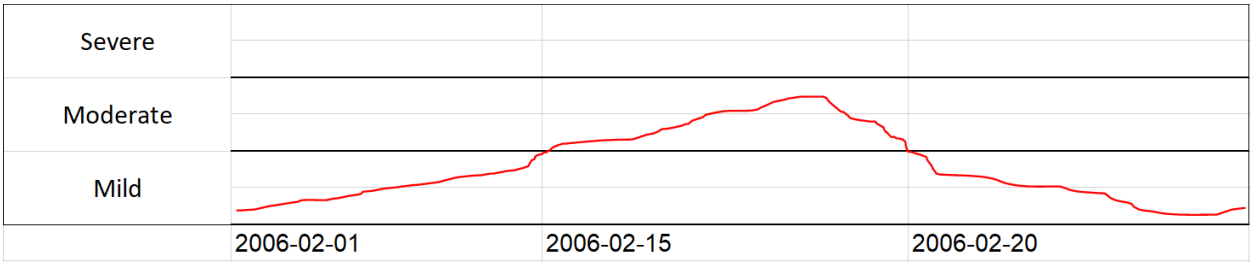


- Dictionary information: MedDRA / CTCAE
- Presentation requirement
  - We need to pay attention to what will be included in AE tables and listings.
    - Summarized by different categories, such as All AE/ Common AE/ AE leading to discontinuation/ AE with CTCAE grade 3 or higher
    - The sort order for output, ex. SOC/PT, international order
    - Other specific requirements, such as to present listing cover patients switching group
    - Result format, like to show out frequency and percentage of patients in each different categories

BUILD UP THE DATA STRUCTURE THAT FITS YOUR STUDY

With the understanding of the analysis requirement from documents, you already had a big picture in your mind about what to do with the AE analysis. The next step is about building up corresponding SDTM and ADaM datasets to fulfill the analysis purpose.

The first thing you need to find out is how will your study collect AE data. Typically the data structure is one record per AE per subject per unique event, which will be collapsed to the highest level of severity cause outcome. For example, you may find your Protocol says “Maximum intensity (mild, moderate, or severe)” in the section of AE data collection. But this is not the fact in real life, for instance, the severity of an adverse event may look like this:



Here we use an example from SDTMIG v3.3 for reference, based on the interest of your protocol mentioned above, you will only see one record of “moderate” nausea collected for the patient. So your SDTM will only have one record for this AE.

Table: SDTM.AE

SUBJID	AESEQ	AETERM	AEDECOD	AESEV	AESTDTC	AEENDTC
1001	1	Morning queasiness	Nausea	MODERATE	2006-02-01	2006-02-23
1001	2	Watery stools	Diarrhea	MILD	2006-02-01	2006-02-15

What about those studies that care about AE severity change? For this situation, not just maximum severity will be collected, you will find out the severity changes over time are also collected and be treated as separate events. Per SDTMIG V3.3's suggestion, these changes are collected in SDTM FA.

Table: SDTM.FA

SUBJID	FASEQ	FATESTCD	FATESTCD	FAOBJ	FAORRES	FADTC
1001	1	SEV	Severity/Intensity	Nausea	MILD	2006-02-01
1001	2	SEV	Severity/Intensity	Nausea	MODERATE	2006-02-15
1001	3	SEV	Severity/Intensity	Nausea	MILD	2006-02-20

Next, we will briefly go through a simple crossover study analyzing AE with toxicity grade change over time, in order to illustrate the end-to-end AE data flow.

STUDY DESIGN

Below shows a simple chart of study trial elements:

Screening	TRT A	Washout	TRT B	Washout	Follow-up

After the screening, the study subject will receive treatment A and then take treatment B after a washout period. In this study, we will collect the maximum AE toxicity grade and also information on grade changes over time including new grades and corresponding dates. The Treatment Emergent AE is defined as “an event that emerges during treatment, having been absent pre-treatment, or worsens

relative to the pretreatment state". Finally, we will present the incidence of TEAE in different treatment groups.

RAW DATA COLLECTION

For this study, we have three AEs. First is Anaemia that happened on 2022-05-29T09:00, with 3 severity grade changes, corresponding dates are collected in AEC01DAT~AEC03DAT, and the grade changes are collected in AEC01TOX~AEC03TOX. Second AE, Fatigue happened on 2022-05-30T09:05 without any toxicity grade change. Third AE, Nausea has a partial start date, without event end date and toxicity grade change.

Table: RAW.AE

row	SUBJID	AEDECOD	AESTDAT	AEENDAT	AETOXGR
1	1001	Anaemia	2022-05-29T09:00	2022-06-02T16:30	1
2	1001	Fatigue	2022-05-30T09:05	2022-06-01T12:00	1
3	1001	Nausea	2022-05		1

row	SUBJID	AEDECOD	AEC01DAT	AEC01TOX	AEC02DAT	AEC02TOX	AEC03DAT	AEC03TOX
1	1001	Anaemia	2022-05-30T09:30	3	2022-05-31T20:30	4	2022-05-31T21:00	5
2	1001	Fatigue						
3	1001	Nausea						

SDTM DERIVATION

Since there will be one record per AE per SUBJECT per unique event (collapsed) to the highest level of severity/toxicity grade, Anaemia will have AETOXGR equal to the maximum toxicity grade which is 5. Fatigue and Nausea will have AETOXGR equal to 1 as there are no toxicity grade changes.

Table: SDTM.AE

SUBJID	AETERM	AESTDTC	AEENDTC	AESPID	AETOXGR
1001	Fatigue	2022-05-30T09:05	2022-06-02T16:30	1	1
1001	Anaemia	2022-05-29T09:00	2022-06-01T12:00	2	5
1001	Nausea	2022-05			

The information on grade changes over time will be mapped into the FA domain.

SUBJID	FAGRPID	FAORRES	FAOBJ	FATEST	FACAT	FASCAT	FADTC
1001	1	1	Anaemia	Toxicity Grade	ADVERSE EVENTS	AE CHANGES	2022-05-29T09:00
1001	2	3	Anaemia	Toxicity Grade	ADVERSE EVENTS	AE CHANGES	2022-05-30T09:30
1001	3	4	Anaemia	Toxicity Grade	ADVERSE EVENTS	AE CHANGES	2022-05-31T20:30
1001	4	5	Anaemia	Toxicity Grade	ADVERSE EVENTS	AE CHANGES	2022-05-31T21:00

ADaM DERIVATION

We will be using both treatment start DateTime which need to be created in ADSL, for subject 1001, treatment A starts from 2022-05-30T09:00, and treatment B starts from 2022-05-31T16:30.

Table: ADaM.ADSL

SUBJID	TR01SDTM	TR02SDTM	TRT01A	TRT02A
1001	2022-05-30T09:00	2022-05-31T16:30	A	B

For deriving ADAE, we need to grab degree change information from FA, which helps us to figure out whether an AE is considered as TEAE or not.

Table: ADaM.ADAE

SUBJID	AETERM	AESTDT	AEENDT	TRT01A	TRT02A	TRTEM01FL	TRTEM02FL
1001	Fatigue	2022-05-30T09:05	2022-06-02T16:30	A	B	Y	
1001	Anaemia	2022-05-29T09:00	2022-06-01T12:00	A	B	Y	Y
1001	Nausea	2022-05-30T09:00		A	B	Y	
1001	Nausea	2022-05-31T16:30		A	B		Y

As we can see from above, Fatigue only happened after taking treatment A, without any worsening information, Fatigue will be treated as TEAE only for treatment A period. However, Anaemia happened before receiving any treatment, but toxicity grade get worsen both after taking drug A and drug B. Obviously, Anaemia will be considered as a TEAE for both treatment A and B periods.

For event Nause, as the start date is partial, the imputation method will be implemented. Since only “day” is missing, “year” and “month” are equal to both treatment A and B. two records will be imputed with AESTDT equal to the start dates of both arms.

OUTPUT PRESENTATION

For our final report, It will be displayed as the number of TEAE that occurred within each treatment arm for subjects with the percentage calculated as the number of patients having adverse events divided by the total number of subjects. As mentioned in previous steps, you will find that Fatigue is only counted for Drug A, but Anaemia and Nausea were counted for both Drug A and B.

Table xx.xx Incidence of Treatment-Emergent Adverse Event by System Organ Class and preferred term (Safety analysis set)

System Organ Class Preferred Term	TRT A (N=XX)	TRT B (N=XX)
General disorders and administration site conditions		
Fatigue	1 (xx.x)	0
Blood and lymphatic system disorders		
Anaemia	1 (xx.x)	1 (xx.x)
Gastrointestinal disorders		
Nausea	1 (xx.x)	1 (xx.x)

From this end-to-end illustration, it’s easy to see it is critical for us to have a good knowledge of AE analysis need from your study, especially the information collected and the rules of TEAE.

CONCLUSION

Adverse Event analysis is a very common part of a clinical trial, AE analysis can be straightforward or very tricky based on different study designs, so it’s very important to get familiar with the study documents. Good knowledge of this information will definitely help you manipulate the data correctly. It is highly recommended to pay attention to what will be collected for AE data, and the rules for identifying a treatment emergent AE (TEAE) because these will be strongly associated with the following analysis and output presentation.

REFERENCES

Referred CDISC documents are available from: http://www.cdisc.org

SDTMIG v3.3 is available from: https://www.cdisc.org/standards/foundational/sdtmig/sdtmig-v3-3

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