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AE: An Essential Part of Safety Summary Table Creation.

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ABSTRACT

Adverse event (AE) summary tables are an imperative part of the study and depict a clear picture of safety of a drug to the patients. Hence, it is very essential that we are clear and very careful while creating these tables and displaying correct counts. This paper will illustrate some basic concepts of the ADaM ADAE dataset and common AE tables created in the study and provide some quick tips to self-validate and cross-check the counts that we display.

INTRODUCTION

AE summary or count tables are very important for physicians and pharmaceutical companies to assess the safety profile of the test drug. These tables usually display the number of adverse events, the number of patients in each treatment group in whom the event occurred. Typically, AEs are grouped by System Organ Class, Preferred Terms and/or other variables of interest. In most clinical studies, we will have overall AE summary, summary tables of severity, outcome created. Before creating these tables it is very important that we are well aware of the ADaM ADAE dataset and necessary variables that will be useful while creating these tables. In the following paper we will be discussing on fundamental structure of ADaM ADAE dataset in brief followed by basic AE table

ADAE: ADaM STEP TOWARDS CREATING TLF.

Analysis of adverse events is one example where the data analyzed does not fit well into the ADaM Basic Data Strucrure (BDS) and are more appropriately analyzed using an occurrences structure with added analysis variables. In particular, for the analysis needs described in this paper:

- There is no need for AVAL or AVALC. Occurrences are counted in analysis.
- A dictionary is used for coding the occurrence, and it includes a well-structured hierarchy of categories and terminology. Mapping this hierarchy to BDS variables PARAM and generic *CAT variables would lose the structure and meaning of the dictionary.
- Dictionary content is typically not modified for analysis purposes. In other words, there is no need for analysis versions of the dictionary hierarchy.

ADVERSE EVENT ANALYSIS

The safety evaluation of a clinical trial includes the analysis of adverse events. An adverse event is defined as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

This definition of an adverse event (AE) includes any unfavorable and unintended sign, symptom, or disease that is temporally associated with the use of an investigational product, regardless of whether the AE is considered to be related to the product.

ADVERSE EVENT ATTRIBUTES

Some important attributes in the ADaM ADAE dataset are whether the adverse event is related to study drug or worsens after taking the study drug. It is also important to check whether the adverse event had what kind of effect like whether the event was mild, moderate or severe. We will also need to check the action taken in response to the events and whether it leads to permanent discontinuation from the investigational product.

CODING OF ADVERSE EVENTS

Medical Dictionary for Regulatory Activities (MedDRA) is a widely used global standard for coding of adverse events. A few other coding dictionaries include WHO Adverse Reaction Terminology (WHO-ART), Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), International Classification of Disease (ICD). Each coding dictionary is characterized by classifying each verbatim term into a hierarchy of medical granularity.

For example, if a verbatim term was recorded as 'Obstipation', using MedDRA V19.0, this verbatim term would result in a System Organ Class (SOC) of 'Gastrointestinal Disorders' and a preferred term (PT) of 'Constipation'.

It is also recommended that all levels of terms in the MedDRA: System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Lowest Level Term (LLT), and Preferred Term (PT) are represented, as these are frequently useful in further analyses of AEs.

STATISTICAL ANALYSIS

The most frequently used method for the comparison of adverse events between treatment groups is the summarization of the number of subjects who experienced a given adverse event at least once by the dictionary derived term. These counts and related percentages are presented for levels of the System Organ Class and preferred term. The denominator used for the calculation of the percentages is often determined by a population flag, such as the total number of subjects at risk or total number of subjects exposed to each treatment (e.g. SAFFL='Y'). Note that some subjects exposed to treatment may not have any adverse events, and therefore these subjects would not be represented in the SDTM AE domain and ADaM ADAE analysis dataset. Thus, the values of the denominator usually need to be obtained from ADSL (subject level analysis dataset) rather than directly from ADAE.

ADAE VARIABLES:

- **Identified Variables：** Include the identifier variables from SDTM:

Name	Label	Core
STUDYID	Study Identifier	Req
USUBJID	Unique Subject Identifier	Req
SUBJID	Subject Identifier for the Study	Perm
SITEID	Study Site Identifier	Perm
AESEQ	Sequence Number	Req

- **Dictionary Coding Variables:** These variables are obtained from MedDRA and should be included as needed for analysis. It is recommended but not required that all levels of terms in the MedDRA hierarchy [System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Lowest Level Term (LLT), and Preferred Term (PT)] are represented, as these are frequently useful in further analysis of AEs.

Name	Label	Core
AEDECOD	Dictionary-Derived Term	Req
AEBODSYS	Body System or Organ Class	Req
AELLT	Lowest Level Term	Cond
AELLTCD	Lowest Level Term Code	Perm
AEHLGT	High Level Term	Cond
AEHLGTCD	High Level Term Code	Perm
AESOC	Primary System Organ Class	Cond

- **Timing Variables:** Timing variables are copied from SDTM and derived within ADaM. Included below are the common timing variables. If other timing variables are collected in SDTM and pertinent for analysis, these should be included in ADaM. Additional timing variables, such as those for analysis period or phase, can be included.

Name	Label	Core
AESTDTC	Start Date/Time of Adverse Event	Perm
ASTDT	Analysis Start Date	Cond
ASTDTM	Analysis Start Date Time	Cond
ASTDTF/ASTTMF	Analysis Start Date Imputation Flag/Date Time Flag	Cond
AENDY/ASTDY	Analysis End Relative Day/Analysis Start Relative Day	Cond
AEENDTC	End Date/Time of Adverse Event	Perm
AENDT	Analysis End Date	Cond
AENDTM	Analysis End Date Time	Cond
AENDTF/AENTMF	Analysis End Date Imputation Flag/Date Time Flag	Cond
ADURN	AE Duration	Perm
APERIOD	Period	Perm
APHASE	Phase	Perm

- **Indicator Variables:** Indicator variables are either copied form SDTM or derived in ADaM ADAE dataset. These variables are used in the analysis and should be included in the dataset. These variables give you a brief idea whether the events occurred due to treatment, before treatment or in a follow- up period.

Name	Label	Core
TRTEMFL	Treatment-Emergent Flag	Cond
PREFL	Pre-Treatment Flag	Cond
FUPFL	Follow-up Flag	Cond

- **Occurrence Flag Variables:** Occurrence flags can be used to prepare data for analysis. They are typically created by sorting the data in the required order and then flagging the first treatment emergent record. These flags are very essential in AE safety reporting. Using these flags we can get the count that needs to be displayed in the summary table. The more common occurrence flags for MedDRA and a structure for additional flags are show below:

Name	Label	Core
AOCCFL	1st Occurrence of Any AE Flag	Perm
AOCCSFL	1st Occurrence of SOC Flag	Perm
AOCCPFL	1st Occurrence of Preferred Term Flag	Perm
AOCCIFL	1st Max Sev./Int. Occurrence Flag	Perm
AOCCSIFL/AOCCPIFL	1st Max Sev./Int. Occur Within SOC Flag/ PT Flag	Perm

- **Descriptive Variables:** Variables that describe the adverse event, including severity, relationship, and toxicity grade, are often used in analysis. These are the variables whose categories are displayed in the output. Below are some common descriptive variables that are often included in ADAE.

Name	Label	Core
AESER	Serious Event	Req
AESEV	Severity/Intensity	Perm
AESEVN	Severity/Intensity(N)	Perm
AEREL	Causality	Perm
RELGRy	Pooled Causality Group y	Perm
AETOXGR	Standard Toxicity Grade	Perm
AEACN	Action Taken with Study Treatment	Perm
AOUT	Outcome	Perm

Please find below snapshot of data:

	SUBJID	TRT01AN	AETERM	AEBODSYS	AEDECOD	ASTDT	AENDT	AESEV	TRTEMFL	AEREL	RELGR1N
1	002	2	Obstipation	Gastrointestinal disorders	Constipation	11DEC2014	15DEC2014	MILD	Y	POSSIBLE	1
2	002	2	intermittent elevated CRP	Investigations	C-reactive protein increased	09DEC2014	.	MODERATE		NOT RELATED	2
3	002	2	nausea	Gastrointestinal disorders	Nausea	15DEC2014	17DEC2014	MILD	Y	UNLIKELY	2
4	002	2	rash in mouth (post chemotherapy known)	Gastrointestinal disorders	Oral mucosal eruption	25DEC2014	08JAN2015	MILD	Y	NOT RELATED	2
5	002	2	rash on body (post chemotherapy known)	Skin and subcutaneous tissue disorders	Rash	19JAN2015	.	MILD	Y	NOT RELATED	2
6	002	2	vomiting	Gastrointestinal disorders	Vomiting	15DEC2014	17DEC2014	MILD	Y	UNLIKELY	2
7	003	2	pathological humerus fract. dext. and sin.	Musculoskeletal and connective tissue disorders	Pathological fracture	09MAR2015	02APR2015	SEVERE	Y	UNLIKELY	2
8	004	1	persisting hypotension	Vascular disorders	Hypotension	02MAY2015	22MAY2015	MILD	Y	POSSIBLE	1
9	005	2	Gastroenteritis	Infections and infestations	Gastroenteritis	03JUN2015	04JUN2015	MILD	Y	NOT RELATED	2
10	005	2	Sciatica	Nervous system disorders	Sciatica	12JUN2015	16JUN2015	MILD	Y	NOT RELATED	2
11	005	2	constipation	Gastrointestinal disorders	Constipation	03JUL2015	.	MILD	Y	PROBABLE/LIKELY	1
12	001	1	diarrhea	Gastrointestinal disorders	Diarrhoea	11NOV2014	12NOV2014	MILD	Y	POSSIBLE	1
13	001	1	difficult swallowing	Gastrointestinal disorders	Dysphagia	29NOV2014	.	MILD	Y	POSSIBLE	1
14	001	1	dizzyness	Nervous system disorders	Dizziness	11NOV2014	.	MILD	Y	POSSIBLE	1
15	001	1	drowsy	Nervous system disorders	Somnolence	25NOV2014	.	MILD	Y	POSSIBLE	1
16	001	1	dry throat	Respiratory, thoracic and mediastinal disorders	Dry throat	29NOV2014	.	MILD	Y	POSSIBLE	1
17	001	1	emotional	Psychiatric disorders	Emotional disorder	27NOV2014	.	MILD	Y	POSSIBLE	1
18	001	1	fatigue	General disorders and administration site conditions	Fatigue	11NOV2014	.	MILD	Y	POSSIBLE	1
19	001	1	fever	General disorders and administration site conditions	Pyrexia	01DEC2014	01DEC2014	MILD	Y	NOT RELATED	2
20	001	1	flulike symptoms	General disorders and administration site conditions	Influenza like illness	11NOV2014	13NOV2014	MILD	Y	POSSIBLE	1
21	001	1	hot flushes	Vascular disorders	Hot flush	13NOV2014	04DEC2014	MILD	Y	NOT RELATED	2
22	001	1	infected right eye	Infections and infestations	Eye infection	22NOV2014	04DEC2014	MILD	Y	POSSIBLE	1
23	001	1	intermittent leucopenia	Blood and lymphatic system disorders	Leukopenia	10NOV2014	.	MILD		NOT RELATED	2
24	001	1	intermittent oedema right foot	General disorders and administration site conditions	Peripheral swelling	17NOV2014	07DEC2014	MILD	Y	POSSIBLE	1
25	001	1	intermittent oedema right foot	General disorders and administration site conditions	Peripheral swelling	08DEC2014	.	MODERATE	Y	POSSIBLE	1

The data snapshot presented will give us a clear idea of the variables that we have discussed in the above section of ADaM ADAE dataset variables. These are the most common variables that will be included in the dataset. Not all the variables could be accommodated in the snapshot but a few are presented in the table.

CODE TO OBTAIN EVENT/SUBJECT COUNTS:

Below is the mock for which we need to obtain counts., using the ADaM ADAE dataset variables described above, to obtain counts will make our task easier.

All TEAEs by primary SOC and PT – SAF

Primary SOC PT	TRTA N = xx n (%)	 E = xx [e] (%)	TRTB N = xx n (%)	 E = x [e] (%)	Total N = xx n (%)	 E = xx [e] (%)
All SOCs	xx (xx.x)	[xx] (100)	xx (xx.x)	[xx] (100)	xx (xx.x)	[xx] (100)
Primary SOC_1	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
PT_1	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
PT_2	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
...	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
Primary SOC_2	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
PT_1	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)

N = number of subjects in population, n = number of subjects. E = total number of TEAEs. e = number of TEAEs.
Adverse events are coded according to MedDRA version 16.1.

- N = xx : This is the safety population count and has to be obtained from ADSL per treatment.

```
proc sql noprint;
     select count(unique(subjid)) into: tt1
     from adsl
     where trtan = 1;
quit;
```

The above piece of code is used to obtain N count for TRTA. A macro variable has been created which will make the task easier to print it in output.

- E = xx/ ALL SOC row count: This represents total number of TEAEs in the ADaM ADAE dataset.

```
proc sql ;
   create table first1 as
   select distinct trtan, "All SOCs" as aebodsys length = 200,
   count(subjid) as cnt1
   from adae
   group by trtan
   order by trtan;
quit;
```

Counts in the body can be obtained from 2 methods:

The counts that are displayed in the output are displayed as: n (%) e (%)

PROC FREQUENCY : To obtain event (e) counts

e counts are the number of events for that particular SOC and PT.

```
PROC FREQ DATA =adae noprint;
     TABLE trtan*aebodsys/out=grade(drop=percent) nocum missing list;
RUN;
```

Please find the below snapshot of the output that will be obtained after executing this code.

	AEBODSYS	TRTAN	ECOUNT
1	Blood and lymphatic system disorders	1	10
2	Cardiac disorders	1	6
3	Ear and labyrinth disorders	1	3
4	Eye disorders	1	4
5	Gastrointestinal disorders	1	58
6	General disorders and administration site conditions	1	32
7	Infections and infestations	1	16
8	Investigations	1	15
9	Metabolism and nutrition disorders	1	16
10	Musculoskeletal and connective tissue disorders	1	10
11	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2
12	Nervous system disorders	1	21
13	Psychiatric disorders	1	17
14	Renal and urinary disorders	1	7
15	Reproductive system and breast disorders	1	2
16	Respiratory, thoracic and mediastinal disorders	1	9
17	Skin and subcutaneous tissue disorders	1	8
18	Vascular disorders	1	3
19	Blood and lymphatic system disorders	2	9
20	Cardiac disorders	2	3
21	Ear and labyrinth disorders	2	4

In above snapshot, using PROC FREQ we have obtained "e"(event) counts. These counts are the number of events a subject has encountered after taking treatment drug and we do not count it as unique event. This is a general approach to derive event counts.

Similar counts can be obtained using PROC SQL.

PROC SQL : To obtain "n" counts

```
proc sql;
      create table soc_count as
      select distinct aesoc, trtan, count(subjid) as ncount
      from adae
      where aesoc ne " " and aoccsfl = "Y" and saffl = "Y"
      group by aesoc, trtan
      order by trtan;
quit;
```

As we have seen the ADaM ADAE dataset variables we also came across occurrence flag variables that are created in the dataset to flag the first occurrence of SOC/ PT/ intensity etc. These occurrence flags are used to obtain the number of count of subjects to be presented in the output. The below table is the output after executing the above code.

	AEBODSYS	TRTAN	NCOUNT
1	Blood and lymphatic system disorders	1	7
2	Cardiac disorders	1	7
3	Ear and labyrinth disorders	1	3
4	Eye disorders	1	3
5	Gastrointestinal disorders	1	24
6	General disorders and administration site conditions	1	27
7	Infections and infestations	1	15
8	Investigations	1	11
9	Metabolism and nutrition disorders	1	9
10	Musculoskeletal and connective tissue disorders	1	9
11	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	8
12	Nervous system disorders	1	13
13	Psychiatric disorders	1	11
14	Renal and urinary disorders	1	6
15	Reproductive system and breast disorders	1	2
16	Respiratory, thoracic and mediastinal disorders	1	9
17	Skin and subcutaneous tissue disorders	1	7
18	Vascular disorders	1	3
19	Blood and lymphatic system disorders	2	9
20	Cardiac disorders	2	4
21	Ear and labyrinth disorders	2	4
22	Eye disorders	2	1

The counts that are displayed in the output are n (%) e (%)

Using PROC SQL we have obtained "n" counts. These counts are the number of subjects having that particular System Organ Class and then the related preferred term. While deriving this count we will be counting the subject once, even if they have multiple events. As occurrence flags mark the very first occurrence of the event, using them will give correct results.

Similar counts can be obtained using PROC FREQ.

ADVERSE EVENT TLF CREATION

The treatment-emergent flag is a key variable while creating AE related tables because we usually display the counts of subjects who had events while on study drug. There are a very few common AE tables that are created nearly in every study and nearly by every client for example:

- Overall TEAE table
- TEAE by SOC and PT
- TEAE by intensity
- TEAE by AREL

In the paper further we will be discussing the above mentioned summary tables in detail.

OVERALL TEAE TABLE

To begin with let us start with the overall AE table. This summary table is the reference table for cross-checking the counts with further subset summary tables created. For example: the overall AE tables have a row for “Subjects with related TEAE” and we also have a separate table where we are displaying the counts of related AEs by SOC and preferred term. The first row in the Related Table i.e. the ALL TEAE count should match to the “Subjects with related TEAE” row in the overall AE Table.

The below snapshot is mock of an overall AE table where we have various category counts to be displayed. The first 2 rows will add up to total number of subjects in the ADaM ADAE dataset. This may not necessarily be the total number of subjects in the study because not all subjects can have adverse events and hence records in ADAE. Depending on the conditions we will filter for the required row to obtain counts. This table is very important as it acts as a reference guide for cross-checking the counts with further AE tables that we create.

Variables used from ADAE ADaM dataset are: TRTEMFL, AESEV, AESER, RELGR1, AEEXPFL. These variables are used to filter respective condition to obtain counts.

Variables from ADSL ADaM dataset are: TRT variables, Population flags.

Overview of number of subjects with TEAE – SAF

	TRTA N = xx n (%)	TRTB N = xx n (%)	Overall N = xx n (%)
Number of subjects without any TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with non-serious TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with serious TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with severe TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with related TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with related serious TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with unexpected TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with TEAE leading to discontinuation from IMP	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with TEAE leading to discontinuation from trial	xx (xx.x)	xx (xx.x)	xx (xx.x)
Deaths	xx (xx.x)	xx (xx.x)	xx (xx.x)}

N = number of subjects in population, n = number of subjects.

Overview of TEAE table has 3 types of counts displayed:

1. N - Number of subjects in the population. The population can be safety, enrolled etc. as described in the SAP. “N” count is always obtained from the ADaM ADSL dataset as it is the population count.
2. n – Number of subjects. This is the count of subjects having adverse events on the table.
3. % - The percentages are obtained by dividing n/N.

Tips for self-validating the overview of TEAE Table:

1. Make sure all TEAE's have been included.

2. Ensure that AE’s with AETERM = “NONE” or “Missing” are not counted.

3. Count for “Subjects with related TEAE” should be less than or equal to count for “Subjects with TEAE”.

4. Number of subjects with “Subjects with TEAE leading to discontinuation from trial” should match with “Adverse Event” row in disposition table.

5. Check the number of subjects with corresponding TEAE listing, if possible. Double check serious adverse event (SAE) counts.

6. Check the percentages. They should not be more than 100%.

SUMMARY TABLE BY SYSTEM ORGAN CLASS AND PREFERRED TERM:

A Second very common table that is created is the summary table displaying the N and E counts by System Organ Class and preferred term. Please find below snapshot for more details. A similar table can be created for AE outcome, relationship to the drug.

Variables used from ADAE ADaM dataset are: TRTEMFL, AEBODSYS, AEDECOD. These variables are used to filter respective condition to obtain counts.

Variables from ADSL ADaM dataset are: TRT variables, Population flags.

All TEAEs by primary SOC and PT – SAF

	TRTA		TRTB		Total	
Primary SOC	N = xx	E = xx	N = xx	E = x	N = xx	E = xx
PT	n (%)	[e] (%)	n (%)	[e] (%)	n (%)	[e] (%)
All SOCs	xx (xx.x)	[xx] (100)	xx (xx.x)	[xx] (100)	xx (xx.x)	[xx] (100)
Primary SOC_1	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
PT_1	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
PT_2	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
…	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
Primary SOC_2	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
PT_1	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)

N = number of subjects in population, n = number of subjects. E = total number of TEAEs. e = number of TEAEs.
Adverse events are coded according to MedDRA version 16.1.

In the table we are displaying an extra count i.e. number of events which means we will display the number of events for that particular AEBODSYS and AEDECOD.

Tips for self-validating the Adverse Event table by SOC and PT:

1. Cross check the numbers against Overview of Adverse Events table (Table 1).

2. Check the sort order. Sorting usually takes place in the descending order of “N” in the active group, followed by the “N” in Placebo group. Or else sorting can be done by arranging the System Organ Class (SOC) terms alphabetically.

3. Check if the denominator should be count of subjects from “Subjects with any drug related adverse event” or the “N” from treatment headers.

4. Ensure there are no “Uncoded" terms in the data after the DBL(database lock). If there are, bring this to the notice of the study statistician.

5. Appropriate footnotes should be present. E.g. Footnotes for Treatment Emergent Adverse Event (TEAE), medical dictionary used etc.

TEAE BY SEVERITY

A third very common table that is created is a count of events or count of subjects by AE intensity. The snapshot below displays the counts of events for each SOC and PT with respective to the severity. A similar table can also present N and n count.

Variables used from ADAE ADaM dataset are: TRTEMFL, AEBODSYS, AEDECOD,AESEV. These variables are used to filter respective condition to obtain counts.

Variables from ADSL ADaM dataset are: TRT variables, Population flags.

TEAEs by primary SOC, PT and intensity – SAF

Primary SOC PT Intensity	TRTA E = xx e (%)	TRTB E = xx e (%)	Total E = xx e (%)
All TEAEs	xx (100)	xx (100)	xx (100)
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary SOC_1	xx (100)	xx (100)	xx (100)
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT_1	xx (100)	xx (100)	xx (100)
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT_2	xx (100)	xx (100)	xx (100)
...			
Primary SOC_2	xx (100)	xx (100)	xx (100)
...			

E = total number of TEAEs. e = number of TEAEs. Adverse events are coded according to MedDRA version 16.1.

Tips for self-validating the TEAE by Severity table:

1. Read the SAP carefully while summarizing by severity/ relationship to the study drug. In some situations subjects are counted only once under maximum severity/ relationship. In some other situations, a subject is counted in all severity/ relationship categories wherever applicable. This condition should be checked in the SAP and there should be a corresponding footnote to explain the same. Also, make sure the intensity of an adverse event is not null. Generally if the intensity is null, it considered as “Severe”, provided it is an AE post drug administration. Else severity is considered as “Mild”. Same is the case with relationship to study drug. Check this with the study statistician.

Note that by changing the “AESEV” variable to the “AEREL” variable, you can easily change the previous adverse event summary to a summary of adverse events by maximum drug relatedness. Also, if you remove the maximum severity steps, you get a typical overall summary of adverse events by body system and preferred term. Since patient medical history data are also often coded with MedDRA, patient medical history data may be summarized much like an overall summary of adverse events.

COSMETIC CHECKS

Once we are confident about the counts that we have displayed in the output the next very important thing is the visual look of the table, or what we call as cosmetic checks of the output.

All TEAEs by primary SOC and PT – SAF

	TRTA		TRTB		Total	
Primary SOC	N = xx	E = xx	N = xx	E = x	N = xx	E = xx
PT	n (%)	[e] (%)	n (%)	[e] (%)	n (%)	[e] (%)
All SOCs	xx (xx.x)	[xx] (100)	xx (xx.x)	[xx] (100)	xx (xx.x)	[xx] (100)
Primary SOC_1	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
PT_1	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
PT_2	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
…	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
Primary SOC_2	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)
PT_1	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)	xx (xx.x)	[xx] (xx.x)

N = number of subjects in population, n = number of subjects. E = total number of TEAEs. e = number of TEAEs.
Adverse events are coded according to MedDRA version 16.1.

- Check the indentation of the primary SOC column heading should match to actual SOC presented in the output. Similarly check for the preferred terms.
- Alignment of N, n in the header should be in sync with that of the counts displayed.
- Align the square brackets and round brackets so that counts in the bracket also look aligned.

CONCLUSION

Maintaining high efficiency without compromising quality is a necessity in the CRO/ Pharmaceutical industry. This paper gives a detailed explanation about ADAE and quick checks one can perform on the AE reports.

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