

Useful Adverse Events (AE) data Diagnostics and Summarization

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ABSTRACT

Safety remains a critical concern in all Clinical trials conducted by the sponsors. Among many aspects to look at for the safety of the patients such as Vital Signs (VS), Laboratory samples (LB), etc, Adverse events (including Serious Adverse events) play a key role in addressing the safety of the drug or biologic under investigation. A typical AE Case Report Form (CRF) collects AE verbatim name, start and stop dates, toxicity, relatedness, action taken, seriousness etc. The paper focusses on data checks that can be done on the AE data and present some useful summarization that can be run as part of routine monitoring reports or submissions. All the results will be reported graphically for easy display using SAS[®] Enterprise Guide 7.1[®].

INTRODUCTION

The data checks presented are inclined with Pinnacle 21 validator checks. Broadly, they are grouped into 4 major categories. For more details please see References section.

- Metadata-level checks
- Value-level checks
- Logical checks
- Cross-reference checks

Some of the key ones are listed below in Diagnostics section. These reports leverage on many of the utilities available in SAS Enterprise Guide[®] (EG). A process flow can be set up in EG and run routinely with each data refresh or transfer for an ongoing trial.

DIAGNOSTICS

Some key data checks are listed below under their respective major categories:

Metadata Level:

- *(Check #1)*: Length of any Variable Name greater than 8 characters
- *(Check #2)*: Length of any Variable Label greater than 40 characters
- *(Check #3)*: Length of any Variable Value greater than 200 characters

Value Level:

- *(Check #4)*: Missing AE Verbatim Name (AETERM) from the CRF
- *(Check #5)*: Missing MedDRA Coding for an AE such as Preferred Term (AEDECOD)
- *(Check #6)*: Missing AE start date (AESTDTC)
- *(Check #7)*: Missing End time-point values. One of the End time-point variables is expected to be populated when an event occurred. (e.g., one of End Date/Time of Event (AEENDTC), End Relative to Reference Period (AEENRF), and End Relative to Reference Period (AEENRTPT) variables values should not be missing, or Occurrence (AEOCCUR) variable value should be set to 'N')
- *(Check #8)*: Presence of any special characters in the data

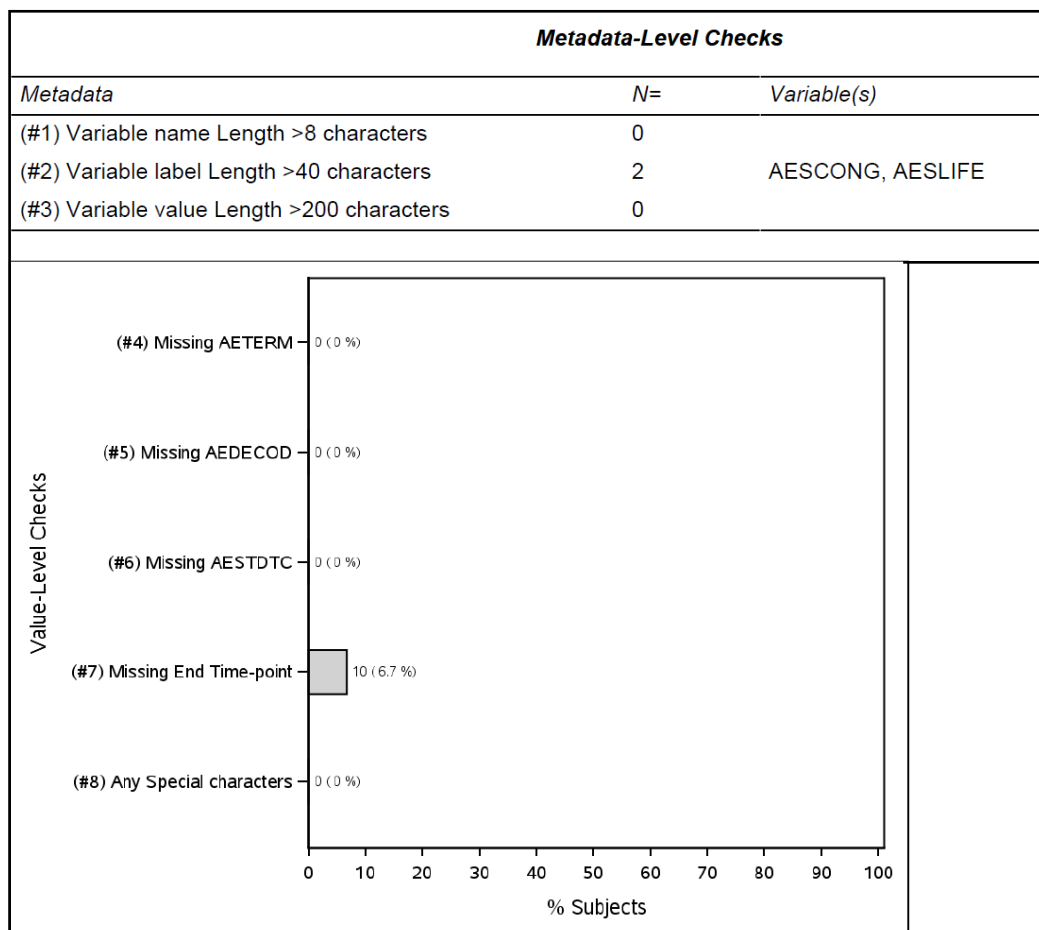
Logical:

- *(Check #9)*: Data entry error when AE start date is greater than the end date

- (Check #10): Inconsistent values between Serious Event (AESER) and related variables (AESCAN, AESCONG, AEDISAB, AESDTH, AESHOSP, AESLIFE, AESMIE). When Serious Event (AESER) variable value is 'Y', then at least one of seriousness criteria variables is expected to have a value 'Y'
- (Check #11): Inconsistent values between Serious Event (AESER) and Overdose variable (AESOD). Serious Event (AESER) variable value is expected to be 'Y', when Occurred with Overdose (AESOD) variable value equals 'Y'
- (Check #12): Inconsistent values between Outcome (AEOU) of "FATAL" and Death (AESDTH). Outcome of AE should equal 'FATAL', when Results in Death (AESDTH) is 'Y'
- (Check #13): Inconsistent values between Toxicity (AETOX) and Toxicity Grading (AETOXGR). A value for a Toxicity (AETOX) variable should be provided, when a Toxicity Grade (AETOXGR) variable value is populated and greater than 0 and vice-versa

Cross Reference:

- (Check #14): AE start date is after the latest Disposition date. AE start date (AESTDTC) should be less than or equal to the latest Disposition date (DSSTDTC)



Logical Checks		
<i>Criteria</i>	<i>N=</i>	<i>Obs No.</i>
(#9) AE Start > AE End	2	21, 89
(#10) AESER and related seriousness variables inconsistency	0	
(#11) AESER ^=Y when AESOD=Y	0	
(#12) AEOU ^=FATAL when AESDTH =Y	0	
(#13) --TOXGR and --TOX inconsistency	1	44
Cross-reference Checks		
<i>Criteria</i>	<i>N=</i>	<i>Obs No.</i>
(#14) AE Start > latest Disposition date (DSSTDTC)	1	112

Display 1: AE Diagnostic checks

SUMMARIZATION

- A. A very high-level summary that is of interest to the reviewers when looking at AE data include: Overall AE, AE with Grade xx (eg. 3) or higher, AE leading to dose discontinuation/interruption due to study drug, Serious AEs etc. Below figure (Figure 1) depicts them conveniently in a bar chart along with counts and percentages in each category.

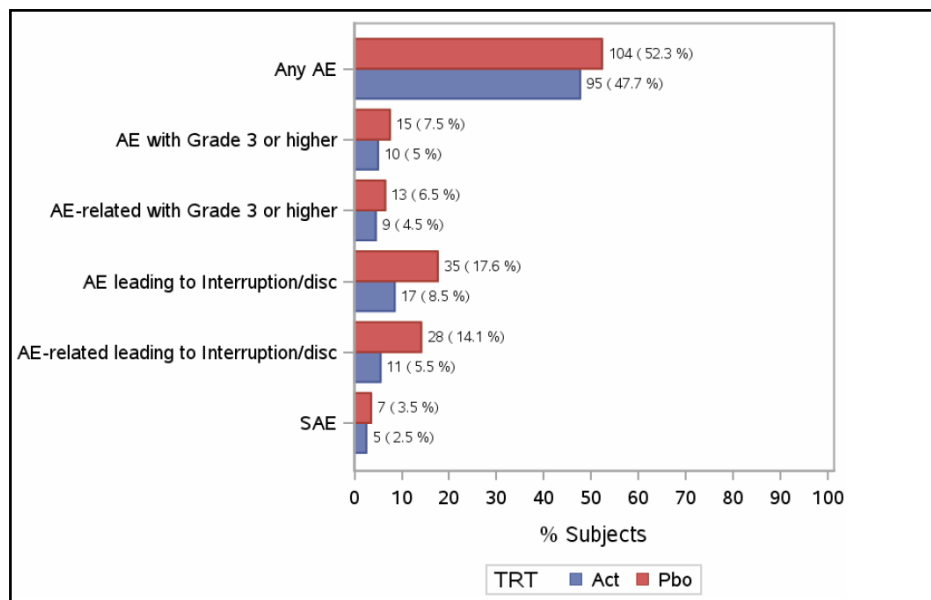


Figure 1: AE Overall Summary

- B. A further drill-down of the above summary within each category can be looked at by some grouping variables like Preferred Term (AEDECOD), System Organ Class (AESOC) to further understand the underlying data.

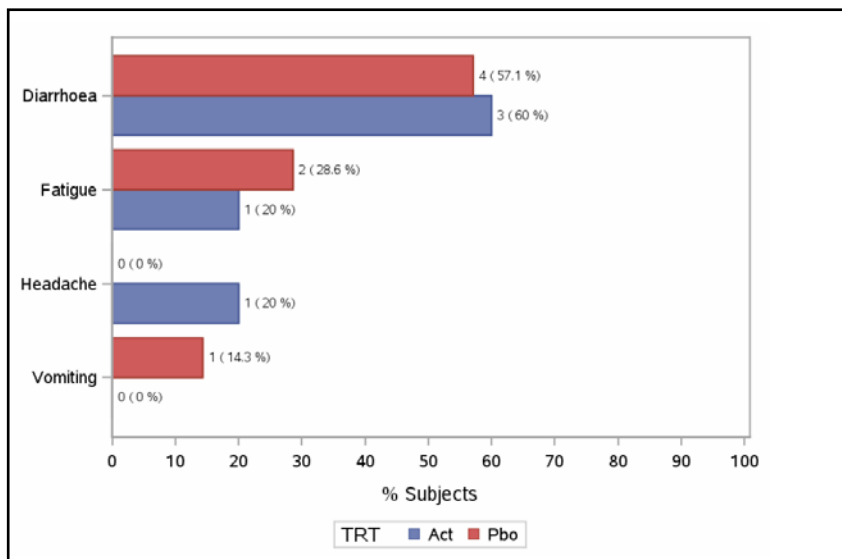


Figure 2: Serious Events (SAE) Summary by Preferred Term

C. AEs can be further narrowed down to look at subject level emphasizing profiles of subjects exhibiting high adverse events. A sample patient-level summary is presented below (Figure 3).

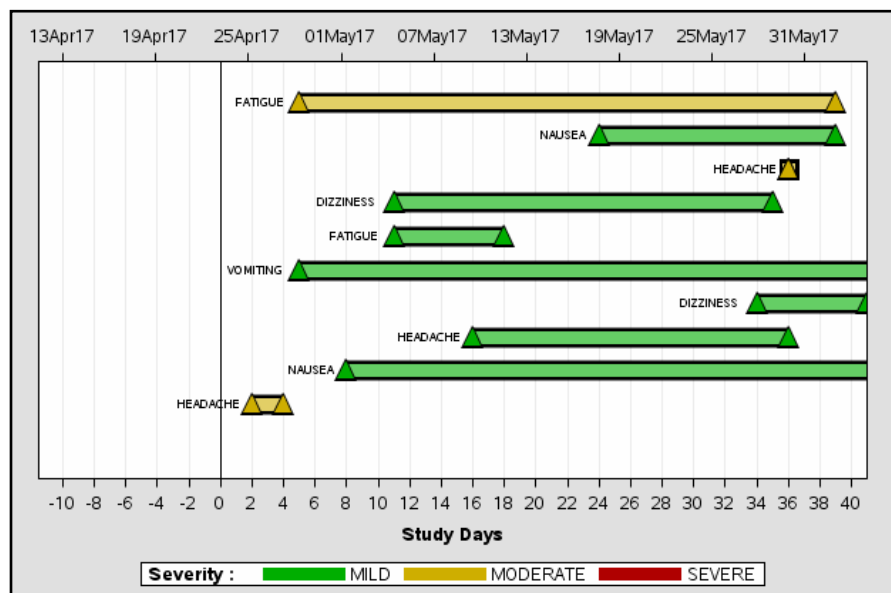


Figure 3: AE Summary for Subject ID= XXXX

D. Some statistical measures such as “Occurrence rate” and “Rate Ratio” can be calculated to compare the risks between treatment groups. The below plot was generated using a log-linear Poisson regression model to present Rate Ratio and 95% CI (Figure 4). Please see Appendix for more details.

$$\text{Rate Ratio} = \frac{\text{the rate of occurrence of any AE in Active group}}{\text{the rate of occurrence of any AE in Placebo group}}$$

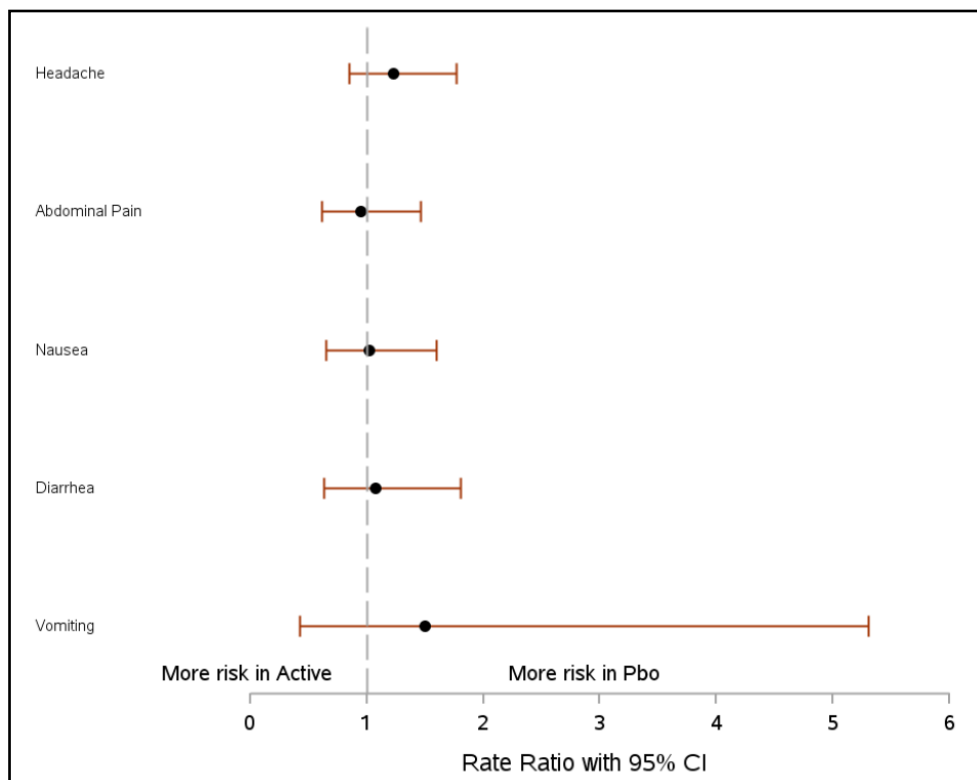


Figure 4: Rate Ratio and 95% CI by Preferred Term by Treatment Group

CONCLUSION

The paper presented some key data checks and summarization which can be expanded as per the individual study needs. While most of the time, AEs are looked at descriptively but it can also have an inferential approach using statistical models. It is recommended to automate the tasks shown in the paper and reviewed periodically.

REFERENCES

- [1] Srivastva, Abhinav, 2016. "Pre-data Checks for SDTM Development", MWSUG 2016.
- [2] Matange, Sanjay, 2013. "Patient Profile Graphs Using SAS", Paper MS14-SAS, PharmaSUG 2013.

CONTACT INFORMATION

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APPENDIX

Sample code for Figure 4: Rate Ratio and 95% CI by Preferred Term by Treatment Group

```
ods output diffs=diffs;

proc genmod data=<model_data> descending;
  class usubjid trt01an(ref='1');
  model aeocc = trt01an / dist=poisson link=log offset=lnPtime;
  lsmeans trt01an / diff exp cl;
run;

/* where, aeocc = 1 when subject has an AE, otherwise 0
      lnPtime = offset calculated as log of person-time (in years) for a subject
      during the study
*/

data stat;
  set diffs;
  *- Rate Ratio and 95% CI -*;
  Rate_Ratio = ExpEstimate;
  Lower_CI   = LowerExp;
  Upper_CI   = UpperExp;
run;
```