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Analyzing Adverse Events of Special Interest using Lab Tests and Toxicity Grades

Elizabeth Thomas, Vamsi Krishna Medarametla, Gokul Vasist
Seattle Genetics, Inc., Bothell, WA

Abstract:

Reporting and analyzing adverse events is one of the most important programming activities in any clinical trial. All adverse events and their severities are captured in the AE dataset. Determination of clinical relevancy and subsequent qualification as an adverse event is at the discretion of the reporting investigator. This allows for a potential bias that can lead to underreporting adverse events. Incorporating additional data sources may enhance the understanding of an agents' emerging risk profile and combat this bias.

When an AE of Special Interest (AESI) has an associated quantifiable laboratory finding, such as thrombocytopenia and low platelet count, laboratory (LB) datasets can be used to complement the adverse events (AE) datasets. Starting with assigning a severity in the form of standardized AE toxicity grades to the LB data, one can define an imputed AE event from the lab data. Grade changes and resolution of the newly defined event are based on how the toxicity grade for the lab test changes over the course of the study, assuming that a lab grade is static until the following lab draw.

This paper demonstrates the use of lab data to compute the grade/severity changes for a lab value corresponding to an AESI. These grade changes will be used to impute additional AEs, which may be tabulated with originally reported AEs as a sensitivity analysis. Utilization of complementary datasets within the same clinical trial database can enhance existing methods of safety surveillance and aid in active monitoring of patients' safety data.

Introduction:

The AE dataset and the related tables are some of the most common sources of identifying adverse events in a clinical trial. Although these provide a fair picture of how safe a drug is, it may not be complete without considering some of the lab results captured in the LB datasets. Certain adverse events, such as thrombocytopenia, can be obtained using the lab test and result from the lab data. The preferred term Thrombocytopenia in adverse events dataset corresponds to the lab term "Platelet count decreased" in the lab dataset. Identifying such similar terms between the datasets helps report adverse events more efficiently and completely in a study. This is represented pictorially in Figure 1 below. Our paper demonstrates the use of lab dataset to provide additional SMQs in a treatment emergent adverse event output. In the scenario where we use lab dataset to

identify AEs, we define treatment emergent adverse events are AEs that occur on or after the start of a treatment. We will describe the process of generating these using the lab dataset, specifically for thrombocytopenia (or low platelet count).

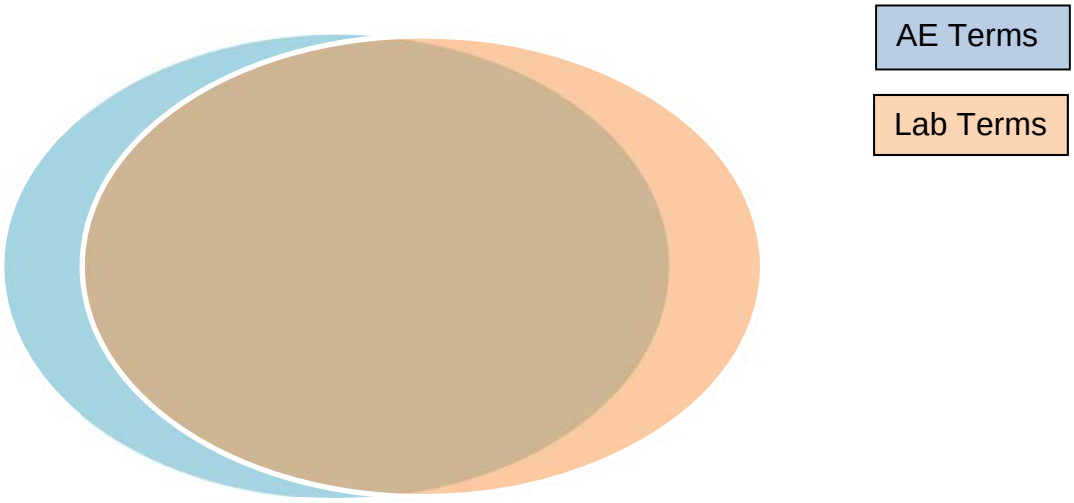

Fig 1: Common adverse events between AE & Lab datasets.

One of the most common treatment emergent adverse events table summarizes AEs by Body System, Preferred Term, and Toxicity Grades. Toxicity grades are usually derived using the CTCAE coding. These indicate the severity of an adverse event with Grade 1 being a mild event while Grade 5 is a death related AE. Similar to these, lab data contains lab toxicity grades ranging from Grade 0 to Grade 4. Toxicity grades for lab tests are based on lab results and the corresponding normal ranges, and are derived using CTCAE coding as well. Identifying these similarities and grading the toxicities appropriately is a required step during the process of reporting safety events. Also the presence of lab date and time variables help us determine the time point at which the lab test was conducted, whether at baseline or during treatment. The timing variables are also crucial while identifying when the lab toxicity grades changed for a subject during the course of a study.

For the purposes of this paper, we assumed that the subject will maintain the same grade until a new grade is observed (LOCF) at a subsequent lab visit. We have represented this in Figure 2 below. We have included a sample of the corresponding lab dataset structure in Table 1.

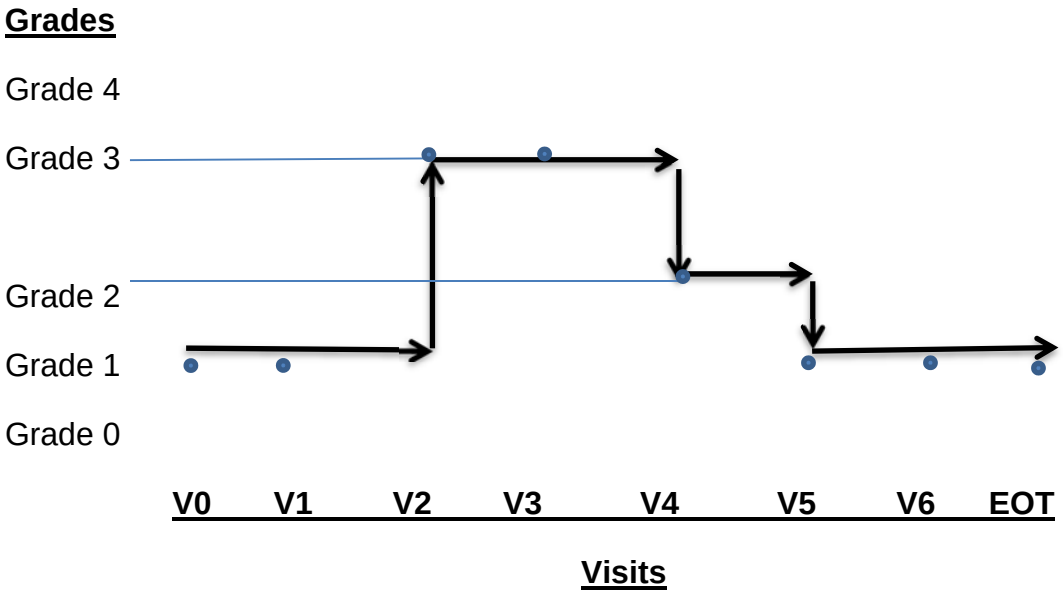

Fig 2: Representation of how lab toxicity grades change for a subject during the course of a study.

SUBJID	Lab Grade	Lab Date	Lab Test	Visit
1	Grade 1	Date of V0	Platelet Count	0
1	Grade 1	Date of V1	Platelet Count	1
1	Grade 3	Date of V2	Platelet Count	2
1	Grade 3	Date of V3	Platelet Count	3
1	Grade 2	Date of V4	Platelet Count	4
1	Grade 1	Date of V5	Platelet Count	5
1	Grade 1	Date of V6	Platelet Count	6
1	Grade 1	Date of EOT	Platelet Count	99

Table 1: Sample of lab data corresponding to Fig 2.

Our lab dataset contained lab date times, visit, toxicity grades and the corresponding lab test along with the subject information. The challenge of converting a lab dataset that

contained a single date-time per record to an adverse event dataset that contains two dates (AE start & AE end date) per record was unique. Our approach was to identify a set of records where the toxicity grade remained the same across visits. The AE start date for such an event would be the first date for that particular grade, and the AE end date would be the last date for that particular grade. The AE terms acquired from the lab datasets were given a unique value depending on which direction the toxicity grade moved. This was a combination of lab test, type of lab (local or central), and the direction of toxicity grade change (I for Increase, D for Decrease). This helped us differentiate the AE terms based on the source, AE dataset or LB dataset. For instance, the preferred term "Platelet count decreased" would appear as "Platelet count decreased-C-D" for data coming out of central lab (C) and a decrease in the toxicity grade direction (D). For the illustration in Fig 2, the corresponding AE dataset would appear as shown in Table 2 below.

SUBJID	Toxicity Grade	AE Start Date	AE End Date	Tmt Emerg.
1	Grade 1	Date of V0	Date of V2	N
1	Grade 3	Date of V2	Date of V4	Y
1	Grade 2	Date of V4	Date of V5	Y
1	Grade 1	Date of V5	EOT	Y

Table 2: The derived AE dataset corresponding to the lab data in Table 1 & Fig 2.

Once we had the data structure in place, we used this interim dataset along with the ADAE dataset to create the treatment emergent adverse events table. One of the differences we noted was the change in the additional AEs that were captured in the "Any Event" category. The sample outputs in Tables 3 & 4 illustrate this difference.

Table xx: Grade 3 or Higher Treatment Emergent Adverse Events by Preferred Term

Safety Population

Preferred Term	Total (N=20)
Any Event	13 (65)
Thrombocytopenia	12 (60)
Platelet count decreased	10 (50)

Table 3: TEAE table generated using just the adverse events dataset

Table xx: Grade 3 or Higher Treatment Emergent Adverse Events by Preferred Term

Safety Population

Preferred Term	Total (N=20)
Any Event	14 (70)
Thrombocytopenia	12 (60)
Platelet count decreased	10 (50)
Platelet count decreased-C-D	1 (5)

Table 4: Same TEAE table generated using the adverse events & lab datasets.

Conclusion:

When it comes to reporting safety events for a drug, it helps to look beyond the adverse events dataset. Identifying commonalities across datasets like AE & LB help ensure adverse events are reported more efficiently and completely. We can utilize the flexibility that SAS programming offers to improve the drug development process.

References:

Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies - U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER)

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CONTACT INFORMATION

Liz Thomas, Vamsi Krishna, and Gokul Vasist worked on this paper during their affiliation with Seattle Genetics. Your comments and questions are valued and encouraged. Contact the authors at:

Vamsi Krishna Medarametla
Seattle Genetics, Inc.
21823 - 30th Drive S.E.
Bothell, WA 98021
kmedarametla@seagen.com

Elizabeth Thomas
liz.g.thomas@gmail.com

Gokul Vasist
Seattle Genetics, Inc.
21823 - 30th Drive S.E.
Bothell, WA 98021
gvasist@seagen.com