PharmaSUG 2022 - Paper DS-054

From the Laboratory Toxicity Data Standardization to CTCAE Implementation

Xiaoyin (Sherry) Zhong, Genmab
Yongjiang (Jerry) Xu, Genmab

ABSTRACT

Oncology is one of the most prevalent therapeutic areas for clinical trials today. One specific method of analyzing oncology data relates to quantify the magnitude of abnormalities of clinical laboratory results. However, laboratory data is often challenging to work with during the analysis data set and output creation, especially when lab limits can be assessed bi-directionally. The lab data process becomes more complicated as the latest CTCAE version 5.0 incorporates grading criteria dependent on baseline measurements. In this paper, we will present the approach to ADLB data set creation, laboratory data presentation (grade shift table) as well as deriving the toxicity grade based on CTCAE version 5.0 and our recommendations on how to handle some common issues.

INTRODUCTION

Oncology studies often collect a significant amount of laboratory data for each subject. Compared to most clinical trials that report lab results only based on normal ranges, Oncology trials take these analyses to the next complexity level. We report not only lab results based on normal ranges, but also the degree of abnormality. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) has defined the degree of abnormality using a range of grades from 1(mild) to 5 (death). Lab toxicity grade shift table is frequently produced in a clinical study report, as it is an important part of safety reporting.

However, processing and presenting lab toxicity grade data is always challenging, especially when lab limits can be assessed bi-directionally. So as developing toxicity grade variables within the ADLB datasets, we need to follow the fundamental principals in CDISC ADaMIG to: 1) facilitate clear and unambiguous communication from datasets to statistical analysis; 2) provide traceability between the analysis data and its source data; 3) be in analysis-ready in order to produce table output; 4) have metadata associated with ADaM data sets; and 5) have datasets that are usable by commonly available software.

Therefore, setting up ADLB and implementing CTCAE appropriately to support the lab toxicity outputs are crucial. In this paper, we explain and provide examples on how ADaM variables can be utilized to handle lab toxicity grade data. In addition, we provide recommendations on CTCAE v5.0 grading rules as well as the examples of our in-house CTCAE macro.

LABORATORY TOXICITY DATA STANDARDIZATION

There are several lab toxicity mock tables frequently used to summarize lab toxicity grade. In this paper, we focus our discussions on lab toxicity shift table (Table 1). Table 1 layout is commonly seen for a clinical study report. Basically, it is a 6X6 table to summarize toxicity grade change of a lab test from baseline to the worst post-baseline (on-treatment) grade with increased and/or decreased lab value. Calcium is an example of bi-directional lab tests that can be graded in both directions: abnormal low values are defined as hypocalcemia whereas abnormal high values are defined as hypercalcemia. As both are of clinical interest, so we focus on summarizing by not only the lab test (Calcium), but also the CTCAE event terms (hypocalcemia and hypercalcemia).

To produce Table 1, we need to have four pieces of information: 1) On treatment flag; 2) bi-directional toxicity grade variables for toxicity grades (low and high); 3) variables to store the baseline grades (low and high) and the worst post-baseline grades (low and high); 4) shift variable to describe the flow from baseline toxicity grade to the worst post-baseline toxicity grade. The details on how to derive them will be discussed in the next section.

Table 1. Shift Table from Baseline to Maximum Post-baseline CTCAE Grade while on-treatment– Safety Analysis Set

CTCAE Grade at Baseline	Worst On-Treatment CTCAE Grade						
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing	Total
Calcium: Hypocalcemia							
Grade 0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Calcium: Hypercalcemia							
Grade 0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Percentages are calculated based on the number of subjects in Safety Analysis Set.

CTCAE: Common Terminology Criteria for Adverse Events v5.0

DATA STRUCTURE AND TOXICITY GRADE VARIABLES

To accommodate summarization of bi-directional lab tests (Table 1), structure of the analysis data set needs to be considered. Historically the BDS structure allowed for a single toxicity grade. Our proposal defines two sets of variables associated with grading; a decision that has been further established with recent guidance from ADAMIG v1.2 regarding ADLB. The guidance included in Table 2 provides instruction for create lab toxicity variables to handled bi-directional information.

Table 2 displays the bi-directional toxicity grading proposed in ADaM IG v1.2. The toxicity descriptions (ATOXDSCL and ATOXDSCH) can help to determine the denominators (Total). For example, if ATOXDSCL is populated then the record is counted for CTCAE grade low, and if ATOXDSCH is populated then the record is counted in CTCAE grade high. In some cases, it can be counted for both when lab test can be assessed in both directions. ATOXDSCL and ATOXDSCH are descriptions of the toxicity being assessed and they can be either based on the LBTOX values in SDTM, or self-defined.

Table 2. Bi-directional Toxicity Variables in ADaM IG 1.2

Variable Name	Variable Label	Type	Comments
ATOXGRL	Analysis Toxicity Grade Low	Char	Low toxicity grade of AVAL or AVALC for analysis
ATOXDSCL	Analysis Toxicity Description Low	Char	The analysis toxicity term used to describe toxicity in the low direction
BTOXGRL	Baseline Toxicity Grade Low	Char	ATOXGRL of the baseline record identified by ABLFL
ATOXGRH	Analysis Toxicity Description High	Char	High toxicity grade of AVAL or AVALC for analysis
ATOXDSCH	Analysis Toxicity Description High	Char	The analysis toxicity term used to describe toxicity in the high direction
BTOXGRH	Baseline Toxicity Grade High	Char	ATOXGRH of the baseline record identified by ABLFL

Under the guidance in Table 2, we develop variables in ADLB to support our lab shift table (Table 1). In additional to the variables in Table 2, we also add ONTRTFL (on-treatment record flag), WTOXGRL/H (worst post-baseline grade low/high), and shift1/shift2 (shift from baseline low/high) for traceability and the ease of the data formatting for display. The metadata of bi-directional toxicity grade variables are presented in Table 3.

Table 3. Metadata Table of Bi-directional Toxicity Grade Variables

Variable Name	Variable Label	Type	Comments
ONTRTFL	On Treatment Record Flag	Char	Set to 'Y' if a subject/param has ADST.TRTSDT <= ADT < ADSL.TRTEDT + lag days (study specific).
ATOXGRL	Analysis Toxicity Grade Low	Char	CTCAE 'Low' grade when applies grading algorithms for ATOXDSCL in grading macro %CTCAE*
ATOXDSCL	Analysis Toxicity Description Low	Char	CTCAE 'Low' grade terms
BTOXGRL	Baseline Toxicity Grade Low	Char	ATOXGRL where ABLFL = ‘Y’
ATOXGRH	Analysis Toxicity Description High	Char	CTCAE 'high' grade when applies grading algorithms for ATOXDSCL in grading macro %CTCAE*
ATOXDSCH	Analysis Toxicity Description High	Char	CTCAE ‘High’ grade terms
BTOXGRH	Baseline Toxicity Grade High	Char	ATOXGRH where ABLFL = ‘Y’
WTOXGRL	Worst Post-Baseline Toxicity Grade Low	Char	highest post baseline value of ATOXGRL by parameter by subject where ONTRTFL = ‘Y’
WTOXGRH	Worst Post-Baseline Toxicity Grade High	Char	highest post baseline value of ATOXGRH by parameter by subject where ONTRTFL = ‘Y’
SHIFT1	Shift Toxicity Grade Low	Char	BTOXGRL||' - '||WTOXGRL
SHIFT2	Shift Toxicity Grade High	Char	BTOXGRH||' - '||WTOXGRH

*See the macro %CTCAE section for details

EXAMPLE OF TOXICITY GRADE VARIABLES FOR CALCIUM IN ADLB

Calcium is a bi-directional lab test and the screenshot in ADLB below illustration the derivation of toxicity grade variables. Subject 0000 has abnormal low value of Calcium so it is graded in the low direction (Hypocalcemia) with ATOXGRL = 'Grade 1', whereas ATOXGRH = 'Grade 0'. Subject 0001 has abnormal high value of Calcium so it is graded in the high direction (Hypercalcemia) with ATOXGRH = 'Grade 1', whereas ATOXGRL = 'Grade 0'. In summary, 'Grade 0' is automatically applied in the opposite direction if one direction has a grade higher than 0.

	SUBJID	AVISIT	PARAM	ONTRTFL	ANRIND	ATOXDSCL	ATOXGRL	ATOXDSCH	ATOXGRH	BTOXGRL	BTOXGRH	WTOXGRL	WTOXGRH	SHIFT1	SHIFT2
1	0000	V1	Calcium Corrected Serum or Plasma (mmol/L)	Y	LOW	Hypocalcemia	Grade 1	Hypercalcemia	Grade 0	1	0	1	0	1-1	0-0
2	0000	V2	Calcium Corrected Serum or Plasma (mmol/L)	Y	LOW	Hypocalcemia	Grade 1	Hypercalcemia	Grade 0	1	0	1	0	1-1	0-0
3	0000	V3	Calcium Corrected Serum or Plasma (mmol/L)	Y	LOW	Hypocalcemia	Grade 1	Hypercalcemia	Grade 0	1	0	1	0	1-1	0-0
4	0001	V1	Calcium Corrected Serum or Plasma (mmol/L)	Y	HIGH	Hypocalcemia	Grade 0	Hypercalcemia	Grade 1	0	0	0	1	0-0	0-1
5	0001	V2	Calcium Corrected Serum or Plasma (mmol/L)	Y	HIGH	Hypocalcemia	Grade 0	Hypercalcemia	Grade 1	0	0	0	1	0-0	0-1
6	0001	V3	Calcium Corrected Serum or Plasma (mmol/L)	Y	HIGH	Hypocalcemia	Grade 0	Hypercalcemia	Grade 1	0	0	0	1	0-0	0-1
7	0001	V4	Calcium Corrected Serum or Plasma (mmol/L)	Y	HIGH	Hypocalcemia	Grade 0	Hypercalcemia	Grade 1	0	0	0	1	0-0	0-1

CTCAE GRADING AND MACROS

Laboratory toxicity grading has been an important part of safety reporting and therefore it is critical to stay up to date with various CTCAE versions. CTCAE version 5.0 adds a layer of complexity with grading criteria dependent on baseline measurements. To implement CTCAE v5.0, we evaluate the updates and develop our own in-house CTCAE implementation guide and the corresponding %CTCAE macro.

CTCAE IMPLEMENTATION GUIDE

While majority of the lab tests can be graded directly based on NCI-CTCAE v5.0, we would like to discuss 4 specific rules we implement for grading (Table 4):

Table 4. CTCAE Implementation Guide

Rule	Description	Example	Implementation
1	All grades were derived based on numeric criteria ONLY and did not take into consideration of clinical signs or symptoms.	**Hypoalbuminemia (ALB)** Grade 1: <LLN - 3 g/dL Grade 2: <3 - 2 g/dL Grade 3: <2 g/dL;<20g/L Grade 4: Life-threatening consequences; urgent intervention indicated	Only grade 1-3 will be graded
2	Worst grade for criteria contains more than one set of criteria	**Creatinine increased (CREAT)** Grade 1: >ULN – 1.5XULN Grade 2: >1.5 – 3.0Xbaseline; >1.5 – 3.0XULN Grade 3: >3.0Xbaseline; >3.0 – 6.0XULN Grade 4:>6.0XULN	If aval meets both >1.5-3.0XULN and >3.0Xbaseline, then worst grade (i.e., Grade 3) is assigned. It is graded based on ULN only when baseline is missing.
3	Criteria contains a dependence on baseline	Alanine aminotransferase increased (ALT)	Baseline and pre-baseline result will not be graded

		Grade 1: >ULN – 3.0XULN if baseline was normal; 1.5 – 3.0Xbaseline if baseline was abnormal Grade 2: >3.0 – 5.0XULN if baseline was normal; >3.0 – 5.0Xbaseline is baseline was abnormal Grade 3: >5.0 – 20.0XULN if baseline was normal; >5.0 – 20.0Xbaseline is baseline was abnormal Grade 4: > 20.0XULN if baseline was normal; >20.0Xbaseline is baseline was abnormal	In the situation if baseline is missing, post-baseline results will be graded using the assumption that baseline was normal Baseline status (Low/Normal/High) replacing baseline grade with footnote added
4	Grade 0 recalibration	Hypercalcemia (calcium graded in high direction) Hypocalcemia (calcium graded in low direction)	High terms (Hypercalcemia): grade 0 is assigned for lab normal indicator (ANRIND) = normal/low Low terms (Hypocalcemia): grade 0 is assigned for lab normal indicator (ANRIND) = normal/high

To implement rule 3 above, we modify the shift table slightly for 6 lab tests (ALT, ALP, AST, BILI, GGT, and EOS) that contains dependence on baseline. The updated shift table (Table 5) is presented below. As the criteria for total bilirubin increased depends on baseline status (normal/high), we display baseline status replacing baseline grade with a footnote added.

Table 5. Shift Table from Baseline to Maximum Post-baseline CTCAE Grade while on-treatment– Safety Analysis Set (MODIFIED)

	Worst On-Treatment CTCAE Grade						
CTCAE Grade at Baseline	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing	Total
Calcium: Hypocalcemia							
Grade 0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total Bilirubin: Increased*							
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

*Grades are derived dependent on baseline. Therefore, baseline results are not graded but baseline status are presented instead.

THE MACRO %CTCAE

A macro has been generated to implement the CTCAE v5.0, following the rules from our in-house implementation guide:

```
%macro ctcae( indsn =
              , outdsn =
              , excelfile =
              , sheetname =CTCV5
               , paramcd_var =LBTESTCD
              , blnrind =BNRIND
               , lln =ANRLO
              , uln =ANRHI
             );
```

The design is set to read in the NCI CTCAE v5 criteria, which has been listed in an excel file for SAS to read in. A merge of the CTCAE criteria dataset with the input dataset will make the comparison of values with criteria possible. The merge variables are LBTESTCD and LBSPEC because of the stability of control terminology in CDISC. PARAMCD could also be a choice if its derivation is well defined in ADLB. The calculation of CTCAE grading for laboratory results will go through each criterion, per each lab test. As the result of the macro, ATOXGRL/ATOXGRH and ATOXDSCL/ATOXDSCH will be created.

Some modifications of the CTCAE toxicity grade are applied to meet the in-house standards. For example, when CTCAE v5.0 criteria consider baseline, the baseline grading is not possible. Thus normal/abnormal/ are populated based on the lab test normal range (see rule 3 in Table 4 in previous section). When a lab result falls within the normal ranges provided by the local lab but the criteria from NCI CTCAE grades it above zero. The normal range from local lab will be honored and the toxicity grading would be reset to 0.

Table 6. The Local Lab Normal Range is Preferred over CTCAE Criteria.

SUBJID	AVISIT	PARAM	AVAL	ANRLO	ANRHI	ANRIND	ATOXGRH	ATOXDSCH	Comments
0000	V1	Prothrombin Intl. Normalized Ratio	1.04	0.9	1.3	Normal	Grade 0	INR Increased	The value is below 1.2 (CTC AE v5 criteria) and within the normal range.
0000	V2	Prothrombin Intl. Normalized Ratio	1.21	0.9	1.3	Normal	Grade 0	INR Increased	The value falls in grade 1 of CTC AE v5 criteria but within normal range, So the ATOXGRH is reset to grade 0
0000	V3	Prothrombin Intl. Normalized Ratio	1.31	0.9	1.3	High	Grade 1	INR Increased	The value falls in grade 1 of CTC AE v5 and above normal range High.
0000	V4	Prothrombin Intl. Normalized Ratio	1.51	0.9	1.3	High	Grade 2	INR Increased	The value falls in grade 2 of CTC AE v5 and above normal range High.

CONCLUSION

This paper demonstrates the approach to ADLB data set creation, laboratory data presentation (grade shift table) as well as deriving the toxicity grade based on CTCAE version 5.0 that was taken within our company. It utilized the guidance for bi-directional toxicity grade in ADaMIG v1.2 and added in other variables in ADLB metadata for better data traceability. At the same time, keeping all data derivation programming in ADLB makes ADLB analysis ready.

As an important part of ADLB, lab tests need to be graded for analysis and reporting in Oncology trials. Although the algorithms are well described in the NCI CTCAE guidelines, there are several operational challenges to be aware of when implementing them globally on all lab results. Therefore, a comprehensive implementation guide and well-defined SAS macro are critical to accomplish this task.

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ACKNOWLEDGMENTS

We would like to acknowledge our colleagues Anna Bladström and Jennifer Gu for their contributions to ADLB initiative. We would also like to thank Genmab leadership team (Chris Velas, Suzanne Viselli, and Jan Skowronski) for the support and endorsement.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Xiaoyin (Sherry) Zhong
Genmab
609-402-7079
shzh@genmab.com

Yongjiang (Jerry) Xu
Genmab
609-402-4019
jexu@genmab.com