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Making Lab Toxicity Tables Less Toxic on Your Brain

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ABSTRACT

Processing and presenting lab data is always challenging, especially when lab limits are assessed in two directions. The lab data process becomes even more complicated when multiple baselines are required due to different analysis criteria or are inherent in the study design. This paper discusses an approach to create lab toxicity grade variables in ADLB for lab bi-directional toxicity report. They are mixed variables defined by Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model Implementation Guide (ADaMIG) v1.1 and draft ADAMIG v1.2 and by sponsor to make ADLB easily interpreted and related summary tables easily produced.

This paper is based on the lab Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade summary, taking into account lab tests with abnormal assessment in either increased direction or decreased direction. In this paper, the authors explain and provide examples showing how ADaMIG v1.1 variables ATOXGR, BTOXGR, SHIFTy, ANLzzFL, MCRITy, and BASETYPE, draft ADaMIG v1.2 new variables ATOXGRH(L) and BTOXGRH(L), and sponsor-defined variables ATOXDIR and WAYSHIFT can be utilized and implemented appropriately. In addition, this paper explains how to handle baseline toxicity grade for analysis sets with more than one baseline in ADLB.

INTRODUCTION

Toxicity grade summary tables and toxicity grade shift tables are frequently produced in a clinical study report. As we develop toxicity grade variables within the ADLB dataset, we need to follow the fundamental principles defined by 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 analysis-ready in order to produce table output, (4) have metadata associated with ADaM datasets, and (5) have datasets that are usable by commonly available software.

How to setup ADLB for lab bi-directional toxicity grade data to support lab toxicity tables is a long-time debatable topic in industry. Shall we add rows with new parameter codes for high and low of the same tests? Or shall we add columns for toxicity grade high and low in the same rows? Or shall we keep a slim and short data structure for ADLB but conduct the derivation of lab bi-directional toxicity grade variables in table program? The pros and cons supporting each approach have been discussed in the past. Due to the unresolved debate, the lab toxicity tables became more or less toxic on one's brain. One of the main purposes of the ADaMIG v1.2 (currently under development) is to provide the guidance for lab bi-directional toxicity grade data. This paper uses an in-house project to illustrate the concepts that will be released with ADaMIG v1.2.The work flow shows the following:

- Lab toxicity grade mock up tables as defined by the Statistical Analysis Plan (SAP)
- Design of the data structure and variables based on both ADaMIG v1.1 and draft ADaMIG v1.2
- The metadata that accompanies the dataset and lab toxicity grade variables
- Illustration of the concepts using examples

LAB TOXICITY GRADE SUMMARY/SHIFT MOCK

In this paper, we present three lab toxicity mock tables frequently used in lab toxicity grade summary. Table 1 lists lab data variables to get the analysis data for table programming per each mock. For example, Under Column Mock 1, there is a check mark for Group #1, Group #2 and Group #3, which means that variables in these three groups are supporting Mock 1.

Table 1. Lab Data Variables Needed for Table Programming

Variable Group and Purpose	Mock 1	Mock 2	Mock 3
#1: Bi-directional toxicity grade variables for toxicity grade low and high	√	√	√
#2: Variables to tag post-baseline records with the worst toxicity grade low and high	√	√	
#3: Variables to tag post-baseline lab records with a worse-than-baseline toxicity grade low and high	√		
#4: Shift variables to describe the flow from baseline toxicity grade to the worst post-baseline toxicity grade low and high		√	
#5: Analysis day category variables			√
#6: Variables to tag the record with the worst toxicity grade low and high, accordingly, in each analysis day category			√

Table 1. Summary of Incidence of Post-baseline Toxicity Grade Shift with Laboratory Value Increases (Decreases)
by Worst Toxicity Grade
Safety Analysis Set

	Worsening Grade Shift from Baseline to Worst Post-baseline Lab Toxicity Grade (<*Decreased/Increased*> Value)							
			Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3
Hemoglobin (mmol/L)			xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Neutrophils (10/L)			xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
.....								

Mock 1. Summary of Incidence of Worsening Grade Shift

Mock 1 is to report the incidence of the worst post-baseline lab toxicity grade worsening from baseline with increased and decreased lab value. As showing in Table 1, Variables of Group #1, #2 and #3 together support this table creation.

Table 2. Shift in Grade from Study Baseline for Analyte
Safety Analysis Set

	Maximum Post-baseline Toxicity Grade for Increased Value						
Baseline Grade	NA n (%)	0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	Total n (%)
Phase x (N=xx)							
NA	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	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)

NA=Not Available

Mock 2. Shift in Grade from Study Baseline for Lab Analyte

Mock 2 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 toxicity grade with increased and decreased lab value. Variables of Group #1, #2 and #4 together provide the information in terms of baseline toxicity grade and the worst post-baseline toxicity grade among lab data of a lab analyte for a subject. From there, we are able to determine the counts in each cell of this 6x6 table.

Table 3. CTCAE Grade 3 or 4 Laboratory Toxicity by Analysis Day Category
by Worst Toxicity Grade
Safety Analysis Set

	Analysis Day Cat. 1 (N=xx))		Analysis Day Cat. 2 (N=xx)		Analysis Day Cat. 3 (N=xx)		Analysis Day Cat. 4 (N=xx)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Chemistry, n (%)								
Increased Alanine Aminotransferase (U/L)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Increased Aspartate Aminotransferase (U/L)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hematology, n (%)								
Decreased Hemoglobin (mmol/L)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Decreased Leukocytes (xx/L)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Mock 3. Summary of Incidence of Grade 3 or Grade 4 by Worst Toxicity Grade by Analysis Day Category

The Mock 3 is to report the incidence of lab toxicity grade as Grade 3 or 4 by worst toxicity grade with increased and decreased lab value within each sponsor-defined analysis day category. This table may reveal severe lab toxicity incidences in each analysis day category. To support this table programming, we need variables of Group #1, #5 and #6 listed in Table 1.

DATA STRUCTURE AND TOXICITY GRADE VARIABLES

DATA STRUCTURE

All bi-directional toxicity variables discussed in this paper are either parameter-level or record-level variables aligned in Basic Data Structure (BDS).

There are considerations for data structure buildup when there are multiple analysis sets with multiple baselines for study report.

Case 1: Data is collected through two study treatment periods and by-treatment-period analysis is required

Case 2: Data is collected through one treatment period and two analyses are conducted with two different baselines.

For both Case 1 and Case 2, the process we use utilizes the toxicity grading that is done in SDTM LB. The toxicity grading done in SDTM LB is based on an original baseline definition. However, the SAP requires an analysis on an alternative baseline definition. In order to allow for this additional analysis that is based on the alternative definition, the data needs to be regraded using the new baseline definition.

DESIGN OF LAB TOXICITY GRADE ANALYSIS VARIABLES

The Rationale and the Design

ADAMIG v1.2 draft for public review introduces three core changes. The guidance for bi-directional toxicity grades is one of them. The guidance included in Table 2 provides instruction for creating lab toxicity variables to handle bi-directional information.

Table 2. Toxicity Variables for BDS Datasets from draft ADaMIG v1.2

Variable Name	Variable Label	Type	CDISC Notes
ATOXGRL	Analysis Toxicity Grade Low	Char	Low toxicity grade of AVAL or AVALC for analysis; may be based on SDTM --TOXGR or an imputed or assigned value. Used to assess when a subject's lab value falls within the low toxicity range.
ATOXGRH	Analysis Toxicity Grade High	Char	High toxicity grade of AVAL or AVALC for analysis; may be based on SDTM --TOXGR or an imputed or assigned value. Used to assess when a subject's lab value falls within the high toxicity range.
BTOXGRL	Baseline Toxicity Grade Low	Char	ATOXGRL of the baseline record identified by ABLFL.
BTOXGRH	Baseline Toxicity Grade High	Char	ATOXGRH of the baseline record identified by ABLFL

Variable Development and Dependency

Under this guidance, we developed variables in ADLB to support our lab summary table programming in a pilot project. Figure 1 illustrates the variable development flow from source data to derived bi-directional toxicity grade variables, and to the final set of variables for the end user, i.e. each table report.

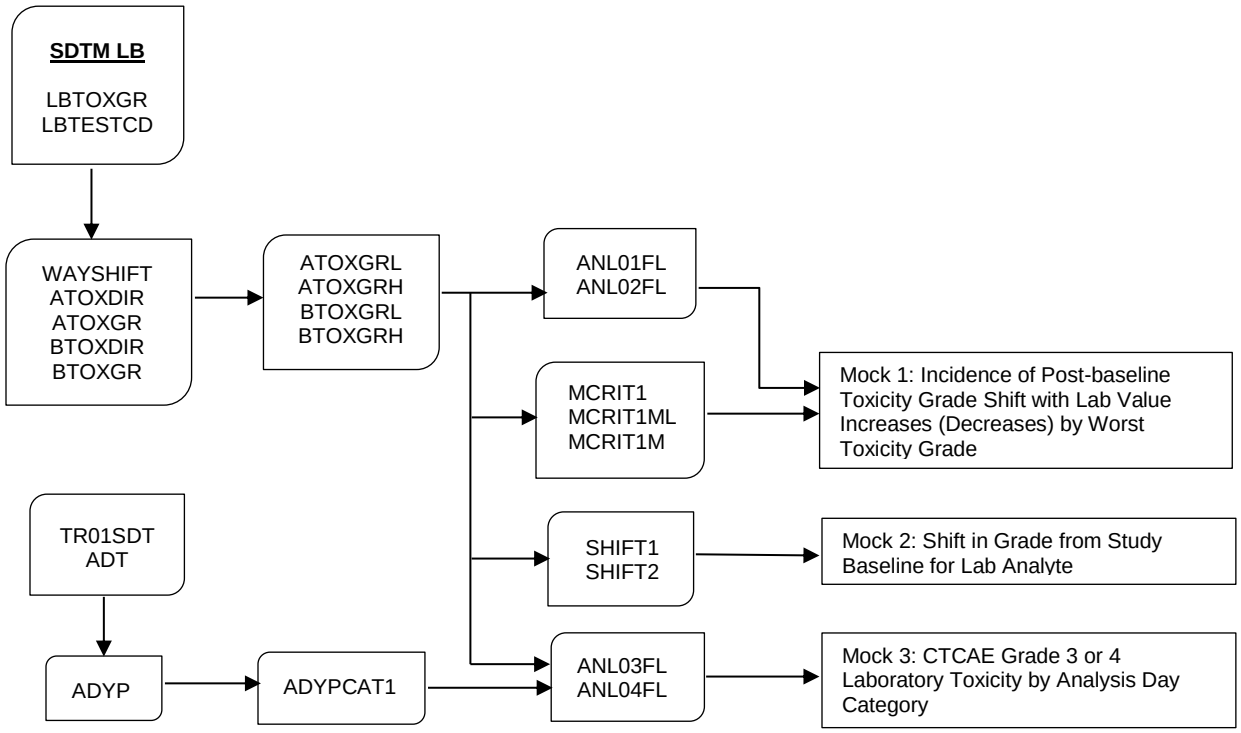

Figure 1. Flow Chart of Derivation and Utilization of Bi-directional Toxicity Grade Variables and the Dependency

Based on the derivation dependency, we group those variables into 6 categories, (1) basic toxicity grade variables, (2) analysis day variables, (3) bi-directional toxicity grade variables, (4) analysis set flag variables, (5) analysis multi-response criterion variables, and (6) shift from baseline variables, as showing in Table 3.

Table 3. Design of Lab Toxicity Variables and Category

Basic Toxicity Grade Variable	Analysis Day Variables	Bi-directional Toxicity Grade Variables	Analysis Set Flag Variables	Analysis Multi-Response Criterion Variables	Shift from Baseline Variables
WAYSHIFT[3] ATOXDIR[3] ATOXGR[1] ATOXGRN[1] BTOXDIR[3] BTOXGR[1] BTOXGRN[1]	ADYP[3] ADYPCAT1[3] ADYPCA1N[3]	ATOXGRL[2] ATOXGRLN[2] ATOXGRH[2] ATOXGRHN[2] BTOXGRL[2] BTOXGRLN[2] BTOXGRH[2] BTOXGRHN[2]	ANL01FL[1] ANL02FL[1] ANL03FL[1] ANL04FL[1]	MCRIT1[1] MCRIT1ML[1] MCRIT1MN[1]	SHIFT1[1] SHIFT1N[1] SHIFT2[1] SHIFT2N[1]

[1] ADaMIG v1.1 variables
[2] Draft ADaMIG v1.2 variables
[3] Sponsor defined variables

Metadata of Lab Toxicity Grade Analysis Dataset

When designing lab toxicity grade analysis variables, we take into account the programming efficiency, clear and unambiguous communication from datasets to statistical analysis, traceability between the analysis data and its source data, and compliance with CDISC ADaM mapping standard. All considerations are transformed as specific rules and criteria in metadata.

The metadata of lab toxicity grade analysis variables as part of ADLB metadata is stored in Data Definition Table (DDT) file, the file serving to create both electronic ADaM SAS ® datasets and define.xml for submission. Table 4 shows the metadata of bi-directional toxicity grade variables and Table 5 has codelist.

In metadata table, ATOXGR and ATOXGRN deserves special attention as they are mapped from SDTM LB.LBTOXGRN and the CTCAE toxicity grade generated in SDTM LB program uses primary baseline. The SAP, by study design, sometimes requires analysis with a different baseline. For example, a primary baseline may be defined as the last value prior to or on baseline visit and a secondary baseline could be the last value prior to or on the first dose visit. In some study design, a subject may have two treatment periods. In this case, one may be interested to know the data change from the time point prior to the time points of the second treatment period. The alternative baseline may be defined as the last value prior to the second treatment start. The variable BASETYPE would help to distinguish different analysis sets with different baseline definitions. In order to obtain toxicity grade with different baseline definition for related analysis set, CTCAE toxicity grading will be processed in SAS program prior to data process for bi-directional toxicity grade variables.

Table 4. Metadata Table of Bi-directional Toxicity Grade Variables

Variable	Label	SAS Type	Mapping Rule	Codelist
ATOXGR[1]	Analysis Toxicity Grade	Char	Original set with common baseline: SDTM.LBTOXGR. Set with alternative baseline: Toxicity regrading is conducted using baseline per SAP.	
MCRIT1[1]	Analysis Multi-Response Criterion 1	Char	“Worse Tox Gr by Abn Dir” Per subject per parameter per base type when WAYSHIFT in (“ONLYLOW”, “ONLYHIGH”, “HIGHLOW”) and POSTFL=Y and ATOXGRN is non-missing.	
MCRIT1ML[1]	Multi-Response Criterion 1 Evaluation	Char	“Worse Toxicity Grade, Low”: ATOXGRLN-BTOXGRLN>0. “Worse Toxicity Grade, High”: ATOXGRHN-BTOXGRHN>0. “Toxicity Grade Not Worse”: neither of above two cases.	MCRIT1MN
ANL01FL[1]	Analysis Flag 01 - Max LTox Post-base	Char	Y - Flag the post-baseline record with the worst toxicity grade low (high). Keep blank when WAYSHIFT=“ONLYHIGH”.	
ANL02FL[1]	Analysis Flag 02 - Max HTox Post-base	Char	Y - Flag the post-baseline record with the worst toxicity grade low (high). Keep blank when WAYSHIFT=“ONLYLOW”.	
ANL03FL[1]	Analysis Flag 03 - Max LTox by ADYP Cat	Char	Y - Flag the post-baseline record with the worst toxicity grade low (high) by ADYPCAT1. Keep blank when WAYSHIFT is “ONLYHIGH”.	
ANL04FL[1]	Analysis Flag 04 - Max HTox by ADYP Cat	Char	Y - Flag the post-baseline record with the worst toxicity grade low (high) by ADYPCAT1. Keep blank when WAYSHIFT is “ONLYLOW”.	
SHIFT1[1]	Shift 1 - in LTox Grade	Char	For the post-baseline records: Concatenation of ATOXGRL and BTOXGRL, such as “Grade 0 to Grade 1” when BTOXGRL is “Grade 0” and ATOXGRL is “Grade 1”.	SHIFTGRN

SHIFT2[1]	Shift 2 - in HTox Grade	Char	For the post-baseline records: Concatenation of ATOXGRH and BTOXGRH, such as “Grade 0 to Grade 1” when BTOXGRH is “Grade 0” and ATOXGRLH is “Grade 1”.	SHIFTGRN
ATOXGRL[2]	Analysis Toxicity Grade Low	Char	Mapped from ATOXGR. Reset to Grade 0 if ATOXDIR is “H”.	
ATOXGRH[2]	Analysis Toxicity Grade High	Char	Mapped from ATOXGR. Reset to Grade 0 if ATOXDIR is “L”.	
WAYSHIFT[3]	Abnormal Direction(s) of Lab Test	Char	“ONLYLOW” a lab test with decreased values only; “ONLYHIGH” for a lab test with increased value only; “HIGHLOW” for a lab test with decreased and increased values.	
ATOXDIR[3]	Analysis Toxicity Direction Indicator	Char	Set to “H” if SDTM.LB.LBTOX contains “HIGH” and set to “L” if SDTM.LB.LBTOX contains “LOW”.	
ADYP[3]	Analysis Day	Num	(ADT-TR01SDT)[4]	
ADYPCAT1[3]	Analysis Day Category 1	Char	“Analysis Day Cat. 1”, “Analysis Day Cat. 2”, “Analysis Day Cat. 3”, Analysis Day Cat. 4”.	ADYPCA1N

[1] ADaMIG v1.1
[2] ADaMIG v1.2 draft for public review
[3] Sponsor defined
[4] (ADT-TR01SDT) is the difference of analysis date minus the first dose date of study treatment.

Table 5. Codelist Referred in Table 4

Codelist Name	Codelist Label	Codelist Value	Codelist Value Decode	Codelist Extensible	Codelist Source
SHIFTGRN	Shift in Toxicity Grade from Baseline	1	NA to NA	N	SPONSOR
SHIFTGRN	Shift in Toxicity Grade from Baseline	2	NA to Grade 0	N	SPONSOR
……	……	……	……	……	……
SHIFTGRN	Shift in Toxicity Grade from Baseline	35	Grade 4 to Grade 3	N	SPONSOR
SHIFTGRN	Shift in Toxicity Grade from Baseline	36	Grade 4 to Grade 4	N	SPONSOR
ADYPCA1N	Analysis Day Catetory 1	1	Analysis Day Cat. 1	N	SPONSOR
ADYPCA1N	Analysis Day Category 1	2	Analysis Day Cat. 2	N	SPONSOR
ADYPCA1N	Analysis Day Category 1	3	Analysis Day Cat. 3	N	SPONSOR
ADYPCA1N	Analysis Day Category 1	4	Analysis Day Cat. 4	N	SPONSOR
MCRIT1MN	ADLB Multi-Response Criterion 1 Evaluation	1	Worse Toxicity Grade Low	N	SPONSOR
MCRIT1MN	ADLB Multi-Response Criterion 1 Evaluation	2	Worse Toxicity Grade High	N	SPONSOR
MCRIT1MN	ADLB Multi-Response Criterion 1 Evaluation	3	Toxicity Grade Not Worse	N	SPONSOR

Clarification of Variable Derivation

WAYSHIFT and ATOXDIR

WAYSHIFT and ATOXDIR are sponsor-defined variables. WAYSHIFT is a parameter-level variable with a value of 'HIGHLOW', 'ONLYLOW', or 'ONLYHIGH' to indicate if a lab test assessment is bi-directional or is uni-directional. ATOXDIR is a record-level variable holding a value of 'L' or 'H' to indicate an increased lab value or decreased lab value of a lab test. Otherwise, the value is null.

ATOXGR, ATOXGRN, ATOXGRL, ATOXGRLN, ATOXGRH, and ATOXGRHN

ATOXGR is initially mapped from SDTM LB domain. ATOXGRL and ATOXGRH are to assess a subject's lab value falling within the low toxicity range and the high toxicity range, accordingly. We apply rules as below for ATOXGRL and ATOXGRH mapping.

- ATOXGRL is mapped from ATOXGR. Reset to 'Grade 0' if ATOXDIR is 'H'.
- ATOXGRH is mapped from ATOXGR. Reset to 'Grade 0' if ATOXDIR is 'L'.

ATOXGRN, ATOXGRLN, and ATOXGRHN are the numeric version of ATOXGR, ATOXGRL, and ATOXGRH, respectively.

BTOXDIR, BTOXGR, BTOXGRN, BTOXGRL, BTOXGRLN, BTOXGRH, and BTOXGRHN

These baseline variables hold baseline values to establish the shift in toxicity level from baseline level. They are populated with the values of ATOXDIR, ATOXGR, ATOXGRN, ATOXGRL, ATOXGRLN, ATOXGRH, and ATOXGRHN from baseline record of the same lab test for each subject.

MCRIT1, MCRIT1ML and MCRIT1MN

To create a table defined in Mock 1, the programmer would look for a subset of ADLB containing records with the worst lab toxicity grade post-baseline that was worsening from baseline with increased lab value and decreased value. We found that the analysis multi-response criterion variables MCRIT1, MCRIT1ML and MCRIT1MN in ADaMIG v1.1 serve this purpose well.

MCRIT1 as 'Worse-than-baseline Tox Gr by Abn Dir' is populated at parameter level for tests with CTCAE toxicity grade. MCRIT1ML has 'Worse Toxicity Grade, Low' if the difference between ATOXGRLN and BTOXGRLN is greater than 0, 'Worse Toxicity Grade, High' if the difference between ATOXGRHN and BTOXGRHN is greater than 0, and 'Toxicity Grade Not Worse' if neither of the previous two cases. MCRIT1MN is the coded version of MCRIT1ML.

ADYP, ADYPCAT1 and ADYPCA1N

This variable group is designed to support table defined in Mock 3. ADYP is the relative analysis day of lab collected date from the first dose date. ADYPCAT1 and ADYPCA1N, the analysis day category variables based on ADYP, are sponsor-defined variables.

ANL01FL, ANL02FL, ANL03FL, and ANL04FL

ANL01FL and ANL02FL are paired variables flagging post-baseline lab records with the worst post-baseline toxicity grade low and high, respectively. ANL03FL and ANL04FL are paired variables tagging records with the worst toxicity grade low and high, respectively, in each analysis day category defined by ADYPCAT1 and ADYPCA1N.

SHIFT1, SHIFT1N, SHIFT2, and SHIFT2N

SHIFT1 and SHIFT2 describe the shift from baseline toxicity grade (NA, Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4) to analysis toxicity grade (NA, Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4) in each direction of low and high, respectively. SHIFT1N and SHIFT2N are the coded version of SHIFT1 and SHIFT2 with 1 for 'NA to NA', 2 for 'NA to Grade 0' …, and 36 for 'Grade 4 to Grade 4'.

The benefit of assigning a numeric code to the shift variables is to allow for the ease of the data formatting for display purposes on the table. The numeric codes allow the decoded values (i.e., the character versions) to be ordered in a specific way according to the table layout.

EXAMPLES OF LAB TOXICITY GRADE ANALYSIS DATASET

In the data presented for each example, both Visit 3 and Visit 6 are highlighted under the condition that, by study design, Visit 3 is the scheduled baseline visit and reference date of the common baseline, and Visit 4 is the schedule visit for the first dose of study treatment. This condition applies to data sets in all examples.

Example 1: Toxicity Grade Variables for Calcium, Albumin, and Alanine Aminotransferase

Example 1 Case 1 – Case 3 illustrate the derivation of bi-directional toxicity grade variable using source data from SDTM LB.LBTOX and LB.LBTOXGR.

Case 1: Bi-directional Toxicity Grade

Row	PARAMCD	WAYSHIFT	AVISIT	SDTM LB LBTOX	SDTM LB LBTOXGR	ATOXDIR	ATOXGR	ATOXGRL	ATOXGRH
1	CA	HIGHLOW	Visit 1	NORMAL	0		Grade 0	Grade 0	Grade 0
2	CA	HIGHLOW	Visit 2	HIGH 1	1	H	Grade 1	Grade 0	Grade 1
3	CA	HIGHLOW	Visit 3	LOW 1	1	L	Grade 1	Grade 1	Grade 0
4	CA	HIGHLOW	Unsch	NORMAL	0		Grade 0	Grade 0	Grade 0
5	CA	HIGHLOW	Unsch	NORMAL	0		Grade 0	Grade 0	Grade 0
6	CA	HIGHLOW	Visit 4	NORMAL	0		Grade 0	Grade 0	Grade 0
7	CA	HIGHLOW	Visit 5	LOW 2	2	L	Grade 2	Grade 2	Grade 0
8	CA	HIGHLOW	Visit 6	LOW 2	2	L	Grade 2	Grade 2	Grade 0
9	CA	HIGHLOW	Visit 7	LOW 3	3	L	Grade 3	Grade 3	Grade 0

Calcium is a bi-directional toxicity test having WAYSHIFT=“HIGHLOW”, indicating calcium is graded both in the low direction and in the high direction. Row 2 record has increased value in “Grade 1” with ATOXDIR set to ‘H’ and ATOXGRL being reset to “Grade 0”. Row 3 and Row 7 - Row 9 records have decreased value with ATOXDIR set to “L” and ATOXGRH being reset to “Grade 0”.

Case 2: Uni-directional Toxicity Grade Low

Row	PARAMCD	WAYSHIFT	AVISIT	SDTM LB LBTOX	SDTM LB LBTOXGR	ATOXDIR	ATOXGR	ATOXGRL	ATOXGRH
1	ALB	ONLYLOW	Visit 1	NORMAL	0		Grade 0	Grade 0	
2	ALB	ONLYLOW	Visit 2	LOW 1	1	L	Grade 1	Grade 1	
3	ALB	ONLYLOW	Visit 3	LOW 1	1	L	Grade 1	Grade 1	
4	ALB	ONLYLOW	Unsch	NORMAL	0		Grade 0	Grade 0	
5	ALB	ONLYLOW	Unsch	NORMAL	0		Grade 0	Grade 0	
6	ALB	ONLYLOW	Visit 4	LOW 1	1	L	Grade 1	Grade 1	
7	ALB	ONLYLOW	Visit 5	LOW 1	1	L	Grade 1	Grade 1	
8	ALB	ONLYLOW	Visit 6	LOW 2	2	L	Grade 2	Grade 2	
9	ALB	ONLYLOW	Visit 7	LOW 2	2	L	Grade 2	Grade 2	

Albumin is a test with uni-directional toxicity grade low so that WAYSHIFT is “ONLYLOW”, indicating that albumin is only graded in the low direction. Row 2, Row 3, and Row 6 - Row 9 records have decreased value in “Grade 1” or “Grade 2” with ATOXDIR set to “L” and ATOXGRH value is set to null for all rows.

Case 3: Uni-directional Toxicity Grade High

Row	PARAMCD	WAYSHIFT	AVISIT	SDTM LB LBTOX	SDTM LB LBTOXGR	ATOXDIR	ATOXGR	ATOXGRL	ATOXGRH
1	ALT	ONLYHIGH	Visit 1	NORMAL	0		Grade 0		Grade 0
2	ALT	ONLYHIGH	Visit 2	NORMAL	0		Grade 0		Grade 0
3	ALT	ONLYHIGH	Visit 3	NORMAL	0		Grade 0		Grade 0
4	ALT	ONLYHIGH	Unsch	NORMAL	0		Grade 0		Grade 0
5	ALT	ONLYHIGH	Unsch	NORMAL	0		Grade 0		Grade 0
6	ALT	ONLYHIGH	Visit 4	NORMAL	0		Grade 0		Grade 0
7	ALT	ONLYHIGH	Visit 5	NORMAL	0		Grade 0		Grade 0
8	ALT	ONLYHIGH	Visit 6	NORMAL	0		Grade 0		Grade 0
9	ALT	ONLYHIGH	Visit 7	HIGH 1	1	H	Grade 1		Grade 1

Alanine Aminotransferase is a test with uni-directional toxicity grade high and so WAYSHIFT is "ONLYHIGH", indicating that alanine aminotransferase is only graded in the high direction. Row 9 record has increased value with ATOXDIR set to 'H' and ATOXGRL is set to null for all rows.

Example 2: Variables of Baseline Toxicity Grade

Example 2 data indicates that Row 3 record is the baseline record with ABLFL=Y. The values of ATOXDIR, ATOXGR, ATOXGRL, and ATOXGRH from Row 3 are populated for BTOXGR, BTOXGRL, and BTOXGRH in Row 1 - Row 9.

Row	PARAMCD	WAYSHIFT	AVISIT	ATOXDIR	ATOXGR	ATOXGRL	ATOXGRH	ABLFL	BTOXGR	BTOXGRL	BTOXGRH
1	CA	HIGHLOW	Visit 1		Grade 0	Grade 0	Grade 0		Grade 1	Grade 1	Grade 0
2	CA	HIGHLOW	Visit 2	H	Grade 1	Grade 0	Grade 1		Grade 1	Grade 1	Grade 0
3	CA	HIGHLOW	Visit 3	L	Grade 1	Grade 1	Grade 0	Y	Grade 1	Grade 1	Grade 0
4	CA	HIGHLOW	Unsch		Grade 0	Grade 0	Grade 0		Grade 1	Grade 1	Grade 0
5	CA	HIGHLOW	Unsch		Grade 0	Grade 0	Grade 0		Grade 1	Grade 1	Grade 0
6	CA	HIGHLOW	Visit 4		Grade 0	Grade 0	Grade 0		Grade 1	Grade 1	Grade 0
7	CA	HIGHLOW	Visit 5	L	Grade 2	Grade 2	Grade 0		Grade 1	Grade 1	Grade 0
8	CA	HIGHLOW	Visit 6	L	Grade 2	Grade 2	Grade 0		Grade 1	Grade 1	Grade 0
9	CA	HIGHLOW	Visit 7	L	Grade 3	Grade 3	Grade 0		Grade 1	Grade 1	Grade 0

Example 3: Variables of Analysis Multi-response Criterion

In Example 3, the value of MCRIT1 is populated for all rows within the same parameter. The value of MCRIT1ML and MCRIT1MN are derived for each post-baseline record in Row 6-Row 9.

Row	PARAMCD	WAYSHIFT	AVISIT	ABLFL	POSTFL	ATOXGRL	BTOXGRL	ATOXGRH	BTOXGRH	MCRIT1	MCRIT1ML
1	CA	HIGHLOW	Visit 1			Grade 0	Grade 1	Grade 0	Grade 0	[a]	
2	CA	HIGHLOW	Visit 2			Grade 0	Grade 1	Grade 1	Grade 0	[a]	
3	CA	HIGHLOW	Visit 3	Y		Grade 1	Grade 1	Grade 0	Grade 0	[a]	
4	CA	HIGHLOW	Unsch			Grade 0	Grade 1	Grade 0	Grade 0	[a]	
5	CA	HIGHLOW	Unsch			Grade 0	Grade 1	Grade 0	Grade 0	[a]	
6	CA	HIGHLOW	Visit 4		Y	Grade 0	Grade 1	Grade 0	Grade 0	[a]	Toxicity Grade Not Worse
7	CA	HIGHLOW	Visit 5		Y	Grade 2	Grade 1	Grade 0	Grade 0	[a]	Worse Toxicity Grade, Low
8	CA	HIGHLOW	Visit 6		Y	Grade 2	Grade 1	Grade 0	Grade 0	[a]	Worse Toxicity Grade, Low
9	CA	HIGHLOW	Visit 7		Y	Grade 3	Grade 1	Grade 0	Grade 0	[a]	Worse Toxicity Grade, Low

[a] "Worse-than-baseline Tox Gr by Abn Dir"

In Row 6, ATOXGRL as "Grade 0" is not worse than BTOXGRL as "Grade 1" and ATOXGRH as "Grade 0" is not worse than BTOXGRH as "Grade 0". So MCRIT1ML has "Toxicity Grade Not Worse". However, in Row 9, ATOXGRL as "Grade 3" is worse than BTOXGRL as "Grade 1" and ATOXGRH as "Grade 0" is not worse than BTOXGRH as "Grade 0" so that MCRIT1ML has "Worse Toxicity Grade Low".

Example 4: Variables of Analysis Flag ANL01FL and ANL02FL for Maximum Post-baseline Toxicity Grade

Example 4 shows that ANL01FL is flagged as "Y" in Row 9 because ATOXGRL as "Grade 3" in Row 9 is the worst post-baseline toxicity grade low. Row 4 - Row 9 have ANL02FL as "Y" because ATOXGRH as "Grade 0" is the worst post-baseline toxicity grade high.

Row	PARAMCD	WAYSHIFT	AVISIT	ABLFL	POSTFL	ATOXGRL	ANL01FL	ATOXGRH	ANL02FL
1	CA	HIGHLOW	Visit 1			Grade 0		Grade 0	
2	CA	HIGHLOW	Visit 2			Grade 0		Grade 1	
3	CA	HIGHLOW	Visit 3	Y		Grade 1		Grade 0	
4	CA	HIGHLOW	Unsch			Grade 0		Grade 0	
5	CA	HIGHLOW	Unsch			Grade 0		Grade 0	
6	CA	HIGHLOW	Visit 4		Y	Grade 0		Grade 0	Y
7	CA	HIGHLOW	Visit 5		Y	Grade 2		Grade 0	Y
8	CA	HIGHLOW	Visit 6		Y	Grade 2		Grade 0	Y
9	CA	HIGHLOW	Visit 7		Y	Grade 3	Y	Grade 0	Y

Example 5: Variables of Analysis Day Category and Analysis Flag ANL03FL and ANL04FL for Maximum Toxicity Grade by Analysis Day Category

By study design, the first dose of study treatment is at Visit 4 (Row 6). In this example, ADYP is calculated as the day from analysis date to the first dose date so that there are two categories, "Analysis Day Cat. 1" and "Analysis Day Cat. 2" for ADYPCAT1. ANL03FL is flagged as "Y" in Row 3 because ATOXGRL as 'Grade 1" is the worst toxicity grade low for "Analysis Day Cat. 1". Row 3 - Row 5 have ANL04FL as "Y" since ATOXGRH as "Grade 0" is the worst toxicity grade high among rows for "Analysis Day Cat. 1".

Row	PARAMCD	WAYSHIFT	AVISIT	ATOXGRL	ANL03FL	ATOXGRH	ANL04FL	ADYP	ADYPCAT1
1	CA	HIGHLOW	Visit 1	Grade 0		Grade 0		-20	
2	CA	HIGHLOW	Visit 2	Grade 0		Grade 1		-14	
3	CA	HIGHLOW	Visit 3	Grade 1	Y	Grade 0	Y	-7	Analysis Day Cat. 1
4	CA	HIGHLOW	Unsch	Grade 0		Grade 0	Y	-5	Analysis Day Cat. 1
5	CA	HIGHLOW	Unsch	Grade 0		Grade 0	Y	-2	Analysis Day Cat. 1
6	CA	HIGHLOW	Visit 4	Grade 0		Grade 0	Y	1	Analysis Day Cat. 2
7	CA	HIGHLOW	Visit 5	Grade 2		Grade 0	Y	14	Analysis Day Cat. 2
8	CA	HIGHLOW	Visit 6	Grade 2		Grade 0	Y	21	Analysis Day Cat. 2
9	CA	HIGHLOW	Visit 7	Grade 3	Y	Grade 0	Y	28	Analysis Day Cat. 2

Example 6: Shift Variables

Example 6 still uses calcium in the example. The value of SHIFT1 is the concatenation of BTOXGRL and ATOXGRL and the value of SHIFT2 uses BTOXGRH and ATOXGRH in each post-baseline row and SHIFT1N and SHIFT2N are the numeric codes for SHIFT1 and SHIFT2.

Row	WAYSHIFT	AVISIT	ABLFL	POSTFL	BTOXGRL	ATOXGRL	SHIFT1	SHIFT1N	BTOXGRH	ATOXGRH	SHIFT2	SHIFT2N
1	HIGHLOW	Visit 1			Grade 1	Grade 0			Grade 0	Grade 0		
2	HIGHLOW	Visit 2			Grade 1	Grade 0			Grade 0	Grade 1		
3	HIGHLOW	Visit 3	Y		Grade 1	Grade 1			Grade 0	Grade 0		
4	HIGHLOW	Unsch			Grade 1	Grade 0			Grade 0	Grade 0		
5	HIGHLOW	Unsch			Grade 1	Grade 0			Grade 0	Grade 0		
6	HIGHLOW	Visit 4		Y	Grade 1	Grade 0	Grade 1 to Grade 0	14	Grade 0	Grade 0	Grade 0 to Grade 0	8
7	HIGHLOW	Visit 5		Y	Grade 1	Grade 2	Grade 1 to Grade 2	16	Grade 0	Grade 0	Grade 0 to Grade 0	8
8	HIGHLOW	Visit 6		Y	Grade 1	Grade 2	Grade 1 to Grade 2	16	Grade 0	Grade 0	Grade 0 to Grade 0	8
9	HIGHLOW	Visit 7		Y	Grade 1	Grade 3	Grade 1 to Grade 3	17	Grade 0	Grade 0	Grade 0 to Grade 0	8

Example 7: Primary Baseline and Alternative Baseline

Example 7 uses creatinine test as example. The data demonstrates the case when data is collected through one treatment period serving two analyses. The first analysis consists of original records and the second set consists of new records from Visit 4 through Visit 7 copied from original set. BASETYPE is applied to distinguish between two sets. The baseline for the 1st set is defined as the last value prior to or on the baseline visit (Visit 3) while the baseline of the 2nd set is defined as the last value prior to or on the first dose of study treatment visit (Visit 4).

The CTCAE toxicity grade for creatinine test result in this example is determined based on CTCAE v4.03 criteria. For visits prior to baseline visit (Visit 3 in the 1st set and Visit 4 in the 2nd set), the assessment will be compared with creatinine abnormal upper limit 1.2 mg/dL (ULN) under the variable ANRHI. For post-baseline visits, the assessment will be compared with baseline value (0.5 mg/dL in the 1st set and 1.2 mg/dL in the 2nd set).

Creatinine Test	CTCAE v4.03 Toxicity Grade			
	1	2	3	4
Assessment Criteria	> 1 - 1.5 x Baseline; > ULN - 1.5 x ULN	> 1.5 – 3 x Baseline; > 1.5 – 3 x ULN	> 3 x Baseline; > 3 – 6 x ULN	> 6 x ULN

Row	PARAM	BASETYPE	AVISIT	AVAL	BASE	ABLFL	WAYSHIFT	ANRHI	ATOXGR	Note
1	Creatinine (mg/dL)	ORIGINAL	Visit 1	0.8	0.5		ONLYHIGH	1.2	Grade 0	
2	Creatinine (mg/dL)	ORIGINAL	Visit 2	1.3	0.5		ONLYHIGH	1.2	Grade 1	AVAL > ULN - 1.5 x ULN
3	Creatinine (mg/dL)	ORIGINAL	Visit 3	0.5	0.5	Y	ONLYHIGH	1.2	Grade 0	
4	Creatinine (mg/dL)	ORIGINAL	Unsch	0.7	0.5		ONLYHIGH	1.2	Grade 1	AVAL > 1.0 x BASE
5	Creatinine (mg/dL)	ORIGINAL	Unsch	0.8	0.5		ONLYHIGH	1.2	Grade 2	AVAL > 1.5 x BASE
6	Creatinine (mg/dL)	ORIGINAL	Visit 4	1.2	0.5		ONLYHIGH	1.2	Grade 2	AVAL > 1.5 x BASE
7	Creatinine (mg/dL)	ORIGINAL	Visit 5	1.6	0.5		ONLYHIGH	1.2	Grade 3	AVAL > 3.0 x BASE
8	Creatinine (mg/dL)	ORIGINAL	Visit 6	1.6	0.5		ONLYHIGH	1.2	Grade 3	AVAL > 3.0 x BASE
9	Creatinine (mg/dL)	ORIGINAL	Visit 7	2.0	0.5		ONLYHIGH	1.2	Grade 3	AVAL > 3.0 x BASE
10	Creatinine (mg/dL)	NEW	Visit 4	1.2	1.2	Y	ONLYHIGH	1.2	Grade 0	
11	Creatinine (mg/dL)	NEW	Visit 5	1.6	1.2		ONLYHIGH	1.2	Grade 1	AVAL > 1.0 x BASE
12	Creatinine (mg/dL)	NEW	Visit 6	1.6	1.2		ONLYHIGH	1.2	Grade 1	AVAL > 1.0 x BASE
13	Creatinine (mg/dL)	NEW	Visit 7	2.0	1.2		ONLYHIGH	1.2	Grade 2	AVAL > 1.5 x BASE

CONCLUSION

The work provided in this paper demonstrates the approach that was taken within our company. It used the guidance for bi-directional toxicity grade found in draft ADaMIG v1.2 and the guidance for analysis flag, analysis multi-response criterion, and shift found in ADaMIG v1.1 to create ADLB dataset for lab toxicity tables.

Sometimes one may go beyond ADaMIG by adapting sponsor-defined variables following CDISC general rules and naming convention. Parameter toxicity direction indicator WAYSHIFT, record toxicity direction indicator ATOXDIR and analysis day category ADYPCAT1 are some examples of sponsor-defined variables.

Having all data derivation in ADLB metadata provides a better data traceability and clear communication for dataset validation and for regulatory data reviewing. At the same time, keeping all data derivation programming in ADLB makes ADLB analysis ready.

When handling multiple baselines for different analyses in ADLB, we need to keep in mind the process of toxicity regrading according to defined baseline and utilize the BASETYPE variable to distinguish between the multi-baseline definitions.

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