Detoxing Toxicity Analysis: Creating Analysis-ready One-proc Away ADLB

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Abstract
Analysis of lab data is one of the major safety evaluations conducted during clinical trials. Lab results are displayed in the data listings and summarized using tables. These reports are customary for longitudinal data analysis (descriptive summary statistics for major lab parameters and their calculated changes from baseline). Another common type of analysis of lab data is evaluating shifts from baseline. In oncology, shift in toxicity (according NCI CTC AE guidance) is commonly used to determine how the categorical result varies from baseline to post-dose. For some of the lab parameters, toxicity is irrelevant; for some, it is expected in only one direction; and for several others, toxicity can be bi-directional (separate types of toxicity due to increase and due to decrease over normal range). This article discusses how to create an effective ADLB that answers all of the challenges in analysis of lab data.

Key Words: CDISC, ADaM, Toxicity Analysis, Oncology, Clinical Trial, Lab Data

1. Introduction

Analysis datasets and associated metadata are critical for the FDA to understand how the specific analyses contained in the study report have been created. ADaM datasets should be used to create and support the results in clinical study reports, as well as other analyses required for a thorough regulatory review. Generally, ADaM facilitates regulatory review. One major benefit to follow ADaM structure is the simplification and consistency of programming steps necessary for performing an analysis. Derived from SDTM datasets, ADaM datasets should have a structure and content that allow statistical analyses to be performed with minimal programming. Such datasets are described as "analysis-ready". In addition, there is no requirement to have separate datasets for different analyses; a single dataset can support multiple analyses.

Section 4.2 in ADaMIG v1.1 lists many situations that require creation of rows not found in SDTM. One of such situation is handling bi-directional toxicity. The idea of having two separate rows, one for toxicity due to decrease over normal range and another for toxicity due to increase over normal range, in case of a specific lab parameters having bi-directional toxicity, was expressed in article "Grading Lab Toxicities using NCI – Common Terminology Criteria for Adverse Events (CTCAE)" of Srinivas Veeragoni and Ankur Mathur, presented at the annual PHUSE conference in 2016. Our work applies this idea, extending the coverage to include generic situations, and provides detailed advice and justifications for how to create an ADLB dataset based on SDTM LB domain that is "analysis-ready" for producing data listings and conducting different statistical analyses.

2. Example of provided SDTM LB records

According to the SDTM Implementation Guidance Version 3.2, raw data are first mapped into SDTM LB domain. Table 1 is a dummy illustrative example including 5 lab tests

(Urinalysis – Occult Blood; Chemistry – Bilirubin; Chemistry – Potassium; Hematology – Hematocrit; and Hematology – Lymphocytes) for the same subject at 3 different visits (Baseline, Week 2, and Week 4).

The results of Urinalysis – Occult Blood Test were collected as character values, while the results of the other 4 tests were collected as numeric values. Note that not each abnormality (result outside of the normal range) leads to assigning a NCI CTC AE Toxicity Grade. The source document ("Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03") has a limited number of cases in which a Toxicity Grade should be assigned.

3. Creating ADaM dataset ADLB from provided SDTM domain LB

To start the process of deriving any dataset, we need to carefully read the study Statistical Analysis Plan and take into consideration the shells of proposed output ("TLG shells") provided by statisticians. All required derivations must be determined based on SAP and TLG shells, and done in ADaM creation code, making ADaM datasets "analysis-ready". Of course, in many cases analysis of lab data can be study/company specific, but we believe that for vast majority of companies conducting clinical trials in oncology, the commonly used lab-related outputs include:

- Data listings that may contain different derivations, such as change from baseline
- Summary tables displaying the descriptive summary statistics for major lab parameters and their changes from baseline. For numeric values, these tables usually include time-point information about numbers of subjects, means, standard deviations, minimums, medians, and maximums (Table 2)
- Shift tables analyzing shifts from baseline, using a Low-Normal-High scale (Table 3).
- Shift tables evaluating shifts in toxicities, from baseline including shift tables to worst post-baseline toxicity. When applying the NCI CTC AE grading scale to laboratory results, grade zero is often used to indicate "normal" or "not a concern", while grade five (death) is not applicable. Again, it is important to note that not all laboratory tests have CTC grade criteria available (Table 4).

Based on CTCAE Version 4.03, we can claim for the lab data in our example:

- Urinalysis – Occult Blood: There are no available CTC grade criteria for this test
- Chemistry – Bilirubin: There is one available CTC grade criteria associated with this test (Blood bilirubin increased)
- Chemistry – Potassium: There are two available CTC grade criteria associated with this test (Hypokalemia and Hyperkalemia)
- Hematology – Hematocrit: There are no available CTC grade criteria for this test
- Hematology – Lymphocytes: There are two available CTC grade criteria associated with this test (Lymphocyte count decreased and Lymphocyte count increased)

To create a One-proc away ADLB that meets all analysis requirements, we recommend:

- If CTCAE Version 4.03 does not have CTC grade criteria associated with the test (e.g.: Hematology – Hematocrit), then each record from SDTM domain LB will result in only one record in ADaM dataset ADLB.
- If CTCAE Version 4.03 has one CTC grade criteria associated with the test (e.g.: Chemistry – Bilirubin), then each record from SDTM domain LB will result in

two records in ADaM dataset ADLB (one record for the collected test result and additional record for assigning toxicity), regardless of whether toxicity was reported in the LB record for this particular test.

- If CTCAE Version 4.03 has two CTC grade criteria associated with the test ("bi-directional toxicity") (e.g.: Chemistry – Potassium), then each record from SDTM domain LB will result in 3 records in ADaM dataset ADLB (one record for collected test result and two additional records for assigning toxicity – one record for each possible direction), regardless of whether toxicity was reported in the LB record for this particular test.

The example ADLB in Table 5 has two Parameter Categories. Original carried forward SDTM LB records are populated with PARCAT1 and these records will be used for producing data listings, descriptive statistics tables, and shift tables by Low – Normal – High Scale. Newly added toxicity related records are populated with PARCAT2, which will be used for shift tables by Toxicity scale.

For the newly added records with PARCAT2, the value of variable PARAM is the name of the toxicity type (e.g.: "Blood bilirubin increased") and AVAL and AVALC contain the reported toxicity grades as numeric and character values, respectively. If no toxicity was reported for the test at a given time point, the values of AVAL = 0 and AVALC = 'Grade 0' are assigned. In the case of bi-directional toxicity, since a lab value toxicity can only go in only one direction for a given time point, the other record in the additional rows approach has to be given a grade of 0 (as an indication that the subject does not have toxicity in the opposite direction). In addition, if there is a need to indicate worst post-baseline toxicity, variable AOCCIFL (1st Max Sev./Int. Occurrence Flag) can be added into ADLB for newly created records (not included in the example).

The created ADLB also contains 2 variables for SHIFT: SHIFT1 (shift using "Low – Normal – High" scale) and SHIFT2 (shift in toxicity). Both shift variables are expected to be populated for post-baseline ADLB records. SHIFT1 is for PARCAT1 records with the original SDTM Reference Range Indicator (LBNRIND) variable, while SHIFT2 is for the newly added ADLB records.

4. Discussion

Let's give an explanation for the proposed ADLB dataset (Table 5) for each of the lab parameters provided in the original example:

For Occult Blood, the results of this test are in character values (captured in AVALC). Since this test does not have Reference Low and Upper Limits, SHIFT1 (shift using a "Low – Normal – High" scale) should not be populated. Also, according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, there is no toxicity associated with this test, so no additional records (in comparison to SDTM) are created.

For Bilirubin, the Reference Low and Upper Limits are available for this test, so we can populate the variable ANRIND (Analysis Reference Range Indicator) for all of the ADLB records that correspond to the original SDTM LB records (assigned with PARCAT1). For post-baseline records of PARCAT1, we can also populate variable SHIFT1. In addition, variables LBTOX and ATOXGRN are used for data listing. There is one-directional toxicity associated with this test (Blood Bilirubin Increased), so for each original SDTM record, we will have one additional record with PARAM = "Blood

Bilirubin Increased". These additional records have populated a variable called LBORTEST (Lab Original Test) with a value of "Bilirubin" to indicate the source. Variables AVAL and AVALC contain Analysis values for the Toxicity Grade in numeric and character forms; variable SHIFT2 is used in post-baseline records to populate shift in toxicity.

For Potassium, the Reference Low and Upper Limits are available for this test, so we can populate variable ANRIND (Analysis Reference Range Indicator) for all of the ADLB records that correspond to the original SDTM LB records (assigned with PARCAT1). For post-baseline records of PARCAT1, we can also populate variable SHIFT1. In addition, variables LBTOX and ATOXGRN are used for data listing. There is bi-directional toxicity associated with this test (Hypokalemia and Hyperkalemia), so for each original SDTM record, we will have two additional records with PARAMs equal to "Hypokalemia" and "Hyperkalemia". These additional records have populated a variable called LBORTEST (Lab Original Test) with a value of "Potassium" to indicate the source. Variables AVAL and AVALC contain Analysis values for Toxicity Grade in numeric and character forms; variable SHIFT2 is used in post-baseline records to populate shift in toxicity. If the initial result indicates toxicity in one direction, there should be no indication of toxicity in the opposite direction. None of the SDTM records provided in the example indicate any toxicity, so for all newly added (in comparison to SDTM) ADLB records, the value of AVAL = 0.

For Hematocrit, the Reference Low and Upper Limits are available for this test, so we can populate variable ANRIND (Analysis Reference Range Indicator) for all of the ADLB records that correspond to the original SDTM LB records. For these post-baseline records, we can also populate variable SHIFT1. According to CTCAE Version 4.03, there is no toxicity associated with this test, so no additional records (in comparison to SDTM) are created.

For Lymphocytes the Reference Low and Upper Limits are available for this test, so we can populate variable ANRIND (Analysis Reference Range Indicator) for all of the ADLB records that correspond to the original SDTM LB records (assigned with PARCAT1). For post-baseline records of PARCAT1, we can also populate variable SHIFT1. In addition, variables LBTOX and ATOXGRN are used for data listing. There is bi-directional toxicity associated with this test (Lymphocyte count decreased and Lymphocyte count increased), so for each original SDTM record, we will have two additional records with PARAMs equal to "Lymphocyte count decreased" and "Lymphocyte count increased". These additional records have populated a variable called LBORTEST (Lab Original Test) with a value of "Lymphocytes" to indicate the source. Variables AVAL and AVALC contain Analysis values for Toxicity Grade in numeric and character forms; variable SHIFT2 is used in post-baseline records to populate shift in toxicity. If the initial result indicates toxicity in one direction, then there should be no indication of toxicity in the opposite direction.

5. Conclusions

The techniques proposed in this paper allow the reader to create "analysis-ready" "one proc away" Analysis Data Model ADLB.

Table 1: Dummy Illustrative Example of SDTM LB Domain

Category for Lab Test (LBCAT)	Lab Test or Examination Name (LBTEST)	Lab Test or Examination Short Name (LBTESTCD)	Visit Name (VISIT)	Character Result/Finding in Std Format (LBSTRESC)	Numeric Result/Finding in Standard Units (LBSTRESN)	Standard Units (LBSTRESU)	Reference Range Lower Limit-Std Units (LBSTNRLO)	Reference Range Upper Limit-Std Units (LBSTNRHI)	Reference Range Indicator (LBNRIND)	Toxicity (LBTOX)	Standard Toxicity Grade (LBTOXGR)
Urinalysis	Occult Blood	OCCBLD	Baseline	Negative							
Urinalysis	Occult Blood	OCCBLD	Week 2	Small (+)							
Urinalysis	Occult Blood	OCCBLD	Week 4	Moderate (++)							
Chemistry	Bilirubin	BILI	Baseline	12.3	12.3	umol/L	3.42	22.23	Normal		
Chemistry	Bilirubin	BILI	Week 2	3.3	3.3	umol/L	3.42	22.23	Low		
Chemistry	Bilirubin	BILI	Week 4	32.1	32.1	umol/L	3.42	22.23	High	Blood bilirubin increased	1
Chemistry	Potassium	K	Baseline	4.1	4.1	mmol/L	3.5	5.0	Normal		
Chemistry	Potassium	K	Week 2	4.2	4.2	mmol/L	3.5	5.0	Normal		
Chemistry	Potassium	K	Week 4	4.3	4.3	mmol/L	3.5	5.0	Normal		
Hematology	Hematocrit	HCT	Baseline	0.33	0.33	L/L	0.4	0.54	Low		
Hematology	Hematocrit	HCT	Week 2	0.44	0.44	L/L	0.4	0.54	Normal		
Hematology	Hematocrit	HCT	Week 4	0.55	0.55	L/L	0.4	0.54	High		
Hematology	Lymphocytes	LYM	Baseline	1.1	1.1	10^9/L	1.0	3.0	Normal		
Hematology	Lymphocytes	LYM	Week 2	0.7	0.7	10^9/L	1.0	3.0	Low	Lymphocyte count decreased	2
Hematology	Lymphocytes	LYM	Week 4	5.5	5.5	10^9/L	1.0	3.0	High	Lymphocyte count increased	2

Table 2: Laboratory Results – Mean and Mean Change from Baseline by Visit

Laboratory Test (Unit) Visit Statistics	Arm A (N = xxx)		Arm B (N = xxx)	
	Actual	Change from Baseline	Actual	Change from Baseline
Parameter Name				
Baseline				
n	xxx		xxx	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Min, Max	xx.x, xx.x		xx.x, xx.x	
Cycle x, Day y				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
…				

Table 3: Laboratory Results – Shifts from Baseline relative to Normal Range by Visit

	Arm A			Arm B		
Laboratory Test Visit Result Category	Low Baseline n (%)	Normal Baseline n (%)	High Baseline n (%)	Low Baseline n (%)	Normal Baseline n (%)	High Baseline n (%)
Laboratory test Name						
Cycle 1 Day 8						
Low	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Normal	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
High	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Cycle 1 Day 15						
…						

Table 4: Laboratory Results – Shifts from Baseline to Worst Post-baseline Grade by CTC AE Grade

Toxicity Type / Laboratory Test Name (e.g. Hypokalemia)	Arm	Worst Post-baseline Grade	Baseline				
			Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
xxxx / yyy	Arm A	Grade 0	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)
		Grade 2	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)
		Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Arm B	Grade 0	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)
		Grade 2	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)
		Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…							

Table 5: Example of Created ADLB Dataset

PARAM	PARAMCD	LBORTEST	PARCAT1	PARCAT2	AVISIT	AVAL	AVALC	ANRIND	BASE	BASEC	SHIFT1	SHIFT2	LBTOX	ATOXGRN
Occult Blood	OCCBLD		Urinalysis		Baseline		Negative			Negative				
Occult Blood	OCCBLD		Urinalysis		Week 2		Small (+)			Negative				
Occult Blood	OCCBLD		Urinalysis		Week 4		Moderate (++)			Negative				
Bilirubin (umol/L)	BILI		Chemistry		Baseline	12.3		Normal	12.3					
Blood bilirubin increased	BILI_I	Bilirubin		Toxicity (Chemistry)	Baseline	0	Grade 0		0	Grade 0				
Bilirubin (umol/L)	BILI		Chemistry		Week 2	3.3		Low	12.3		Normal – Low			
Blood bilirubin increased	BILI_I	Bilirubin		Toxicity (Chemistry)	Week 2	0	Grade 0		0	Grade 0		Grade 0 – Grade 0		
Bilirubin (umol/L)	BILI		Chemistry		Week 4	32.1		High			Normal – High		Blood bilirubin increased	1
Blood bilirubin increased	BILI_I	Bilirubin		Toxicity (Chemistry)	Week 4	1	Grade 1		0	Grade 0		Grade 0 – Grade 1		
Potassium (mmol/L)	K		Chemistry		Baseline	4.1		Normal	4.1					
Hypokalemia	K_D	Potassium		Toxicity (Chemistry)	Baseline	0	Grade 0		0	Grade 0				
Hyperkalemia	K_I	Potassium		Toxicity (Chemistry)	Baseline	0	Grade 0		0	Grade 0	Normal – Normal			
Potassium (mmol/L)	K		Chemistry		Week 2	4.2		Normal	4.1					
Hypokalemia	K_D	Potassium		Toxicity (Chemistry)	Week 2	0	Grade 0		0	Grade 0		Grade 0 – Grade 0		
Hyperkalemia	K_I	Potassium		Toxicity (Chemistry)	Week 2	0	Grade 0		0	Grade 0		Grade 0 – Grade 0		
Potassium (mmol/L)	K		Chemistry		Week 4	4.3		Normal	4.1		Normal – Normal			

Table 5: Example of Created ADLB Dataset (Continued)

PARAM	PARAMCD	LBORTEST	PARCAT1	PARCAT2	AVISIT	AVAL	AVALC	ANRIND	BASE	BASEC	SHIFT1	SHIFT2	LBTOX	ATOXGRN
Hypokalemia	K_D	Potassium		Toxicity (Chemistry)	Week 4	0	Grade 0		0	Grade 0		Grade 0 – Grade 0		
Hyperkalemia	K_I	Potassium		Toxicity (Chemistry)	Week 4	0	Grade 0		0	Grade 0		Grade 0 – Grade 0		
Hematocrit (L/L)	HCT		Hematology		Baseline	0.33		Low	0.33					
Hematocrit (L/L)	HCT		Hematology		Week 2	0.44		Normal	0.33		Low – Normal			
Hematocrit (L/L)	HCT		Hematology		Week 4	0.55		High	0.33		Low – High			
Lymphocytes (10^9/L)	LYM		Hematology		Baseline	1.1		Normal	1.1					
Lymphocyte count decreased	LYM_D	Lymphocytes		Toxicity (Hematology)	Baseline	0	Grade 0		0	Grade 0				
Lymphocyte count increased	LYM_I	Lymphocytes		Toxicity (Hematology)	Baseline	0	Grade 0		0	Grade 0				
Lymphocytes (10^9/L)	LYM		Hematology		Week 2	0.7		Low	1.1		Normal – Low		Lymphocyte count decreased	2
Lymphocyte count decreased	LYM_D	Lymphocytes		Toxicity (Hematology)	Week 2	2	Grade 2		0	Grade 0		Grade 0 – Grade 2		
Lymphocyte count increased	LYM_I	Lymphocytes		Toxicity (Hematology)	Week 2	0	Grade 0		0	Grade 0		Grade 0 – Grade 0		
Lymphocytes (10^9/L)	LYM		Hematology		Week 4	5.5		High	1.1		Normal - High		Lymphocyte count increased	2
Lymphocyte count decreased	LYM_D	Lymphocytes		Toxicity (Hematology)	Week 4	0	Grade 0		0	Grade 0		Grade 0 – Grade 0		
Lymphocyte count increased	LYM_I	Lymphocytes		Toxicity (Hematology)	Week 4	2	Grade 2		0	Grade 0		Grade 0 – Grade 2		

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