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Bidirectionality to LOINC: Handling the Nitty Gritty of Lab Data

Bhargav Koduru, Seattle Genetics, Inc.

ABSTRACT

Laboratory data is often challenging to work with during tabulation and analysis data set creation. This paper will include solutions to some of these complexities encountered during the LB (SDTM) and ADLB (ADaM) data set structure, including but not limited to:

- How to use the Model Permissible variables of the Findings class in the LB SDTM data set (Ex: __SPCCND, __SPCUFL)
- How to identify the tests that could be graded by CTCAE 4.0 or higher, and determine the directionality
- How to plan and execute the ADaM dataset to support the shift tables associated with bidirectional tests (Ex: Glucose-High and Low)
- How to derive "Treatment Emergent" records in the ADLB ADaM datasets, bidirectional tests in particular
- How to associate the preferred terms between CTCAE and MedDRA to establish the clinical connection between the adverse event and the lab result. (Ex: Neutropenia (MedDRA) and Neutrophil Count Decreased (CTCAE) can both be linked to the lab test "Neutrophils".)

With the requirement for LOINC (Logical Observation Identifiers Names and Codes) beginning for studies that start after March 15, 2020 for U.S. NDAs, ANDAs and certain BLAs, and on March 15, 2021 for certain INDs, I would like to share some thoughts on the LOINC implementation in the LB data. For example, glucose identified in serum/plasma or urine would both have the same TESTCD "GLUC" and often the units are also same (mg/dL), however, only the variable LBSPEC would differ between them. LOINC is proposed to address potential confusion by having a unique 6-part name.

INTRODUCTION

Safety data collected through the laboratory tests is required to be included in the trial submission package submitted to the FDA, if collected as a part of the trial. Laboratory data collected in the CRFs or electronically received from independent central laboratories are captured in the LB SDTM domain, which belongs to the Findings class of the SDTM. Laboratory data also often complements the adverse event data, as both use the same Common Terminology Criteria for Adverse Events (CTCAE) grading system.

There are various excellent papers on how to capture data in the LB domain and the challenges associated with it (Meier, 2014) (Veeragoni & Mathur, 2016). With this paper, I would like to add some of our recent experiences and strategies we have adopted in designing our LB and ADLB datasets, and also elaborate on the connection between LB and AE domains. I would also add in some details on LOINC, a novel aspect associated with LB that has been introduced in the recent past, and the need to embrace it with open arms for future trials.

MODEL PERMISSIBLE VARIABLES

Programmers often limit themselves to the variables mentioned in the SDTM IG though we have a wealth of additional model permissible variables in the SDTM that can help us in correctly mapping the CRF variables. However, you will receive a *"SD1076/FDAC031: Model permissible variable added into standard domain"* warning in your Pinnacle 21 report. It is just a preventive message to check if it was an intentional addition and not added by mistake. Table 1 has some of the interesting variables from the Findings Observation Class of SDTM v1.7 (SDTMIG v3.3), which can be used in further fortifying your LB rather than moving them to SUPPLB and re-merging them later at the ADaM level.

Variable Name	Variable Label	Type	Role	Description
--LLOQ	Lower Limit of Quantitation	Num	Variable Qualifier of --STRESC and --STRESN	Indicates the lower limit of quantitation for an assay. Units will be those used for --STRESU.
--ULOQ	Upper Limit of Quantitation	Num	Variable Qualifier of --STRESC and --STRESN	Indicates the upper limit of quantitation for an assay. Units will be those used for --STRESU.
--REPNUM	Repetition Number	Num	Record Qualifier	The instance number of a test that is repeated within a given timeframe for the same test. The level of granularity can vary (e.g., within a time point or within a visit). For example, multiple measurements of blood pressure or multiple analyses of a sample.
--ANMETH	Analysis Method	Char	Record Qualifier	Analysis method applied to obtain a summarized result. Analysis method describes the method of secondary processing applied to a complex observation result (e.g., an image or a genetic sequence).
--TSTDTL	Measurement, Test, or Examination Detail	Char	Variable Qualifier of --TESTCD and --TEST	Further description of --TESTCD and --TEST. Example: "The percentage of cells with +1 intensity of staining" when MITEST = "Thyroid Transcription Factor 1".
--RUNID	Run ID	Char	Record Qualifier	A unique identifier for a particular run of a test on a particular batch of samples.
--SPCUFL	Specimen Usability for the Test	Char	Record Qualifier	Describes the usability of the specimen for the test. The value will be "N" if the specimen is not usable, and null if the specimen is usable.
--ANTREG	Anatomical Region	Char	Variable Qualifier of --SPEC	Defines the specific anatomical or biological region of a tissue, organ specimen or the region from which the specimen is obtained, as defined in the protocol, such as a section or part of what is described in the --SPEC variable. Examples: "CORTEX", "MEDULLA", "MUCOSA".

Table 1: Example Model Permissible variables for Findings Observation Class of SDTM v1.7

An example LB dataset incorporating some of the model permissible variables from Table 1 is shown below in Table 2. This example has been adopted from section 4.2.1 of the Virology TAUG v2.0 (CFAST Virology v2.0 Standards Team, 2015), and it summarizes the complete results of HIV viral load analyzed using the qRT-PCR without using SUPPLB at all. LBREPNUM shows that the test has been repeated thrice for the same sample in this visit. The sample is initially tested as a duplicate, as understood from the repeated LBRUNID value for the first two rows. As the results were contradicting each other, the sample was re-run under the LBRUNID “2101” to confirm the result from the earlier run. The LBANTREG value elucidates that the “RNA” specimen used for the test has been obtained from “LIVER, LEFT LOBE”. qRT_PCR results can be analyzed using the Double delta CT Method or by relative standard curve method. In this example, the value of variable LBANMETH specifies which of the two methods has been used for the analysis. Finally, LBLLOQ qualifies the LBORRES value of “DETECTED, BELOW LLOQ”. The sensitivity of qRT-PCR can vary across instruments and hence LBLLOQ becomes a meaningful companion to LBORRES for this test. Also, note that LBSTRESU is generated even though LBORRESU is blank, in order to support LBLLOQ.

Row	STUDYID	DOMAIN	USUBJID	LBREFID	LBREPNUM	LBRUNID	LBTEST
1	HIV456	LB	HIV456-02	3896	1	2100	Ribonucleic Acid
2	HIV456	LB	HIV456-02	3896	2	2100	Ribonucleic Acid
3	HIV456	LB	HIV456-02	3896	3	2101	Ribonucleic Acid

Row	LBTESTCD	LBCAT	LBORRES	LBORRESU	LBSTRESC	LBSTRESN	LBSTRESU
1 (cont)	RNA	VIRAL LOAD	TARGET NOT DETECTED		TARGET NOT DETECTED		log10 copies/mL
2 (cont)	RNA	VIRAL LOAD	DETECTED, BELOW LLOQ		DETECTED, BELOW LLOQ		log10 copies/mL
3 (cont)	RNA	VIRAL LOAD	TARGET NOT DETECTED		TARGET NOT DETECTED		log10 copies/mL

Row	LBMETHOD	LBANMETH	LBSPEC	LBANTREG	LBLLOQ	VISIT	LBDTC
1 (cont)	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	DOUBLE DELTA CT METHOD	RNA	LIVER, LEFT LOBE	1.5	VISIT2	2011-08-13
2 (cont)	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	DOUBLE DELTA CT METHOD	RNA	LIVER, LEFT LOBE	1.5	VISIT2	2011-08-13
3 (cont)	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	DOUBLE DELTA CT METHOD	RNA	LIVER, LEFT LOBE	1.5	VISIT2	2011-08-13

Table 2: Example LB dataset using --REPNUM, --RUNID, --ANMETH, --ANTREG, and --LLOQ variables.

A CLOSER LOOK AT CTCAE

HOW TO GRADE YOUR LAB TESTS?

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) is a descriptive terminology which can be utilized for adverse event (AE) reporting (including abnormal laboratory findings) in clinical trials. A grading (severity) scale is provided for each AE term. For lab toxicities, general practice is that the investigators assess the toxicity grades using clinical evaluation and lab data and enter their assessment into the AE CRF. The lab values could be later graded programmatically and reconciled with AEs, which would be helpful to verify that critical lab toxicities are appropriately reported as AEs. However, assigning lab toxicity grades following CTCAE criteria is not a straightforward task. The rationale within CTCAE was to apply greater clinical significance to the descriptions of grade because of clinical management decisions that are made based on the assignment of grade. Consequently, grading is not always based on pure numeric values. While many grading scales include only numeric values/ranges, some grading scales also include clinical assessment and/or intervention text.

CTEP (Cancer Therapy Evaluation Program), NCI's Investigational Drug Branch, has provided additional guidance regarding computer usage as a component of grade assignment for CTCAE AE terms with quantitative severity scales. Based on this guidance, the lab related CTCAE findings are classified into 2 groups: (1) Investigator input required: Grade should not be assigned based on numeric values alone; and (2) Potential use of lab interface: Grade potentially could be assigned using an electronic lab interface if the system is capable of managing the variables of baseline, ULN (Upper Limit of Normal), and LLN (Lower Limit of Normal) across patients and laboratories. (CTEP Guidance, 2010). There is a thin line between the tests that are purely based on numerical and those that require clinical assessments and it is in the best interest of the sponsor to clarify the approach used for assigning the laboratory grades. Adopting either of the below options, and adding in the appropriate language in the SAP/ Protocol or as footnotes in the outputs will help to maintain the clarity and integrity of data:

Option 1:

Assign grades only to those lab values that fit in the grades devoid of clinical assessments (e.g., only Grade 1 is considered while assigning the grades for hypernatremia, as per the Table 3 below. Grade 2 - 4 have some clinical assessments along with numerical ranges. So, they are left as missing in LB).

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					

Table 3: Hypernatremia definition and grading scale as per CTCAE v5.0

Option 2:

Ignore clinical assessments completely while assigning the grades (i.e. assign grade 1 - 4 in reference to the numerical ranges from the Table 3 above). Subsequently, any potential clinical assessment associated to the lab test is reported by the investigator in the AE CRF. Option 2 is more optimal than 1 and it rules out the possibility of underreporting the adverse events.

Another slippery slope of clinical assessments is handling the overlapping numerical ranges of some AEs in the CTCAE criteria. The only difference between them is the clinical assessment, such as a concomitant medication. One such AE is shared in the Table 4, as an example.

When we encounter such AEs, the recommendation is to choose the AE of higher grade, to avoid accidental under-reporting (Veeragoni & Mathur, 2016).

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					

Table 4: Hypokalemia, showing the overlapping numerical ranges in Grade 1 and Grade 2

There are some AEs, an example is shared in Table 5, that require a baseline value and Upper Limit of Normal (ULN). For these tests, it is essential to derive the baseline values prior to grading in a manner consistent with analysis-driven baseline values.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen. Navigational Note: Also consider Renal and urinary disorders: Acute kidney injury					

Table 5: Creatinine increased, with the grades that consider "Baseline" in assessment

Until SDTM IG 3.2, there could be some challenges in deriving these baselines and making them consistent with the analysis baseline values depending on where they are derived (i.e., raw data/SDTM or ADaM). However, in SDTM IG 3.3, a new variable "LBLOBXFL" has been added, which relies on RFXSTDTC in deriving the baseline flag, as shown in Table 6. Addition of this variable does bring in clarity on how "baseline" is defined. Our old faithful friend "LBBLFL" has been deprecated as a "Permissible" variable, moving forward.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
LBLOBXFL	Last Observation Before Exposure Flag	Char	(NY)	Record Qualifier	Operationally-derived indicator used to identify the last non-missing value prior to RFXSTDTC. The value should be "Y" or null.	Exp
LBBLFL	Baseline Flag	Char	(NY)	Record Qualifier	Indicator used to identify a baseline value. Should be "Y" or null. Note that LBBLFL is retained for backward compatibility. The authoritative baseline for statistical analysis is in an ADaM dataset.	Perm

Table 6: Variable LBLOBXFL, from SDTM IG 3.3

THE PREFERRED TERM CONFUSION

A consolidated table which combines the AEs from AE and LB domains, especially those of special interest, is commonly included in the clinical study report. When generating such a table, special attention has to be attributed to the AEs under the "Investigations" class in CTCAE. The AEs under this class are often purely based on laboratory values, but their clinical equivalents captured in the AE CRF belong to other SOCs of MedDRA, that are not included in CTCAE. Hence, when generating the numbers for the AEs of special interest, they might dilute the numbers across two preferred terms, leading to underreporting.

For example, let us consider "Thrombocytopenia" of the SOC "Blood and lymphatic system disorders" as an AE of special interest. In this scenario, the "Platelet count decreased" CTCAE term in the "Investigations" class is closely associated with "Thrombocytopenia". When reporting the numbers, the counts will be distributed across these two preferred terms, but only a combined percentage of these two terms would provide a better picture of the AE. In such scenarios, we propose to combine the counts under a single preferred term, and add a footnote clarifying the approach, to make it clear to the reviewer.

It is also a good practice to get such questions clarified with your regulatory review division in a Type C or Type B meeting well in advance, to avoid confusion during submission.

TIME TO UPVERSION YOUR CTCAE

CTCAE version 5.0 was published in November 2017 (U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, 2017). There are many updates in the latest version compared to the previously published v4.0 in 2009. Effective April 1, 2018, all protocols of CDUS submitters are converted to CTCAE v5.0 for both Clinical Data Update System (CDUS) and CTEP-AERS reporting (DEPARTMENT of HEALTH & HUMAN SERVICES, 2018). Table 7 summarizes all the updates to the numerically gradable tests, as per CTCAE v5.0.

Lab Tests	CTCAE Term (Increase/Decrease)		Lab Tests	CTCAE Term (Increase/Decrease)
Body Temperature	Fever/Hypothermia		Creatine kinase	CPK increased
Calcium	Hypercalcemia/Hypocalcemia		Creatinine	Creatinine increased
Glucose	Hyperglycemia*/Hypoglycemia		Diarrhea	Diarrhea
Hemoglobin	Hemoglobin increased*/Anemia		eGFR	Chronic kidney disease
Lymphocytes	Lymphocyte count increased/Lymphocyte count decreased		Ejection Fraction (Cardiology Test)	Ejection fraction decreased
Magnesium	Hypermagnesemia/Hypomagnesemia		Eosinophils	Eosinophilia**
PH	Alkalosis/Acidosis		FEV (Lung Test)	Forced expiratory volume decreased
Potassium	Hyperkalemia*/Hypokalemia*		Fibrinogen	Fibrinogen decreased*
Sodium	Hypernatremia*/Hyponatremia		GGT	GGT increased*
Weight	Weight gain/Weight loss		Haptoglobin	Haptoglobin decreased
White blood cell count	Leukocytosis/White blood cell decreased		INR	INR increased
Alanine aminotransferase	Alanine aminotransferase increased		Lactate dehydrogenase	Blood lactate dehydrogenase increased**
Albumin	Hypoalbuminemia		Lipase	Lipase increased*
Alkaline phosphatase	Alkaline phosphatase increased*		Methemoglobin	Methemoglobinemia**
Amylase	Serum amylase increased*		Neutrophils	Neutrophil count decreased
Aspartate aminotransferase	Aspartate aminotransferase increased		PFT (Lung Test)	Vital capacity abnormal
Bicarbonate	Blood bicarbonate decreased		Phosphorus	Hyperphosphatemia
Blood Pressure	Hypertension		Platelets (thrombocytes)	Platelet count decreased
BMI	Obesity		PTT	Activated partial thromboplastin time prolonged
cardiac dysrhythmia (Cardiology Test)	Electrocardiogram QT corrected interval prolonged		Sperm Count	Oligospermia
Cardiac troponin I	Cardiac troponin I increased		Total Bilirubin	Blood bilirubin increased
Cardiac troponin T	Cardiac troponin T increased		Triglycerides	Hypertriglyceridemia
CD4 lymphocytes	CD4 lymphocytes decreased		Uric acid	Hyperuricemia
Cholesterol	Cholesterol high		Urinary Protein	Proteinuria
CO Diffusion (Lung Test)	Carbon monoxide diffusing capacity decreased		Urine Quantity	Urine output decreased
*Grades updated in CTCAE v5.0 ** Newly added terms in CTCAE v5.0				

Table 7: Compilation of lab tests that are numerically gradable, partially or completely, as per the CTCAE v5.0

CHALLENGES WITH BIDIRECTIONALITY

Often, counts of the laboratory grades are summarized using a table shell as shown in Table 8. In case the request is to summarize only the treatment-emergent laboratory events, then the question arises about dealing with bidirectional tests in which the baseline value was in one direction, while the post-baseline value is in another direction. For example, the Potassium value at baseline is grade -2, where

'-'indicates it is hypokalemia, whereas the post-baseline value is +2, where '+' indicates that it is hyperkalemia. In this scenario, we would treat any post-baseline event with a change of direction as a 'treatment-emergent' event.

Parameter	Drug of Interest (N =)								Control (N =)							
	G 0		G 1-2		G ≥ 3		G 4		G 0		G 1-2		G ≥ 3		G 4	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
CHEMISTRY																
Hyperkalemia																
Hypokalemia																

Table 8: Example table shell summarizing the laboratory grades by each direction.

Another challenge with bidirectional tests is getting the total counts of the subjects in each direction when the subjects do not have events in both directions. For example, in a situation where the subject never had any events in one direction of a bidirectional test, the total 'n' under 'G 0' would be equal to 'N'. Conceptually it is very simple but the issue is in representing it at ADaM level, when virtually no data exists for the subjects in that direction at the SDTM level (LB). Following is a strategy we have applied by leveraging MCRIT variables at the ADaM level. In the below Table 9, the subject has no data associated with "Hyperkalemia". In this case, we enter a value of Grade 0 for Hyperkalemia and it can be used for the counts in the Table 5.

Row	USUBJID	PARAM	VISIT	ADT	AVISIT	AVAL	ABLFL
1	XYZ-001	Potassium (mEq/L)	Cycle 1 Day 1	26Jul2016	Baseline	3.7	Y
2	XYZ-001	Potassium (mEq/L)	Cycle 2 Day 1	16Aug2016	Cycle 2 Day 1	4.1	
3	XYZ-001	Potassium (mEq/L)	Cycle 3 Day 1	06Sep2016	Cycle 3 Day 1	3.1	

Row	BASE	CHG	ATOXGR	BTOXGR	ANRIND	BNRIND	BNRINDIR
1(Contd)	3.7	0	0	0	NORMAL	NORMAL	0
2(Contd)	3.7	0.4	0	0	NORMAL	NORMAL	0
3(Contd)	3.7	-0.6	1	0	LOW	NORMAL	0

Row	ANRINDIR	SHIFT1	LBTRTMFL	MCRIT1	MCRIT1ML	MCRIT2	MCRIT2ML
1(Contd)	0						
2(Contd)	0	0 to 0		Hyperkalemia		Hypokalemia	
3(Contd)	-1	0 to -1	Y	Hyperkalemia	Grade 0	Hypokalemia	Grade 1-2

Table 9: An example ADLB dataset highlighting the use of MCRIT variables

SAY NO TO SPECIAL CHARACTERS

Always ensure that LBSTRESC and controlled terminology extensions in LBTEST do not contain byte values 160-191, as some character mappings in that range may interfere with FDA processes (FDA, 2019).

WHEN SIZE IS AN ISSUE

The size of the LB domain dataset submitted by sponsors is often too large to process by FDA. This issue can be addressed by splitting a large LB dataset into smaller datasets according to LBCAT and LBSCAT, using LBCAT for initial splitting. If the size is still too large, then LBSCAT can be leveraged for further splitting. For example, use the dataset name lb1.xpt for chemistry, lb2.xpt for hematology, and lb3.xpt for urinalysis. Splitting the dataset in other ways (e.g., by subject or file size) makes the data less useable. Sponsors should submit these smaller files in addition to the larger non-split standard LB domain file. Sponsors should submit the split files in a separate sub-directory (/split) that is clearly documented in addition to the non-split standard LB domain file in the SDTM datasets (FDA, 2019).

LOINC

By March of 2020, FDA expects that all SDTM data sets include the LOINC codes; the support for LOINC code to the sponsors has started already. To understand the need for LOINC code we have to take a step back into the complexities of mapping involved in LB. As per Paul Vervuren, “One has to find candidates in the extensive controlled terminology list. Then there can be multiple lab tests that map to a single SDTM controlled term. This means additional variables must be used in order to produce a unique test definition (e.g. LBCAT, LBSPEC, LBMETHOD and/or LBELTM). Finally, it can occur that a controlled term is not available and a code needs to be defined in agreement with the rules for Lab tests" (Vervuren, 2010). Currently, we leverage multiple variables, such as LBCAT, LBSPEC, etc., as mentioned above to distinguish the tests. For example, a glucose test done in urine or serum would have the same units of “mg/dL”. We can only distinguish these using the LBSPEC variable which would have different values of “Urine” or “Serum”. LBLOINC is a single variable that applies rule-based uniqueness represented in all the aforementioned variables, for maintaining the distinction between tests.

LOINC is a system (not just a list of terms) used worldwide for test codes in healthcare, not only for lab tests but also for vital signs and many other tests. LOINC coding is found (or even mandated) to be used in (Aerts, 2017):

- HL7-v2 messages in hospital information systems (HIS)
- Interoperable electronic health records (HL7-v3, CDA/CCD, FHIR)

A LOINC code is just a number for the LOINC name, which consists of 5-6 parts ("dimensions"). The LOINC name of code 2345-7 is "Glucose:MCnc:Pt:Ser/Plas:Qn" with each part being separated by a colon (":"). So the parts are:

- Component: Glucose
- Property measured: MCnc ("Mass concentration")
- Time aspect: Pt ("point in time")
- System/Specimen: Ser/Plas (Serum/Plasma)
- Scale: Qn (quantitative)

Thus, the use of LOINC codes maintains the traceability of the test with a wide range of details including specimen type used, to the FDA reviewer. Do note that though the SDTM already supports the exchange of LOINC codes using the LBLOINC variable, LOINC codes should not be added to SEND datasets (FDA, 2019).

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CONTACT INFORMATION

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

Bhargav Koduru
Seattle Genetics, Inc.
425-527-4715
bkoduru@seagen.com