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Clinical Laboratory Results, Old and New Pains

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ABSTRACT

Analyzing clinical trial laboratory results should be a straightforward task; however, a quick perusal of industry papers and presentations contradicts this statement. Issues surfaced over ten years ago continue to plague industry. Further, adoption of the CDISC SDTM Laboratory Test Results (LB) domain adds another level of complexity. In this paper, the authors will readdress old challenges associated with laboratory data including variability of reported units and reference ranges and their impact on analyzability as well as discuss the new task of tabulating laboratory data in a standard model.

Keywords: Laboratory results, lab unit conversion, normal ranges, WBC differentials, NCI grades, SDTM, LB

INTRODUCTION

In addition to the traditional difficulties, unit conversions, normal range harmonization, toxicity grade calculations, etc., the FDA "is strongly encouraging sponsors to submit data in a standard form …" Tabulating laboratory results in the CDISC Study Data Tabulation Model (SDTM) Laboratory Test Results (LB) domain introduces new challenges and requirements.

OLD PAINS

There have been lab related tasks since the original days of clinical trials. Publications on how to address them date as far back as we want to look.

UNIT CONVERSION

We learned in school about converting metric units to pound system and as soon as we memorize the conversion factors it become close to trivial, perhaps converting from Fahrenheit to Celsius added a little twist. For lab results, however, it seems a consistently problematic story. We could create a look-up table with conversion factors but still we may get unpredictably creative unit spelling making any table obsolete every time a new variety is present. And sometimes these spellings happen to be ambiguous where it will depend on the particular lab test, making them context sensitive. Another such a case is for example those lab units using molecular weights. We could get things like "g", "G", "Gram", "gr", "grm", "Grm", and every possible –sometimes impossible—combination of characters to represent grams. The case of "G" is particularly interesting because it is ambiguous as it could be grams or GIGA becoming context sensitive and it is necessary to know the lab test to make a determination of what unit actually is. Similarly, but not ambiguous, when the units are in terms of molecular weights it is also necessary to know the lab test. For example Bilirubin has conventional units mg/dL and SI units µmol/L where the conversion factor 17.1 applies only to this test. Most conventional units are metric and many SI standard units are metric also, for all those test the same conversion factor will apply to any pair of units.

Other interesting cases: the lab test measurement is biological activity like "IU" (International Units, e.g. Insulin), or enzyme activity measured in "U/L" (e.g. ALT, Alkaline Phosphatase).

A couple of methods for unit conversion are described by Carlson 2006.

NORMAL RANGES

On a multi-center clinical trial with local labs there will likely be multiple reference ranges which may come from several different reasons. Instruments from different manufacturers or different assays or different methods to calculate the local reference limits, and some other reasons can be found.

The process to transform lab results for adjusted homogeneous limits has been called "normalization" and also "harmonization" of ranges. There have been a number of attempts to harmonize normal ranges.

Analysis tables where those lab results are summarized may have questionable results as it could be inappropriate to aggregate values that potentially belong to different scales. Several methods have been developed to address this problem: In 1986 Sogliero-Gilbert et al proposed computing a unit-less score based on each lab test patient result and upper limit where a positive score would indicate the severity of any abnormality, and a score of zero indicated a

normal result.

Later in 1992 Chuang-Stein proposed two methods of normalizing reference ranges, the first is somehow a refinement of Sogliero-Gilbert where the transformation consisted on taking the result minus the lower limit and divided by the width of the range, so normal values would be between 0 and 1. The other method is based on the same ideas as some ranges are constructed: take two standard deviations up and down from the mean of a large set of individuals considered normal and set the limits.

In 2001 Chuang-Stein came with a new proposal to transform the ranges. It consists of converting the upper and lower limits to some predefined values and then convert the result in a way to preserve its relative position within the range. The method produces a new transformed result that is proportionally equivalent to the new limits as the original result within the original limits. With this method however it is possible to obtain negative values which according to the method should be set to zero, to be interpreted as a value too small to be measured.

All these method above allow to display figures where all results belong to the same scale, however there are some problems, as we will see below: when transforming WBC differentials the sum of the components may no longer add up to 100%, also when computing CTC grades using the new adjusted normal limits may not match the original CTC grades.

These problems are reduced significantly when using a central lab, but there are some risks such as the central lab changing instruments and therefore normal ranges. And very often is not feasible or practical to have a central lab.

In 2003 Karvanen presented a solution to avoid negative converted results based on a statistical foundation.

Also in 2003 Ravuna reports the flaws on the methods described above and suggests another solution.

These methods above have a common problem in that the converted results, have little or no clinical meaning.

However, another quite different approach was offered by Jansen 1999, this method allows to have as many local labs as needed but have a central lab to process the results before they are entered in the clinical database. The main idea is that the central labs gets their own known samples analyzed in the local labs instruments and use them as reference to adjust the local labs results and ranges. Since then the major central labs offer such a service.

BLOOD DIFFERENTIALS

A CBC (complete blood count) test will count the following components of our blood:

RBC – Red blood cells- , WBC – White blood cells-, HGB – amount of hemoglobin- and hematocrit -the fraction of RBC in the blood-.

In turn WBC has its own components, showing the normal percent within the total WBC count.

- Neutrophils: 40% to 60%
- Lymphocytes: 20% to 40%
- Monocytes: 2% to 8%
- Eosinophils: 1% to 4%
- Basophils: 0.5% to 1%
- Band (young neutrophil): 0% to 3%

For a particular blood sample, the sum of the percent differentials should add up to 100%, as each percent corresponds to the fraction of WBC. Our problems start when we get results which may be given as percent and as absolute counts, we may have the corresponding normal ranges, but very often we do not.
If results had been modified to accommodate harmonized normal ranges, because the transformations could have used different scales, the sum of percent differentials will not add up to 100. Similarly after range harmonization the sum of absolute differential counts may not match the total WBC count. This is a case where the authors do not know any solutions, other than using a central lab.

TOXICITY CTC GRADES

For background information and some explanation regarding how the NCI defines CTC adverse event grades see Niland 2012.

For something more related to SAS programming see Matthews 2009, who explains the difficulties to compute CTC grades version 4 and also presents a method to calculate a few case examples.

In previous versions, in particular version 2 and version 3, the grade limits were defined using only absolute values in some specific units or based on some factor of the normal limits. This made it fairly straight forward to create a table

with all absolute limits and the factors with an additional variable to distinguish each case. Since you only needed one row per lab test it was easy to merge the corresponding record from this table to the lab dataset and then compute the grade.

With NCI CTC-AE version 4 the process became a bit more complicated as there are absolute limits and relative to normal limits as before but also grades that are defined as an offset of normal limits and grades where de definition is in terms of some increase or decrease on the normal limits or from the patient baseline result. This makes our old grade table somehow impractical.

Dayog 2011 explain further the additional difficulties of CTC AE version 4 for laboratory events when input from the investigator is part of the grade definition specification.

URINALYSIS

Urinalysis refers to lab test done to find specific target parameters in urine. Urinalysis seems to have been somehow neglected as it seems difficult to find SAS papers that talk about it.

There are several methods, among the most common we have:

Urine test strip. Used to determine the presence of leukocytes, nitrite, protein, blood and measure the specific gravity and pH. In the figure the lab operator is comparing colors of the dipstick against the reference chart. The lab results may look like '+' or '1+' or '++' or '2+' or just '2' or any possible variation challenging the strongest imagination.

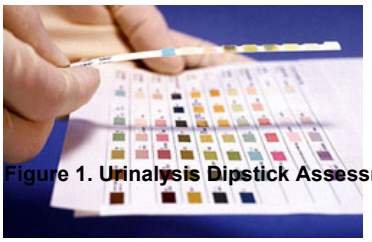

Figure 1. Urinalysis Dipstick Assessment

Microscopic examination. Allows to determine type and number of cells associated with kidney stones, infections, tumors, nephritis, vasculitis and some other conditions.

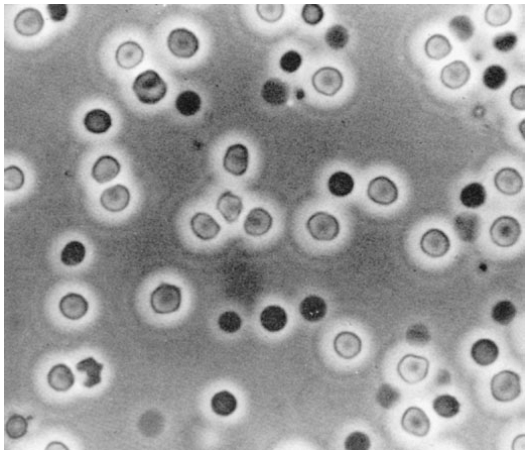

Figure 2. Urine Microscopic Examination and Results

Urine casts and crystals. Allow the detection of urinary infections, red blood cells, and other parameters.

Urinalysis data could be interpreted as a special case of the unit conversion process, with the caveat that typically they do not have units.

NEW PAINS

Tabulating laboratory results in SDTM LB domain expedites analysis; however, the actual tabulation introduces new challenges.

CONTROLLED TERMINOLOGY

Certain SDTM variables require a discrete set of values or controlled terminology. The CDISC Controlled Terminology Team, sponsors, or external sources (e.g. MSSO) define these values sets. Additionally, certain codelists defined by the CDISC Controlled Terminology Team may be extended by sponsors. CDISC defined codelists bind the Lab Test or Examination Short Name (LBTESTCD), Laboratory Test or Examination Name (LBTEST), Original Units (LORRESU), and Standard Units (LBSTRESU).

Test Short Name and Test Name:

CDISC codelists for LBTESTCD and LBTEST are extensive, but not exhaustive. Further, the terminology is not specific to biological matrix, testing method or result type (quantitative or qualitative). For example, LBTESTCD is assigned to "GLUC" for serum glucose, plasma glucose, and urine glucose. Additional qualifier variables including Category (LBCAT), Subcategory (LBSCAT), Specimen Type (LBSPEC), and Method (METHOD) exist that enable the differentiation between tests. Tabulating laboratory results requires mapping unique test codes provided by vendors or developed by sponsors to a fully qualified representation.

Sponsor Code	LBESTCD	LBTEST	LBCAT	LBSPEC	LBMETHOD
GLUC_SER	GLUC	Glucose	CHEMISTRY	SERUM	
GLUC_PLA	GLUC	Glucose	CHEMISTRY	PLASMA	
UGLUCQL	GLUC	Glucose	URINALYSIS	URINE	QUALITATIVE ASSESSMENT
UGLUCQN	GLUC	Glucose	URINALYSIS	URNE	

Developing and storing this "laboratory transformation metadata" simplifies tabulation and minimizes the impact of CDISC controlled terminology updates. As mentioned, the CDISC codelists for LBTESTCD and LBTEST are not exhaustive and sponsors will need to extend the value set. If the CDISC Controlled Terminology Team adds values for which sponsor extensions have been previously defined, updating the conversion metadata makes the change available across the sponsor organization.

Original Units and Standard Units:

Original Units (LBORRESU) and Standard Units (LBSTRESU) must be represented using CDISC defined controlled terminology. As a result, "original" units reported by a laboratory must first be translated to a controlled terminology value prior to unit conversion. As such, industry use of the terms "reported unit" and "original unit" are no longer synonymous. "Original unit" is now defined as the reported unit translated into CDISC controlled terminology.

Similar to LBTESTCD and LBTEST controlled terminology, the CDISC controlled terminology for units is not exhaustive and sponsors will need to extend the value set. Again, tabulating laboratory results is simplified by developing and storing laboratory transformation metadata to translate reported units into CDISC controlled terminology.

Original Unit	Reported Unit
%	PCT
%	PERCENT
%	PERCENTAGE

RESULTS REPORTED BY A LABORATORY MAY NOT BE LABORATORY TEST RESULTS

All results reported by a laboratory may not be appropriate for the LB domain. For example, SDTM domains have been defined for pharmacokinetic concentrations and pharmacokinetic parameters. Differentiation becomes more problematic for genomic biomarkers, complements, diagnostic assays, etc. Spirited discussions occur within the CDISC community and sponsors regarding the appropriate domain(s) in which to tabulate said data. The CDISC Submission Data Standards Team has issued a draft version of Pharmacogenomics/Pharmacogenetics domains (PGx) and has a sub-team exploring the tabulation of biomarkers. Sponsors have developed their own CDISC-aligned domains for results reported by laboratories that require qualifiers not defined within SDTM.

CONCLUSION

Ideally, sponsors would leverage expertise like central laboratories to solve both the issues that have existed for years as well as more recent challenges. For example, central laboratories can harmonize reference ranges, convert units including urinalysis results, standardize differentials, and provide data in a CDISC-compliant format.

Unfortunately, target audience for this paper may not be able to influence these operational decisions. As such, legacy solutions will continue to address the old pains; however, analysts should consider developing transformation metadata to enable the scalable conversion of laboratory results to the SDTM LB domain.

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