

Implementing Laboratory Toxicity Grading for CTCAE Version 5

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ABSTRACT

Laboratory toxicity grading has been an important part of safety reporting since the FDA began accepting electronic data in 1999. Staying up to date with the various CTCAE versions can be a challenge. CTCAE Version 5.0 adds a layer of complexity with new grading criteria dependent on baseline measurements. We will present a practical method for deriving toxicity grades in the SDTM LB domain based on the new CTCAE, as well as reporting toxicity events in an OCCDS dataset derived separately from the BDS dataset with the laboratory findings.

INTRODUCTION

Toxicity grading for laboratory results began in 1999 with CTCAE version 2.0. In this version, toxicity grading was based on absolute ranges relative to the upper and lower limits of normal. With these simplistic criteria, deriving the toxicity grades was a simple task. However, the grading criteria became more complex with the release of CTCAE version 4.0 in 2009 quickly replaced by version 4.03 in 2010. In this version, the change in the laboratory measurement from baseline also became a factor in deriving the toxicity grade. More interesting, however, was the introduction of the MedDRA preferred term and system organ class associated with the toxicity. With this, it became possible to treat laboratory toxicity measurements as adverse events. When CTCAE version 5.0 was released in 2017, another layer of complexity was added in that the subject's status at baseline became a factor in deriving toxicity grades. For some laboratory measurements, the grading is different depending on whether the subject's baseline measurement was normal or abnormal. With this addition, we cannot rely solely on ranges to derive the toxicity grade. The purpose of this paper is to demonstrate how to derive toxicity grades with the new CTCAE 5.0 criteria. Additionally, we will discuss how to leverage the MedDRA information introduced in CTCAE 4.03 to represent lab toxicities as events in an ADaM OCCDS dataset.

EVOLUTION IN COMPLEXITY

Consider the lab parameter Alkaline Phosphatase commonly captured in the SDTM LB domain with LBTESTCD = "ALP". Abnormally high values of this parameter can result in an adverse event with the CTCAE term "Alkaline phosphatase increased". In CTCAE version 4.03, toxicity grades for this adverse event are calculated explicitly in ranges related to the upper limit of normal (ULN) as shown below in Table 1.

| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|------------------|------------------|-------------------|-------------|
| >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |

Table 1: "Alkaline Phosphatase Increased" grading criteria from CTCAE version 4.03

This is very simple to program. With the result stored in LBSTRESN and the ULN stored in LBSTNRHI, one simply needs to compare the two SDTM values to determine the grade. (Note that toxicity grade of 5 was excluded. That grade cannot be computed based just on values in LB as it only applies when the event results in death.)

Now compare this to the "Alkaline phosphatase increased" criteria for CTCAE version 5.0 as shown below in Table 2.

| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|--|---|---|---|
| >ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal | >2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal | >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal |

Table 2: “Alkaline Phosphatase Increased” grading criteria from CTCAE version 5.0

In addition to LBSTRESN and LBSTNRHI from a single record as needed with CTCAE Version 4.03, we also need the LBSTRESN value from the associated baseline ALP record. First, it needs to be determined whether the baseline LBSTRESN is greater than the ULN. If the baseline LBSTRESN is at or below the ULN, then the toxicity grade is derived based on the ULN as was done in version 4.03. However, if the baseline LBSTRESN is greater than the ULN, then the grades are derived by comparing the current LBSTRESN value to the baseline LBSTRESN value instead of the ULN. (Note that the baseline records themselves are graded according to the ULN, since an abnormal baseline value cannot be compared to itself to get a meaningful grade.)

DERIVING THE TOXICITY GRADES

Deriving these more complex grade criteria can be frontloaded into an Excel spreadsheet and then called programmatically in a SAS macro. The grading criteria are specified in the spreadsheet as macro variables that are then applied using a Call Execute routine. The ALP increased criteria from version 5.0 appear in the spreadsheet as shown below in Table 3.

| TESTCD | TOX | DIR | G1 | G2 |
|--------|--------------------------------|------------------------|--|---|
| ALP | Alkaline phosphatase increased | (&R > &ULN OR &R > &B) | ((&BVISN = &VISN OR &B <= &ULN) AND &ULN < &R <= 2.5*&ULN) OR (&B > &ULN AND 2*&B <= &R <= 2.5*&B) | ((&BVISN = &VISN OR &B <= &ULN) AND 2.5*&ULN < &R <= 5*&ULN) OR (&B > &ULN AND 2.5*&B < &R <= 5*&B) |

Table 3: “Alkaline Phosphatase Increased” grading criteria from CTCAE version 5.0 written in SAS macro variables. (Note that Grades 3 and 4 are excluded from this display.)

The macro variables are defined as follows:

- &R is the result from the record being graded, assumed to be captured in LBSTRESN.
- &ULN is the upper limit of normal, assumed to be captured in LBSTNRHI.
- &VISN is the visit number of the record being graded, captured in VISITNUM.
- &B is the baseline result found in LBSTRESN of the associated baseline record.
- &BVISN is the baseline visit number found in VISITNUM of the associated baseline record.

The DIR column specifies a grading direction. In this case, the direction criterion is met if the result is greater than the ULN or the baseline result. While only increases are relevant for this specific test, specifying directionality is necessary as there are lab tests that need to have grades assigned based on both increases and decreases. (An example of bidirectional grading will be provided later.)

The SAS macro for performing these derivations (see appendix for the code) starts by defining a dataset name, a CTCAE version, and the various macro parameters described above:

A parameter (“ds”) refers to an SDTM domain name. In most cases, this will be “LB”, but other SDTM findings domains may require toxicity grading. The input will be an SDTM domain without the xxTOXGR and xxTOX variables, and the output will be the same SDTM domain with the toxicity variables added. As a default, the CTCAE version is set to 5.0, but this can be manually set to other versions as needed. Like the ULN parameter, the LLN parameter refers to the lower limit of normal, assumed to be collected in the SDTM variable LBSTNRLO. This is not needed for the ALP test, but it is needed for low-graded CTCAE terms such as “Hypocalcemia”.

First, the macro determines the baseline result values. This can be customized for specific definitions of baseline. For this example, baseline is being defined as the last populated record before initial treatment. The SDTM IG 3.3 variable LBLOXFL (last observation before treatment flag) is used to simplify the derivation. Adjustments are required if an earlier SDTM IG version is being followed.

The next step requires that the grading criteria written in macro variables as shown in Table 3 be available in a SAS dataset. This can be done by reading in the associated CTCAE grading criteria excel file each time the macro is run using proc import. Alternatively, as in this example, the grading criteria for version 5.0 can be stored as a SAS dataset (here named ctcae5). Similarly, the version 4.03 criteria are stored in a SAS dataset named ctcae4. The version can be selected based on the macro call. The associated grading criteria are transposed for downstream use.

The resulting transposed table for CTCAE version 5.0 for the “Alkaline phosphatase increased” event is shown below in Table 4.

| TESTCD | TOX | DIR | GRADE | CODE |
|--------|--------------------------------|---------------------------|-------|--|
| ALP | Alkaline phosphatase increased | (&R > &ULN OR &R > &B) | G1 | ((&BVISN = &VISN OR &B <= &ULN) AND &ULN < &R <= 2.5*&ULN) OR (&B > &ULN AND 2*&B <= &R <= 2.5*&B) |
| ALP | Alkaline phosphatase increased | (&R > &ULN OR &R > &B) | G2 | ((&BVISN = &VISN OR &B <= &ULN) AND &ULN < &R <= 2.5*&ULN) OR (&B > &ULN AND 2*&B <= &R <= 2.5*&B) |
| ALP | Alkaline phosphatase increased | (&R > &ULN OR &R > &B) | G3 | ((&BVISN = &VISN OR &B <= &ULN) AND 5*&ULN < &R <= 20*&ULN) OR (&B > &ULN AND 5*&B < &R <= 20*&B) |
| ALP | Alkaline phosphatase increased | (&R > &ULN OR &R > &B) | G4 | ((&BVISN = &VISN OR &B <= &ULN) AND &R > 20*&ULN) OR (&B > &ULN AND &R > 20*&B) |

Table 4: SAS dataset containing transposed grading criteria for the “Alkaline phosphatase increased” event

Using this dataset, we use a Call Execute routine to run the code stored in the CODE variable (when the associated criteria are met).

Lastly, a new LB dataset is created with LBTOX and LBTOXGR added, and intermediate datasets used for processing are dropped from the WORK library.

With this approach, the derivations for each CTCAE and grade only need to be written out once in terms of macro variables. Then the Call Execute routine applies that code where needed.

EXAMPLES WITH MOCK LABORATORY DATA

Consider the mock laboratory SDTM LB dataset shown in Table 5 below:

| Row | USUBJID | LBSEQ | LBTESTCD | LBTEST | LBSTRESN | LBSTRESU | LBSTNRLO | LBSTNRHI |
|-----|---------|-------|----------|----------------------|----------|----------|----------|----------|
| 1 | 001 | 1 | ALP | Alkaline Phosphatase | 110 | U/L | 31 | 106 |
| 2 | 002 | 1 | ALP | Alkaline Phosphatase | 100 | U/L | 35 | 131 |
| 3 | 003 | 1 | ALP | Alkaline Phosphatase | 200 | U/L | 95 | 385 |
| 4 | 001 | 2 | CREAT | Creatinine | 0.6 | mg/dL | 0.4 | 1.1 |
| 5 | 002 | 2 | CREAT | Creatinine | 0.7 | mg/dL | 0.5 | 1.2 |

| Row | USUBJID | LBSEQ | LBTESTCD | LBTEST | LBSTRESN | LBSTRESU | LBSTNRLO | LBSTNRHI |
|-----|---------|-------|----------|----------------------|----------|----------|----------|----------|
| 6 | 003 | 2 | CREAT | Creatinine | 2.4 | mg/dL | 0.67 | 1.17 |
| 7 | 001 | 3 | CACR | Calcium Corrected | 2.2 | mmol/L | 2.15 | 2.55 |
| 8 | 002 | 3 | CACR | Calcium Corrected | 2.8 | mmol/L | 2.15 | 2.55 |
| 9 | 003 | 3 | CACR | Calcium Corrected | 1.6 | mmol/L | 2.15 | 2.55 |
| 10 | 001 | 4 | ALP | Alkaline Phosphatase | 540 | U/L | 31 | 106 |
| 11 | 002 | 4 | ALP | Alkaline Phosphatase | 300 | U/L | 35 | 131 |
| 12 | 003 | 4 | ALP | Alkaline Phosphatase | 8000 | U/L | 95 | 385 |
| 13 | 001 | 5 | CREAT | Creatinine | 0.84 | mg/dL | 0.4 | 1.1 |
| 14 | 002 | 5 | CREAT | Creatinine | 2.22 | mg/dL | 0.5 | 1.2 |
| 15 | 003 | 5 | CREAT | Creatinine | 7.1 | mg/dL | 0.67 | 1.17 |
| 16 | 001 | 6 | CACR | Calcium Corrected | 3.5 | mmol/L | 2.15 | 2.55 |
| 17 | 002 | 6 | CACR | Calcium Corrected | 2.03 | mmol/L | 2.15 | 2.55 |
| 18 | 003 | 6 | CACR | Calcium Corrected | 2.4 | mmol/L | 2.15 | 2.55 |

| Row (cont) | LBNRIND | LBLOBXFL | VISITNUM | VISIT | LBTOX | LBTOXGR |
|------------|---------|----------|----------|-------|-------|---------|
| 1 | HIGH | Y | 2 | Day 1 | | |
| 2 | NORMAL | Y | 2 | Day 1 | | |
| 3 | NORMAL | Y | 2 | Day 1 | | |
| 4 | NORMAL | Y | 2 | Day 1 | | |
| 5 | NORMAL | Y | 2 | Day 1 | | |
| 6 | HIGH | Y | 2 | Day 1 | | |
| 7 | NORMAL | Y | 2 | Day 1 | | |
| 8 | HIGH | Y | 2 | Day 1 | | |
| 9 | LOW | Y | 2 | Day 1 | | |
| 10 | HIGH | | 3 | Day 2 | | |
| 11 | HIGH | | 3 | Day 2 | | |
| 12 | HIGH | | 3 | Day 2 | | |
| 13 | NORMAL | | 3 | Day 2 | | |
| 14 | HIGH | | 3 | Day 2 | | |
| 15 | HIGH | | 3 | Day 2 | | |
| 16 | HIGH | | 3 | Day 2 | | |
| 17 | LOW | | 3 | Day 2 | | |
| 18 | NORMAL | | 3 | Day 2 | | |

Table 5: Mock SDTM laboratory data used as a demonstration. (Note that some columns not shown.)

We have data for three lab tests: Alkaline Phosphatase, Creatinine, and Calcium Corrected. For each of these tests, we will examine the CTCAE derivations written in SAS macro variables for both versions 4.03 and 5.0, and we will look at results that give a different grade between the two versions. We will show how to populate the LBTOX and LBTOXGR columns.

ALKALINE PHOSPHATASE

The toxicity grading criteria for the term “Alkaline phosphatase increased” for CTCAE version 5.0 is shown above in Table 3. The simpler toxicity grading criteria for version 4.03 is shown below in Table 6.

| TESTCD | TOX | DIR | G1 | G2 | G3 | G4 |
|--------|--------------------------------|-----------|-------------------------|-----------------------------|----------------------------|----------------|
| ALP | Alkaline phosphatase increased | &R > &ULN | &ULN < &R <= 2.5 * &ULN | 2.5 * &ULN < &R <= 5 * &ULN | 5 * &ULN < &R <= 20 * &ULN | &R > 20 * &ULN |

Table 6: “Alkaline Phosphatase Increased” grading criteria from CTCAE version 4.03 written in SAS macro variables

The version 4.03 criteria only compare to the ULN, while the version 5.0 criteria vary depending on whether the baseline assessment was normal or abnormal.

Table 7 below shows the toxicity grades derived for subject 001 using the version 4.03 criteria, and Table 8 shows the same records with the toxicity grades derived using the version 5.0 criteria.

| USUBJID | LBTESTCD | LBSTRESN | LBSTNRHI | LBLOBXFL | VISITNUM | VISIT | LBTOX | LBTOXGR |
|---------|----------|----------|----------|----------|----------|-------|--------------------------------|---------|
| 001 | ALP | 110 | 106 | Y | 2 | Day 1 | Alkaline phosphatase increased | 1 |
| 001 | ALP | 540 | 106 | | 3 | Day 2 | Alkaline phosphatase increased | 3 |

Table 7: Sample “Alkaline phosphatase increased” derived using CTCAE version 4.03 criteria

| USUBJID | LBTESTCD | LBSTRESN | LBSTNRHI | LBLOBXFL | VISITNUM | VISIT | LBTOX | LBTOXGR |
|---------|----------|----------|----------|----------|----------|-------|--------------------------------|---------|
| 001 | ALP | 110 | 106 | Y | 2 | Day 1 | Alkaline phosphatase increased | 1 |
| 001 | ALP | 540 | 106 | | 3 | Day 2 | Alkaline phosphatase increased | 2 |

Table 8: Sample “Alkaline phosphatase increased” derived using CTCAE version 5.0 criteria

For these records, the baseline ALP measurement is 110 (as indicated by LBLOBXFL), the ULN is 106, and the post-baseline measurement is 540. By simply looking at 5 times the ULN (530) and 20 times the ULN (2120), we see that that the post-baseline measurement has a toxicity grade of 3 according to the version 4.03 criteria. However, since the baseline measurement was above the ULN, we compare to 2.5 times the baseline value (275) and 5 times the baseline value (550) and determine that the post-baseline measurement has a toxicity grade of 2 according to the version 5.0 criteria.

CREATININE

We will now consider the lab parameter with LBTESTCD = “CREAT”, and it’s associated CTCAE term “Creatinine increased”. The version 4.03 criteria are shown below in Table 9, and the version 5.0 criteria are shown below in Table 10.

| TESTCD | TOX | DIR | G1 | G2 | G3 | G4 |
|--------|----------------------|------------------------|--|--|--|-------------|
| CREAT | Creatinine increased | (&R > &ULN OR &R > &B) | (&ULN < &R <= 1.5*&ULN) OR (&B < &R <= 1.5*&B) | (1.5*&ULN < &R <= 3*&ULN) OR (1.5*&B < &R <= 3*&B) | (3*&ULN < &R <= 6*&ULN) OR (&R > 3*&B) | &R > 6*&ULN |

Table 9: CTCAE Version 4.03 toxicity grading criteria for “Creatinine increased” written in terms of SAS macro variables

| TESTCD | TOX | DIR | G1 | G2 | G3 | G4 |
|--------|----------------------|------------------------|-----------------------|--|--|-------------|
| CREAT | Creatinine increased | (&R > &ULN OR &R > &B) | &ULN < &R <= 1.5*&ULN | (1.5*&ULN < &R <= 3*&ULN) OR (1.5*&B < &R <= 3*&B) | (3*&ULN < &R <= 6*&ULN) OR (&R > 3*&B) | &R > 6*&ULN |

Table 10: CTCAE Version 5.0 toxicity grading criteria for “Creatinine increased” written in terms of SAS macro variables

While there is no major change in complexity between version 4.03 and version 5.0 in this example (unlike with “Alkaline phosphatase increased”) there is a subtle difference in the way a toxicity grade of 1 is derived that can cause errors if care is not taken when applying the different CTCAE versions. In version 4.03, a record with a result that is greater than the baseline value but not greater than the ULN can be given a toxicity grade of 1. This relationship was removed in version 5.0 so that records in the normal range are not given a toxicity grade unless they are greater than 1.5 times the baseline value.

Table 11 below shows the toxicity grades derived for subject 001 using the version 4.03 criteria, and Table 12 below shows the same records with the toxicity grades derived using the version 5.0 criteria.

| USUBJID | LBTESTCD | LBSTRESN | LBSTNRHI | LBLOBXFL | VISITNUM | VISIT | LBTOX | LBTOXGR |
|---------|----------|----------|----------|----------|----------|-------|----------------------|---------|
| 001 | CREAT | 0.6 | 1.1 | Y | 2 | Day 1 | | |
| 001 | CREAT | 0.84 | 1.1 | | 3 | Day 2 | Creatinine increased | 1 |

Table 11: Sample “Creatinine increased” derived using CTCAE version 4.03 criteria

| USUBJID | LBTESTCD | LBSTRESN | LBSTNRHI | LBLOBXFL | VISITNUM | VISIT | LBTOX | LBTOXGR |
|---------|----------|----------|----------|----------|----------|-------|-------|---------|
| 001 | CREAT | 0.6 | 1.1 | Y | 2 | Day 1 | | |
| 001 | CREAT | 0.84 | 1.1 | | 3 | Day 2 | | |

Table 12: Sample “Creatinine increased” derived using CTCAE version 5.0 criteria

In this example, the post-baseline measurement of 0.84 is below the ULN of 1.1. However, since the result is greater than the baseline result of 0.6, the post-baseline measurement is given a toxicity grade of 1 using the version 4.03 criteria. With the version 5 criteria, the post-baseline measurement is still less than 1.5 times the baseline measurement ($0.6 \times 1.5 = 0.9$), so the record is not given a toxicity grade at all. When transitioning from version 4.03 to version 5.0, failure to notice subtle changes like this can result in unnecessary toxicity events appearing in the study data.

CALCIUM

While calcium toxicity grading is simple and identical between CTCAE versions 4.03 and 5.0, this example is included to show how this method handles lab tests that can be graded in two directions. Calcium has two associated CTCAE terms; “Hypocalcemia” and “Hypercalcemia”. The CTCAE criteria for these terms are shown in Table 13 and Table 14 below.

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|--------------|---|---|---|--|---------|
| Hypocalcemia | Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L | Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic | Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated | Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences | Death |

Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.

Table 13: Hypocalcemia toxicity grading criteria (versions 4.03 and 5.0)

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---------------|--|--|--|---|---------|
| Hypercalcemia | Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L | Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic | Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated | Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences | Death |

Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.

Table 14: Hypercalcemia toxicity grading criteria *Versions 4.03 and 5.0)

Please note that this technique does not handle descriptive terms such as “symptomatic”, “hospitalization indicated”, “life-threatening consequences”, or “Death”, since these cannot be determined from lab data alone. Also notice that there are multiple lab tests and units that can lead to a CTCAE term of “Hypocalcemia” or “Hypercalcemia”. The mock data in this example assumes that corrected serum calcium (LBTESTCD = “CACR”) is collected with a standardized unit of LBSTRESU = “mmol/L”.

These grading criteria in both versions 4.03 and 5.0, written in terms of SAS macro variables, are shown in Table 15 below.

| TESTCD | TOX | DIR | G1 | G2 | G3 | G4 |
|--------|---------------|-----------|------------------|-----------------|------------------|----------|
| CACR | Hypercalcemia | &R > &ULN | &ULN < &R <= 2.9 | 2.9 < &R <= 3.1 | 3.1 < &R <= 3.4 | &R > 3.4 |
| CACR | Hypocalcemia | &R < &LLN | 2 <= &R < &LLN | 1.75 <= &R < 2 | 1.5 <= &R < 1.75 | &R < 1.5 |

Table 15: CTCAE grading criteria for “Hypocalcemia” and “Hypercalcemia” (Versions 4.03 and 5.0)

This scenario shows the utility for the DIR column. By checking the result against the ULN and the LLN in the beginning of the Call Execute portion of the macro, we can ensure that toxicity grades are only derived for the appropriate LBTOX value. For reference, the CACR records from the mock LB dataset with LBTOXGR and LBTOX derived is included below in Table 16.

| USUBJID | LBSEQ | LBTESTCD | LBSTRESN | LBSTNRLO | LBSTNRHI | LBNRIND | LBLOBXFL | VISIT | LBTOX | LBTOXGR |
|---------|-------|----------|----------|----------|----------|---------|----------|-------|---------------|---------|
| 001 | 3 | CACR | 2.2 | 2.15 | 2.55 | NORMAL | Y | Day 1 | | |
| 001 | 6 | CACR | 3.5 | 2.15 | 2.55 | HIGH | | Day 2 | Hypercalcemia | 4 |
| 002 | 3 | CACR | 2.8 | 2.15 | 2.55 | HIGH | Y | Day 1 | Hypercalcemia | 1 |
| 002 | 6 | CACR | 2.03 | 2.15 | 2.55 | LOW | | Day 2 | Hypocalcemia | 1 |
| 003 | 3 | CACR | 1.6 | 2.15 | 2.55 | LOW | Y | Day 1 | Hypocalcemia | 3 |
| 003 | 6 | CACR | 2.4 | 2.15 | 2.55 | NORMAL | | Day 2 | | |

Table 16: Corrected Calcium data with toxicity grades derived

LAB TOXICITIES AS EVENTS IN AN OCCDS DATASET

With the addition of MedDRA terminology into the CTCAE criteria, it is now possible to treat lab toxicities as events in an OCCDS dataset. Consider the output below in Table 17

**Table 3
Clinical Laboratory Events by NCI-CTCAE Grade
Number of Subjects (%) by Body System and MedDRA Term
Safety-Evaluable Subjects**

| MedDRA System Organ Class/ Preferred Term | NCI CTCAE Grade | Group 1 (n=nn) | Group 2 (n=nn) |
|---|-----------------|----------------|----------------|
| Any Instance | | | |
| Total | Total | nn (xx.x%) | nn (xx.x%) |
| | 4 | nn (xx.x%) | nn (xx.x%) |
| | 3 | nn (xx.x%) | nn (xx.x%) |
| | 2 | nn (xx.x%) | nn (xx.x%) |
| | 1 | nn (xx.x%) | nn (xx.x%) |
| Blood and Lymphatic System Disorders | | | |
| Total | Total | nn (xx.x%) | nn (xx.x%) |
| | 4 | nn (xx.x%) | nn (xx.x%) |
| | 3 | nn (xx.x%) | nn (xx.x%) |
| | 2 | nn (xx.x%) | nn (xx.x%) |
| | 1 | nn (xx.x%) | nn (xx.x%) |
| Hypoalbuminemia | | | |
| Total | Total | nn (xx.x%) | nn (xx.x%) |
| | 4 | nn (xx.x%) | nn (xx.x%) |
| | 3 | nn (xx.x%) | nn (xx.x%) |
| | 2 | nn (xx.x%) | nn (xx.x%) |
| | 1 | nn (xx.x%) | nn (xx.x%) |

Table 17: Laboratory toxicities analyzed as events using the MedDRA System Organ Class and Preferred Term (Minjoe and Widell, 2013)

With the creation of the OCCDS standard, there is now a formal compliant and official format for supporting analysis data for events other than AEs. With the MedDRA terms available in LBTOX and an

official standard available for occurrence data, it is now possible to summarize lab toxicities as events as shown in Table 17 in a compliant manner. Sample records from the associated ADaM dataset, which we call ADLBTOX, are shown below in Table 18.

| USUBJID | LBTESTCD | LBSEQ | LBTOX | ASOC | LBTOXGR | TRTP |
|---------|----------|-------|-----------------|--------------------------------------|---------|------|
| 001 | ALB | 3 | Hypoalbuminemia | Blood and Lymphatic System Disorders | 2 | 1 |
| 002 | ALB | 6 | Hypoalbuminemia | Blood and Lymphatic System Disorders | 3 | 1 |
| 003 | ALB | 7 | Hypoalbuminemia | Blood and Lymphatic System Disorders | 4 | 2 |

Table 18: Sample records from an OCCDS ADLBTOX dataset that can support analysis of lab toxicity events

Only selected columns are shown in order to support the analysis in Table 17. The SDTM variables LBTESTCD and LBSEQ are included to maintain traceability from LB to ADLBTOX.

CONCLUSION

Even with the additional complexity added to the definitions of laboratory toxicity grades that comes from considering baseline values, deriving these grades can still be handled easily and consistently with proper planning. By housing all the grade derivations into a reference metadata as macro variables and utilizing the Call Execute routine in SAS, these grades (regardless of CTCAE version) can be derived automatically and efficiently. Additionally, since this process requires that all toxicity grade definitions be stored in a single file, that file can be maintained (or at least easily reviewed) by an expert in laboratory assessments.

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APPENDIX

```
%macro tox(ds,version=5,R=lbstresn,B=base,Uln=lbstnrhi,LLN=lbstnrlo,
          VISN=visitnum,BVISN=basevisit);

/*get baseline values in the same row*/
proc sql;
create table base as
  select usubjid, &ds.testcd, &ds.stresn as base, visitnum as basevisit
  from &ds.
  where &ds.lobxfl = 'Y'
;

/*join back to the dataset*/
create table &ds._base as
  select a.*, b.base, b.basevisit
  from &ds. a
  left join base b
  on a.usubjid = b.usubjid
  and a.&ds.testcd = b.&ds.testcd
;
quit;
/*sort CTCAE dataset for transpose*/
proc sort data = %if &version = 4 %then %str(ctcae4); %else %if &version =
5 %then %str(ctcae5);;
  by testcd tox dir;
run;

/*transpose to get grading in a single column*/
proc transpose data =
  %if &version = 4 %then %str(ctcae4); %else %if &version = 5 %then
%str(ctcae5);
  out = ctcae (rename = (_NAME_ = GRADE COL1 = CODE) drop = _LABEL_);
  by testcd tox dir;
  var g;;
run;
/*Data step that executes another data step by reading in code form the
CTCAE dataset*/
data _null_;
  set ctcae end=eof;
  if _n_ = 1 then
    do;
      call execute('data &ds._tox;');
      call execute('  set &ds._base;');
    end;

    call execute('if &ds.testcd = ""||strip(testcd)||" and
||strip(dir)||" then do;');
    call execute(' if ""||strip(code)||" then &ds.TOXGR =
""||substr(strip(grade),2)||";');
    call execute(' if lbttoxgr ne "" then &ds.TOX =
""||strip(tox)||";');
    call execute('end;');

  if eof then
    do;
```

```
        call execute('run;');
    end;
run;

/*Create new dataset with toxicity variables added*/
data &ds.;
    set &ds._tox (drop = base basevisit);
run;

/*delete intermediate processing datasets*/
proc datasets nolist;
delete base ctcae lb_base lb_tox;

%mend;
```