Paper DH16

Get to the Bottom of Lab Toxicity Grading: Challenges and Implementation of CTCAE Version 5

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ABSTRACT

The NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) is a set of criteria to assign laboratory toxicity grades in Oncology trials. A laboratory toxicity grading is an important part of safety reporting, therefore it is critical to stay up to date with various CTCAE versions. Compared with CTCAE version 4.03, the latest CTCAE version 5.0 contains 54 new/updated algorithms in 19 lab parameters. Additionally, it adds a layer of complexity with grading criteria dependent on baseline measurements. In this paper, we will present the approach used for deriving the toxicity grade based on CTCAE version 5.0, as well as challenges we encountered.

INTRODUCTION

Oncology is one of the most prevalent indications for clinical trials today. One specific method of analyzing oncology data relates to clinical laboratory results. Compared to most clinical trials that report lab results only based on normal ranges, oncology trials take these analyses to the next complexity level. We not only report lab results based on normal ranges, but also report the degree of abnormality. The degree of abnormality is defined by NCI-CTCAE, which uses a range of grades from 1 (mild) to 5 (death).

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) is a descriptive terminology which can be utilized for laboratory toxicity grading (including an abnormal lab reporting). Lab toxicity grade summary tables and lab grade shift tables are frequently produced in a clinical study report and it is an important part of safety reporting. Therefore, there is a need to establish a standard process to assign and derive lab toxicity grades. However, assigning lab grades following CTCAE v5.0 is not an easy task, as the complexity of CTCAE criteria has evolved over time. In particular, CTCAE v5.0 adds another layer of complexity that subject's status at baseline become a factor in deriving toxicity grades. For some lab parameters, the assigned grading is dependent on whether baseline is normal or abnormal. The purpose of this paper is to introduce the new CTCAE v5.0 criteria, as well as discuss the challenges encountered on implementing CTCAE v5.0 and the proposed solutions.

EVOLUTION IN COMPLEXITY

CTCAE v2.0 (1999) is the first version for lab toxicity grading. In this version, toxicity grading was easy to implement and was based on upper limit normal (ULN) and lower limit normal (LLN) only. However, the grading criteria became more complex in CTCAE v4.0 released in 2009, which was soon replaced by CTCAE v4.03 in 2010. In this version, there are three major updates: 1) change from baseline became a factor in deriving the toxicity grade; 2) there was an introduction of the MedDRA terms associated with the toxicity; 3) The clinical assessments were part of the grading criteria. Finally, with the release of CTCAE v5.0 in 2017, another layer of complexity was added in that the baseline status (normal/abnormal) became a factor in deriving toxicity grades. Table 1 demonstrates the evolvement of grading criteria for Hyperkalemia.

CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
V3.0	>ULN-5.5 mmol/L	>5.5-6.0 mmol/L	>6.0-7.0 mmol/L	>7.0 mmol/L	Death
V4.03	>ULN-5.5 mmol/L	>5.5-6.0 mmol/L	>6.0-7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
V5.0	>ULN-5.5 mmol/L	>5.5-6.0 mmol/L; intervention initiated	>6.0-7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death

Table 1: Hyperkalemia grading criteria in CTCAE v3.0, CTCAE v4.03 and CTCAE v5.0

NEW CTCAE V5.0 CRITERIA

Compared with CTCAE v4.03, there are 54 new algorithms for 19 lab parameters in CTCAE v5.0. To implement CTCAE v5.0, we first evaluate the updates and changes in this version and further classify these 54 new algorithms into three scenarios: 1) algorithms with updated numeric thresholds only; 2) algorithms consisting with clinical assessments or mixture of numeric thresholds and clinical assessments; 3) algorithms dependent on baseline status. Table 2 provides an example for each of the scenario.

Scenarios	Grade 1	Grade 2	Grade 3	Grade 4
Scenario 1: Hemoglobin Increased	Increased in >0 - 2 g/dL	Increase in >2 – 4 g/dL	Increase in > 4 g/dL	-
Scenario 2: Lipase Increased	> ULN – 1.5 X ULN	> 1.5 – 2.0 X ULN; > 2.0 – 5.0 X ULN and asymptomatic	> 2.0 – 5.0 X ULN with signs or symptoms; > 5.0 X ULN and asymptomatic	> 5.0 X ULN and with signs or symptoms
Scenario 3: Alanine Aminotransferase Increased	> ULN – 3.0 X ULN if baseline was normal; 1.5 – 3.0 X baseline if baseline was abnormal	> 3.0 – 5.0 X ULN if baseline was normal; > 3.0 – 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: Examples of three scenarios for new grading algorithms in CTCAE v5.0

Based on the three scenarios defined above, our objective is to tackle each scenario one by one and come up with the solutions for each of them.

- **Scenario 1**: algorithms based on quantitative values only. It is easy to implement algorithms in this scenario, as everything can stay the same in the existing program, with only updates on the actual numeric values.
- **Scenario 2**: algorithms with investigator assessments in additional to quantitative values. Since the lab toxicity grades in this scenario are not determined from the lab data alone, therefore they cannot be handled programmatically. After discussed with the clinical team, we made our decisions based on different cases (Table 3). Additionally, all lab grade summary tables are updated with footnote: “Grades were derived based on numeric criteria as defined in CTCAE Vx.x and did not take into consideration of clinical signs or symptoms which is needed for the final grade associated with the adverse event.”. All toxicity grades derived under this scenario are flagged for further clinical review.

Case	CTCAE v5.0 criteria (Scenario 2)	Decision
1	Contains mutually exclusive numeric thresholds, and clinical signs or symptoms are included in the criteria	Assign grade to the lab value based on the thresholds only and do not consider the clinical signs or symptoms information within the CTCAE v5.0. The summaries of AEs by grade will be used to review the definitive grade.
2	Contains mutually inclusive numeric thresholds when depend on assessment of clinical signs or symptoms are included	Lab test will not be assigned a grade programmatically.
3	Contains more than one set of criteria for the grade of the lab tests	Worst case grade will be assigned.
4	Contains character lab results	We do not standardize character lab results at a global level. The grading will be based on numeric values only.

Table 3: Decisions for implementation of CTCAE v5.0 in scenario 2

- **Scenario 3**: algorithms dependent on baseline status. In this scenario, in addition to only upper limit normal and lower limit normal from a single record as needed with CTCAE v4.03, we also need the associated baseline assessment to determine if it is normal or abnormal. To implement this scenario, the baseline information needs to incorporate in the current lab reference data structure. It poses several challenges in our current process and we will discuss them in the next session.

CURRENT PROCESS AND THE CHALLENGES

We currently derive lab toxicity grades in External Data Utility (EDU) on raw LAB data and the resulting lab grades are carried over in SDTM (LBTOX/LBTOXGR) and ADaM. EDU utilizes the reference dataset LBGRADE that contains all grading algorithms in each of CTCAE version. To help understand, we will use 'Alanine aminotransferase increased' as an example (Table 4).

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase increased	> ULN – 3.0 X ULN	> 3.0 – 5.0 X ULN	> 5.0 – 20.0 X ULN	> 20.0 X ULN

Table 4: Alanine aminotransferase increased toxicity grading criteria (NCI CTCAE v4.03)

The grading criteria in table 4 is translated and stored in the reference dataset LBGRADE. Below is the screenshot of 'Alanine aminotransferase increased' event in LBGRADE.

LBGRDVER	LBTESTCD	LBSTUNIT	LBTOX	LBTOXTX	LBGRDSEQ	LBGRDLO	LBGRDHI	LBALG	LBGRIE
CTCAE04.03	ALT_PLC	IU/L	1	Alanine aminotransferase increased	2	1.0000000	3.0000000	N3	2
CTCAE04.03	ALT_PLC	IU/L	2	Alanine aminotransferase increased	3	3.0000000	5.0000000	N3	2
CTCAE04.03	ALT_PLC	IU/L	3	Alanine aminotransferase increased	4	5.0000000	20.0000000	N3	2
CTCAE04.03	ALT_PLC	IU/L	4	Alanine aminotransferase increased	5	20.0000000	.	N3	2

LBGRDVER: CTCAE version
LBTESTCD: Test code (in raw LAB data)
LBSTUNIT: Lab result unit
LBTOX: Grade code
LBTOXTX: Description quantified by grade
LBGRDSEQ: Grade sequence
LBGRDLO: Criteria lower limit value or factor
LBGRDHI: Criteria upper limit value or factor
LBALG: Algorithm type code (N3 = Assign grade by multiplying lab normal high value by criteria low and high limits to obtain the low and high ends)
LBGRIE: Endpoint inclusion/exclusion type code (2 = Exclusive on low end, inclusive on high end)

In CTCAE v5.0, baseline status becomes a factor in assigning toxicity grades. As a result, a multi-disciplinary workstream was created to decide on the possible solutions as well as evaluate the pros and cons of each solution. The initial discussion was around where we should derive lab toxicity grades, for instance in SDTM or in ADaM data set. Per FDA feedback: it is recommended to populate LBTOX and LBTOXGR variables in SDTM LB. Therefore, our challenges are not only to incorporate baseline in the current LBGRADE dataset, but also to have the stakeholders agree upon a generic baseline definition across all studies.

SOLUTIONS AND NEXT STEPS

To bring in the baseline status, we need to: 1) define the baseline; 2) include additional lab grading algorithms, which can be customized for specific definitions of baseline.

After discussions with our stakeholders, it is decided that the default definition for baseline is the last non-missing pre-dose lab assessment. The SDTM variable LBBLFL is used to identify the baseline assessment. In addition, we will keep the collected visits and timepoints from the raw data for the potential alternative baseline definition.

After the baseline is defined, the next step is to add new algorithms in LBGRADE reference dataset for CTCAE v5.0.

We will again use 'Alanine aminotransferase increased' as an example for illustration (Table 5).

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase increased	> ULN – 3.0 X ULN if baseline was normal; 1.5 – 3.0 X baseline if baseline was abnormal	> 3.0 – 5.0 X ULN if baseline was normal; > 3.0 – 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 5: Alanine aminotransferase increased toxicity grading criteria (NCI CTCAE v5.0)

To implement the updated grading criteria, new algorithms considering baseline status are added in LBGRADE, and they are represented by the additional values of LBALG (Algorithm type code) in Table 6.

LBALG	Definition
B5	If baseline value is <= lab normal high value or baseline is missing, then assign grade by multiplying the lab normal high value criteria low and high limits to obtain the low and high ends
B6	If baseline value is > lab normal high value or baseline is missing, then assign grade by multiplying the baseline value by criteria low and high limits to obtain the low and high ends

Table 6: Additional lab algorithms used for baseline status

The resulting LBGRADE for 'Alanine aminotransferase increased' event is shown below. Please note that the new algorithms (B5 and B6) are employed.

LBGRDVER	LBTESTCD	LBSTUNIT	LBTOX	LBTOXTX	LBGRDSEQ	LBGRDLO	LBGRDHI	LBALG	LBGRIE
CTCAE05.00	ALT_PLC	IU/L	1	Alanine aminotransferase increased	2	1.0000000	3.0000000	B5	2
CTCAE05.00	ALT_PLC	IU/L	2	Alanine aminotransferase increased	3	3.0000000	5.0000000	B5	2
CTCAE05.00	ALT_PLC	IU/L	3	Alanine aminotransferase increased	4	5.0000000	20.0000000	B5	2
CTCAE05.00	ALT_PLC	IU/L	4	Alanine aminotransferase increased	5	20.0000000	.	B5	2
CTCAE05.00	ALT_PLC	IU/L	1	Alanine aminotransferase increased	6	1.5000000	3.0000000	B6	2
CTCAE05.00	ALT_PLC	IU/L	2	Alanine aminotransferase increased	7	3.0000000	5.0000000	B6	2
CTCAE05.00	ALT_PLC	IU/L	3	Alanine aminotransferase increased	8	5.0000000	20.0000000	B6	2
CTCAE05.00	ALT_PLC	IU/L	4	Alanine aminotransferase increased	9	20.0000000	.	B6	2

GRADING PROCESS FOR OUTSOURCED STUDIES

As the process of lab grading is ongoing and still subjects to changes, it gets more complicated with fully outsourced studies. Prior to rolling out the final process, each study utilized CTCAE v5.0 may be allowed to have different ways to handle lab grading. Careful oversight is required to ensure the correctness of implementation. After the standard process is established, all CRO partners are expected to derive lab grades based on the updated LBGRADE reference data set, with the CTCAE v5.0 grading criteria incorporated.

CONCLUSION

As majority of the protocols utilize CTCAE v5.0 for reporting, there is an urgent need for implementing CTCAE v5.0 grading criteria. Although the algorithms are well defined, there are still several operational challenges due to the additional complexity. Despite all the challenges of implementation, we eventually come up with the solutions moving forward by housing all the updated grade algorithms into the reference dataset, where all the grades can be derived automatically and efficiently.

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