

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

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Introduction and Objective

- Oncology trials report lab results not only based on normal range, but also report the degree of abnormality (i.e. lab grades: grade 1 (mild) to grade 5 (death))
- Laboratory toxicity grading is an important part for safety reporting and thus it is critical to keep up to date with various CTCAE versions
- The complexity of toxicity grading evolves over time. CTCAE v5.0 adds a layer of complexity with new algorithms dependent on baseline measurements (normal/abnormal)

Objective: Introduce **new grading algorithms (3 scenarios)**, challenges to implement, as well as the proposed solutions.

Lab Grading: Evolution in CTCAE complexity

1999 **V2.0** Simplistic criteria - Lab grading based on ULN and LLN.

2010 **V4.03** More complex criteria:

1. Change from Baseline factor
2. Correspondence to MedDRA terms
3. Clinical assessments and/or intervention text

2017 **V5.0** Another layer of complexity - Status at Baseline (normal or abnormal)

Lab Parameters CTCAE v3.0 / v4.03/ v5.0

Example: 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

Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.

NEW Algorithms in CTCAE Version 5.0

– Scenario 1: Algorithms with only numeric thresholds – easy to implement

Hemoglobin increased	Grade 1	Increase in >0 - 2 g/dL
Hemoglobin increased	Grade 2	Increase in >2 - 4 g/dL
Hemoglobin increased	Grade 3	Increase in >4 g/dL

– Scenario 2: Algorithms with clinical text/mixture of thresholds and text

Lipase increased	Grade 2	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic
Lipase increased	Grade 3	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic
Lipase increased	Grade 4	>5.0 x ULN and with signs or symptoms

– Scenario 3: Algorithms dependent on baseline status

Alanine aminotransferase increased	Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Alanine aminotransferase increased	Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Alanine aminotransferase increased	Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Alanine aminotransferase increased	Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Note: Compared with CTCAE v4.03, there are 54 **NEW** algorithms in 19 lab parameters. To prevent re-inventing the wheels, we only focus on implementing the **NEW** algorithms.

Scenario 2: Algorithms with Clinical Assessment and Numeric Thresholds



- Lab toxicity grades are not determined by the data alone, therefore they **cannot** be handled programmatically.
 - We reviewed the lab parameters case by case with clinical team and it is decided to assign preliminary grade based on **numeric values** and all grades derived under this scenario are flagged for further clinical review.
 - 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.”.
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Scenario 2: Decisions by Case

Case 1: Contains mutually exclusive numeric thresholds, and clinical signs or symptoms are included in the criteria → **thresholds only**

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Activated partial thromboplastin time prolonged	> ULN – 1.5 X ULN	>1.5 – 2.5 X ULN	>2,5 X ULN; bleeding	-	-

Case 2: Contains mutually inclusive numeric thresholds depend on assessment of clinical signs or symptoms → **do NOT grade**

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperuricemia	> ULN without physiologic consequences	-	> ULN with physiologic consequences	Life-threatening consequences	Death

Case 3: Contains more than one set of criteria for the grade of the lab tests → **Worst case grade will be assigned.**

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	-

Case 4: Contains character lab results → **numeric values only**

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proteinuria	1+ proteinuria; urinary protein $\geq$ ULN - <1.0g/24 hours	Adult: 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5g/24 hours Pediatric: Urine P/C ratio 0.5-1.9	Adult: Urinary protein $\geq$ 3.5 g/24hrs; 4+ proteinuria Pediatric: Urine P/C ratio > 1.9	-	-

Understanding the Current Process

– Current process

- Lab toxicity grades are derived by External Data Utility (EDU) on raw lab data
- EDU utilizes the reference dataset LBGRADE
- Lab grades are carried over from raw data to SDTM (LBTOX/LBTOXGR) and ADaM

– Example: Alanine aminotransferase increased (CTCAE v4.03)

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	> ULN – 3.0 X ULN	> 3.0 – 5.0 X ULN	> 5.0 – 20.0 X ULN	> 20.0 X ULN	-

LBGRADE Reference Dataset

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	> ULN – 3.0 X ULN	> 3.0 – 5.0 X ULN	> 5.0 – 20.0 X ULN	> 20.0 X ULN	-

The Grading criteria is translated and store in LBGRDAE

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 (ULN) 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)

Scenario 3: Algorithms Dependent on Baseline Status

– Example: Alanine aminotransferase increased (CTCAE v5.0)

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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	-

– Challenges

- Requires to incorporate baseline in the current LBGRADE dataset
- The stakeholders need to agree upon a generic baseline definition across all studies

– Solutions

- Baseline: the default definition is the last non-missing pre-dose lab assessment (LBBLFL)
- Add new algorithms in LBGRADE for implementation

Updated LBGRADE Reference Dataset

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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	-

New algorithms considering baseline status are added in LBGRADE, representing by the new values of LBALG (B5 & B6)

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	1	Alanine aminotransferase increased	3	1.5000000	3.0000000	B6	3
CTCAE05.00	ALT_PLC	IU/L	2	Alanine aminotransferase increased	4	3.0000000	5.0000000	B5	2
CTCAE05.00	ALT_PLC	IU/L	2	Alanine aminotransferase increased	5	3.0000000	5.0000000	B6	2
CTCAE05.00	ALT_PLC	IU/L	3	Alanine aminotransferase increased	6	5.0000000	20.0000000	B5	2
CTCAE05.00	ALT_PLC	IU/L	3	Alanine aminotransferase increased	7	5.0000000	20.0000000	B6	2
CTCAE05.00	ALT_PLC	IU/L	4	Alanine aminotransferase increased	8	20.0000000	.	B5	2
CTCAE05.00	ALT_PLC	IU/L	4	Alanine aminotransferase increased	9	20.0000000	.	B6	2

B5: If baseline value is $\leq$ 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

Conclusion

- There is an urgent need for implementing CTCAE v5.0. The letter from CTEP (Cancer Therapy Evaluation Program) in NCI states that effective **April 1 2018**, all protocols will be converted to CTCAE v5.0 for reporting and patient data submit using CTCAE v4.0 will no longer be accepted.
 - Although the new algorithms are well-defined, there are still several operational challenges due to the additional complexity (i.e. baseline measurements). We come up with solutions by housing all updated algorithms into the reference dataset, where all the grades can be derived automatically and efficiently.
 - Final note: similar approach may be applied to studies in other therapeutic areas.
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Q & A



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