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Decoding Laboratory Toxicity Grading: Unlocking the Potential and Overcoming Challenges of CTCAE

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ABSTRACT

Toxicity grading is a critical tool for assessing the severity of adverse events and ensuring clinical trial safety. The Common Terminology Criteria for Adverse Events (CTCAE), developed by the National Cancer Institute (NCI), provides standardized criteria for grading adverse events. Originally designed for oncology, CTCAE has since been applied across various therapeutic areas. Despite its widespread use, significant challenges remain in interpreting and implementing CTCAE criteria, particularly in the context of laboratory toxicity grading. Existing publication provides limited guidance on these complexities, including the concepts of CTCAE for laboratory toxicity, the integration of CTCAE grading into analysis data models, and the application of CTCAE criteria to laboratory results at baseline or post-baseline. This paper aims to address these gaps by comparing CTCAE to other dictionaries such as MedDRA, examining the contents of CTCAE, exploring its practical implementation in Analysis Data Model (ADaM) Laboratory Test Result Analysis dataset (ADLB) data and corresponding SHIFT tables, and proposing strategies to address the challenges in laboratory toxicity grading. By doing so, this paper provides a critical framework for improving the accuracy and consistency of laboratory toxicity assessments.

INTRODUCTION

The Common Terminology Criteria for Adverse Events (CTCAE) provides standardized criteria to grade adverse events (AEs) for safety analysis in clinical trials. Initially developed for cancer therapy, CTCAE now has extended its application to other therapeutic areas. And it's often referenced in clinical trial study protocol to guide investigators to assess AE severity.

A comparison of CTCAE version 5.0 [1] vs. MedDRA version 27.1 highlights the unique value of CTCAE in AE grading (Table 1). CTCAE includes a subset of MedDRA Lowest Level Terms (LLTs) for AE grading: CTCAE version 5.0 contains 26 system organ classes (SOCs) and a total of 837 MedDRA LLTs, whereas MedDRA version 27.1 includes 27 SOCs and 88,985 LLTs [2].

As CTCAE evolves, its application in grading laboratory toxicity has become more feasible yet increasingly complex. The integration of MedDRA preferred terms and SOCs into CTCAE, beginning with version 4.0, facilitated the classification of laboratory assessments as AEs. However, in CTCAE 5.0 However, with the introduction of baseline assessment normality in CTCAE 5.0, new challenges have emerged [1, 7].

While the majority of the CTCAE AE terms do not directly involve laboratory tests, total 56 AE terms in CTCAE 5.0 explicitly reference laboratory test results in their definitions. Furthermore, 39 CTCAE AE terms incorporate Lower Limit of Normal (LLN) or Upper Limit of Normal (ULN) in their grading criteria (21 terms use ULN, 18 use LLN). Among these, only 9 AE terms incorporate baseline evaluation in the criteria.

This paper will elaborate the usage, challenges, and strategies of applying CTCAE to laboratory toxicity grading, with a focus on the evolving criteria and their implications in clinical trials.

Table 1: The comparison of CTCAE 5.0 and MedDRA 27.1

MedDRA v27.1 (2024 May)	CTCAE v5.0
International Conference on Harmonization (ICH) standard	National Cancer Institute (NCI) standard
Wide range of indications	Oncology, expanded to other fields

No AE grading	AE Grading criteria
Coding and analysis of clinical data	Standardize and compare AE severity
Wide range of clinical information: 27 System Organ Classes (SOC) 337 High Level Group Terms (HLGT) 1,738 High Level Terms (HLT) 26,641 Preferred Terms (PT) 88,985 Lowest Level Terms (LLT)	AE terms: 26 System Organ Classes (SOC) 837 AE terms (MedDRA LLTs)
5-Level hierarchy (SOC, HLGT, HLT, PT, LLT). >88,000 LLT	2-Level hierarchy (MedDRA SOCs and 837 MedDRA LLTs)
English and multiple languages	English

Source: Modified from [9]

THE USAGE OF CTCAE FOR LABORATORY TOXICITY GRADING

Monitoring patient safety in clinical trials often involves analyzing changes in laboratory toxicity grading after treatment initiation, as well as identifying new or worsening laboratory abnormalities. These changes are typically demonstrated by a shift table (Table 2.1), which shows toxicity grade changes from baseline to post-baseline, and a lab table (Table 2.2), which summarizes treatment-emergent laboratory abnormalities [4]. It is important to note that CTCAE does not include a Grade 0 category. Instead, Grade 0 refers to laboratory values that do not meet the criteria for Grade 1 or higher.

Table 2.1 Shift Table from Baseline to Maximum Post-baseline CTCAE Grade

CTCAE at Baseline	**Worst On-Treatment CTCAE Grade**						
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Missing**	**Total**
Blood bilirubin increased							
Grade 0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 2.2 Treatment-Emergent laboratory Abnormalities by Maximum Grade

Lab Category		
Term (lab increase/decrease)	**All-grade, n (%)**	**Grade 3-4, n (%)**
Hematology		
Hemoglobin decrease	xx(xx.x)	xx(xx.x)
Platelet decrease	xx(xx.x)	xx(xx.x)
Etc.		
Chemistry		
Alanine Aminotransferase increase	xx(xx.x)	xx(xx.x)
Etc.		

Footnote: Treatment-emergent laboratory abnormalities are defined as post-treatment laboratory abnormalities with a higher grade (based on CTCAE v5.0) compared to baseline.

To support these analyses, CTCAE grading-related variables will be derived in the ADaM dataset ADLB. These variables include ATOXGR (Analysis Toxicity Grade), BTOXGR (Baseline Toxicity Grade), and SHIFT (defined as the change of grades from BTOXGR to ATOXGR). Detailed descriptions of these variables can be found in the CDISC Analysis Data Model Implementation Guide (1.3) [3].

THE CHALLENGES OF CTCAE AND STRATEGIES

The challenges encountered in deriving CTCAE toxicity grading for lab parameters are discussed below.

Table 3.1 CTCAE Grading Criteria

MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Investigations	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Investigations	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	-
Blood and lymphatic system disorders	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences: urgent intervention indicated	Death
Investigations	Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-

Source: [1] NIH National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017

In these above examples, the CTCAE grading for decrease in platelet count is relatively straightforward to derive as the lab values are directly compared with the lower limit of normal or absolute values. However, grading an increase in alanine aminotransferase (ALT) is more complex. The subject's baseline status must first be evaluated.

- If baseline ALT is normal, post-baseline results will be compared to the upper limit of normal (ULN), and the fold-change of ULN will determine the grading.
- If baseline ALT is abnormal, post-baseline results will be compared to baseline values, and the fold-change of baseline will determine the grading.

While some lab abnormalities are single-directional (i.e., they either increase or decrease), others are bi-directional. For example, hemoglobin abnormalities can involve either a decrease or an increase, both of which can be quantified.

CHALLENGE #1: SINGLE-DIRECTIONAL VS. BI-DIRECTIONAL CTCAE TERMS

Along with the CDISC Analysis Data Model Implementation Guide V1.2, we will demonstrate how bi-directional lab toxicity results are mapped into ADLB. Two options will be considered.

Option 1:

A positive or negative integer would be assigned to the toxicity grade (ATOXGR), with positive integers indicating the high direction and negative integers indicating the low direction.

For example (Table 3.2.1), ATROXGR as -2 would indicate Grade 2 anemia, while +1 would indicate Grade 1 in hemoglobin increase.

For one-directional CTCAE terms, grading numbers will only yield a single sign. For example, platelet count decrease will always be represented with negative values, while alanine aminotransferase increased will be represented only with positive values.

Table 3.2.1 SINGLE-DIRECTIONAL VS. BI-DIRECTIONAL CTCAE TERMS (1)

ROW	USUBJID	PARAM	PARAMCD	AVISIT	AVAL	ANRIND	ANRLO	ANRHI	BASE	BNRIND	ATOXGR	BTOXGR	SHIF1
1	999-001	Platelets (10^9/L)	PLAT	Month 1	42	LOW	150	400	296	NORMAL	-3	0	0 to -3
2	999-001	Alanine Aminotransferase (U/L)	ALT	Month 1	121	HIGH	0	32	23	HIGH*	3	0*	0 to 3
3	999-001	Hemoglobin (g/dL)	HGB	Month 1	9	LOW	12	15.5	7.5	LOW	-2	-3	-3 to -2
4	999-001	Hemoglobin (g/dL)	HGB	Month 2	16	HIGH	12	15.5	7.5	LOW	1	-3	-3 to 1

Option 2:

A different set of analysis variables can be used for each direction (Table 3.2.2). Taken the same parameters from Table 3.2.1, in table 3.2.2, ATOXGRL, BTOXGRL, ATOXSCL, and SHIFT1 represent toxicity grades in the low direction, while ATOXGRH, BTOXGRH, ATOXSCH, and SHIFT2 represent toxicity grades in the high direction. This approach has been demonstrated in the CDISC Analysis Data Model Implementation Guide (1.3) [3,5].

Table 3.2.2 SINGLE-DIRECTIONAL VS. BI-DIRECTIONAL CTCAE TERMS (2)

ROW	USUBJID	PARAM	AVISIT	ATOXDSCL	ATOXGRL	BTOXGRL	SHIF1	ATOXDSCH	ATOXGRH	BTOXGRH	SHIF2
1	999-001	Platelets (10^9/L)	Month 1	Platelets count decrease	3	0	0 to 3				
2	999-001	Alanine Aminotransferase (U/L)	Month 1					Alanine aminotransferase increased	3	0*	0 to 3
3	999-001	Hemoglobin (g/dL)	Month 1	Anemia	2	3	3 to 2	Hemoglobin increased	0	0	0 to 0
4	999-001	Hemoglobin (g/dL)	Month 2	Anemia	0	3	3 to 0	Hemoglobin increased	1	0	0 to 1

CHALLENGE #2: GRADING THE BASELINE LABORATORY RESULTS WHEN BASELINE VALUE IS INVOLVED

There were limited guidelines on how to use CTCAE to grade laboratory results at baseline, as criteria were designed for post-baseline assessments. A couple examples of CTCAE criteria involving baseline are Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Bilirubin (BILI). This poses a challenge when determining treatment emergent status for laboratory toxicity, as postbaseline grades needs to compare with baseline grades to assess the new onset or worsening in grading. Several options are demonstrated below.

Option 1: Grade baseline results based on the criteria without considering the baseline status [6]. This however often means that the lab values will be compared to the lower or high limit of normal, modifying the CTCAE grading criteria. In the example of Alanine aminotransferase increased, the grading criteria will only be only based on the ULN fold changes.

Option 2: Do not grade baseline results [8]. Instead, baseline status (Low/Normal/High) or a missing category (Table 2.1) will be shown in the SHIFT table. However, it remains unclear how to quantify the treatment emergent status for these cases.

Option 3: Apply the same CTCAE criteria to all results (including the baseline results). With this practice, all baseline results will be considered Grade '0', given that the baseline result values are always 1xbaseline if baseline is abnormal or always meet the criterial of less than ULN or greater than LLN if baseline is normal. For example, alanine aminotransferase is abnormal high at baseline, however based on the CTCAE criteria, it would be deemed as Grade 0 (Table 3.2.1 and 3.2.2) for alanine aminotransferase increased. As a result, any lab records with post-baseline Grade >0 for these cases will be considered as new or worsen lab abnormalities.

CHALLENGE #3: THE STATUS OF BASELINE NORMALITY IMPACTS THE GRADING

The status of baseline normality can be controversial, and the fold change of ULN vs. fold change of baseline may lead to different toxicity grading.

For example, based on CTCAE 5.0, alanine aminotransferase (ALT) increase is graded as CTCAE grade 3 if: >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal. Note that the normal range of Alanine Aminotransferase (ALT) may vary slightly across different laboratories due to different assays or different types of samples.

In this example (Table 4), the normal range at the baseline differs from the post-baseline. If baseline is deemed normal, this lab record will be assigned to Grade 2. If baseline is deemed abnormal based on normal range at baseline, this lab record will be assigned to Grade 3. Thus, the determination of baseline normality will pose impact on the grading. Misclassification of baseline normality may lead to potential underestimation or overestimation of the post-treatment adverse events. This will require careful considerations from the sponsor.

Table 4. The status of baseline abnormality impact on toxicity grading

Visit	Alanine Aminotransferase (U/L)	Normal Range	Baseline status considered as	Fold change	ATOXGR
Baseline	23	0-16			
Post-Treatment	121	0-32	Normal	3.8XULN	Grade 2
			Abnormal	5.2Xbaseline	Grade 3

LIMITATION OF CTCAE FOR LABORATORY TOXICITY GRADING

The CTCAE have several limitations when applied to laboratory toxicity grading. First, most of the CTCAE terms required assessment of clinical interventions or symptom severity. Laboratory test results are often not sufficient to define the grades. Second, CTCAE only covers a subset of MedDRA terms, and among which, AE terms that can be assessed with laboratory tests are even a smaller portion. Finally, only a small portion of the common laboratory assessments can be found in CTCAE dictionary.

Despite these limitations, CTCAE remains a valuable tool for patient safety monitoring, offering an opportunity to enhance laboratory assessments through its standardized and objective grading criteria.

SUMMARY

CTCAE has expanded its application to numerous therapeutic areas, serving as a vital tool in clinical trials and adverse event toxicity assessments. This paper has explored the fundamental concepts of CTCAE, highlighted its application, identified key challenges, and proposed strategies to address these challenges for laboratory toxicity grading.

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