

CTCAE v6.0: The Good, the Bad, and the Ugly

Elizabeth Dennis, EMB Statistical Solutions, LLC;
Grace Fawcett, Independent Contractor

ABSTRACT

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) is an important tool for reporting the severity of adverse events as grades. In many clinical trials, these grades are applied to lab results, and they are often programmatically determined in the production of the ADaM lab results dataset.

In 2025, version 6.0 of CTCAE was released. As compared to version 5.0, it contains additions, deletions, and revisions. The release included an Excel version, with a tab that shows a comparison to version 5.0, and the type of change. In January 2026, an errata was issued with a few corrections.

These criteria have evolved over time, with many of the criteria becoming clearer. Unfortunately, some ambiguities remain, which leave questions on how the grades should be programmatically determined. This paper will walk through some of the grades that have been revised and now have clear guidelines, and others where the interpretation is murky.

An overview of the ADaM bi-directional toxicity variables will be discussed, along with a possible limitation in common lab shift tables.

INTRODUCTION

A common task for the statistical team is to grade lab results using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). To accurately assign the grades, clear criteria are necessary. Unfortunately, despite multiple versions and continual feedback, ambiguities remain in the definitions.

GRADE 0

The CTCAE do not use the term 'Grade 0', but it's a common and useful way to refer to values that do not meet the criteria. If a record contains all the necessary information to make a grading determination, and it does not meet any of the grading criteria, then it's labeled as 'Grade 0'. This is sometimes explained as a 'normal' record, but that's not quite correct. For bi-directional grades, a lab value that is abnormally high will qualify as Grade 0 in the low direction, but the record is not normal.

THE GOOD

The CTCAE are presented in an Excel file. One tab shows the differences from version 5.0, making changes easy to spot. Version 6.0 certainly has some improvements, when compared to version 5.0.

ASSOCIATED MEDDRA

Each criteria row is specifically linked to a MedDRA System Organ Class and Lowest Level Term, along with their associated codes. The MedDRA version is now provided. This granularity is a welcome addition. Since abnormal lab results are often linked to a reported adverse event, details about the lowest level term can be helpful in verifying the correct recording of the adverse event.

HEMOGLOBIN INCREASED

The criteria for this term have been clarified. Here's the version 5.0 text.

MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-

Table 1 Hemoglobin increased v5.0

This is confusing because of the word 'increase' in the criteria. It implies a change over time, which in clinical studies usually refers to change from baseline. At first glance, Grade 1 in g/dL could be interpreted in programming language as this:

$0 < \text{CHG} \leq 2$

However, version 6.0 makes it clear that the word 'increase' is better viewed as 'elevated'. The criteria provided in version 6.0 are below.

MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Hemoglobin increased	Increase in >0 - 2 g/dL above ULN	Increase in >2 - 4 g/dL above ULN	Increase in >4 g/dL above ULN	-

Table 2 Hemoglobin increased v6.0

Grade 1 in g/dL could be interpreted in programming language as this:

$\text{ULN} < \text{AVAL} \leq \text{ULN} + 2$

ALANINE AMINOTRANSFERASE INCREASED

This term has criteria that change depending on where the baseline value falls with respect to the reference range. The version 5.0 text is below.

MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
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

Table 3 Alanine aminotransferase increased v5.0

The issue here is the phrase 'if baseline was abnormal'. Alanine aminotransferase usually has both low and high reference ranges. Implementing the Grade 1 criterion exactly as written would mean that if a baseline value is below the lower reference range (i.e., 'abnormal'), then the value is judged against baseline instead of ULN.

Version 6.0 has corrected this.

MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal or less than normal; 1.0 - 1.5 x baseline if baseline was >ULN	>3.0 - 5.0 x ULN if baseline was normal or less than normal; >1.5 - 2.0 x baseline if baseline was >ULN	>5.0 - 20.0 x ULN if baseline was normal or less than normal; >2.0 - 4.0 x baseline if baseline was >ULN up to 5 x ULN	>20.0 x ULN if baseline was normal or less than normal; >4.0 x baseline if baseline was >ULN

Table 4 Alanine aminotransferase increased v6.0

A value is now judged against baseline only if the baseline value is abnormally high.

This change also applies to the terms Aspartate aminotransferase increased and Blood bilirubin increased.

THE BAD

Unfortunately, not all of the criteria are clear. Here are some examples of grades where the conditions are murky.

DEPENDENCE ON BASELINE

There are a number of CTCAE terms where the grading criteria depend on the value at baseline. This leads to the obvious question of how the baseline value itself can be graded. An example is below.

MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal or less than normal; 1.0 - 1.5 x baseline if baseline was >ULN	>1.5 - 3.0 x ULN if baseline was normal or less than normal; >1.5 - 2.5 x baseline if baseline was >ULN	>3.0 - 10.0 x ULN if baseline was normal or less than normal; >2.5 - 10.0 x baseline if baseline was >ULN	>10.0 x ULN if baseline was normal or less than normal; >10.0 x baseline if baseline was >ULN

Table 5 Blood bilirubin increased

There are two possible ways to handle this. The first method is to never assign a grade to the baseline value. The result of this is that the lab test cannot be summarized in a standard shift table. The second method is to grade the baseline value using the criteria that is based on ULN. The drawback is that the authors of the CTCAE haven't indicated that this is a clinically appropriate method.

The CTCAE terms Alanine aminotransferase increased, Aspartate aminotransferase increased, Alkaline phosphatase increased, Blood bilirubin increased, Creatinine increased, and GGT increased, and Fibrinogen decreased all contain criteria that rely on the value at baseline.

THE UGLY

There are two terms where the criteria seem to create a hole where certain records would not receive a toxicity grade. Looking only at cases where the baseline value is above the upper limit of normal, the table below shows the grading criteria. The highlight has been added here for emphasis.

MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Alanine aminotransferase increased	1.0 - 1.5 x baseline if baseline was >ULN	1.5 - 2.0 x baseline if baseline was >ULN	>2.0 - 4.0 x baseline if baseline was >ULN up to 5 x ULN	>4.0 x baseline if baseline was >ULN
Investigations	Aspartate aminotransferase increased	1.0 - 1.5 x baseline if baseline was >ULN	1.5 - 2.0 x baseline if baseline was >ULN	>2.0 - 4.0 x baseline if baseline was >ULN up to 5 x ULN	>4.0 x baseline if baseline was >ULN

Table 6

Consider the following records for a subject:

BASE = 280 U/L

ULN = 55 U/L (5 x ULN = 275 U/L)

AVAL = 840 U/L (3 x BASE)

This record would not qualify for any of these criteria. While this may be an impossible value, it still exposes a hole in this grading scale. It's possible that the Grade 3 criteria contain a mistake, and the text 'up to 5 x ULN' should be removed.

ITEMS FOR CONCERN

DESCRIPTORS OF 'INCREASE' AND 'DECREASE'

Many of the Lowest Level Terms include 'increased' and 'decreased' as part of the description. This can cause confusion, since the criteria don't include change from baseline. These words aren't used uniformly though, and sometimes the longer definition provided by the NCI adds clarity. The yellow highlights have been added to the original NCI text to emphasize the inconsistency.

CTCAE Term	Grade 1	Definition
HDL decreased	<LLN	A finding based on laboratory test results that indicate a decrease in HDL in a blood specimen.
Vitamin D decreased	Vitamin D decreased <LLN	A finding based on laboratory test results that indicate a low concentration of Vitamin D in the blood.

Table 7 Increase/Decrease

It's important to note that a CTCAE Term is a term for an adverse event. The FDA defines an adverse event as "any undesirable experience associated with the use of a medical product in a patient." In general, clinical studies specify that an event qualifies as an adverse event if it either begins or worsens after the introduction of the medical product. The CTCAE term includes the words 'increase' and

'decrease' because the continuation of a toxicity grade from pre-baseline to post-baseline is a continuation of a medical history event, not an adverse event.

CRITERIA FOR CALCIUM

CTCAE version 6.0 contains the CTCAE terms regarding calcium. It's important to note that these terms refer to Corrected serum calcium and Ionized calcium, not simply calcium.

CTCAE Term	Grade 1	Definition
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.

Table 8 Calcium v6.0

The table below displays the relevant calcium tests. In general, records with LBTESTCD='CA' should not be used to determine Hypercalcemia or Hypocalcemia, since these are different assessments.

SDTM.LB.LBTESTCD	SDTM.LB.LBTEST
CA	Calcium
CACRALB	Calcium Corrected for Albumin
CAION	Calcium, Ionized

Table 9 Calcium test codes

STANDARD LAB GRADE SHIFT TABLES

Common lab grade shift tables display the categorical changes from baseline to post-baseline in toxicity grades. They often look like this

Shift from Baseline to Worst Post-Baseline Grade in Lab Parameters Safety Analysis Set					
CTCAE Term Cohort Baseline Grade	Worst post-baseline grade				
	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hypomagnesemia					
Active Drug (N=53)					
Grade 0	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)
Grade 2	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)
Grade 4	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Hypermagnesemia					
Active Drug (N=53)					
Grade 0	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)
Grade 2	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)
Grade 4	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Table 10 Standard shift table

It's important to note that this table, however, does have a limitation. A record is assigned to Grade 0 if it doesn't qualify for Grade 1 – Grade 4. The baseline grade, however, could be a value in the opposite direction. Here's an example record, using ADaM's standard bi-directional lab toxicity variables.

SUBJID	ATOXDACL	BTOXGRL	ATOXGRL	ATOXDSCH	BTOXGRH	ATOXGRH
001	Hypomagnesemia	Grade 2	Grade 0	Hypermagnesemia	Grade 0	Grade 3
909	Hypomagnesemia	Grade 0	Grade 0	Hypermagnesemia	Grade 0	Grade 3

Table 11 Example subject shift from baseline

For the Hypermagnesemia section on a standard shift table, both subjects would show a shift from Grade 0 to Grade 3. The table doesn't capture the fact that subject 001 started at a value below the lower limit of normal. Subject 001 had a much greater shift than subject 909, but this table doesn't display that information.

CONCLUSION

CTCAE version 6.0 contains some improvements compared to version 5.0. Some ambiguities still remain, making it difficult to interpret the criteria. The NCI does solicit feedback here: ncictcaehelp@mail.nih.gov. Any feedback received will be discussed during CTCAE v7.0 updated. CTCAE v7.0 is expected to be developed and released between 2027 and 2030.

REFERENCES

NCI CTCAE v5.0 and v6.0 <https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events>

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

Elizabeth Dennis
 EMB Statistical Solutions LLC
edennis@embstats.com

Grace Fawcett
 Independent Contractor
gracefawc@gmail.com