

Grading Lab Toxicities using NCI- Common Terminology Criteria for Adverse Events (CTCAE)

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ABSTRACT

In Oncology trials, the NCI-CTCAE, V4.0 is a set of criteria for the standardized classification of AEs (including laboratory abnormalities) used in cancer therapy. While some grading scales include only numeric values/ranges, some grading scales also include clinical assessment and/or intervention text. This paper focuses on one approach of using programming techniques where the lab toxicities could be graded using the numerical component alone without clinical assessment even though it is required. This poses some challenges such as identical reference limits applicable for multiple grades for the same lab finding (clinical input needed) or multiple conditions referenced in CTCAE within a single grade (one using ULN, one using baseline values). What if information is missing (reference ranges, units)? How do we collaborate with CROs for outsourced studies to implement these strategies? The full paper offers strategic suggestions for assigning overlapping grades, CRF design implications, the use of standard units and more.

INTRODUCTION

The National Cancer Institute Common Terminology Criteria, Version 4.0 for Adverse Events (NCI CTCAE) is a descriptive terminology which can be utilized for Adverse Event (AE) reporting (including an abnormal laboratory finding) in Oncology trials. A grading (severity) scale is provided for each AE term. For lab toxicities, general practice is that the investigators assess the toxicity grades using clinical evaluation and lab data and enter those into AE CRF (Case Report Form). The lab values could be later graded programmatically and reconciled with AEs which would be helpful to verify that critical lab toxicities are appropriately reported as AEs. However assigning lab toxicity grades following CTCAE v4.0 criteria is not a straight forward task. "The rationale within CTCAE v4.0 was to apply more clinical significance to the descriptions of grade because of clinical management decisions that are made based on the assignment of grade. Consequently grading is not always based on pure numeric values. While some grading scales include only numeric values/ranges alone, some grading scales also include clinical assessment and/or intervention text".^[2] CTEP (Cancer Therapy Evaluation Program), NCI Investigation Drug Branch has provided additional guidance regarding computer usage as a component of grade assignment for CTCAE v4.0 AE terms with quantitative severity scales. Based on this guidance the lab related CTCAE findings are classified into 2 groups. (1) Investigator input required: Grade should not be assigned based on numeric values alone. (2) Potential use of lab interface: Grade potentially could be assigned using an electronic lab interface if the system is capable of managing the variables of baseline, ULN (Upper Limit of Normal), and LLN (Lower Limit of Normal) across patients and laboratories. Sponsors could contact the CTEP helpdesk to clarify their questions during this process. This paper focuses on one strategic transparent approach of grading the lab findings under both classes and the challenges in implementing this approach.

PURPOSE AND SCOPE OF CTCAE^[3]

Adverse Events could be reported using CTCAE, MedDRA (Medical Dictionary for Regulatory Activities), LOINC (Logical Observation Identifiers Names and Codes) or SNOMED (Systematized Nomenclature of Medicine) terminology. However LOINC and SNOMED are currently not applicable standards for AE reporting within the ICH community. Both CTCAE and MedDRA data are currently submitted to FDA.

The purpose of the CTCAE is:

- to provide standards for the description and exchange of safety information in oncology research
- to define protocol parameters (such as maximum tolerated dose and dose-limiting toxicity) and provide eligibility assessment and guidelines for dose modification.
- to facilitate the evaluation of new cancer therapies and treatment modalities, and the comparison of safety profiles between interventions.

The CTCAE v4.0 standards include:

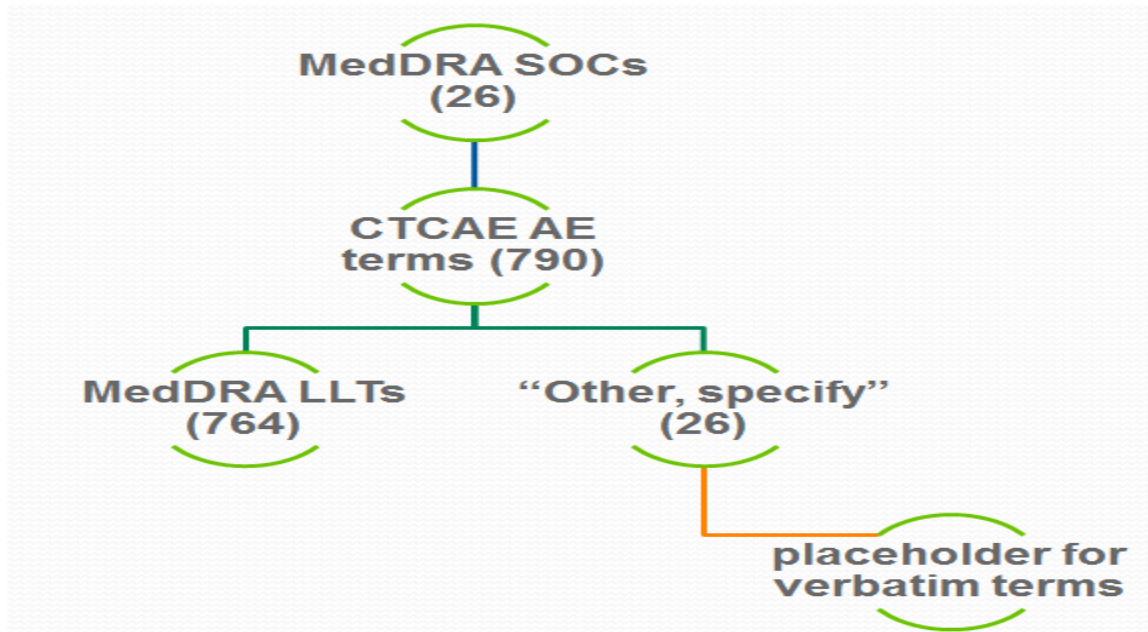
- AE terms that correspond to MedDRA Lowest Level Terms (LLTs), are organized in MedDRA System Organ Class (SOC) groupings and that are signs, symptoms, laboratory values, and diagnoses of AEs commonly monitored in oncology research studies
- A severity grading scale that:

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- Provides a scale to measure severity of clinical findings and the impact on the study participant.
- Promotes consistency within a given grade across all AEs.
- Provides guidance in the evaluation and documentation of severity of the AE.
- Facilitates a common understanding of AE data shared among academic, commercial, and regulatory entities.
- Provide framework to compare AEs across different studies

STRUCTURE AND CONTENT OF CTCAE ^[3]:

- AE terms are grouped by 26 SOC's corresponding to the 26 MedDRA SOC's; the SOC's replace the historical CTCAE CATEGORY.
- CTCAE AE terms are all MedDRA LLTs, with the exception of the 26 "Other, specify" a place-holder intended to elicit either other MedDRA terms or verbatim terms.
- There are 790 AE terms, including 764 corresponding to MedDRA LLTs and 26 MedDRA SOC terms as a placeholder for verbatim terms via "Other, specify."

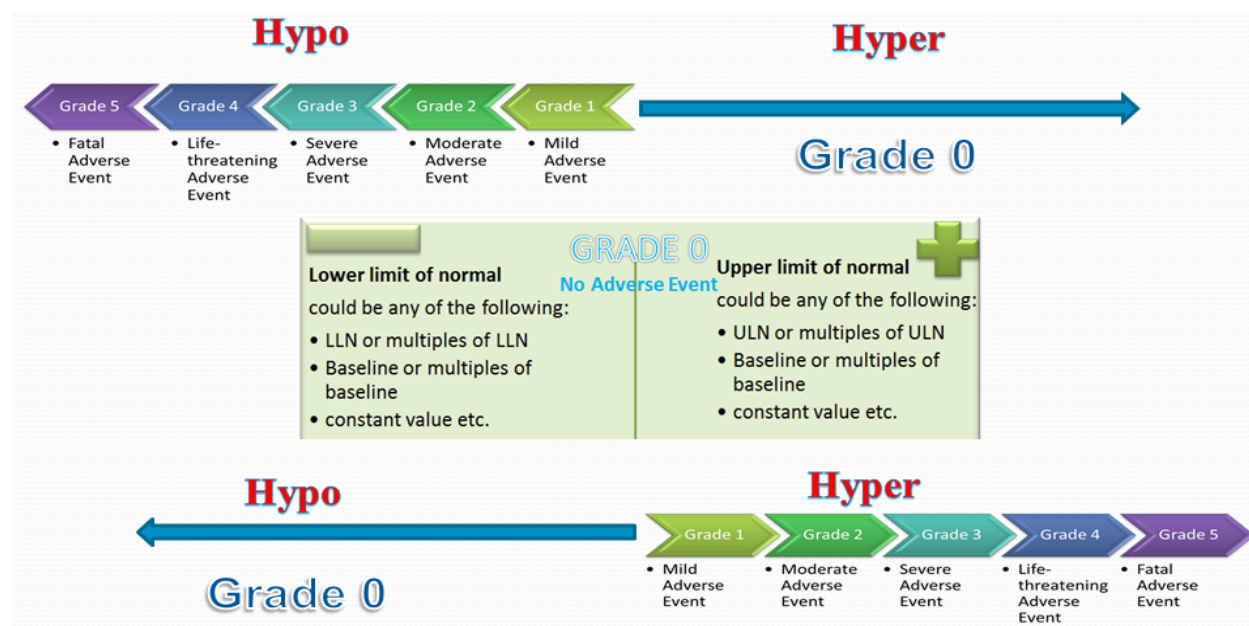


General Grade Guidelines

Grade 0 No Adverse Event	Grade 1 Mild Adverse Event (any of the following)	Grade 2 Moderate Adverse Event (any of the following)	Grade 3 Severe Adverse Event (any of the following)	Grade 4 Life-threatening Adverse Event (any of the following)	Grade 5 Fatal Adverse Event
Sign/symptom within normal limits	Minor; Mild symptoms and intervention not indicated; Non-prescription intervention indicated; No specific medical intervention; Asymptomatic laboratory finding only; Radiographic finding only; Marginal clinical relevance	Intervention indicated; Minimal, local, noninvasive intervention (e.g. packing, cautery); Limiting instrumental ADL (e.g., shopping; laundry; transportation; conduct finances)	Medically significant but not life-threatening; Inpatient or prolongation of hospitalization indicated; Important medical event that does not result in hospitalization but may jeopardize the patient or may require intervention either; to prevent hospitalization or; to prevent the AE from becoming life-threatening or potentially resulting in death; Disabling - results in persistent or significant disability or incapacity; Limiting self-care ADL (e.g., getting in and out of bed; dressing; eating; getting around inside; bathing; using the toilet)	Life-threatening consequences; Urgent intervention indicated; Urgent operative intervention indicated; Patient is at risk of death at the time of the event if immediate intervention is not undertaken	Death

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A semicolon is read as "or" within the description of a grade. NCI recommends assigning highest grade when a clinical finding/situation fulfills any of the conditions in the grade descriptions for more than one grade level. When programmatically grading lab toxicities, Grade 5 cannot be assigned for any laboratory abnormality because death does not result from abnormal diagnostic tests themselves, but rather from the medical conditions that the tests detect. The medical conditions, listed as AEs in their appropriate disorder SOC, may include a Grade 5 Death.



The CTCAE grading scale describes severity, not seriousness. Serious and severe are not the same. "Serious" is associated with AEs that pose a threat to a patient's life or functioning. On the other hand, "severe" describes the intensity (severity) of a specific AE (as in mild, moderate, severe). The AE itself, however, may be of relatively minor medical significance, such as severe headache, and therefore is not serious. Most AEs in CTCAE include clinical criteria that describe patient/event outcomes or indicated interventions to more clearly substantiate severity. Seriousness, not severity, serves as a guide for defining FDA regulatory reporting obligations. ^[4]

CHALLENGES

"Common Terminology Criteria for Adverse Events (CTCAE): Is designed as an instrument to be used to document AEs identified through a combination of clinical and laboratory evaluation. CTCAE is NOT a tool to assist with data extraction from source documents without the direct participation and supervision of clinical investigators. AE grading and attribution require documentation by medical personnel who are directly involved in the clinical care of protocol subjects." ^[5] However it has become a common practice in the industry to also supplement the AE grading with laboratory toxicity grading which is complex and poses several challenges. It is also important to note that not all laboratory tests have CTC grade criteria available. Below are some of the challenges along with some suggestions to deal with those.

STRUCTURE OF OUTPUT DATASET

As per SDTMIG v3.2 the description of toxicity quantified could be stored in the LBTOX variable and the toxicity grade value in LBTOXGR variable in the LB domain which are both permissible. ^[6]

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
LBTOX	Toxicity	Char	*	Variable Qualifier	Description of toxicity quantified by LBTOXGR. The sponsor is expected to provide the name of the scale and version used to map the terms, utilizing the define.xml external codelist attributes.	Perm
LBTOXGR	Standard Toxicity Grade	Char	*	Variable Qualifier	Records toxicity grade value using a standard toxicity scale (such as the NCI CTCAE). If value is from a numeric scale, represent only the number (e.g., "2" and not "Grade 2"). The sponsor is expected to provide the name of the scale and version used to map the terms, utilizing the define.xml external codelist attributes.	Perm

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This SDTM structure might not be ready for easy analysis and needs further processing at the ADaM level. Even in the ADaM structure it is tricky on how to organize the toxicity grading. There are several reasons for this. One of the main challenges is that the same lab parameter could be graded in two directions i.e. bi-dimensional. For example lower levels of Glucose in the blood could lead to grading it under CTCAE term 'Hypoglycemia', whereas elevated levels of Glucose would fall under CTCAE term 'Hyperglycemia'. So in this case there are several possibilities in presenting these records in ADaM like within ADLB or as a separate dataset. The same lab parameter could be either duplicated in two rows one for 'Hypoglycemia' and another for 'Hyperglycemia' or within one record two separate variables could be added for each term and toxicity grading. As a lab value could only go in one direction for a given time point the other record in the duplicate records approach has to be graded as 0 (as the value could be considered as normal in this direction) or missing. The ADaM team is working on finding a solution for this. But in the meanwhile sponsors are taking different approaches to handle this.

At Bayer we have a bidirectional structure in a separate dataset i.e. a separate record for each possible CTCAE term and where a lab value could be graded in both directions then one of them will be graded as "Grade 0". This approach is mainly useful in the analysis of toxicity grades in Tables and figures where the availability of the lab value is used as denominator in calculating percentages.

Variable name	Type	Derivation
STUDYID	C	LB.STUDYID
DOMAIN	C	Set to 'XT'
USUBJID	C	LB.USUBJID
SUBJIDN	N	LB.USUBJID
XTSEQ	N	Derived
XTLBSEQ	N	LB.LBSEQ
XTTESTCD	C	CTCAE term code
XTTEST	C	CTCAE term
XTCAT	C	System Organ Class
XTSTRESN	N	Derived according to CTCAE criteria (values 0-4)
VISITNUM	N	LB.VISITNUM
VISIT	C	LB.VISIT
XTSTAT	C	Completion Status
XTSTATN	N	Completion Status (N)
XTREASND	C	Reason Test Not Done
XTRESNDN	N	Reason Test Not Done (N)
Other identifier and relational variables from LB as needed		

Table: Metadata of XT domain

Event category (alphabetical order)	NCI CTCAE term (alphabetical order within event category)	Worst CTCAE grade	Treatment A N= x	Treatment B N=x	Treatment C N=x	Total N=x
Number (%) of subjects		Grade 1	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%)
		Grade 3	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%)
		Grade 1-4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Grade 3-4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		All	xx (100%)	xx (100%)	xx (100%)	xx (100%)
		Not Graded	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Investigations	Lipase increased	Grade 1	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%)
		Grade 3	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%)
		Grade 1-4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		All	xx (100%)	xx (100%)	xx (100%)	xx (100%)
		Not Graded	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Denominator and rates for each lab based on is the number of subjects with a specific lab value available.

All = number of subjects with a specific lab values available. It does not include 'Not graded'.

Only laboratory values (no clinical assessments) were used for the grading.

Table: Example of laboratory toxicity grade table

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ADVERSE EVENTS THAT NEED BOTH QUANTITATIVE VALUES AND CLINICAL FINDINGS

There are some AEs that could be graded purely based on quantitative values (lab values and lab reference ranges) (ex: Blood bilirubin increased) while some others would need investigator assessments in addition to the quantitative values (i.e. Hyperkalemia). In these scenarios Sponsors have a few options with regards to those AEs that need clinical assessment:

- Assign grades only to those AEs that are independent of clinical assessments (i.e. Grade 1 or 2 only for Hyperkalemia)
- Ignore clinical assessments completely and assign Grades 1-4.

Adverse Event	1	2	3	4	5
Hyperkalemia	>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
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.					

At Bayer we have decided to continue to depict laboratory abnormalities in laboratory tables based on actual laboratory values alone. Any potential associated clinical assessment by investigator to be reported as (S)AE. The approach taken by the company was the most accurate representation that can be given with confidence and the lab toxicity tables were footnoted accordingly that the grades are based on pure quantitative lab results.

ADVERSE EVENTS THAT REQUIRE FASTING STATUS

When grading Glucose for Hyperglycemia, CTCAE criteria ranges for Grades 1 and 2 require subject's fasting status whereas the other Grades (3 and 4) do not mention fasting. This could lead to multiple issues. For example if the lab value falls in the range of Grade 1 or 2 and the fasting status is unknown or not collected on CRF then it could lead to completely not grading the records.

CTCAE term	1	2	3	4	5
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.					

As you can see in the guidance above, the fasting status is only required for Grade 1&2 assessments but not for Grades 3&4 assessments. If we are uncertain whether or not a fasting sample taken was measured then it is assumed that sample was a fasting sample. It is possible that this could be reporting more Grade 1 or 2 Hyperglycemias with this approach. It was also decided to collect the fasting status in CRFs as a mandatory variable especially for Oncology studies.

ADVERSE EVENTS WITH OVERLAPPING RANGES

Some AEs (ex: Hypokalemia, Hyperuricemia.) have overlapping numeric ranges in the CTCAE criteria, and the difference between the grades is a clinical assessment such as a concomitant medication. However in the approach we are taking where we use only the numeric result to grade, what grade should be assigned when the ranges overlap for example if we had a potassium value of 3.7 and LLN = 4 mmol/L ?

Adverse Event	1	2	3	4	5
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					

In cases like the example above where both Grades 1 and 2 have same numeric reference ranges we have assigned them to higher grade (i.e. 2 in this case).

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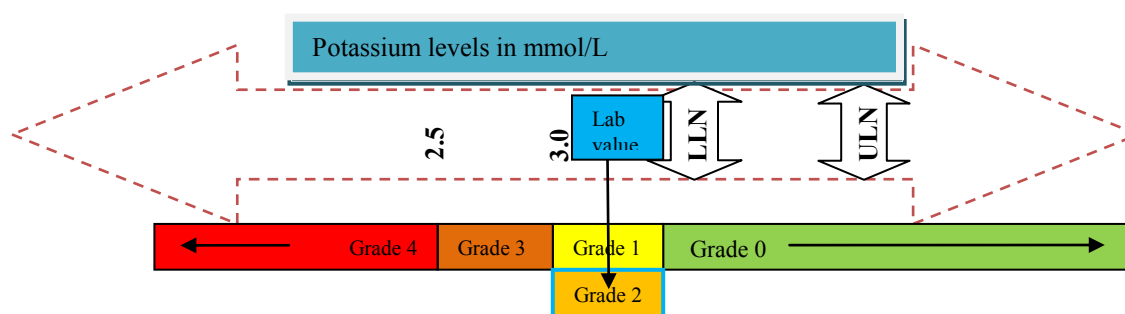


Figure: Grading of Hypokalemia using CTCAE criteria

ADVERSE EVENTS THAT NEED BASELINE VALUES

The criteria for grading some of the AEs (ex: Hemoglobin increase, Creatinine increase etc.) need baseline values and ULN (Upper Limit of Normal) in order to grade some of the grades. So for these tests it would be necessary to derive the baseline values which in general are expected to be consistent with the analysis baseline values. There could be challenges in deriving these baselines and making them consistent with the analysis baseline depending on where they are derived (i.e. raw data/SDTM or ADaM). Also if there are multiple baseline values at same time point or if baseline is missing it is not clear if the ULN value alone could be used.

Adverse Event	1	2	3	4	5
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.					

In these cases the first step is to derive baseline and if there are multiple values at baseline then the latest value is taken. Also if the baseline values are missing then the grading is done based on ULN alone. Likewise, the grading is done based on baseline values alone if ULN is missing. When both baseline and ULN are available then grades are calculated separately using baseline and ULN and then the worst grade of these two is assigned to the AE.

ADVERSE EVENTS THAT NEED AGE GROUP AND/OR BASED ON CHARACTER VALUES

Some AEs like Proteinuria are graded based on age group for certain grades. In this case Grades 2 and 3 of Proteinuria could be assigned only if the age group (adult or pediatric) is known. This leads to multiple questions like what to do with Grade 1? Should we use the informed consent date or randomization date or lab sample collection date in calculating age? This is of special interest in pediatrics studies where the subject could have started the study when he/she was less than 18 years old and at the age of lab sample collection the subject could have attained 18 years of age. Also not all studies would collect subject's date of birth due to several reasons like the country regulatory restrictions etc. In addition the Grades 1 and 2 could also be graded based on character results (dip stick results). What if there are other character results like 1++ or 2++ or 3+++ etc. and the urinary protein is not collected in the desired numeric units? Would a 3+ qualify for Grade 3?

Adverse Event	1	2	3	4	5
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein ≥3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.					

For deriving the age group, if a subject's complete birth date is available we use the date of lab sample collection to derive the age. If either the complete birth date or date of sample taken is not available then we take the age recorded from the CRF demographics. For the character dipstick results all variations of 1+ and 2+ were graded under Grade 1 and 2 respectively for adults. Also we have clarified with CTEP Help desk that both 3+ and 4+ dipstick results could be considered Grade 3 for CTCAE version 4 and this is applicable to adults and pediatric subjects. Results of "Normal" or "Abnormal" are not graded.

ADVERSE EVENTS WITH CRITERIA DEFINED IN UNITS THAT ARE DIFFERENT THAN SPONSORS STANDARD UNITS

AEs in CTCAE criteria that are based on lab results have a numeric range and a standard unit. If the sponsor is using a different unit for this test then it poses additional questions like if the units should be converted to grade appropriately or skip grading that test. In general it is required and a common practice to standardize lab results into appropriate units as lab values come from various sources. So the same principle could be applied in converting either the CTCAE reference ranges to sponsor units or vice versa for grading purpose and care should be taken to use appropriate conversion factors and rounding. It is important that a standard rounding process be established before grading the lab toxicities as minor differences in the decimals could lead to assigning a higher or lower grade when the lab results are very close to the reference range values.

On the same lines, in order to properly grade 'Hypercalcemia' and 'Hypocalcemia' one must know which specific calcium was tested as the scales have different criteria for corrected serum calcium and ionized calcium. For laboratories, where it is not known if total, ionized or corrected calcium is reported, we assumed that calcium was corrected which can lead to a potential over-reporting of hypocalcemia.

CTCAE version 3 requested correction based on albumin levels, but only if levels are below 4.0 g/dl. In CTCAE version 4 (4.03) there is no mention of the condition that calcium levels are only to be corrected if below 4.0 g/dl, suggesting that ALL measured total calcium values should be corrected for albumin, irrespective of an albumin cut-off. However we discussed with the CTEP Help Desk and they confirmed calcium levels are to be corrected only if albumin levels are low and they assumed that a physician will know to correct calcium levels only if albumin levels are low.

When Total Calcium (or Calcium) is collected the following conversion method is used to convert it into corrected calcium.

If serum albumin is available at the same time point and its value is <4.0 g/dL then

$$\text{Corrected Calcium (mg/dL)} = \text{Total Calcium (mg/dL)} - 0.8 [\text{Albumin (g/dL)} - 4]$$

If the type of calcium is unknown or if Total Calcium is collected and Albumin value is ≥ 4.0 g/dL then it was assumed that these value are equivalent to Corrected Calcium for grading purpose and lab toxicity tables are footnoted accordingly.

Adverse Event	1	2	3	4	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.					

Another example is when the WBC(White Blood Cell) differentials (Neutrophil, lymphocytes and CD4 Lab Values) reported only as percentages especially common in local labs whereas the AEs "neutrophil count decreased", "lymphocyte count decreased" and "CD4 lymphocytes decreased" need absolute counts to grade them. If the percentages are not converted and graded then we would not be reporting any of these AEs under lab toxicities. By referring to standard algorithms in research papers and taking internal clinical input we have used the following algorithms to convert the percentages to absolute counts.

Absolute Lymphocytes: $\text{WBC} \times (\% \text{ differential Lymphocytes/Leukocytes}) / 100$

Absolute Neutrophils : $\text{WBC} \times (\% \text{ differential Neutrophils/Leukocytes}) / 100$

CD4 lymphocytes : absolute value of lymphocyte (Giga/L) $\times$ % of CD4

These converted records could be stored in the lab data as derived records and then appropriate grades could be assigned.

ADVERSE EVENTS THAT NEED REFERENCE RANGES

Most of the lab tests that are graded using CTCAE criterion require reference ranges. However there could be missing reference ranges due to several reasons. The question arises if these records with missing ranges should be graded or not, especially when only Grade 1 for any term requires reference ranges. In cases where grades do not require reference ranges these should be graded normally and every effort should be made to query and get the reference ranges from the sites and/or labs. At Bayer, we will use textbook ranges for the derived absolute neutrophils, lymphocytes and CD4 lymphocytes if the site and/or lab did not provide the ranges in absolutes. This is because this is a transformation of source data to calculate grading similar to other calculations we perform. We

should not apply textbook ranges to missing ranges because this is missing source. In these cases, the study teams will need to query the missing ranges. We do not currently have a missing source data policy that would allow us to provide this data. Also this practice should be documented appropriately in all relevant analysis.

THE IMPORTANCE OF ASSIGNING 'GRADE 0'

As described under the grading guidelines 'Grade 0' events are those signs or symptom which are within normal limits and not considered as AEs. However there are no explicit criteria defined in the CTCAE criterion for Grade 0. In order to conduct a consistent analysis with a reasonable determination of subjects at risk for the toxicity (i.e. the denominator for calculating percentages in the summary reports) it is required that we Grade 0s when the lab values are within the normal ranges. This again could pose some challenges depending on the requirement of each AE. For example toxicities like Proteinuria refer to character values for dipstick results and thorough review of the different unique value for this data has to be done by the medical team in order to assign them as Grade 0. In other cases where a constant value or LLN or ULN are mentioned, Grade 0 could be assigned by algorithms like in the following examples by consulting the clinical teams:

- If the lowest grade defined in the scale (ex: Grade 1) has a lower limit of ULN and the CTCAE term is based on elevated values of this lab test (i.e. 'Hyper') then values that are below ULN could be assigned as Grade 0.

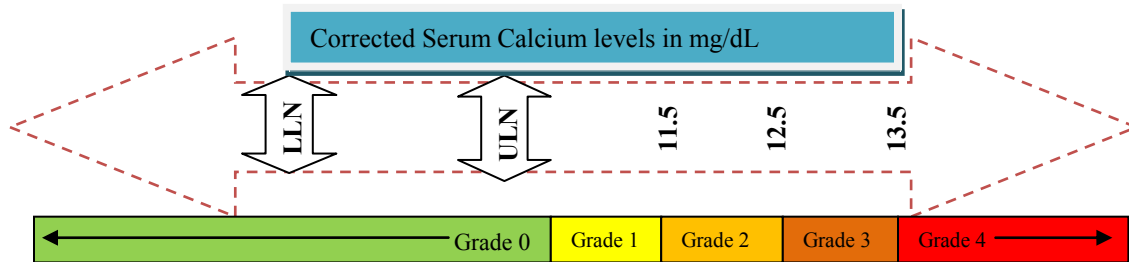


Figure: Grading of Hypercalcemia using CTCAE criteria

- Similarly if the lowest grade defined in the scale (ex: Grade 1) has a higher limit of LLN and the CTCAE term is based on decreased values of this lab test (i.e. 'Hypo') then values that are above LLN could be assigned as Grade 0.

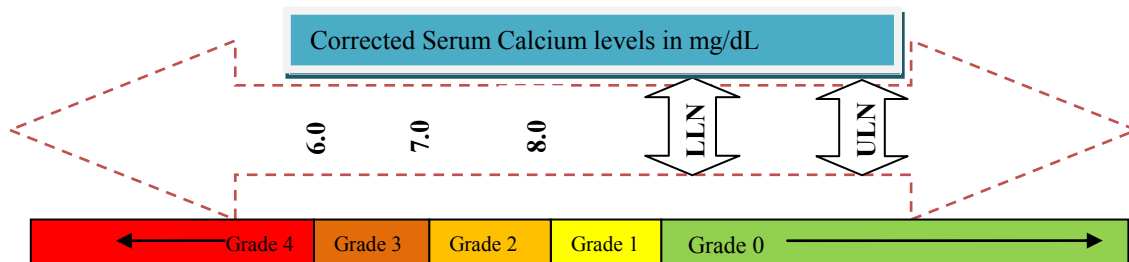
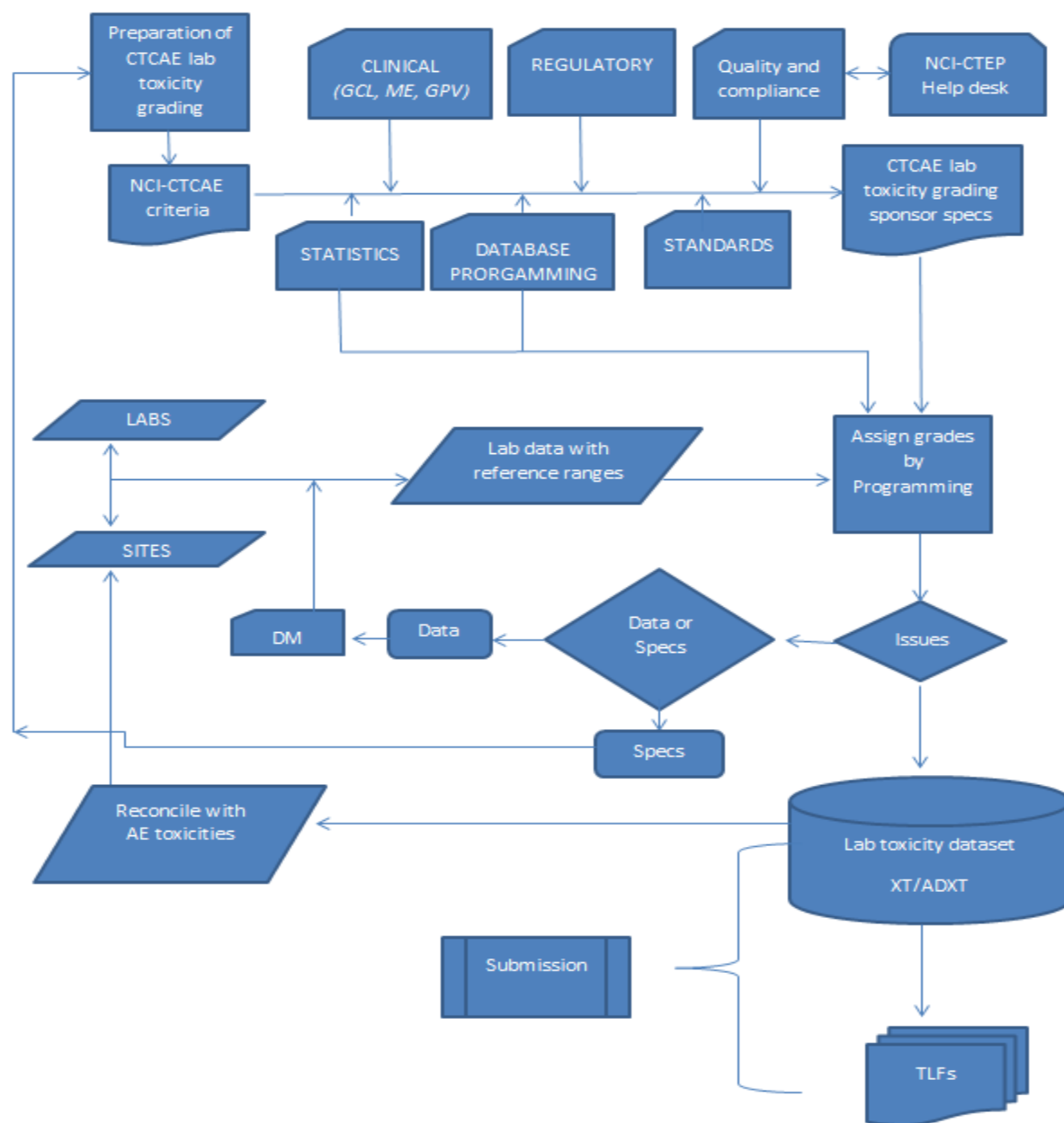


Figure: Grading of Hypercalcemia using CTCAE criteria

GRADING PROCESS AND DEALING WITH VENDORS

All these processes of grading lab values involves many stake holders and could be quite challenging if a proper process is not established. This gets further complicated when this is outsourced to CROs (Clinical Research Organizations) and getting them on the same page and asking them to program by giving the sponsored defined specs or asking them to come up with their specifications based on CTCAE criteria. The below flow diagram shows how different stake holders are involved at various stages.



Abbreviations: DM= Data Management; GCL= Global Clinical Leader; GPV = Global Pharmacovigilance; ME = Medical Expert; TLFs = Tables, Listings and Figures

Figure: Flow chart for the process of grading Lab values using CTCAE criteria

CONCLUSION

CTCAE criteria were defined by NCI to standardize grading of AEs in oncology trials using clinical and lab data. However it has become a common practice in the industry to also supplement the AE grading with laboratory toxicity grading which is complex and poses several challenges. If sponsors decide to grade lab toxicities by using the CTCAE criteria then it is critical to consider the challenges described such as baseline handling, overlapping grading ranges, conversions etc. which could be subjective. We also would recommend that these assumptions made are documented in an appropriate location i.e. Statistical Analysis Plan, sponsor driven CTCAE grading guidance document, and/or footnotes in the summary tables. Data collection process (ex. CRFs) should also be streamlined in order to collect information that aids in assigning CTCAE grades with minimal efforts. When not sure about handling a scenario sponsors should contact the NCI-CTEP help desk to clarify their questions. When the lab toxicities are analyzed appropriate documentation should be prepared to explain the sponsor process in grading these values. Comment period on 'CTCAE v5.0 Final Draft' has recently ended and its publication is expected by mid-September 2016. Sponsors should be prepared to embrace any updates made to the guidance from version 4.03 to 5.0.

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CONTACT INFORMATION

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