DH03
Grading Lab Toxicities using NCI-Common Terminology Criteria for Adverse Events (CTCAE)

PhUSE 2016
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NCI CTCAE v4.0

- Descriptive terminology for AEs (+ abnormal labs) in Oncology trials.
- A grading (severity) scale - for each AE term
- Severity, not seriousness
- Investigators assess the grades - clinical evaluation + lab data
- Both CTCAE and MedDRA data are currently submitted to FDA
Purpose of the CTCAE

- Standards for exchange of safety information in oncology research
- To define protocol parameters:
  - maximum tolerated dose and dose-limiting toxicity
  - eligibility assessment and guidelines for dose modification.
- Evaluation of new cancer therapies
  - comparison of safety profiles between interventions.
STRUCTURE

- MedDRA SOCs (26)
- CTCAE AE terms (790)
  - MedDRA LLTs (764)
  - “Other, specify” (26)

placeholder for verbatim terms
## GENERAL GRADE GUIDELINES

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0 - No Adverse Event</td>
<td>• Sign/symptom within normal limits</td>
</tr>
<tr>
<td>Grade 1 - Mild Adverse Event</td>
<td>• Minor; Mild symptoms and intervention not indicated</td>
</tr>
<tr>
<td>Grade 2 - Moderate Adverse Event</td>
<td>• Intervention indicated; Minimal, local, noninvasive intervention; Limiting instrumental ADL</td>
</tr>
<tr>
<td>Grade 3 - Severe Adverse Event</td>
<td>• Medically significant but not life-threatening; Inpatient/prolongation of hospitalization; Important medical event; Disabling; Limiting self care ADL…</td>
</tr>
<tr>
<td>Grade 4 - Life-threatening Adverse Event</td>
<td>Life-threatening consequences • Urgent intervention indicated; Urgent operative intervention indicated; Patient is at risk of death…</td>
</tr>
<tr>
<td>Grade 5 - Fatal Adverse Event</td>
<td>• Death</td>
</tr>
</tbody>
</table>
STRUCTURE

**Hypo**
- Grade 5: Fatal Adverse Event
- Grade 4: Life-threatening Adverse Event
- Grade 3: Severe Adverse Event
- Grade 2: Moderate Adverse Event
- Grade 1: Mild Adverse Event

**Hyper**
- Grade 5: Fatal Adverse Event
- Grade 4: Life-threatening Adverse Event
- Grade 3: Severe Adverse Event
- Grade 2: Moderate Adverse Event
- Grade 1: Mild Adverse Event

**Grade 0**

**Lower limit of normal** could be any of the following:
- LLN or multiples of LLN
- Baseline or multiples of baseline
- Constant value etc.

**Upper limit of normal** could be any of the following:
- ULN or multiples of ULN
- Baseline or multiples of baseline
- Constant value etc.
CHALLENGES

- CTCAE - NOT to use without clinical investigators
- Common practice - supplement with laboratory toxicity grading
- Grading scales - numeric values/ranges +/- clinical assessment
  - identical reference limits
  - multiple conditions referenced
  - missing reference ranges, units
  - Age group, baseline, Rounding etc.
- Note:
  - not all laboratory tests have CTC grade criteria available
  - Grade 5 not applicable for lab values
## STRUCTURE OF OUTPUT DATASET

### ISSUE

- **SDTMIG v3.2**

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Variable Label</th>
<th>Type</th>
<th>Role</th>
<th>CDISC Notes</th>
<th>Core</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBTOX</td>
<td>Toxicity</td>
<td>Char</td>
<td>Variable Qualifier</td>
<td>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.</td>
<td>Perm</td>
</tr>
<tr>
<td>LBTOXGR</td>
<td>Standard Toxicity Grade</td>
<td>Char</td>
<td>Variable Qualifier</td>
<td>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.</td>
<td>Perm</td>
</tr>
</tbody>
</table>
STRUCTURE OF OUTPUT DATASET

- Might not be ready for easy analysis
- Bi-dimensional ex: Glucose: Hypoglycemia- Hyperglycemia
- ADLB or separate dataset?
- Single row vs Multiple rows or multiple variables?

Issue handling

- Bi-directional structure in a separate dataset
  - A separate record for each possible CTCAE term
  - Lab value in both directions - one will be “Grade 0”
    - Useful for analysis – included in denominators
## STRUCTURE OF OUTPUT DATASET

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Type</th>
<th>Derivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDYID</td>
<td>C</td>
<td>LB.STUDYID</td>
</tr>
<tr>
<td>DOMAIN</td>
<td>C</td>
<td>Set to ‘XT’</td>
</tr>
<tr>
<td>USUBJID</td>
<td>C</td>
<td>LB.USUBJID</td>
</tr>
<tr>
<td>SUBJIDN</td>
<td>N</td>
<td>LB.USUBJID</td>
</tr>
<tr>
<td>XTSEQ</td>
<td>N</td>
<td>Derived</td>
</tr>
<tr>
<td>XTLBSEQ</td>
<td>N</td>
<td>LB.LBSEQ</td>
</tr>
<tr>
<td>XTTESTCD</td>
<td>C</td>
<td>CTCAE term code</td>
</tr>
<tr>
<td>XTTEST</td>
<td>C</td>
<td>CTCAE term</td>
</tr>
<tr>
<td>XTCAT</td>
<td>C</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>XTSTRESN</td>
<td>N</td>
<td>Derived according to CTCAE criteria (values 0-4)</td>
</tr>
<tr>
<td>VISITNUM</td>
<td>N</td>
<td>LB.VISITNUM</td>
</tr>
<tr>
<td>VISIT</td>
<td>C</td>
<td>LB.VISIT</td>
</tr>
<tr>
<td>XTSTAT</td>
<td>C</td>
<td>Completion Status</td>
</tr>
<tr>
<td>XTSTATN</td>
<td>N</td>
<td>Completion Status (N)</td>
</tr>
<tr>
<td>XTREASND</td>
<td>C</td>
<td>Reason Test Not Done</td>
</tr>
<tr>
<td>XTRESNDN</td>
<td>N</td>
<td>Reason Test Not Done (N)</td>
</tr>
</tbody>
</table>

Other identifier and relational variables from LB as needed
### Table: Example of laboratory toxicity grade table

<table>
<thead>
<tr>
<th>Event category (alphabetical order)</th>
<th>NCI CTCAE term (alphabetical order within event category)</th>
<th>Worst CTCAE grade</th>
<th>Treatment A N= x</th>
<th>Treatment B N=x</th>
<th>Treatment C N=x</th>
<th>Total N=x</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects</td>
<td>Grade 1</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>xx (100%)</td>
<td>xx (100%)</td>
<td>xx (100%)</td>
<td>xx (100%)</td>
<td>xx (100%)</td>
</tr>
<tr>
<td></td>
<td>Not Graded</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Investigations</td>
<td>Lipase increased</td>
<td>Grade 1</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>xx (xx.x%)</td>
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</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>xx (xx.x%)</td>
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<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>xx (xx.x%)</td>
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<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
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<td>xx (100%)</td>
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<tr>
<td></td>
<td>Not Graded</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
</tbody>
</table>

**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.
AEs that need both Quantitative Values and Clinical Findings. **Issue**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia</td>
<td>&gt;ULN - 5.5 mmol/L</td>
<td>&gt;5.5 - 6.0 mmol/L</td>
<td>&gt;6.0 - 7.0 mmol/L; hospitalization indicated</td>
<td>&gt;7.0 mmol/L; life-threatening consequences</td>
</tr>
</tbody>
</table>

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.
AEs that need both Quantitative Values and Clinical Findings. **Issue handling**

- Assign Grades 1-4 based on actual laboratory values alone
- potential associated clinical assessment by investigator to be reported as (S)AE
- lab toxicity tables were footnoted - the grades are based on pure quantitative lab results

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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hospitalization indicated</td>
<td></td>
</tr>
</tbody>
</table>

**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.
AEs That Require Fasting Status

**Issue**

Hyperglycemia:

- ranges for Grades 1 and 2 - fasting status
- other Grades (3 and 4) do not mention fasting

lab value - in the range of Grade 1 or 2 and the fasting status is unknown or not collected on CRF?

Should we grade 3 and 4 if fasting is unknown?

<table>
<thead>
<tr>
<th>CTCAE term</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td><strong>Fasting glucose value &gt;ULN - 160 mg/dL;</strong> <strong>Fasting glucose value &gt;ULN - 8.9 mmol/L</strong></td>
<td><strong>Fasting glucose value &gt;160 - 250 mg/dL;</strong> <strong>Fasting glucose value &gt;8.9 - 13.9 mmol/L</strong></td>
<td>&gt;250 - 500 mg/dL; &gt;13.9 - 27.8 mmol/L; hospitalization indicated</td>
<td>&gt;500 mg/dL; &gt;27.8 mmol/L; life-threatening consequences</td>
</tr>
</tbody>
</table>

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.
AEs That Require Fasting Status

**Issue handling**

- Lab value - in the range of Grade 1 or 2 and fasting = U
  - Assume fasting = Y
  - Make Fasting collection mandatory on CRFs
  - Might be over reporting

- Should we grade 3 and 4 if fasting is known/unknown?
  - Yes
  - Not dependent on fasting

---

**CTCAE term**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
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<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Hyperglycemia</strong></td>
<td><strong>Fasting glucose value &gt;ULN - 160 mg/dL</strong>; <strong>Fasting glucose value &gt;ULN - 8.9 mmol/L</strong></td>
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</table>

**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.
AEs With Overlapping Ranges

**Issue**

**Hypokalemia:**

Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.

**Adverse Event**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>&lt;LLN - 3.0 mmol/L</td>
<td>&lt;LLN - 3.0 mmol/L; symptomatic; Intervention Indicated</td>
<td>&lt;2.5 mmol/L; life-threatening consequences</td>
</tr>
</tbody>
</table>

Ex: potassium 3.7 mmol/L and LLN=4 mmol/L

Grade 1: <LLN - 3.0 mmol/L

Grade 2: <LLN - 3.0 mmol/L; symptomatic; intervention indicated
AEs With Overlapping Ranges

Issue handling

- when both Grades have same numeric reference ranges - assigned them to higher grade

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<td>&lt;LLN - 3.0 mmol/L; symptomatic; Intervention Indicated</td>
<td>&lt;3.0 - 2.5 mmol/L; hospitalization indicated</td>
<td>&lt;2.5 mmol/L; life-threatening consequences</td>
</tr>
</tbody>
</table>

Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.
AEs That Need Baseline Values

**Issue**

Hemoglobin increased: need baseline and ULN.

- Consistent with the ABLFL if derived in SDTM?
- If multiple baseline values at same time point?
- If baseline missing - ULN value alone?

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<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin increased</td>
<td>Increase in &gt;0 - 2 gm/dL above ULN or above baseline if baseline is above ULN</td>
<td>Increase in &gt;2 - 4 gm/dL above ULN or above baseline if baseline is above ULN</td>
<td>Increase in &gt;4 gm/dL above ULN or above baseline if baseline is above ULN</td>
<td>-</td>
</tr>
</tbody>
</table>

Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.
AEs That Need Baseline Values

**Issue handling**

- Hemoglobin increased
  - SDTM - consistent with the ABLFL?
    - LBBLFL based on rule specified in SAP
  - multiple baselines at same time point?
    - value closest to treatment start date/time or average
  - if baseline missing or ULN value missing?
    - Grading based on ULN alone or baseline alone

<table>
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<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin increased</td>
<td>Increase in &gt;0 - 2 gm/dL above ULN or above baseline if baseline is above ULN</td>
<td>Increase in &gt;2 - 4 gm/dL above ULN or above baseline if baseline is above ULN</td>
<td>Increase in &gt;4 gm/dL above ULN or above baseline if baseline is above ULN</td>
<td>-</td>
</tr>
</tbody>
</table>

Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.
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.
Proteinuria: Grades 2 and 3 - age group

Proteinuria: Grades 2 and 3 - age group

Grade 1?

Both Adults / pediatric

Age = the informed consent/ randomization/ lab date?

Lab date – DOB

Full DOB is not collected - country regulatory restrictions

If any of the dates missing use age from CRF

Dipstick results (Char) not in specs: 1++ or 2++ or 3+++ etc.?

All variations of 1+ = Grade 1
2+ = Grade 2
3+ / 4+ = Grade 3
AEs with units that differ from criteria

- Unit is different?
  - Standardize the unit (generally done in SDTM process)
  - If sponsor’s standard unit is different then map to CTCAE specified unit for grading

- Rounding?
  - Yes
  - minor differences in the decimals could lead to assigning a higher or lower grade
AEs with units that differ from criteria

‘Hypercalcemia’ and ‘Hypocalcemia’: ionized or corrected calcium

If Unknown Calcium?

- Assume corrected Calcium
  - Potential over-reporting of hypocalcemia

Total Calcium?

- If serum albumin < 4.0 g/dL then
  - Corrected Calcium (mg/dL) = Total Calcium (mg/dL) - 0.8 [Albumin (g/dL) - 4]

- If serum albumin >= 4.0 g/dL then
  - Assume equivalent to Corrected Calcium

<table>
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<tr>
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<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia</td>
<td>Corrected serum calcium of &gt;ULN - 11.5 mg/dL; &gt;ULN - 2.9 mmol/L; Ionized calcium &gt;ULN - 1.5 mmol/L</td>
<td>Corrected serum calcium of &gt;11.5 - 12.5 mg/dL; &gt;2.9 - 3.1 mmol/L; Ionized calcium &gt;1.5 - 1.6 mmol/L; symptomatic</td>
<td>Corrected serum calcium of &gt;12.5 - 13.5 mg/dL; &gt;3.1 - 3.4 mmol/L; Ionized calcium &gt;1.6 - 1.8 mmol/L; Hospitalization indicated</td>
<td>Corrected serum calcium of &gt;13.5 mg/dL; &gt;3.4 mmol/L; Ionized calcium &gt;1.8 mmol/L; life-threatening consequences</td>
</tr>
</tbody>
</table>

Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.
**AEs with units that differ from criteria**

“Neutrophil / lymphocyte / CD4 lymphocytes decreased” need absolute counts to grade

If WBC differentials reported only as percentages?

- Could lead to not reporting the respective grades

Convert %s to absolute counts

- Absolute Lymphocytes: \( WBC \times \left( \frac{\% \text{ differential Lymphocytes/Leukocytes}}{100} \right) \)
- Absolute Neutrophils: \( WBC \times \left( \frac{\% \text{ differential Neutrophils/Leukocytes}}{100} \right) \)
- CD4 lymphocytes: absolute value of lymphocyte (Giga/L) x % of CD4
AEs That Need Reference Ranges

- Most of the lab based CTCAE require reference ranges
- Missing reference ranges - local labs, data issues etc.
  - query and get the reference ranges
  - Text book ranges?
    - Only for derived parameters like absolute neutrophils, lymphocytes and CD4 lymphocytes or to others as well?

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</tr>
</tbody>
</table>

Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.
The Importance of assigning ‘Grade 0’

- 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.

---

Corrected Serum Calcium levels in mg/dL

- ULN
- LLN

Grade 0, Grade 1, Grade 2, Grade 3, Grade 4
The Importance of assigning ‘Grade 0’

- 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.

![Corrected Serum Calcium levels in mg/dL](image)
**Table: Example of laboratory toxicity grade table**

<table>
<thead>
<tr>
<th>Event category (alphabetical order)</th>
<th>NCI CTCAE term (alphabetical order within event category)</th>
<th>Worst CTCAE grade</th>
<th>Treatment A N=x</th>
<th>Treatment B N=x</th>
<th>Treatment C N=x</th>
<th>Total N=x</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>xx (xx.x%)</td>
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**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.
Grading process

**Preparation of CTCAE lab toxicity grading**

- **NCI-CTCAE criteria**
- **CLINICAL (GCL, ME, GPV)**
- **REGULATORY**
- **Quality and compliance**
- **NCI-CTEP Help desk**

**STANDARDS**

- **DATABASE PROGRAMMING**

**STATISTICS**

- **Lab data with reference ranges**

**DM**

- **Data**

**Data or Specs**

- **Specs**

**Assign grades by Programming**

- **Issues**

**Lab toxicity dataset XT/ADXT**

- **Submission**

**TLFs**

**SITES**

- **LABS**

**Reconcile with AE toxicities**
Summary

CTCAE - defined by NCI to standardize grading of AEs in oncology trials using clinical and lab data.

Common practice - supplement with laboratory toxicity grading

- critical to consider - baseline handling, overlapping grading ranges, conversions, missing ranges etc.
- Streamline Data collection process (ex. CRFs)
- contact the NCI-CTEP help desk to clarify their questions
- Documentation and transparency

Be prepared to embrace CTCAE v5.0
REFERENCES


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Thank You!