



DH03

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

PhUSE 2016

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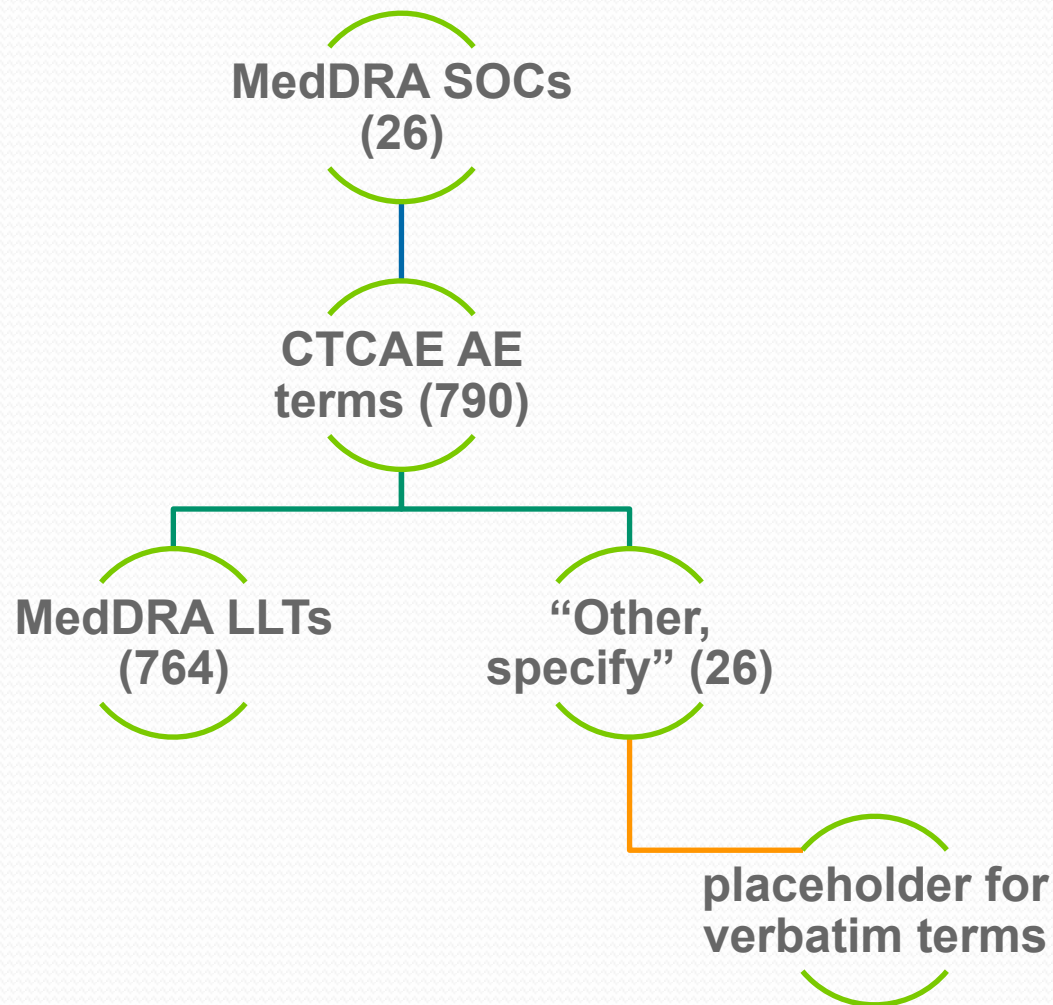
NCI CTCAE v4.0

- 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



GENERAL GRADE GUIDELINES

Grade 0 - No Adverse Event

- Sign/symptom within normal limits

Grade 1 - Mild Adverse Event

- Minor; Mild symptoms and intervention not indicated.....

Grade 2 - Moderate Adverse Event

- Intervention indicated; Minimal, local, noninvasive intervention; Limiting instrumental ADL

Grade 3 - Severe Adverse

- Medically significant but not life-threatening; Inpatient/prolongation of hospitalization; Important medical event; Disabling; Limiting self care ADL ...

Grade 4 - Life-threatening Adverse Event Life-threatening consequences

- Urgent intervention indicated; Urgent operative intervention indicated; Patient is at risk of death ..

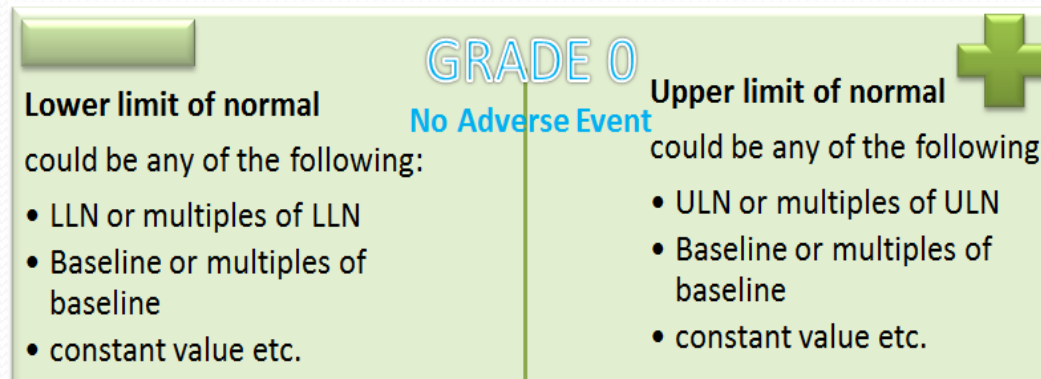
Grade 5 - Fatal Adverse Event

- Death

STRUCTURE

Hypo

Hyper



Hypo

Hyper



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

Variable Name	Variable Label	Type	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

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

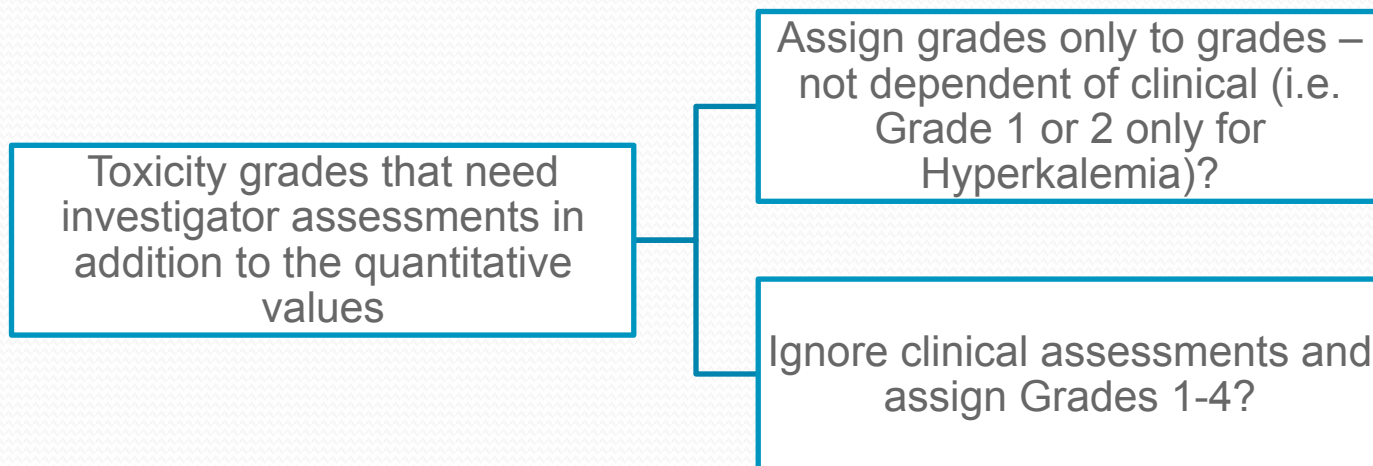
Variable name	Type	Derivation
STUDYID	C	LB.STUDYID
DOMAIN	C	Set to 'XT'
USUBJID	C	LB.USUBJID
SUBJIDN	N	LB.USUBJID
XTSEQ	N	Derived
XTLBSEQ	N	LB.LBSEQ
XTTESTCD	C	CTCAE term code
XTTEST	C	CTCAE term
XTCAT	C	System Organ Class
XTSTRESN	N	Derived according to CTCAE criteria (values 0-4)
VISITNUM	N	LB.VISITNUM
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: Example of laboratory toxicity grade table

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.

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



Adverse Event	1	2	3	4
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
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.				

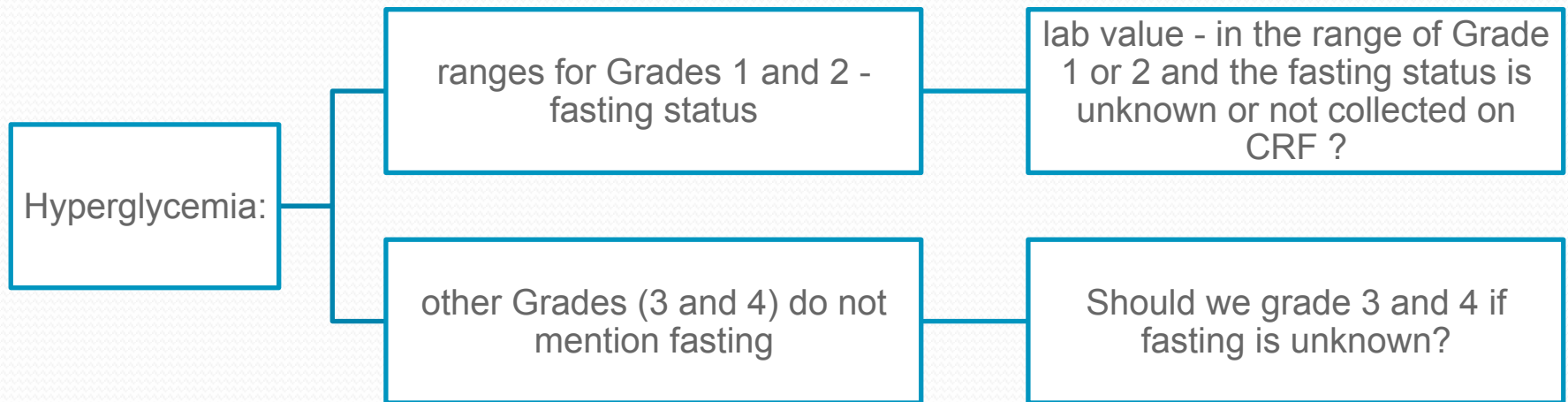
AEs that need both Quantitative Values and Clinical Findings. **Issue handling**

- 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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AEs That Require Fasting Status

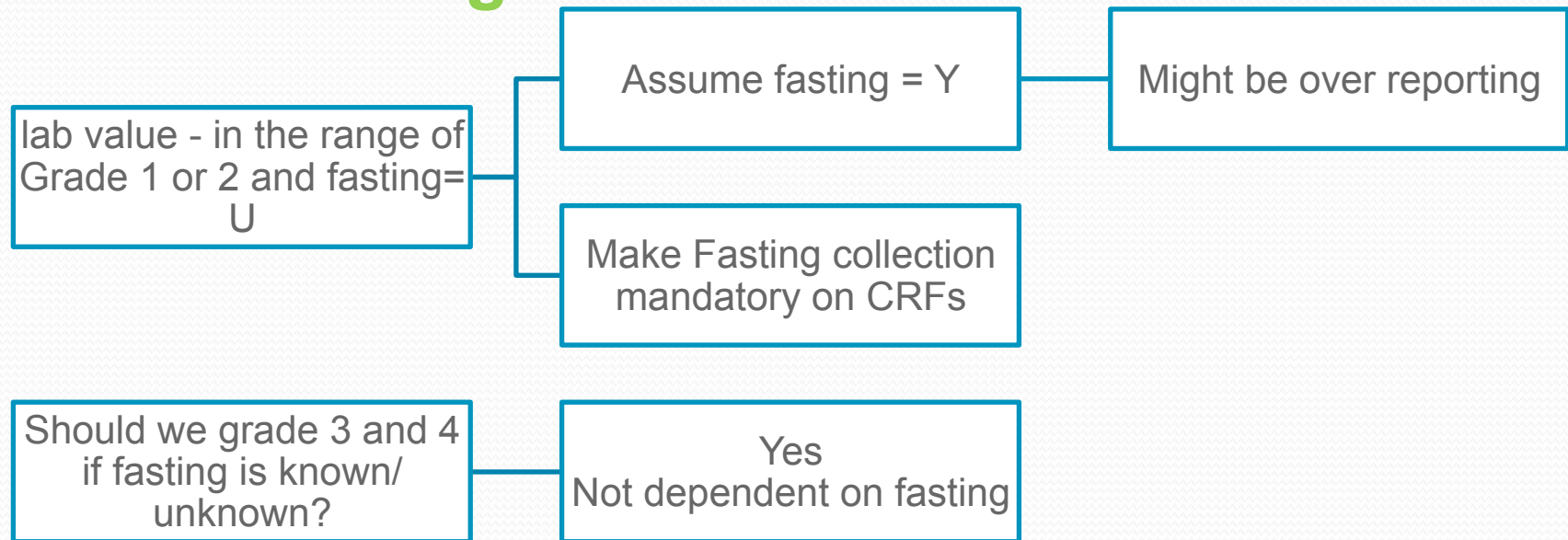
Issue



CTCAE term	1	2	3	4
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
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

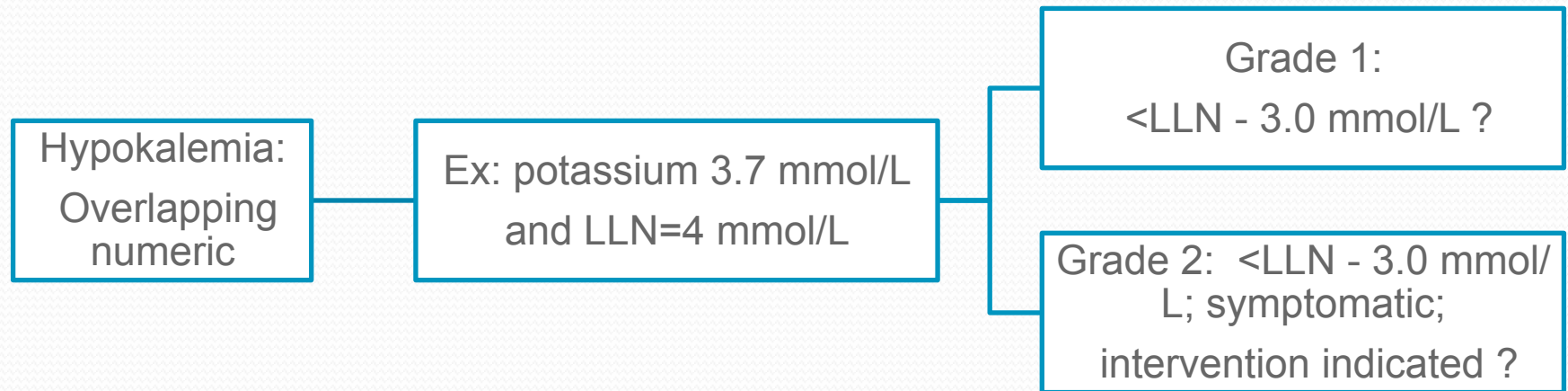


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AEs With Overlapping Ranges

Issue



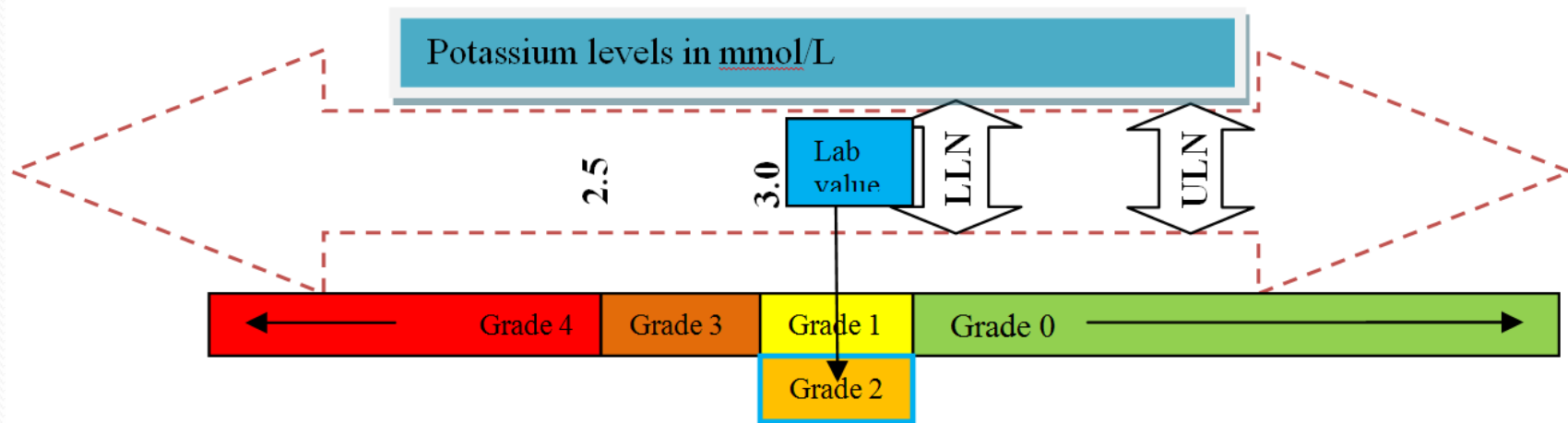
Adverse Event	1	2	3	4
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; Intervention Indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences

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

AEs With Overlapping Ranges

Issue handling

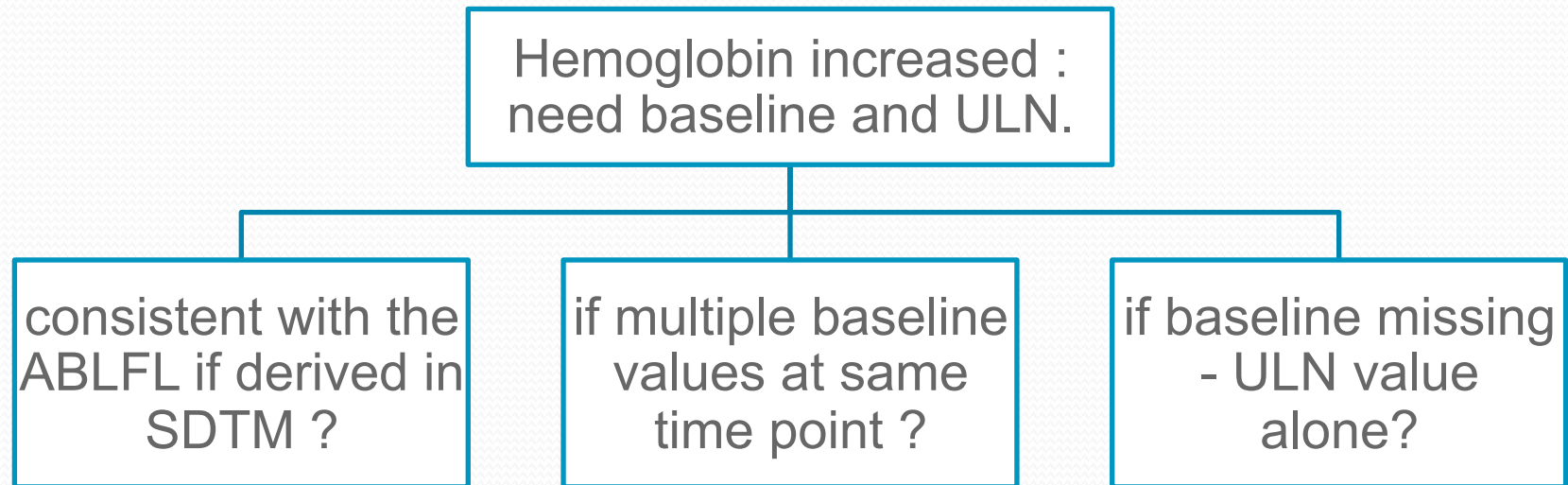
- when both Grades have same numeric reference ranges - assigned them to higher grade



Adverse Event	1	2	3	4
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
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.				

AEs That Need Baseline Values

Issue

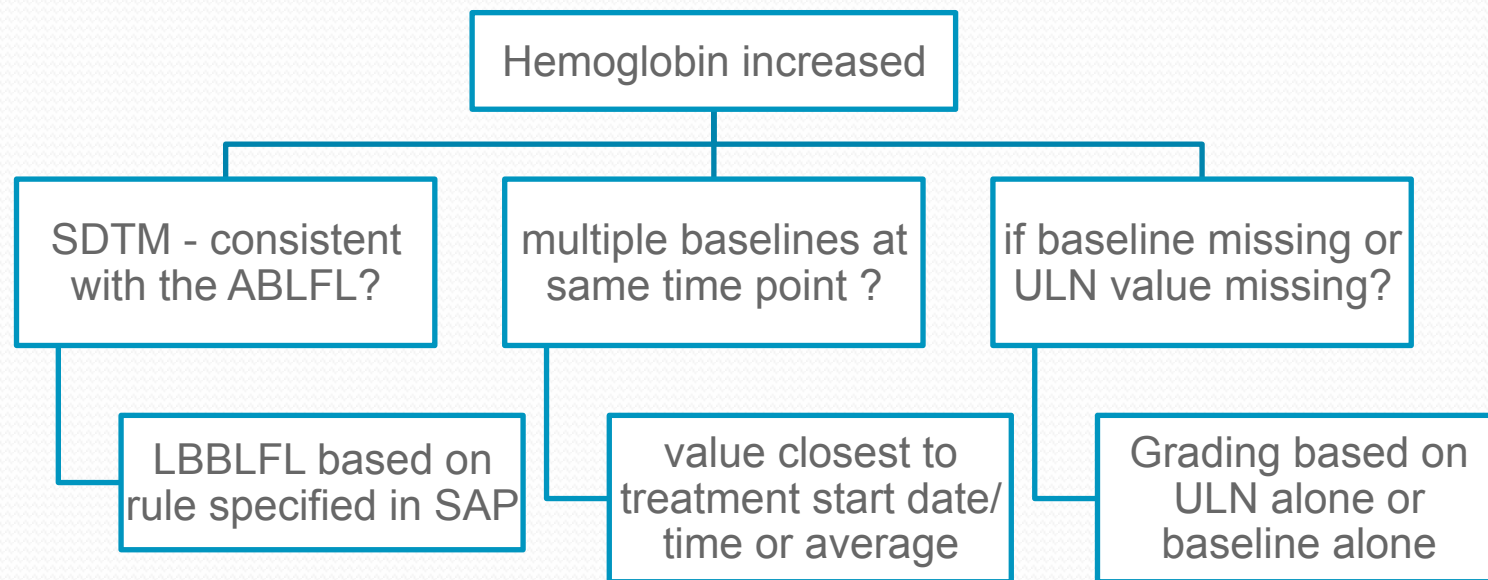


Adverse Event	1	2	3	4
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-

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

AEs That Need Baseline Values

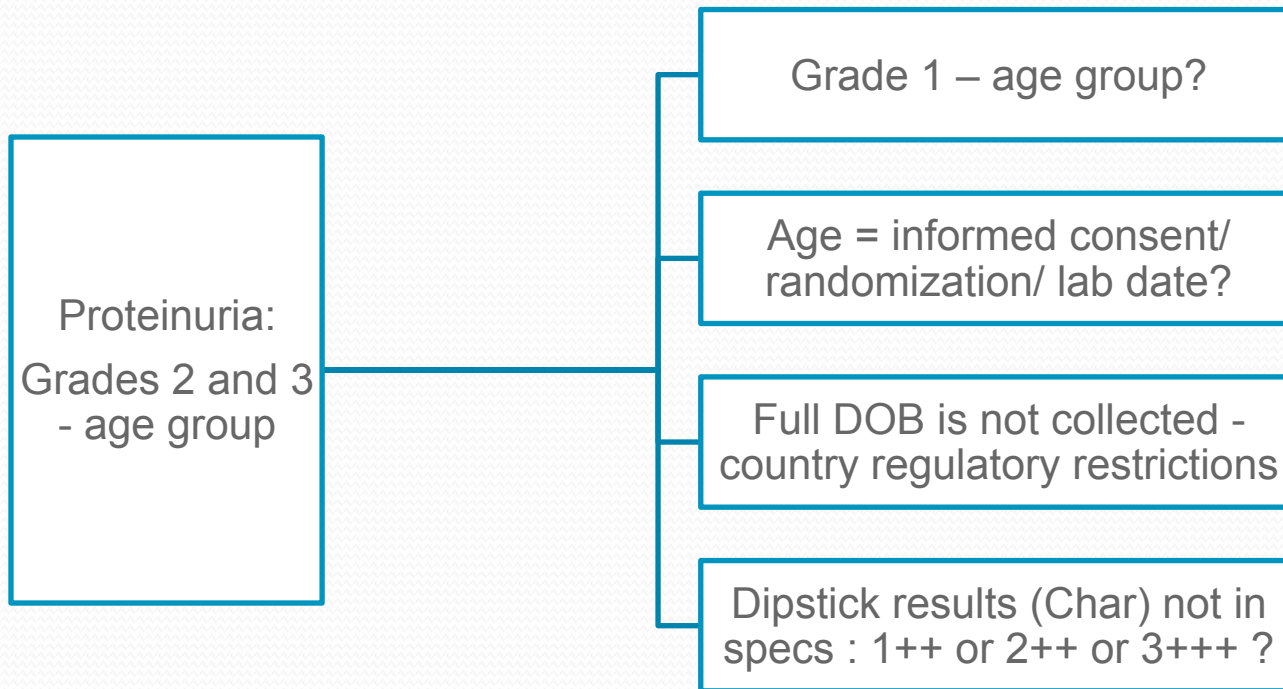
Issue handling



Adverse Event	1	2	3	4
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	-

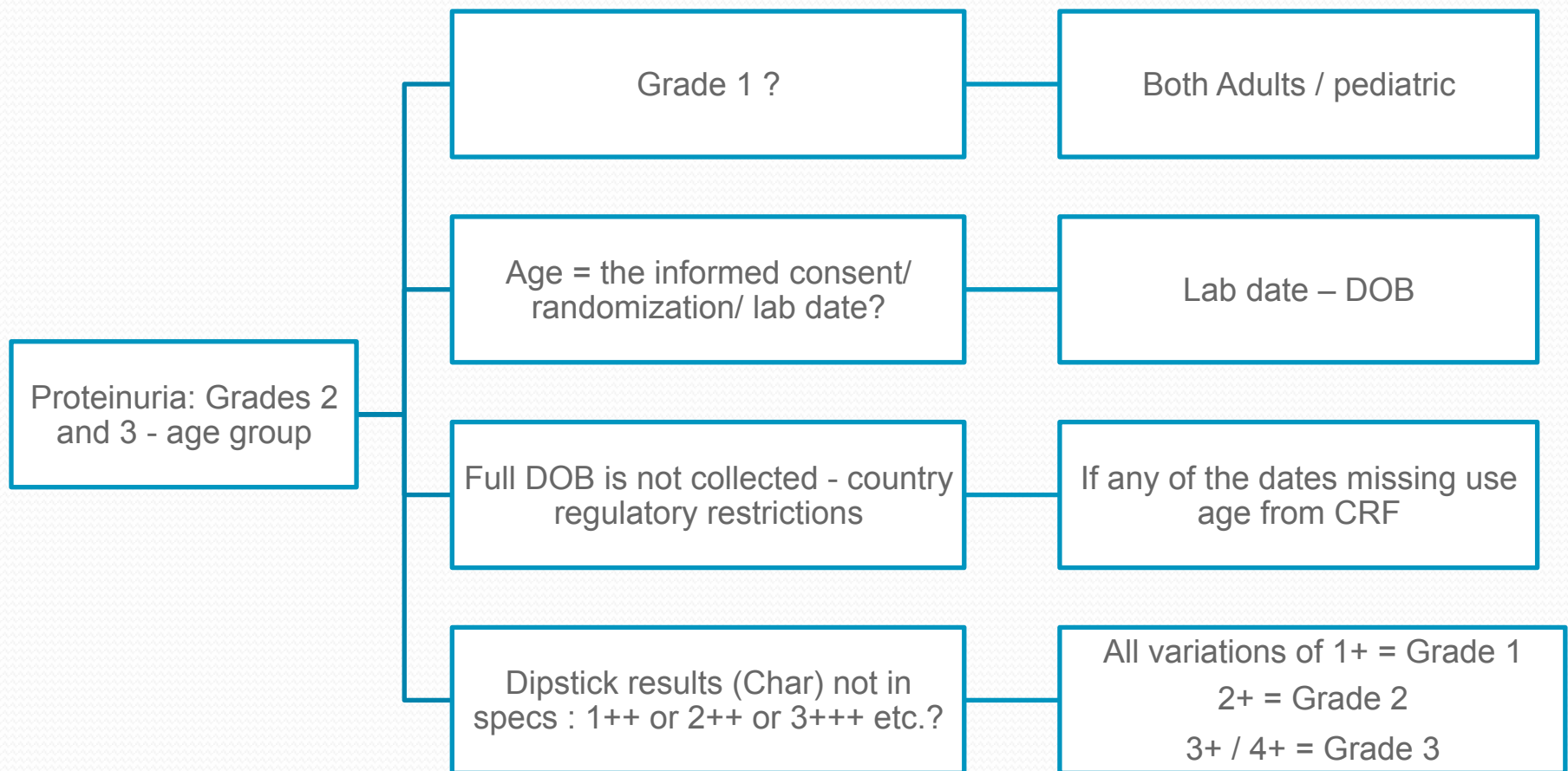
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.

AEs That Need Age Group and/or Based on Character Values **Issue**



Adverse Event	1	2	3	4
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.				

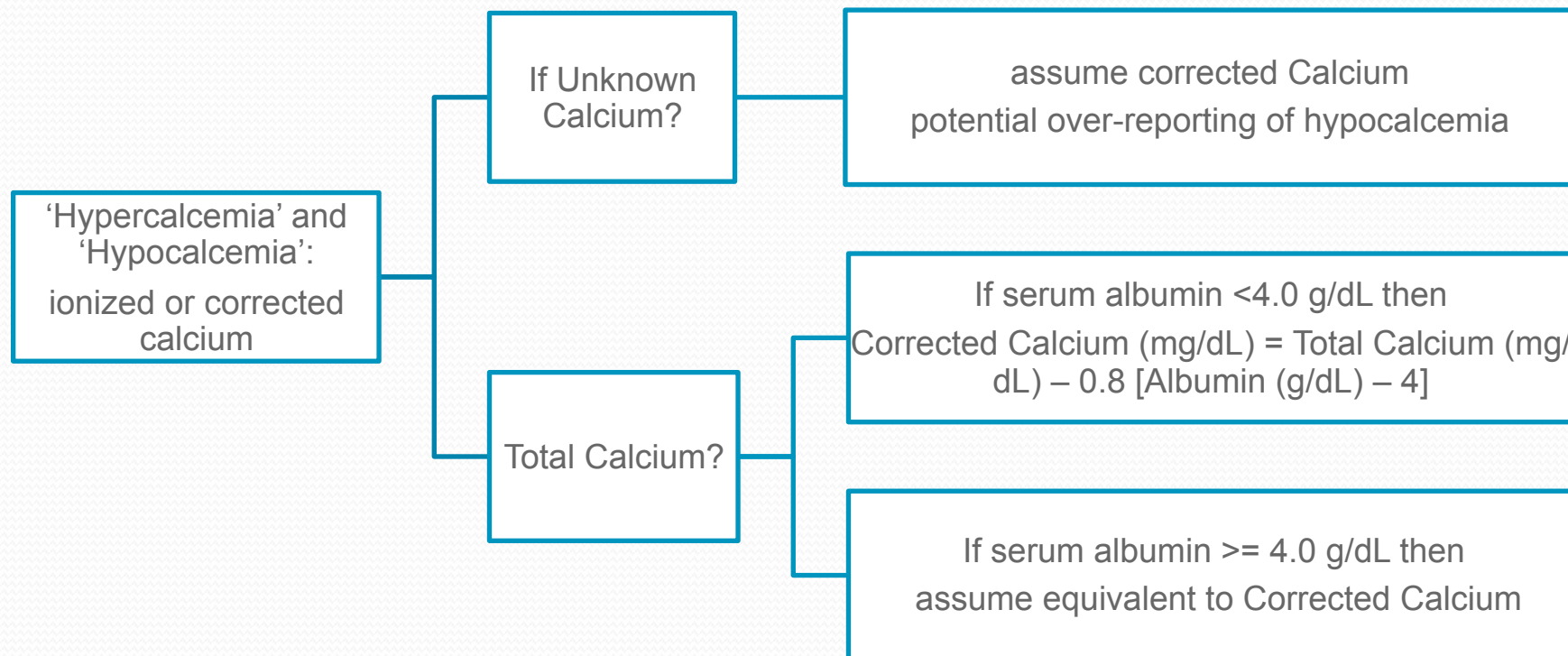
AEs That Need Age Group and/or Based on Character Values **Issue handling**



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



Adverse Event	1	2	3	4
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

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: $\text{WBC} \times (\% \text{ differential Lymphocytes/Leukocytes}) / 100$
- Absolute Neutrophils : $\text{WBC} \times ((\% \text{ differential Neutrophils/Leukocytes})/100$
- CD4 lymphocytes : absolute value of lymphocyte (Giga/L) x % of CD4

AEs That Need Reference Ranges

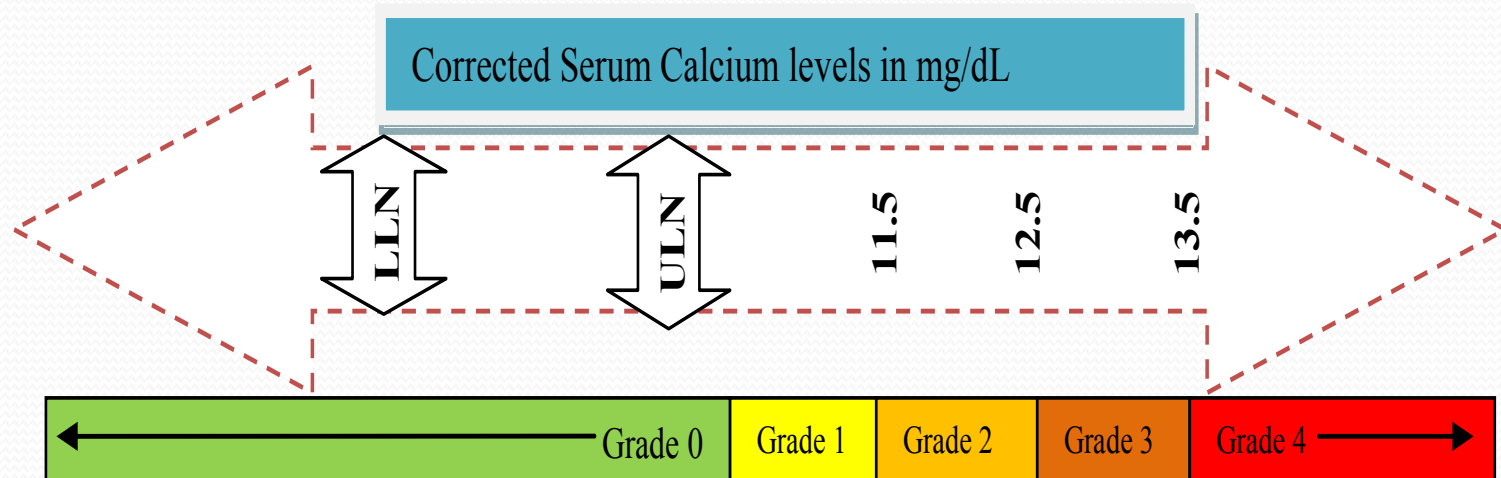
- Most of the lab based CTCAE require reference ranges
- Missing reference ranges - local labs, data issues etc.
 - query and get the reference ranges
 - Text book ranges ?
 - Only for derived parameters like absolute neutrophils, lymphocytes and CD4 lymphocytes or to others as well?

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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.



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.

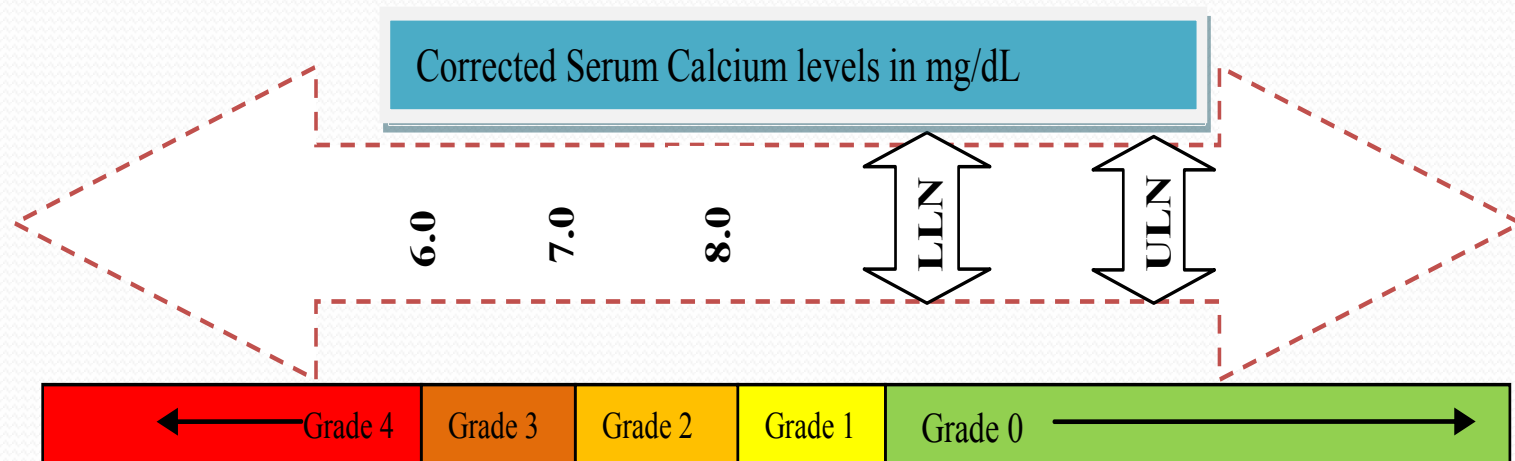
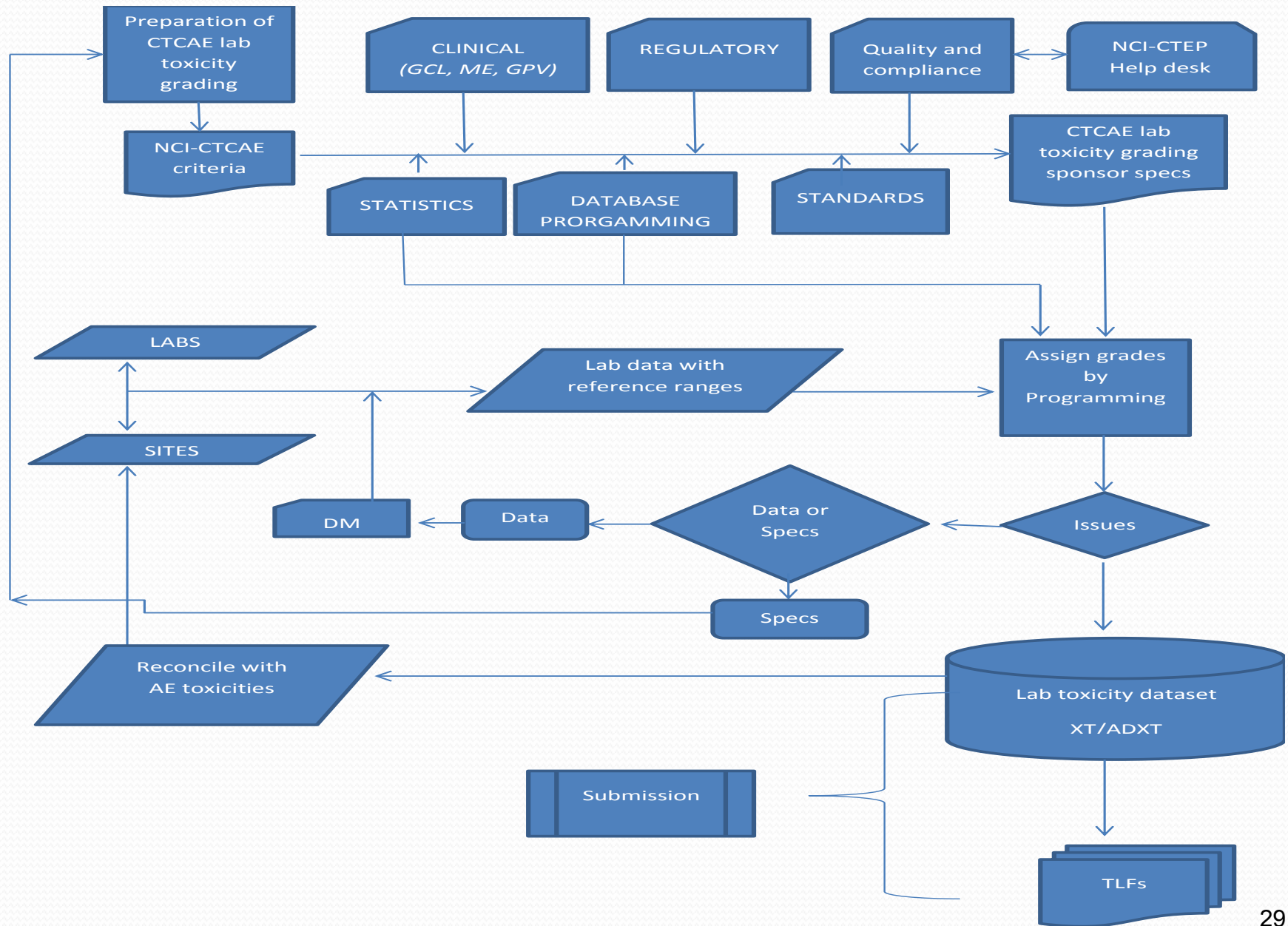


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All = number of subjects with a specific lab values available. It does not include 'Not graded'.
Only laboratory values (no clinical assessments) were used for the grading.

Grading process



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

[1] Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; Published: May 28, 2009 (v4.03: June 14, 2010) by National Cancer Institute.

Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

[2] CTEP Guidance: CTCAE v4.0 Grading Scales with Numeric Component; Published: May 17, 2010 by CTEP, NCI Investigation Drug Branch.

Available at: http://evs.nci.nih.gov/ftp1/CTCAE/Documentation/CTEP_Guidance_Quant-Grade_2010-05-17.doc

[3] CTCAE Redesign and Life Cycle Management; Published: March 11, 2010.

Available at: http://evs.nci.nih.gov/ftp1/CTCAE/Documentation/CTCAE_Governance_2010-03-11.pdf

[4] CTCAE FAQ.

Available at: <https://wiki.nci.nih.gov/display/VKC/Common+Terminology+Criteria+for+Adverse+Events+FAQ>

[5] NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDS and IDES.

Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ae guidelines.pdf

[6] CDISC SDTM Implementation Guide (Version 3.2)

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Thank You!