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Review of Recent DAIDS Tox Table Clarification

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Goals of the August Clarification

- **Address comments and questions received from site investigators, SDMCs, and Medical Officers within DAIDS**
- **Provide additional explanation of the Tox Table**
- **Clarify several of the clinical and laboratory parameters included in the Table**





When should I start using the information included in the Clarification?

- **Now!**
- **The “version” of the Tox Table remains 1.0. DAIDS noted that there is no requirement to change any references to the Table in already approved protocols.**





Is this AE “severe” or “serious”?

- **“Severity” is an indication of how intense an event may be (i.e. mild, moderate, severe, life-threatening).**
- **“Seriousness” refers to an outcome or action criteria associated with an AE (i.e. hospitalization)**






I see “Grade 5” as an option on the AE Log CRF, but where does the Tox Table define Grade 5 events?

- **DAIDS clarified, on Page 1 of the Tox Table, that for any AE where the outcome is death, the severity of the AE is classified as a Grade 5.**





How do I grade Lab events that fall in between two different severity grades?

- **DAIDS previously stated that if a clinical event could fall under one of two severity grades, select the higher of the two for the AE.**
- **Similarly, this is how lab events should be handled when ULNs or LLNs are used.**
 - ▶ If Grade 1 is 2.5x ULN and Grade 2 is 2.6x ULN, what grade would a lab value of 2.53x ULN be?
 - Grade 2





What do I do if my LLN overlaps with a Grade 1 value?

- **The severity grade is based on the ranges in the Tox Table, even if there is overlap with your site normal ranges.**
 - ▶ Example: A site's LLN for Phosphate is 2.3. The Grade 2 range in the Tox Table is 2.0 - 2.4. If a ppt's Phosphate value comes back as 2.4. What grade would this event be?
 - ▶ Although this is “normal” for the site, this would be considered a Grade 2 event.





Specific Updates/Clarifications Made to the Tox Table



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Hypertension

Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
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- **Grading parameters are inclusive.**
 - ▶ Grade 2 starts at 160 systolic and 100 diastolic.
 - ▶ Grade 3 starts at 180 systolic and 110 diastolic.





Anorexia

Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
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Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
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- DAIDS clarified that while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is NOT required and should not take the place of clinical judgment**





Lab Event Age Parameter Clarifications

- **DAIDS clarified that they have not issued grading ranges for CD4 count and Lymphocyte count for children ≤ 13 since the counts are so variable**
- **Many “Infant, <1 day” parameters updated to be “Infant, ≤ 1 day”.**





Hemoglobin

Adult and Pediatric ≥ 57 days (HIV <u>NEGATIVE</u> ONLY)	10.0 – 10.9 g/dL <i>6.18 – 6.79 mmol/L</i> OR Any decrease 2.5 – 3.4 g/dL <i>1.58 – 2.13 mmol/L</i>	9.0 – 9.9 g/dL <i>5.55 - 6.17 mmol/L</i> OR Any decrease 3.5 – 4.4 g/dL <i>2.14 – 2.78 mmol/L</i>	7.0 – 8.9 g/dL <i>4.34 - 5.54 mmol/L</i> OR Any decrease ≥ 4.5 g/dL <i>> 2.79 mmol/L</i>	< 7.0 g/dL <i>< 4.34 mmol/L</i>
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- **“Any decrease” refers to a decrease from the ppt’s baseline value.**
 - ▶ Example: A ppt enrolls with a screening HgB of 14 and at Visit 4 his HgB value is 11. Is this an AE?
 - ▶ Although the absolute value is still “non-gradeable”, because there has been a 3.0 decrease from baseline, this would meet Grade 1 AE criteria.
- **HgB values in mmol/L have changed because the conversion factor has been updated.**





Clarification related to Bicarbonate

Bicarbonate, serum, low	18.0 mEq/L - < LLN 16.0 mmol/L - < LLN	11.0 - 15.9 mEq/L 11.0 - 15.9 mmol/L	8.0 - 10.9 mEq/L 8.0 - 10.9 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
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- DAIDS clarified that since “Bicarbonate” and “Total Carbon Dioxide” are the same tests, sites should use the “Bicarbonate, serum, low” parameter to grade AEs.**

Clarifications related to Calcium and Lactate



- **DAIDS no longer requires sites to adjust Calcium values for Albumin. Grading should be based on unadjusted Calcium values.**
- **DAIDS added a ULN to the Grade 1 AE parameter for Lactate**
 - ▶ ULN - $<2.0 \times$ ULN without acidosis





Any Questions?

**Please feel free to e-mail
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