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(REVIEW ARTICLE)

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BIDIRECTIONAL LABORATORY TOXICITY REPORTING USING CTCAE V5.0 AND ADAMIG V1.2

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ABSTRACT

Background: Laboratory results are frequent safety observations, but a value outside a reference interval is not itself a complete description of clinical severity. Reproducible reporting requires a versioned grading reference, explicit time-window rules, and a traceable path from analysis records to participant summaries.

Objective: To describe a practical workflow for laboratory toxicity outputs aligned with the directional toxicity approach in CDISC ADaM Implementation Guide (ADaMIG) v1.2 and the term-specific criteria in National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Methods: This focused narrative review synthesizes the CTCAE v5.0 reference, ADaMIG v1.2, clinical-trial reporting guidance, and selected methodological literature available by 31 December 2020. A synthetic serum-sodium example illustrates directional grading, treatment-emergent selection, an analysis listing, and participant-level summary counts. No participant data or empirical performance results were used.

Results: The proposed workflow separates lower- and higher-direction grades for parameters with bidirectional toxicity, retains record-level evidence in a listing, and summarizes each participant's maximum eligible grade by analyte anddirection. The example applies a protocol-defined postbaseline window through 30 days after last dose and uses an analyte-specific evaluable denominator; both are illustrative conventions requiring study-level specification.

Conclusion: A reviewable laboratory toxicity output depends on harmonized units and reference limits, explicit grade criteria and boundary handling, documented treatment-emergent and follow-up rules, and reconciliation between subject-level records and summary counts. ADaMIG variable names can support implementation, while study metadata and specifications determine the final analysis dataset.

Keywords: CTCAE, Laboratory Toxicity, CTCAE v5.0; ADaMIG v1.2; ADaM; Clinical Trial Safety; Synthetic Data; Analysis Dataset; Clinical Programming, Safety Reporting, Laboratory Abnormalities

1 INTRODUCTION

Clinical laboratory data are central to safety review because they can reveal treatment-associated changes before symptoms are evident. Their interpretation is not automatic: reference intervals vary by laboratory, clinically relevant grading criteria are term-specific, and repeated measurements can produce multiple grades for one participant [5]. A useful output must therefore show both the individual results and a clearly defined participant-level summary.

CTCAE v5.0, published in 2017, provides adverse-event terminology and severity criteria, including criteria for selected laboratory abnormalities [1]. It does not define a universal programming rule for every analyte or study. CDISC ADaMIG v1.2, published in 2019, describes analysis dataset structures and recommends an approach for bidirectional laboratory toxicity grades [2]. Together, these standards provide a foundation for derivation and traceability, while the protocol and statistical analysis plan (SAP) still govern study-specific analysis choices.

This article develops a practical workflow based on the supplied laboratory-toxicity slide deck, with confidential names, file paths, and implementation details removed. It focuses on the derivation and presentation of Grades 1–4 laboratory toxicity. A Grade 5 outcome, where present in CTCAE criteria, should not be inferred from a numeric result alone; the clinical outcome and adverse-event reporting process require separate review. The article is a focused narrative review and methods proposal, not a systematic review or validation study.

2 REVIEW SCOPE, SOURCE SELECTION AND GRADING PRINCIPLES

We used targeted searches of official NCI Cancer Therapy Evaluation Program (CTEP), CDISC, and International Council for Harmonisation (ICH) materials, PubMed, and clinical-programming conference literature. The source set was limited to materials published on or before 31 December 2020, including CTCAE v5.0 (2017), ADaMIG v1.2 (2019), ICH E3 (1995), ICH E9 (1998), and selected methodological discussion. Search terms combined "CTCAE v5.0," "laboratory toxicity," "ADaMIG v1.2," "bidirectional toxicity," and "clinical trial laboratory data." We prioritized authoritative standards and papers directly relevant to laboratory data or ADaM implementation. This targeted narrative approach was intended to establish a practical workflow; it was not designed to identify every publication, and no systematic screening counts or risk-of-bias assessment are claimed.

CTCAE grades describe severity on a scale from Grade 1 through Grade 5. The general definitions progress from mild findings at Grade 1 to death related to the adverse event at Grade 5, while the criteria for an individual term provide the operational thresholds [1]. Laboratory grading therefore requires a term-specific mapping rather than one universal numeric rule. The example workflow uses Grades 1 through 4 for laboratory toxicity. It does not derive a Grade 5 laboratory category from a result value; any fatal outcome is handled through the applicable adverse event reporting process.

The source material uses CTCAE v5.0, so the applicable version must be confirmed against the study protocol and reporting requirements before programming begins [1]. The threshold reference must match that version, the units in the analysis data, and the study's agreed conventions. This review uses v5.0 only to describe the source workflow and does not recommend it as the default version for new studies.

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin below LLN to 10.0 g/dL (<LLN to 6.2 mmol/L; <LLN to 100 g/L)	Hemoglobin <10.0 to 8.0 g/dL (<6.2 to 4.9 mmol/L; <100 to 80 g/L)	Hemoglobin <8.0 g/dL (<4.9 mmol/L; <80 g/L); transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limits instrumental ADL	Fatigue not relieved by rest; limits self-care ADL	—	—

Figure 1: CTCAE v5.0 grading criteria for anemia and fatigue

Note. A dash means CTCAE v5.0 specifies no criterion for that grade. Anemia is graded using hemoglobin and, at Grade 3, the transfusion criterion. Fatigue is graded clinically by its effect on daily activities.

3 STANDARDS AND DERIVATION PRINCIPLES

3.1 CTCAE grading is term-specific

CTCAE grade criteria must be applied to the matching term, direction, unit, and clinical qualifiers [1]. For example, CTCAE v5.0 defines separate criteria for hyponatremia and hypernatremia. The lower-direction sodium criteria use the lower limit of normal (LLN) and clinically relevant absolute thresholds; the higher-direction criteria use the upper limit of normal (ULN), numeric thresholds, and in some grades intervention or hospitalization criteria. Thus, a laboratory value can support a grade, but some criteria also require clinical context. A derivation should not replace that context with an assumed value.

For laboratory-only summaries, Grades 1–4 can be presented as severity categories when that matches the analysis plan. The presence of Grade 5 in the general CTCAE scale does not mean a grade should be assigned from an extreme laboratory value alone. For a term whose Grade 5 criterion is death, the event requires clinical outcome adjudication and appropriate safety reporting.

3.2 ADaMIG v1.2 and directional grades

For a parameter that can be toxic in both directions, ADaMIG v1.2 recommends representing low and high toxicity separately [2]. In the BDS context, directional analysis and baseline toxicity variables commonly use names such as ATOXGRL and ATOXGRH, with corresponding BTOXGRL and BTOXGRH baseline grades. The names should be implemented consistently with the applicable ADaMIG version and study metadata; this article does not assert that a particular set of variables alone establishes conformance. A 2019 programming paper also illustrates the developing ADaMIG v1.2 approach to bidirectional laboratory grading [6].

Separate direction variables preserve interpretability. A participant can have low-direction toxicity at one visit and high-direction toxicity at another. Combining the two into a single maximum grade may hide that pattern or imply that the direction is clinically interchangeable. Listings may display both directions together for review, while summary tables should report them separately when specified by the SAP.

3.3 Treatment emergence, baseline, and window

The source slide deck specifies selection of parameters with treatment-emergent laboratory abnormality records and a post-last-dose follow-up period of 30 days. Those choices are examples, not universal requirements. The protocol and SAP should define baseline selection, treatment-emergent status, start and end dates, whether the final day is inclusive, and whether the window is applied to collection date, analysis date, or another date field. The definition should also distinguish a postbaseline abnormal result from a treatment-emergent abnormality; those concepts are related but not identical [4].

The example below uses a last-dose date of 15 January 2020 and an inclusive 30-day post-dose period through 14 February 2020. A result collected on 15 February is outside this illustrative window. If a study applies a different rule, both the derivation and the mock-up should change together.

4 METHODS/ PRACTICAL WORKFLOW

Table 1: Core derivation decisions and review evidence

Stage	Specification	Evidence for review
Map	Match test, CTCAE term, direction, units, and criteria version.	Versioned threshold reference; unmatched tests and units reported for resolution.
Normalize	Convert units only under documented, validated conversion rules; retain original values as required.	Conversion factors, precision, and source units can be reproduced.
Select	Apply baseline, treatment-emergent, and protocol-defined analysis-window rules.	Eligible records and exclusion reasons can be traced.
Grade	Apply exact CTCAE criteria, including qualifiers and boundary operators.	Threshold source and grade can be independently checked.

Summarize	Select participant maximum by analyte and direction; use the prespecified denominator.	Listing and table counts reconcile, including no-grade participants.

4.1 Mapping and unit harmonization

A controlled reference should identify the analyte or parameter code, source terminology, corresponding CTCAE term, direction, criterion version, expected analysis unit, thresholds, comparison operators, and any clinical qualifier required [1,2]. Where local reference intervals are part of the grade rule, store the applicable LLN or ULN and the source laboratory context. Confirm that unit conversion does not change the intended comparison. An unresolved mapping or unsupported unit should be flagged for resolution rather than assigned a guessed grade.

4.2 Record-level grading and participant maximum

For each eligible result, determine whether the low or high criterion applies and assign the matching grade. A value satisfying no reportable toxicity criterion should remain distinguishable from missing data and from a result that could not be graded. For a participant, analyte, and direction, select the maximum eligible postbaseline grade in the reporting window. Preserve all eligible observations in the listing so the selected maximum can be reviewed. The analysis specification should say how ties, duplicate records, unscheduled assessments, and multiple laboratory sources are handled.

4.3 Treatment-emergent period and participant grade

For the worked example, a postbaseline result is eligible when it occurs after baseline and on or before 30 days after the last dose. The 30-day extension comes from the supplied presentation and should be replaced when the protocol or SAP specifies another window. The analysis also applies the study-defined indicator that restricts reportable parameters to those with treatment-emergent laboratory abnormality records. The indicator's definition and derivation must be documented in the analysis specification.

For each participant, analyte, and toxicity direction, the program assigns a grade to every eligible result using the mapped threshold. It then selects the maximum grade observed in the reporting period. When both low and high results can be toxic for an analyte, the listing can display both directions together for review, while summary counts are produced separately by direction. This preserves the distinction between clinically different abnormality patterns and prevents a low-value grade from being obscured by a high-value result.

4.4 Denominator and table construction

The example follows the source deck's denominator convention: the analyte-specific denominator is the number of participants with at least one non-missing postbaseline result for that test. Each participant contributes once to each directional grade distribution, based on their maximum eligible grade in that direction. To make the denominator reconcile, include a "No Grade 1–4 event" category for participants with evaluable results but no grade in that direction, or state another mutually exclusive accounting convention. The SAP and table shell should make this choice explicit.

4.5 Listings and summary tables

The listing supports traceability with participant, analyte, date, baseline value where applicable, postbaseline result and unit, reference range, toxicity direction, CTCAE grade, and visit context. A marker can identify the maximum grade in the reporting window. The displayed observations should allow reviewers to reproduce that maximum.

The summary first reports participants with at least one postbaseline laboratory result. Each analyte row reports participants with a postbaseline result for that test and their maximum-grade distribution. Its denominator is the number with a non-missing postbaseline result for that analyte. Count one maximum grade per participant and analyte-direction combination so repeated visits do not inflate counts.

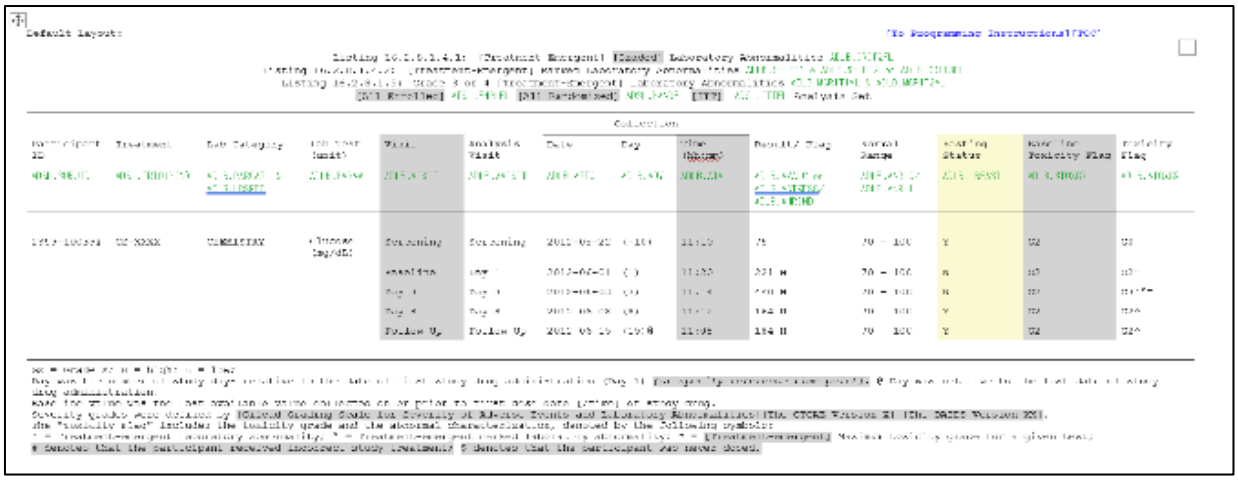


Figure 2: Listing Mock-up

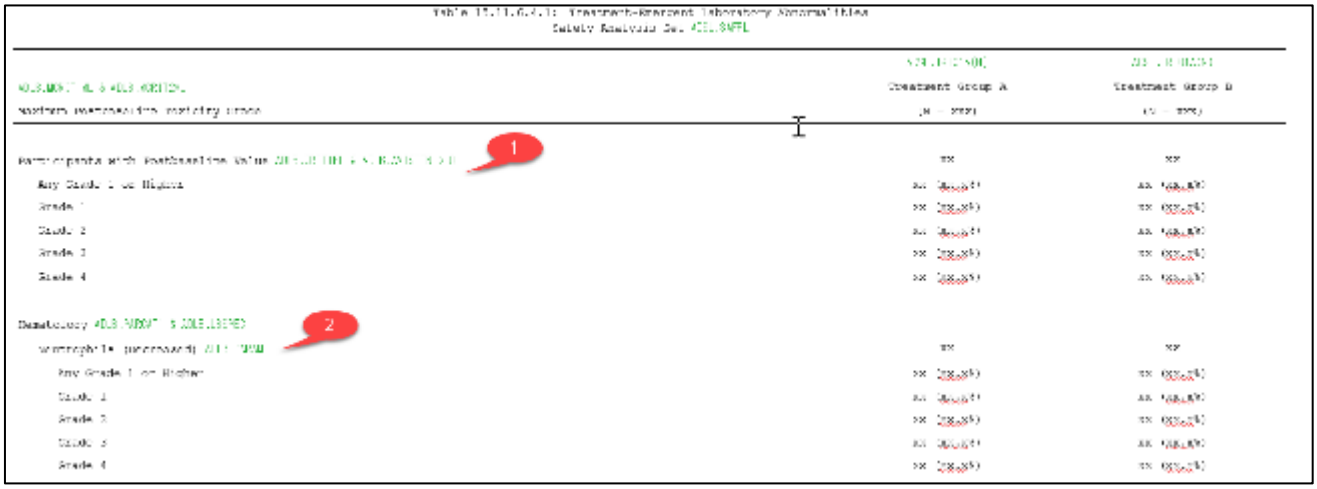


Figure 3: Table Mock-up

5 SYNTHETIC WORKED EXAMPLE

The mock-up uses four entirely synthetic participants and serum sodium (mmol/L), with a hypothetical local reference interval of 135–145 mmol/L. CTCAE v5.0 criteria are applied directionally. The low-direction Grade 1 example is 132 mmol/L; the low-direction Grade 3 example is 123 mmol/L. The high-direction Grade 1 example is 148 mmol/L. No clinical qualifier is needed for these selected example grades. Five observations are within the illustrative analysis window, and one is deliberately shown outside it. These records are fabricated for demonstration and do not describe actual trial participants.

Table 2: Synthetic participant-level listing mock-up

Subject	Visit/ day	Date	Baseline	Sodium	Direction	ATOXGRL	ATOXGRH	Window
SYN-001	Day 3	2020-01-18	140	132	Low	Grade 1	—	In
SYN-001	Day 14	2020-01-29	140	148	High	—	Grade 1	In
SYN-002	Day 7	2020-01-22	139	136	Within range	—	—	In
SYN-003	Day 7	2020-01-22	138	123	Low	Grade 3	—	In
SYN-004	Day 30	2020-02-14	140	140	Within range	—	—	In
SYN-004	Day 31	2020-02-15	140	152	High	—	Grade 2*	Out

Illustrative study rules: first dose 15 January 2020; last dose 15 January 2020; baseline is the last nonmissing value

before first dose; the post-last-dose window is inclusive through 14 February 2020. "—" means no grade assigned for that direction in the displayed record, not missing laboratory data. *The synthetic Grade 2 value is outside the reporting window and is shown only to demonstrate the date rule; it is excluded from the participant maximum and summary. For this illustrative value, assume the CTCAE v5.0 hypernatremia intervention criterion was met and documented; the example does not imply that concentration alone establishes this grade.

Table 3: Synthetic maximum-grade summary by direction

Analyte / direction	Evaluable N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	No Grade 1– 4 n (%)
Sodium low	4	1 (25.0)	0	1 (25.0)	0	2 (50.0)
Sodium high	4	1 (25.0)	0	0	0	3 (75.0)

The denominator is four for each direction because all four synthetic participants have at least one nonmissing postbaseline sodium result inside the analysis window. SYN-001 contributes a maximum Grade 1 to both directions on separate visits; SYN-003 contributes a maximum low Grade 3; SYN-002 and SYN-004 contribute to the no-grade categories. The Day 31 sodium result for SYN-004 is excluded. Counts are participant counts, not observation counts, and therefore do not increase with repeat testing.

6 QUALITY CONTROL AND TRACEABILITY

Quality Validation should cover both the grade derivation and the participant-level summary. A practical test set includes values immediately below, exactly at, and immediately above every numeric boundary; both directions for bidirectional tests; and cases that exercise any required intervention, symptom, hospitalization, or life-threatening qualifier. Confirm that the programmed operators match CTCAE v5.0 exactly and that values outside a parameter's supported criteria are not assigned an invented grade.

Time-window checks should include baseline records, the first eligible postbaseline date, the last included date, the first excluded date, and records with missing or conflicting dose dates. Verify treatment-emergent selection against its documented definition. Review unit conversion and reference-limit provenance. Missing, below-quantification, invalid, or unmapped records need explicit dispositions; they should not be conflated with a normal result.

At the output level, reproduce selected participant maxima from the listing, confirm one contribution per participant per analyte-direction category, and reconcile grade counts plus the no-grade category to the analyte-specific denominator. Keep the source criteria, mapping version, analysis dataset metadata, derivation code version, and output version linked in the study's traceability records [2,4]. ICH E3's emphasis on by-patient safety listings complements this analysis-data approach by supporting inspection of individual laboratory observations [3].

7 DISCUSSION

This workflow links three decisions that are often scattered across programming specifications: the grading reference and direction, the analysis period, and the rule that converts repeated results into a subject-level summary. Using ADaMIG v1.2 directional variables can preserve the distinction between lower and higher abnormalities in the analysis data. A listing then provides observation-level context, while a summary table gives a mutually exclusive maximum-grade distribution.

The synthetic example makes the denominator explicit and shows why a participant with no graded abnormality must still be represented when the denominator is all participants with evaluable postbaseline results. It also illustrates that eligibility is independent of apparent severity: a high result after the prespecified window is excluded even when it could meet a grade criterion. Conversely, a reportable grade can depend on clinical qualifiers not present in the numeric laboratory record, so a lookup table alone may be insufficient for all CTCAE terms [1].

Several limitations apply. This is a focused narrative methods article based on standards and selected literature available through 2020, not a systematic evidence synthesis. No protocol, SAP, validated threshold workbook, production code, or participant-level data were provided. Consequently, the example cannot establish that its mock reference interval, time window, variable attributes, or table shell is appropriate for a particular study. The 30-day extension and Grade 1–4 laboratory summary follow the supplied slide deck as illustrative conventions. A study team must confirm them against its protocol, SAP, safety conventions, and applicable standards. Laboratory toxicity grades support review and do not replace investigator assessment or adverse-event reporting.

8 CONCLUSION

A reproducible laboratory toxicity output starts with a version-controlled CTCAE mapping, separates low and high directions where both are clinically relevant, applies prespecified baseline and treatment-period rules, and selects a participant maximum without losing the observations behind it. A table should state its evaluable denominator and account for participants without a graded event. Boundary testing and reconciliation between listings and summaries make the result easier to review and reproduce under ADaMIG v1.2 and CTCAE v5.0.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The author declares no conflicts of interest regarding this manuscript.

Disclaimer

The views are the author's own; no proprietary or confidential employer information is included.

REFERENCES

[1] U.S. Department of Health and Human Services, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Published November 27, 2017. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

[2] Clinical Data Interchange Standards Consortium (CDISC). Analysis Data Model Implementation Guide (ADaMIG), Version 1.2. Published October 3, 2019. Available from: https://www.cdisc.org/standards/foundational/adam/adamig-v1-2

[3] International Council for Harmonisation. ICH Harmonised Tripartite Guideline E3: Structure and Content of Clinical Study Reports. November 30, 1995. Available from: https://database.ich.org/sites/default/files/E3_Guideline.pdf

[4] International Council for Harmonisation. ICH Harmonised Tripartite Guideline E9: Statistical Principles for Clinical Trials. February 5, 1998. Available from: https://database.ich.org/sites/default/files/E9_Guideline.pdf

[5] Chuang-Stein C. Laboratory data in clinical trials: a statistician's perspective. Controlled Clinical Trials. 1998;19(2):167–177. doi:10.1016/S0197-2456(97)00123-2.

[6] Xie L, Wang J, Sun J, Lai R, Watson R. Making lab toxicity tables less toxic on your brain. In: Proceedings of PharmaSUG 2019; Paper SS-306. Available from: https://www.pharmasug.org/proceedings/2019/SS/PharmaSUG-2019-SS-306.pdf