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Bridging Toxicity Grading and Data Standards: Evolution of CTCAE and Expansion of SDTM and ADaM Frameworks

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Introduction

Background and Purpose

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What is CTCAE?

- Common Terminology Criteria for Adverse Events
- A common framework for AE severity grading (Grade 1–5)
- Widely used in oncology, including laboratory-based toxicities

- Example of CTCAE v6.0

CTCAE v6.0 MedDRA 28.0 LLT Code	CTCAE v6.0 MedDRA 28.0 SOC	CTCAE v6.0 MedDRA 28.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
10029366	Investigations	Neutrophil count decreased	<1500 – 1000/mm3; <1.5 – 1.0 x 10^9/L	<1000 – 500/mm3; <1.0 – 0.5 x 10^9/L	<500 – 100/mm3; <0.5 – 0.1 x 10^9/L	<100/mm3; <0.1 x 10^9/L	–

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Purpose of the Presentation

CTCAE (the standard system for grading adverse-event severity in oncology trials) has evolved toward baseline-aware, bidirectional, mechanism-specific assessment — but SDTM and ADaM have only partially kept pace in capturing how those grades are derived.

This talk will:

1. Trace the evolution of CTCAE across major versions and the drivers behind each change
2. Examine how these changes are reflected — and where gaps remain — in SDTM and ADaM standards
3. Propose directions for closer alignment between clinical grading practice and data standards

This isn't just a terminology update — it changes how you build derivations and interpret safety data.

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EVOLUTION OF CTCAE AND TOXICITY GRADING

From Version 4.0 to 6.0

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Therapeutic diversification is increasing the complexity of laboratory safety assessment

Small-molecule drugs
Established mechanisms, well-characterized safety

+

Biologics
e.g., monoclonal antibodies

CAR-T cell therapy
Engineered immune cells

Immunotherapies
e.g., checkpoint inhibitors

Increasing clinical trial complexity
More — and more varied — laboratory assessments are needed to evaluate patient safety

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CTCAE Version Evolution at a Glance

v 4.0	v 4.3	v 5.0	V 6.0
MedDRA alignment, harmonization	Errata(clarifications only)	Terminology standardization, improved navigation	Paradigm shift(change in the grading logic itself)

Overall trend: CTCAE is moving from fixed reference-range-based assessment toward more context-aware, clinically nuanced assessment.

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What Actually Changed in CTCAE v6.0: Two Real Examples

ALT — branching logic refined

Baseline-dependent branching already existed in v5.0,but the condition for using it was ambiguous("baseline was abnormal" — either direction). v6.0 narrowed this to a clinically meaningful condition:

Grade 1
v5.0
>ULN - 3.0 x ULN if baseline was normal
1.5 - 3.0 x baseline if baseline was abnormal

v6.0
>ULN - 3.0 x ULN if baseline was normal or less than normal
1.0 - 1.5 x baseline if baseline was >ULN

Thrombocytopenia (Platelet count decreased) — criteria restructured

Numeric bands widened, and a clinical-action criterion was added — not just a different number:

V5.0
Grade3: <50,000 - 25,000/mm3
Grade4: <25,000/mm3

V6.0
Grade3: <50,000 - 10,000/mm3; transfusion indicated
Grade4: <10,000/mm3; life-threatening consequences; urgent intervention indicated

Across roughly 60% of CTCAE's 850 terms, grading criteria changed in v6.0 — not only thresholds, but in some cases the structure of the criteria itself.

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The Same Lab Value, Two Different Grades

Example: a patient with Absolute Neutrophil Count (ANC) = 300/mm³

CTCAE v5.0
ANC 300/mm³ falls in the
"<500/mm³" band
→ Grade 4

Grade CTCAE v6.0
ANC 300/mm³ falls in the
"<500 – 100/mm³" band
→ Grade 3

This is grade migration: the same patient, the same lab value — a different severity grade, purely because of which CTCAE version was used.

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When Grade Migration Changes a Trial Decision

Many early-phase trials define a Dose-Limiting Toxicity (DLT) as a treatment-related Grade ≥4 adverse event.

Under CTCAE v5.0:
ANC 300/mm³ = Grade 4
→ COUNTS as a DLT

Under CTCAE v6.0:
ANC 300/mm³ = Grade 3
→ Does NOT count as a DLT

Dose-escalation decisions and Maximum Tolerated Dose (MTD) determination can differ solely because of which CTCAE version a protocol specifies.

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DATA STANDARDS SUPPORTING TOXICITY GRADING

SDTM & ADAM

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Why This Creates New Demands on Data Standards

CTCAE concepts

- Reference range
- Baseline
- Direction of change
- Clinical context

Data needs

- Traceability
- Derivation logic
- Version tracking
- Reproducibility

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SDTM: The Foundation, but Not the Full Solution

Test	Result	Reference range	Normality indicator	Toxicity grade
LBTEST / LBTESTCD	LBORRES / LBSTRESN	LBSTNRLO / LBSTNRHI	LBNRIND	LBTOX / LBTOXGR

- Good for traceability and submission
- LBTOX / LBTOXGR can record a toxicity grade value, but not how it was derived
- Limited for baseline linkage and longitudinal, bidirectional derivation logic

Good foundation — not the whole solution

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ADaM Grading Variables in Action: A Worked Example

Toxicity grade

ATOXGRL / ATOXGRH
Analysis toxicity grade in the LOW / HIGH direction for this record

BTOXGRL / BTOXGRH
The baseline record's grade in that same direction — kept on every row for shift-table analysis

ATOXDSCL / ATOXDSCH
Plain-language label for what is being graded in each direction (e.g., "Anemia" vs. "Hemoglobin increased")

- Example: Visit 1 (baseline): Hgb = 7.4, below the normal range (11–16.1) → graded LOW direction as Grade 3 (Anemia). Visit 2: Hgb rises to 20.5, above the normal range → now graded HIGH direction as Grade 3 (Hemoglobin increased); the LOW-direction grade returns to 0.

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
PARAMCD	AVISITN	AVAL	BASE	ABLFL	ANRLO	ANRHI	ATOXDSCL	ATOXGRL	BTOXGRL	ATOXDSCH	ATOXGRH	BTOXGRH
HGB	1	7.4	7.4	Y	11	16.1	Anemia	Grade 3	Grade 3		Grade 0	Grade 0
HGB	2	20.5	7.4		11	16.1		Grade 0	Grade 3	Hemoglobin increased	Grade 3	Grade 0

Why this matters: a single lab test can be clinically meaningful in BOTH directions — these variables let ADaM capture that without ambiguity.

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ADaM: Grading Variables and Their Evolution

ADaM IG 1.0 / 1.1

Foundational Phase

- ATOXGR / BTOXGR (single-direction grade) already present
- Limited explicit guidance beyond this core pair
- Grading often implemented via sponsor-specific conventions

ADaM IG 1.2 / 1.3

Expansion Phase / Maturity Phase

- Introduction of bidirectional variables: ATOXGRL/ATOXGRH, BTOXGRL/BTOXGRH
- Introduction of ATOXDSCL / ATOXDSCH (toxicity description, low/high)
- Improved alignment with SDTM structures

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Where the Gaps Still Remain

What standards already support

- Structured lab results & reference ranges (SDTM)
- Baseline, change, derived grade variables (ADaM)
- Bidirectional grading variables, as standard Permissible ADaM variables (IG 1.2+)

What still remains difficult

- No baseline-linkage variable in SDTM itself
- Bidirectional ADaM variables are optional (Permissible), so adoption may vary by sponsor
- No standardized algorithm for baseline-dependent branching (e.g., the ALT case)
- Cross-TA harmonization limited

Not a study-specific inconvenience — a systemic data-standard issue.

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Conclusion

Toward Better Alignment

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Proposal: What Could Improve Next

CTCAE and CDISC may be able to evolve more smoothly when their evolution is kept in sync.

- Strengthen SDTM-level capture of source evidence behind grade derivation
- Strengthen collaboration between CTCAE clinical experts and CDISC developers
- Build reusable, algorithm-level derivation guidance for lab-based grading

Sponsors may benefit from building internal standards proactively.

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Conclusion

- **How CTCAE and SDTM/ADaM have evolved together**
  As CTCAE grading became more baseline-aware, bidirectional, and mechanism-specific, SDTM supplied the foundational structures while ADaM IG progressively added grading-specific variables.
- **Where gaps remain**
  Baseline-adjusted grading logic, bidirectional grading variables, and cross-therapeutic-area harmonization are not yet fully standardized.
- **What improvement is needed going forward**
  Stronger SDTM-level traceability, closer collaboration between CTCAE clinical experts and CDISC developers, and reusable, algorithm-level derivation guidance.

As the concept of safety assessment evolves, the data standards that capture it must continue to evolve as well.

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