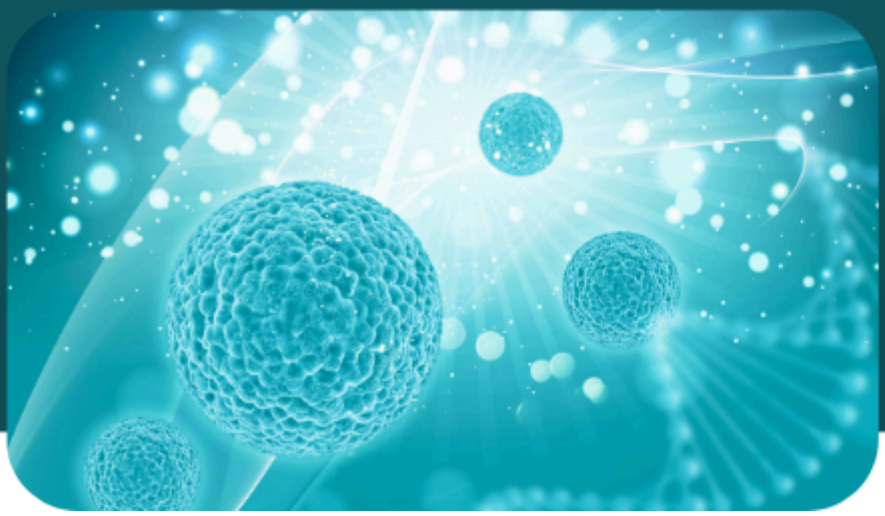
CRS Adjudication Guide

Recommended elements for structured CRS event review following CAR-T and T-cell engager therapies

September 2026



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Purpose

The CRS Adjudication Guide defines the recommended outputs generated following structured review and characterization of cytokine release syndrome (CRS) events following CAR T-cell and T-cell engager (TCE) therapy.

The purpose of these outputs is to create a consistent, longitudinal representation of CRS events across clinical trials and clinical practice. Standardized outputs support reproducible safety assessment, cross-study analyses, and future development of data-driven approaches for improved CRS characterization and clinical decision support.

This specification complements, but does not replace, established clinical standards for CRS identification and grading, including ASTCT consensus definitions and grading criteria.

This specification is intended to be used in conjunction with the **CRS Adjudication Flowchart** to support consistent documentation, review, and reporting of CRS events.

SCOPE

The outputs described below represent recommended information elements generated through structured clinical review. They are not intended to establish a minimum required dataset for CRS adjudication. CRS events are reconstructed from heterogeneous clinical sources whose completeness varies across sites, studies, and care settings; mandating a fixed set of elements would risk excluding well-supported events where a specific element is unavailable, or forcing adjudication where the evidence is insufficient. Instead, an event can be adjudicated whenever the available information is sufficient for clinical interpretation, even if any individual element is missing.

Availability of individual data elements may vary depending on clinical documentation, available data sources, and clinical context. The practical trigger for review is evidence of a change in clinical status or management, rather than any specific measurement; the elements below characterize the event once review is underway.

Core principles

CRS Is a longitudinal clinical event

CRS should be represented as an evolving clinical event rather than a single diagnosis or severity classification.

A complete CRS event representation includes:

- Evidence supporting event identification
- Timing of clinical findings
- Changes in CRS severity over time
- Operational definitions of how severity or progression was assessed
- Interventions and clinical responses
- Resolution of the event
- Clinical rationale supporting interpretation

The final maximum CRS grade is an important summary output; however, it does not replace documentation of the underlying time-resolved clinical course.

ASTCT remains the clinical standard

The ASTCT consensus definition and grading system provides the current clinical standard for CRS identification and severity assessment.

This framework does not introduce new CRS definitions or modify established grading criteria. Instead, it provides a structured methodology for applying current standards consistently and documenting the clinical trajectory of CRS events.

As additional data sources become available, including continuous physiologic monitoring, future research will be needed to determine how these data may enhance CRS event characterization and whether refinement of operational approaches is warranted.

Clinical judgment remains central

CRS event outputs represent structured interpretation of available clinical evidence.

The framework supports transparency and consistency in review but does not replace investigator or adjudicator clinical assessment.

Incomplete data should not preclude review

The absence of a specific data element should not prevent CRS event assessment when available clinical evidence supports interpretation.

When information is incomplete, the limitation should be documented along with the rationale supporting the final determination.

CRS event output structure

A completed CRS event record should include the following domains:

- ✔ Treatment Context
- ✔ CRS Event Determination
- ✔ CRS Onset
- ✔ Time-Resolved CRS Grade Assessments
- ✔ Clinical Interventions
- ✔ Alternative Diagnosis Assessment
- ✔ CRS Resolution
- ✔ Data Availability and Confidence

Definitions

Definitions used within this framework align with established consensus criteria, including ASTCT consensus grading criteria and CTCAE Version 5.0 terminology for cytokine release syndrome (CRS).

Additional documentation-specific terms introduced within this framework are defined to support consistent interpretation, data capture, and adjudication of CRS events across clinical studies.

These definitions are intended to provide a common reference for CRS event identification, grading, documentation, and review. See **Section 10** for the complete list of definitions.

Data source hierarchy and data review considerations

CRS event assessments may require integration of information from multiple clinical sources, including vital signs, laboratory data, medication records, and clinical documentation. Differences may occur across source records due to timing, documentation practices, or data availability.

The data source hierarchy is intended to guide review toward the most objective and contemporaneous information available. It does not imply that one data source automatically supersedes all others; clinical context and the complete event timeline should be considered.

When evaluating potentially conflicting information, consider:

- Timing of documentation relative to the CRS event
- Objective measurements versus clinical interpretation
- Completeness and consistency of the clinical timeline
- Relationship between clinical findings and interventions provided

The clinical data source(s) reviewed and the evidence supporting the CRS assessment and final determination should be documented. Recommended data sources and documentation considerations are described in **Section 8**.

1. Treatment context

Purpose

Establish the clinical setting and temporal relationship between immune effector therapy administration and subsequent findings.

Recommended outputs

Data element	Description
Therapy name / agent	Name of the CAR T-cell therapy, bispecific TCE, or other immune effector therapy
Administration date / time	Date and time the therapy was administered
Treatment cycle / dose	Treatment cycle, dose, or dose level administered, as applicable
Relevant clinical history / confounding factors	Baseline conditions and history that may influence CRS presentation, interpretation, or management (for example, high tumor burden, relevant comorbidities (e.g., COPD), prior immune effector therapy, or prior CRS history). Informs the clinical rationale for determination and grading.
Premedication	Medications administered prior to or in anticipation of therapy that may influence CRS presentation or grading (for example, antipyretics or corticosteroids). Timing relative to therapy and to subsequent findings should be noted where available.

2. CRS event determination

Purpose

Document the overall conclusion following structured review.

Recommended outputs

Data element	Description
CRS event status	Final determination of whether CRS occurred (likely, unlikely, indeterminate, or alternative diagnosis identified)
Supporting evidence	Clinical findings and data reviewed to support the CRS event determination
Clinical rationale	Clinical rationale supporting the final CRS event determination
Alternative diagnoses considered	Alternative diagnoses evaluated during the CRS event assessment

3. CRS onset

Purpose

Document the earliest evidence supporting CRS onset.

Recommended outputs

Data element	Description
CRS onset date / time	Date / time onset assigned
Supporting evidence	Clinical findings and data sources reviewed to support CRS onset determination
Clinical rationale	Clinical rationale for why CRS onset was assigned to this date/time, including the reasoning behind the specific timestamp (for example, whether onset reflects the first qualifying fever versus a temperature rise following antipyretic administration).

4. CRS grade assessment

Principle

Each CRS grade assignment represents a discrete clinical assessment and should be documented as an individual time-stamped event.

The maximum CRS grade should be retained as a summary measure; however, the underlying grade trajectory should be preserved.

Required documentation for each CRS grade assessment

Data element	Description
Assessment date / time	Date / time associated with CRS grade assignment
CRS grade	Grade assigned at the assessment time point
Supporting evidence	Clinical findings and data sources reviewed to support the CRS grade assignment (e.g., laboratory results, vital signs, imaging, clinical notes)
Clinical actions	Clinical interventions or management actions associated with the CRS grade assessment, as applicable
Clinical rationale	Clinical rationale supporting the assigned CRS grade including how the applicable ASTCT grading criteria were operationalized in this case (e.g., how 'hypotension' or 'hypoxia' was interpreted for this assessment).

Example grade trajectory output

Date/Time	CRS grade	Supporting evidence	Clinical actions	Clinical rationale
Day 2 08:30	Grade 1	Fever 38.5°C; no hypotension; no hypoxia	Acetaminophen; increased monitoring	Increased monitoring; CRS criteria met (fever ≥38°C)
Day 2 15:00	Grade 2	Hypotension confirmed by SBP < 90 (flagged by patient-reported dizziness)	IV fluids initiated (15:15); continued monitoring	Escalation to Grade 2 based on confirmed hypotension requiring intervention, without vasopressor support
Day 2 18:00	Grade 2	Persistent Grade 2 CRS (fever plus hypotension responsive to IV fluids; no vasopressor required)	Tocilizumab administered; continued monitoring	Tocilizumab administered for CRS for persistent Grade 2 CRS
Day 3 10:00	Grade 1	Blood pressure stabilized as measured at 10:00 (Day 3), temperature 38.1°C	Continued monitoring; supportive care	Improvement to Grade 1 after intervention, fever persists

5. Clinical intervention

Principle

Interventions should be captured as time-stamped clinical events linked to the findings that prompted management changes.

Required documentation for each intervention

Data element	Description
Intervention date / time	Date / time intervention administered or initiated
Intervention type	Type of intervention taken in response to the event, including supportive or pharmacologic treatment (e.g., antipyretic, intravenous fluids, tocilizumab, corticosteroid therapy), changes in monitoring intensity, and modifications to immunotherapy (e.g., delaying or holding a step-up dose).
CRS grade at intervention	Grade assigned at time of intervention
Clinical response	Clinical outcome following the intervention
Clinical rationale	Clinical rationale supporting the intervention decision

Example intervention output

Date/ Time	Intervention	CRS grade	Clinical response	Clinical rationale
Day 2 15:15	IV fluids	Grade 2	Partial, transient improvement in BP after fluids as indicated by symptom resolution and SBP ≥ 90 at 15:15	IV fluids initiated to manage hypotension associated with CRS identified through patient reported dizziness at 15:15 (Day 2)
Day 2 18:00	Tocilizumab	Grade 2	Clinical improvement	tocilizumab administered for persistent Grade 2 CRS; hypotension remained responsive to IV fluids without vasopressor support

6. Alternative diagnosis assessment

Purpose

Document evaluation of competing explanations for clinical findings.

Recommended outputs

Data element	Description
Alternative diagnosis considered	Alternative diagnosis evaluated as a potential explanation for the clinical findings
Supporting evidence	Clinical findings and data supporting the alternative diagnosis
Evidence supporting CRS	Clinical findings and data supporting a CRS interpretation
Final assessment	Final clinical determination based on the available evidence

Examples

- ✔ Infection/sepsis
- ✔ Disease progression
- ✔ infusion-related reaction
- ✔ HLH/MAS
- ✔ ICANS
- ✔ Other adverse event

7. CRS resolution

Purpose

Document completion of the CRS event.

Recommended outputs

Data Element	Description
Resolution status	Status of CRS resolution, categorized as: resolved; ongoing; resolved with sequelae; fatal; or unknown.
Resolution date / time	Date / time resolution assigned
Supporting evidence	Clinical findings and data supporting the resolution determination
Clinical rationale	Clinical rationale supporting the resolution determination

8. Supporting data sources

Purpose

Document the information sources reviewed during CRS event assessment.

Recommended sources

Data element	Description
Vital signs	Temperature, heart rate, blood pressure, oxygen saturation
Medication administration records	Administration of medications including tocilizumab, corticosteroids, antipyretics, vasopressors, and other supportive therapies
Laboratory data	Relevant laboratory results reviewed during CRS assessment
Clinical notes	Physician notes, nursing documentation, specialist assessments, and other relevant clinical documentation
Hospitalization records	Hospital admission, ICU transfer, escalation of care, and other hospitalization-related information
Site-reported CRS documentation	Investigator-reported CRS assessments, grading, and supporting documentation
Continuous physiologic monitoring	High-frequency physiologic monitoring data, when available (e.g., continuous core body temperature monitoring)

9. Data availability and confidence

Purpose

Provide transparency regarding the evidence available for CRS assessment.

Recommended outputs

Data Element	Description
Data availability	Sufficient, insufficient
Assessment confidence	High, moderate, or low
Supporting rationale	Explanation of limitations or uncertainty

10. Definitions

Purpose

ASTCT (2019) remains the reference standard for CRS identification and grading. Because certain ASTCT criteria are operationalized differently across sites and clinicians in practice, this specification captures the clinical rationale behind each determination — preserving ASTCT as the standard while documenting how it was applied.

Term	Definition
Cytokine release syndrome (CRS)	A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction.[1]
Fever	Temperature ≥ 38°C not attributable to any other cause.[1]
Grade 1 CRS	Fever (≥ 38.0°C) with or without constitutional symptoms.[1]
Grade 2 CRS	Fever (≥ 38.0°C) with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula (≤ 6 L/min) or blow-by. Fever is not required if CRS has previously been documented and antipyretic or anticytokine therapy has been received.[1]
Grade 3 CRS	Fever (≥ 38.0°C) with hypotension requiring one vasopressor with or without vasopressin, and/or hypoxia requiring high-flow nasal cannula (>6 L/min), facemask, nonrebreather mask, or venturi mask, not attributable to any other cause. Fever is not required if CRS has previously been documented and antipyretic or anticytokine therapy has been received.[1]
Grade 4 CRS	Fever (≥ 38.0°C) with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, mechanical ventilation), not attributable to any other cause. The use of multiple vasopressors constitutes Grade 4 CRS irrespective of total cumulative dose. Fever is not required if CRS has previously been documented and antipyretic or anticytokine therapy has been received.[1]
Hypotension	A disorder characterized by blood pressure below the normal expected level for an individual in a given environment. An individual requiring IV fluid boluses or vasopressors to maintain normal blood pressure may be considered to have hypotension.[2]

Term	Definition
Hypoxia	A disorder characterized by a decrease in the level of oxygen in the body, considered relative to the individual's baseline. Events requiring supplemental oxygen to correct an oxygenation deficit should be considered for CRS grading.[2]
CRS Resolution	A patient with CRS in whom fever, oxygen, and pressor requirements have resolved for 24 hours is assumed to have resolved CRS, unless there are alternative causes for the fever, hypoxia, and/or hypotension.
CRS Event Status — Likely	Structured review determined that clinical findings meet ASTCT criteria for a CRS event.
CRS Event Status — Unlikely	Structured review determined that available evidence does not support a CRS event.
CRS Event Status — Indeterminate	Available evidence is insufficient, or is conflicting, such that a likely or unlikely determination cannot be supported; the limitation and rationale should be documented.
CRS Event Status — Alternative diagnosis identified	Structured review determined that a competing diagnosis (see **Section 6**) better explains the clinical findings than CRS.
CRS Recurrence	A new CRS event, meeting ASTCT onset criteria, occurring after a previously documented CRS event has met the CRS resolution definition.
Assessment Confidence — High	Supporting evidence is complete and internally consistent (e.g., vital signs, laboratory data, clinical notes) such that limited additional information would be expected to change the determination.
Assessment Confidence — Moderate	Supporting evidence is adequate to reach a determination but includes gaps, inconsistencies, or reliance on a narrower evidence base than "High."
Assessment Confidence — Low	Supporting evidence is limited, conflicting, or largely indirect; the determination is more susceptible to revision if further information becomes available.

Sources:

1. Lee DW, Santomasso BD, Locke FL, et al. (2019) ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 25(4):625-638.

2. *U.S. Department of Health and Human Services, National Cancer Institute. (2017). Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Published November 27, 2017.*

Continuous data considerations

Continuous physiologic data may provide additional resolution regarding CRS onset, progression, and resolution.

Current CRS definitions and grading approaches are primarily based on discrete clinical observations, vital signs, and therapeutic interventions. Therefore, continuous data should be considered supporting clinical evidence and interpreted within the context of the overall clinical timeline and established CRS grading criteria.

The framework supports preservation and evaluation of continuous data to enable future research and improved characterization of CRS events while maintaining alignment with current ASTCT standards.

When available, continuous data may contribute to:

- Characterization of CRS event timing and trajectory
- Evaluation of physiologic trends relative to patient-specific baseline status and changes observed during CRS onset, progression, and resolution including sustained changes as distinct from transient fluctuations.
- Development of future data-driven approaches for CRS monitoring and clinical decision support

Continuous data availability and limitations should be documented as part of the overall assessment of data completeness and confidence.

Principles for adjudicator use

Principle	Description
Complements clinical assessment	A continuous/DHT-derived data is treated as supporting evidence, the same as a lab value or charted vital sign. It may corroborate or inform onset, grade, or resolution determinations as appropriate. Clinical correlation and adjudicator judgment remain required, consistent with the "Clinical Judgment Remains Central" principle.
Foster a comprehensive clinical narrative	Where a DHT data source and a discrete clinical observation disagree (e.g., a DHT-flagged fever not reflected in a charted vital sign, or vice versa), the discrepancy and how it was resolved should be noted in the clinical rationale.
Gaps are a completeness issue, not a review blocker	Missing or incomplete continuous data should be reflected in Data Availability and Confidence (**Section 9**), not treated as a reason to withhold or delay assessment, consistent with the "Incomplete Data Should Not Preclude Review" principle.
DHT-generated alerts	An automated alert or threshold-crossing flag from a DHT or platform is not a clinical finding. If cited as supporting evidence, the record should reflect that the alert was reviewed and clinically correlated.

Final CRS event summary output

The final CRS event record should contain both:

- ✔ Summary outputs for analysis
- ✔ Underlying time-resolved event data for clinical interpretation

Summary outputs

Data element	Description
CRS event determination	Likely / Unlikely / Indeterminate
CRS onset	Date / time and supporting clinical rationale
CRS resolution	Date / time and supporting clinical rationale
Maximum ASTCT CRS grade	Highest grade reached
CRS duration	Time from onset to resolution
CRS recurrence	New CRS event following documented resolution
Alternative diagnosis	Competing explanation identified

Underlying time-resolved outputs

Data element	Description
CRS onset event	Date / time, supporting evidence, clinical rationale
Grade assessments	Every grade assignment with date / time and clinical rationale
Grade changes	Date / time of escalation or improvement events
Intervention events	Date / time, intervention type, clinical response, clinical rationale
Resolution event	Date / time and supporting evidence

Future applications

Consistent CRS event outputs may support:

- ✔ Improved safety analyses
- ✔ Cross-study comparisons
- ✔ Pharmacovigilance activities
- ✔ Research on CRS trajectories
- ✔ Development of predictive models
- ✔ Future digital clinical decision support tools

Standardized CRS event outputs provide a structured representation of clinical events that supports reproducible analysis while preserving the role of clinical expertise and judgment in CRS assessment and interpretation.

Reporting template

Protocol Header

Protocol number:

Site name / ID:

Subject / participant ID:

Date of report:

Site awareness date:

Investigator name:

1. Treatment Context

Therapy name / agent	
Administration date/time	
Treatment cycle/dose	
Relevant clinical history / confounding factors	
Premedication	

2. CRS Event Determination

CRS Event Status	
Supporting evidence	
Clinical rationale	
Alternative diagnoses considered	

3. CRS Onset

CRS onset Date / Time	
Supporting evidence	
Clinical rationale	

4. CRS Grade Assessment

Complete one row per grade assessment. See Section 4 for a worked example.

Assessment Date/Time	CRS Grade	Supporting Evidence	Clinical Actions	Clinical Rationale

5. Clinical Intervention

Date/Time	Intervention	CRS Grade	Clinical Response	Clinical Rational

6. Alternative Diagnosis Assessment

Alternative diagnosis considered	
Supporting evidence	
Evidence supporting CRS	
Final assessment	

7. CRS Resolution

Resolution status	
Resolution date / time	
Supporting evidence	
Clinical rationale	

8. Supporting Data Sources

Vital signs	☐	**Hospitalization records**	☐
Medication administration records	☐	**Site-reported CRS documentation**	☐

Laboratory data	☐	**Continuous physiologic monitoring**	☐
Clinical notes	☐	**Other:_____**	☐

9. Data Availability and Confidence

Data availability	Sufficient, insufficient
Assessment confidence	High, moderate, or low
Supporting rationale	Explanation of limitations or uncertainty

10. Form Signatures and Verification

Adjudicator name / identifier	
Adjudication date	
Adjudicator signature	
Adjudicator comments	