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# Harmonizing the Definition and Reporting of Cytokine Release Syndrome (CRS) in Immuno-Oncology Clinical Trials

## Shaping the Future of Emerging Immunotherapies and Cell Therapies

## Objective

This white paper focuses on establishing a standardized approach for defining and capturing cytokine release syndrome (CRS). It also provides considerations for categorizing the variety of adverse events (AEs) that may accompany CRS, recognizing that presentations of CRS may differ among various immunotherapeutics (e.g., monoclonal antibodies, CAR T-cell therapies, and T-cell engagers, which can include bispecific antibodies and other constructs). The ultimate goal is to ensure accurate and consistent identification of CRS in patients receiving immunotherapies in clinical studies to aid in reporting; enable a more precise evaluation of the therapeutic risk-benefit profile; support evidence-based monitoring and management of novel toxicities; and improve patient care and outcomes. This will be of increasing importance as the number and variety of molecular targets for these therapies expands and immunotherapies with novel mechanisms of action are tested either as a monotherapy or in combinations.

## Introduction

The emergence of cancer immunotherapies has resulted in transformational advances across solid and hematological malignancies, bringing new hope to patients with serious, life-threatening diseases. Cancer immunotherapies provide clinically beneficial alternatives and additions to traditional cytotoxic treatments. Recent U.S. Food and Drug Administration (FDA) approvals and the rapid expansion of indications for existing agents are enabling broader availability of immunotherapies to cancer patients.

The immuno-oncology (IO) drug development pipeline continues to grow, and cancer immunotherapies are quickly being integrated into the standard of care for many cancers.[1] Importantly, our increasing clinical experience with these immunotherapeutic agents has brought greater awareness to several unique toxicities when compared to traditional cytotoxic agents. With the success of newer immunotherapies like T-cell engagers and chimeric antigen receptor (CAR) T-cells in several hematologic malignancies, there has been growing recognition of cytokine

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release syndrome (CRS) as a distinct clinical entity. Cytokine release syndrome represents one of the most common toxicities of these therapies and occurs with varying frequency, severity, and presentation among immunotherapeutic agents.[2] The incidence of CRS is relatively low for conventional monoclonal antibodies, but there is a higher risk of CRS (incidence of 17% to 94%) with CAR T-cell therapies and T-cell engagers.[3] While early in the development of immunotherapies, the term CRS was used more generally to describe a syndrome with a dramatic presentation requiring intensive care, it has been increasingly recognized that CRS presents with a spectrum of severities, ranging from a self-limited low grade fever to serious multiorgan collapse requiring intensive care.

Although CRS is increasingly recognized as an on-target effect associated with CAR T-cells and T-cell engagers, the scope of this syndrome, including effects on end organ function, has not been fully characterized. A standardized approach is needed for diagnosing and reporting CRS and its manifestations in clinical trials, published literature, and in clinical practice. More importantly there is a need to distinguish CRS from other clinical entities, such as acute infusion-related reactions (IRR). Acute IRRs and CRS can have overlapping symptoms and temporality but likely have different pathophysiology and treatments with different prognoses. Inconsistent or inadequate characterization of these toxicities in clinical trials impact how data are presented in publications and prescribing information, potentially resulting in suboptimal description and management of these clinical events. This can put patients at risk if their treatment side effects are not properly managed.

## Growing Clinical Experience of Infusion Reactions and CRS

Adverse events (AEs) known broadly as IRRs have been long defined, diagnosed, and reported in an ambiguous and inconsistent manner.[4] This arises, in part, from the fact that the term IRR came into use at a time when few biological therapies were available and acute reactions to an infusion of a biologic agent were reported. Additionally, little was known about the exact mediators involved in these reactions. Since the introduction of therapeutic monoclonal antibodies into clinical practice, IRR continues to be used as a term to describe a variety of symptoms occurring during or shortly after the infusion of the medicinal product. Infusion related reactions following CAR T-cell administration are infrequent and generally mild. However, with the emergence of T-cell-engaging therapeutics, in particular T-cell engagers and fusion proteins, distinguishing CRS from IRR has been a challenge, in that the signs and symptoms may partially overlap.

Infusion-related reaction is a broad term traditionally used to encompass acute findings during or shortly after an infusion that may include hypersensitivity/anaphylaxis, complement activation-related pseudoallergy (CARPA), CRS, or more nonspecific signs and symptoms.[4] During clinical development, IRRs are generally defined as AEs occurring within the first 24 hours after infusion of a therapy, with causality deemed by the investigator as related to the therapy. This operational definition has resulted in this term being used to define a wide array of symptoms with potentially disparate pathophysiology whose main commonality is occurrence within 24 hours of infusion. The majority of IRRs reported with therapeutic monoclonal antibodies are self-limited and treated symptomatically.[5–8] However, a primary clinical concern within the con-

text of IRR is whether the reaction is mediated by immunoglobulin E (IgE) because this specific type of reaction can increase in severity with additional infusions. For that reason, re-challenging is contraindicated with IgE mediated hypersensitivity.[4,9,10]

CRS is a supraphysiologic response driven by the immune system, which is also observed commonly in sepsis and other infections and most recently with COVID-19. CRS is T-cell mediated and can occur within several hours to days after infusion, but rarely presents beyond 14 days after initiation of therapy. CRS can be short lived, but often lasts for several days. Because symptoms of CRS can overlap with other toxicities that have generally been classified as IRRs, and because both CRS and IRR can occur within a day after infusion, careful examination of the signs and symptoms, their attribution, and the response to therapy is important. The presentation of CRS may differ depending on the immunotherapeutic. The timing of the onset of CRS can coincide closely with infusion of T-cell engagers, but for cellular products where T-cell expansion precedes clinical CRS, there may be a significant lag between infusion and CRS symptom onset.11 CRS typically presents with a fever and may progress to hypotension and/or hypoxia. Flushing and rash may accompany both anaphylactic reactions and CRS, although specific skin and mucosal changes such as hives and mucosal swelling predominate in anaphylactic reactions, occurring in 80% of cases.[12] An underlying factor associated with CRS is the release of cytokines, and this has been identified as a differentiating criterion in the Common Terminology Criteria for Adverse Events (CTCAE) v.5 definition for CRS and IRRs. However, the measurement of cytokines is not yet a routine element in clinical practice, nor are there reliable cytokine thresholds for CRS diagnosis. Thus, this distinction alone may not be helpful to clinicians at the bedside, and emergent clinical interventions are still largely based on the clinical manifestations and severity of CRS as well as response to therapeutic interventions. For example, the role of the IL-6 pathway in CAR T-cell therapy has been characterized and use of IL-6 blocking agents is the primary treatment of CRS.[13,14]

## CRS Definition and Severity

In light of our evolving clinical experience with emerging immunotherapeutics, several efforts to update and harmonize grading criteria for CRS in clinical trials have occurred (**Table 1**). Additionally, the elements described in each grading system offer information on what defines severity.

Fever is a CRS-defining characteristic but does not dictate the severity. Therefore, the MSKCC grading system initially relied on the availability of released cytokine levels measured from patients in real-time to distinguish severe versus non-severe CRS.[21] However, cytokine testing may be limited to specific health care research settings, and there is currently poor correlation between cytokine levels and the intensity of CRS signs and symptoms. The presence and severity of hypotension and hypoxia are most commonly used to assign the grade of severity for CRS, as these two events drive the need for higher level of care (e.g., intensive care). One unique aspect of CRS grading is that the severity is often attributed based on practitioner intervention. For example, the utilization of one or more vasopressor agents to treat hypotension or use of supplemental oxygen or mechanical ventilation for hypoxia would dictate the CRS severity grade.

## Table 1: Evolving Definitions and Criteria for Grading and Managing CRS

| Lee Criteria[15] |
|---|
| Grade 1: Symptoms are not life-threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgias, malaise)<br><br>Grade 2: Symptoms require and respond to moderate intervention; Oxygen requirement <40% or hypotension responsive to IV fluids or low-dose single vasopressor or grade 2 organ toxicity<br><br>Grade 3: Symptoms require and respond to aggressive intervention; Oxygen requirement of ≥40% or hypotension requiring high-dose or multiple vasopressors or grade 3 organ toxicity or grade 4 transaminitis<br><br>Grade 4: Life-threatening symptoms; Requirements for ventilator support OR grade 4 toxicity (excluding transaminitis) |
| CTCAE v5.0[16] |
| Grade 1: Fever with or without constitutional symptoms<br><br>Grade 2: Hypotension responding to fluids; Hypoxia responding to <40% oxygen<br><br>Grade 3: Hypotension managed with one vasopressor; Hypoxia requiring ≥40% oxygen<br><br>Grade 4: Life-threatening consequences; Urgent intervention indicated |
| Memorial Sloan Kettering Cancer Center (MSKCC)[17] |
| Grade 1: Mild symptoms requiring observation or supportive care only (e.g., antipyretics, antiemetics, pain medication)<br><br>Grade 2: Hypotension requiring any vasopressors <24 h; Hypoxia or dyspnea requiring supplemental oxygen <40%<br><br>Grade 3: Hypotension requiring any vasopressors ≥24 h; Hypoxia or dyspnea requiring supplemental oxygen ≥40%<br><br>Grade 4: Life-threatening symptoms; Hypotension refractory to high-dose vasopressors; Hypoxia or dyspnea requiring mechanical ventilation |
| Chimeric Antigen Receptor Toxicity (CARTOX)[18] |
| Grade 1: Temperature ≥38°C Grade 1 organ toxicity<br><br>Grade 2: Hypotension responds to intravenous fluids or low-dose vasopressor; Hypoxia requiring oxygen <40%; Grade 2 organ toxicity<br><br>Grade 3: Hypotension needing high-dose or multiple vasopressors; Hypoxia requiring oxygen ≥40%; Grade 3 organ toxicity or Grade 4 transaminitis<br><br>Grade 4: Life-threatening hypotension; Needing ventilator support; Grade 4 organ toxicity except Grade 4 transaminitis |

| Penn Criteria[19] |
| --- |
| Grade 1: Mild reaction: Treated with supportive care, such as antipyretics, antiemetics<br><br>Grade 2: Moderate reaction: Some signs of organ dysfunction (Grade 2 creatinine or Grade 3 liver function tests [LFTs]) related to CRS and not attributable to any other condition; Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for IV therapies (not including fluid resuscitation for hypotension)<br><br>Grade 3: More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction, including Grade 4 LFTs or Grade 3 creatinine, related to CRS and not attributable to any other condition; Hypotension treated with multiple fluid boluses or low-dose vasopressors; Coagulopathy requiring fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate; Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)<br><br>Grade 4: Life-threatening complications, such as hypotension requiring high-dose vasopressors; Hypoxia requiring mechanical ventilation |
| American Society for Transplantation and Cellular Therapy (ASTCT)[20] |
| Grade 1: Temperature ≥38°C<br><br>Grade 2: Temperature ≥38°C; Hypotension not requiring vasopressor; Hypoxia requiring low-flow nasal cannula or oxygen blow-by<br><br>Grade 3: Temperature ≥38°C; Hypotension requiring one vasopressor with or without vasopressin; Hypoxia requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask<br><br>Grade 4: Temperature ≥38°C; Hypotension requiring multiple vasopressors (excluding vasopressin); Hypoxia requiring positive pressure ventilatory support (CPAP, BiPAP, intubation, and mechanical ventilation) |

This is important to remember as the use of vasopressors or respiratory support is based on the clinical judgement of the physician, which may vary and lead to individual bias in CRS grading. The presence of other organ function abnormalities is included in some but not all grading systems. These abnormalities of other organs could be reported either as separate AEs with no relationship to CRS or as preferred terms encompassing CRS. Thus, it is important to clarify whether CRS definition would consider these abnormalities to capture the full extent of CRS and minimize the possibilities of under-documenting and/or reporting. Additionally, if a therapeutic modality has the potential to cause clinically severe CRS that requires treatment with fluids, vasopressors, supplemental oxygen, and anti-cytokine therapy, we should assume that low-grade events related to these manifestations that may occur initially are part of that spectrum and define them as CRS. While there are a variety of published manuscripts, descriptions, and adapted grading criteria and management strategies for CRS[20], it is noted that published definitions and grading criteria do not readily articulate the distinctions among CRS and other clinical entities that may have overlapping symptoms and temporality (e.g., IRR, macrophage activation syndrome/hemophagocytic lymphohistiocytosis [MAS/HLH]).

**Given the current variations in defining and reporting CRS, the working group feels an urgent need to harmonize grading, collecting, and reporting CRS. Below are our recommended proposals.**

### 1. Alignment on Defining and Grading CRS

The ASTCT defines CRS as "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."[20] ASTCT's definition for CRS represents an opportunity for alignment, prioritization of grading of clinically relevant events, and can be inclusive of currently available and emerging immunotherapies with some considerations noted below.

While each CRS grading scale in Table 1 has advantages and limitations, the working group recommends the utilization of a harmonized definition and grading scale as well as collection of common data elements within and across development programs. An informal sponsor survey indicated that out of eight sponsors, seven are utilizing/planning to utilize ASTCT criteria for new protocols. Several sponsors indicated that some programs have been underway prior to the release of the ASTCT 2019 grading criteria, and CTCAE and Lee Criteria 2014 were predominantly being used to grade CRS. (see Appendix for Survey Summary). This is likely driven by efforts to simplify the characterization and categorization of the severity of CRS in the ASTCT criteria. Some limitations exist, such as the overlapping nature of oxygen requirements between Grade 1 and Grade 2 hypoxia due to the reliance on the oxygen delivery method and exclusion of end organ toxicities (e.g., renal or hepatic injury) from the grading that results from CRS. Additionally, the use of proactive premedication (e.g., corticosteroids) may limit or minimize the presence of some symptoms, such as fever, which is used as a defining characteristic of CRS in the ASTCT 2019 definition.

Since these guidelines have been developed based mainly on the clinical experience with CAR T-cell therapy, they may prove, with additional clinical experience, to be incomplete for all cancer immunotherapies and may need to be revised as new data become available from existing and novel therapies.[20] As such, it is important that data collection is aimed at more than meeting the requirements of any one grading system. Therefore, establishing core principles for defining CRS that consider the therapeutic modality, symptom manifestation, timing, and response to intervention will be important to enable flexibility and maximize utility of a harmonized definition for CRS to adequately assess safety profiles of therapeutics being offered to patients (Table 2).

## Table 2: Principle Components for Defining Cytokine Release Syndrome

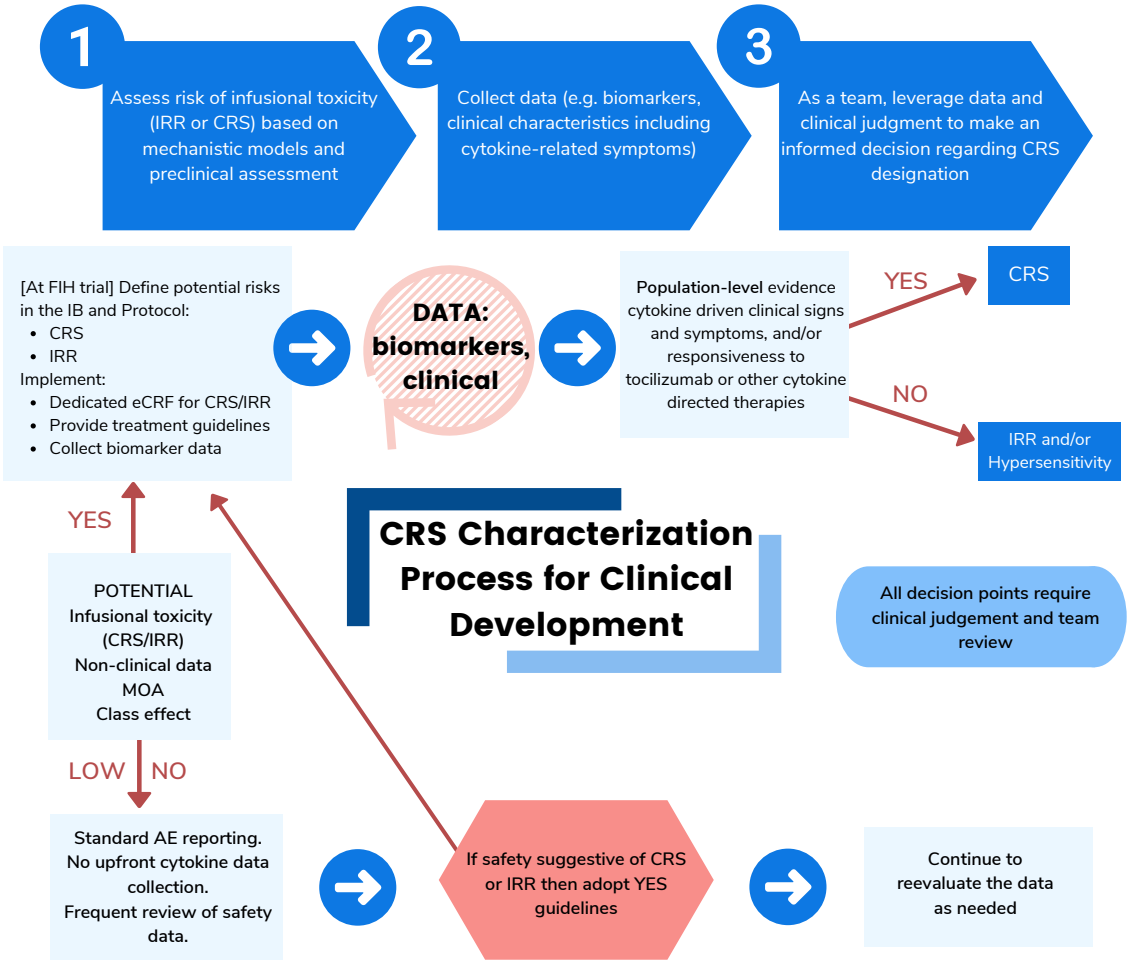
| Principles | Considerations |
|---|---|
| Therapeutic Modality | The spectrum of CRS and symptoms may change as different antigen targets and the methods to engage the immune system evolve; therefore, the definition of CRS may evolve |
| Therapeutic Schedule | The onset of CRS and severity can differ based on treatment administration (i.e., one-time infusion vs. multiple infusions). Kinetics of CRS may differ by both disease state and therapeutic platform (e.g., cellular products vs T-cell engagers). |
| Temporal Association | The timing of development of CRS depends on patient-, disease-, and treatment-related factors. In the setting of CAR T-cells, in vivo expansion of CAR T-cells is associated with the onset and maximum severity. A reasonable temporal relationship to the therapy must be present. |
| Symptom Manifestation | A suspected diagnosis of CRS should be made based on clinical signs and symptoms. Hallmarks of CRS are fever with or without hypotension and hypoxia; however, symptoms of CRS are not unique and overlap with other toxicities. Careful evaluation is required to ensure that the symptoms are associated with the cancer therapy, and other information such as blood cultures, fever workup, etc. should be collected and may help justify an alternate diagnosis. |
| Laboratory Evaluation | Baseline assessment of inflammatory markers can assist in comparing with post therapy increase. Laboratory evaluation including C-reactive protein and ferritin are routinely available. Other cytokine level assessments (IL-6, IL-1, IL-8, TNFα, and IFNγ), if available, can be helpful in further characterizing this syndrome. |
| Interventional Care | CRS infers the toxicity may be effectively treated with anti–IL-6 therapy or other cytokine-directed therapies given in conjunction with corticosteroids depending on the type of immunotherapy. |

## 2. Strategy for Assessing CRS Over the Course of a Clinical Development Program

The characterization of CRS for a given experimental therapeutic in the course of a clinical development program is crucial to ensure the correct diagnosis and deployment of appropriate toxicity management. This is particularly important since some of the therapies used to manage conditions other than CRS can mitigate the effectiveness of immunotherapy. During the development of protocols for safety data collection and monitoring strategies as it relates to CRS, consideration should be given for how toxicities will be identified and managed in routine clinical care. Recognizing the association between the immunotherapeutic agent and CRS will inform the framework on how best to collect these data.

The collection of a broad dataset for characterizing CRS is resource intensive for both sponsors and investigators; however, assessing the risk of an IRR or CRS during preclinical and early clinical development of a new therapy will help assess the robustness of data collection required during clinical development to characterize the potential risk of CRS (**Figure 1**). The robustness of data collection can be assessed using a decision tree approach, which includes (1) an initial assessment of the risk of IRR or CRS based on mechanistic models and preclinical assessment; (2) biomarker and clinical data collection; and (3) iterative review of aggregate data to make an informed decision regarding CRS designation.

### Figure 1. Decision Tree for Assessing a Population-level CRS Risk during Product Development of an Experimental Agent




FIH: first in human, CRF: case report form

If there is a low risk or no risk of IRR or CRS based on mechanistic models, known class effects, and non-clinical data, "LOW/NO" guidelines would be followed (**Figure 1**). In this instance, standard AE reporting and no upfront cytokine and other biomarker data collection would be recommended initially. With ongoing frequent safety data review and consideration for inclusion of cytokine and biomarker data collection, the data collection plan should be adapted if the clinical data are suggestive of potential IRR or CRS toxicity.

For therapeutic classes that are known to be associated with CRS or at particularly high risk for inducing CRS based on mechanism of action or preclinical data, the implementation of a dedicated clinical and safety monitoring plan may be required from the onset. The potential risks of IRR and CRS should be defined in the Investigator Brochure and protocol for the first-in-human trial, with a dedicated case report form (CRF) for IRR/CRS that collects the associated signs and symptoms. In addition, special preparation may be warranted as part of the protocol such as specific site training on CRS and the requirement of certain clinical interventions (e.g., inpatient monitoring, ICU availability, and readily available tocilizumab). In most circumstances, the provision for the physicians to report either IRR or CRS as the preferred term is recommended until human data at the population level are available. If there is evidence at the population level of cytokine-driven clinical signs and symptoms, and/or responsiveness to tocilizumab or other cytokine-directed therapies, it would be concluded that CRS is an identified risk and can be characterized accordingly. Lack of such evidence may suggest that the reaction is a manifestation of IRR or hypersensitivity.

As more data are collected in a harmonized fashion, the field can better decide at which point and with which factors an event is determined to be a high-grade IRR versus a low-grade CRS. Understanding if there are implications on patient management will be important.

### 3. Harmonized Data Elements for Characterizing CRS

Given the likely evolution of defining and grading CRS in the field, the medical community should ensure that the appropriate data elements are collected to allow derivation with different grading systems. Collection of common data variables using aligned protocols will be important to enable comparison with different therapies in the future. A suspected diagnosis of CRS will most likely be based on clinical signs and symptoms. However, the collection of certain data variables, such as laboratory assessments, cytokine profiles, and biomarkers will be important for future retrospective analyses to assess the relationship of certain signs and symptoms with CRS, the severity of CRS, natural history of the event including response to therapy, or the identification of predictive biomarkers. CRS should be considered as an adverse event of special interest (AESI) whenever there is an association of the IO product and CRS.

CRS is most often characterized by fever, hypotension, hypoxia, and increased release of inflammatory cytokines.[22] The use of proactive premedication (e.g., corticosteroids) may limit or minimize the presence of some symptoms, such as fever, associated with CRS. In addition, the signs and symptoms associated with CRS may represent other adverse events from non-CRS etiologies (i.e., IRR, infection). Early in the clinical development of a novel therapy it is important to collect individual signs and symptoms associated with each case of CRS, since the definition of CRS has evolved and is likely to continue to evolve as more experience is gained with immu-

notherapies. A confirmatory diagnosis could be made at a later date and in the context of the evolution of clinical symptoms and cytokine data or response to cytokine-directed interventions (see section "Harmonized Approach for Recording and Reporting CRS Events").

**Table 3** outlines key data elements driven largely in part by ASTCT 2019. Review of key data variables from published severity scales should inform the components of a dedicated CRF for CRS. These represent minimal data collection elements for sponsors. Comprehensive data capture will be critical to facilitate new iterations of grading criteria and past criteria to ensure the safe monitoring and administration of T-cell engaging immunotherapies.

## Table 3: Harmonized Collection of Discrete Data Elements

| Parameter | Data Collection |
|---|---|
| Signs/Symptoms | Minimum signs and symptoms to collect include fever, nausea, chills, vomiting, diarrhea, confusion, dizziness, dyspnea, tachycardia, headache, hypotension, hypoxia, but the eCRF should allow an investigator to enter any symptom thought to be a CRS symptom.<br><br>Date/time onset (e.g., x hour[s] post infusion of dose); initial grade; maximum grade; date/time resolution; outcome; intervention |
| Hypotension management | No intervention required, blood pressure values, intravenous fluids, use of vasopressors and dose, start/stop date of treatment, and duration of treatment |
| Hypoxia management | No oxygen supplementation required, regular flow nasal cannula, high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask; Positive pressure ventilatory support (CPAP, BiPAP, intubation, and mechanical ventilation). |
| Organ toxicity | Liver function tests, creatinine, amylase, lipase, rash, neurotoxicity cardiac, pulmonary, renal, hepatic toxicities |
| Cytokines | IL-6, IL-1, IL-8, TNFα, and IFNγ are recommended as a core cytokine panel, if available and considered in a research setting |
| Other laboratory assessments | Routine hematology analysis, including complete blood count and differential, serum chemistries, coagulation factors, ferritin, and C-reactive protein (CRP) |
| Care setting | Admitted to hospital or ICU; Duration, including distinguishing ICU from non-ICU duration |
| Intervention for management | Tocilizumab or other cytokine-directed therapy administered for management, as well as corticosteroids other supportive care, such as antipyretics, and type of prophylaxis, if any. If applicable, permanent discontinuation of therapy or ability to rechallenge and administer therapy, if applicable. |

Vital sign assessment should include body temperature, pulse (heart rate), blood pressure, and oxygen saturation. It is important to note the ASTCT grading depends on the use of supplemental oxygen or positive pressure ventilation and the use of vasopressors. Because the criteria to use these interventions are not standardized, it could introduce some bias into the grading of CRS. Once CRS is further characterized, biomarker testing can be reduced to key time points and biomarkers. Capturing these core data elements may be important for drug label descriptions and management guideline development.

Additional laboratory tests should be considered among patients who experience a more severe manifestation of CRS without initial response to interventional therapy. This can include fibrinogen and complete blood counts, if not already included in the routine hematologic laboratory assessments, triglycerides, and a bone marrow biopsy. The latter being necessary to confirm the diagnosis of MAS/HLH, which likely has a worse prognosis.

In the setting of CAR T-cell therapy, one important determinant associated with CRS and its severity is the in vivo expansion of these cells after infusion. Patients with CRS symptoms with increasing acute phase reactants and expansion of cells might require a different therapeutic approach compared to patients with the same severity of CRS in whom laboratory values are normalizing. While to date treatment guidelines are based on symptoms, it is important to capture the lab value information, including cytokine biomarkers, as lab values and cytokines help improve our understanding of the pathophysiology and may inform future development of management guidelines. Though currently there are no commercially available assays to determine expansion and persistence of CAR T-cells, and real-time cytokine analysis is also not typically available, correlative analyses in the context of clinical trials may allow retrospective analyses to interrogate CRS cases and direct future guidelines for toxicity management.

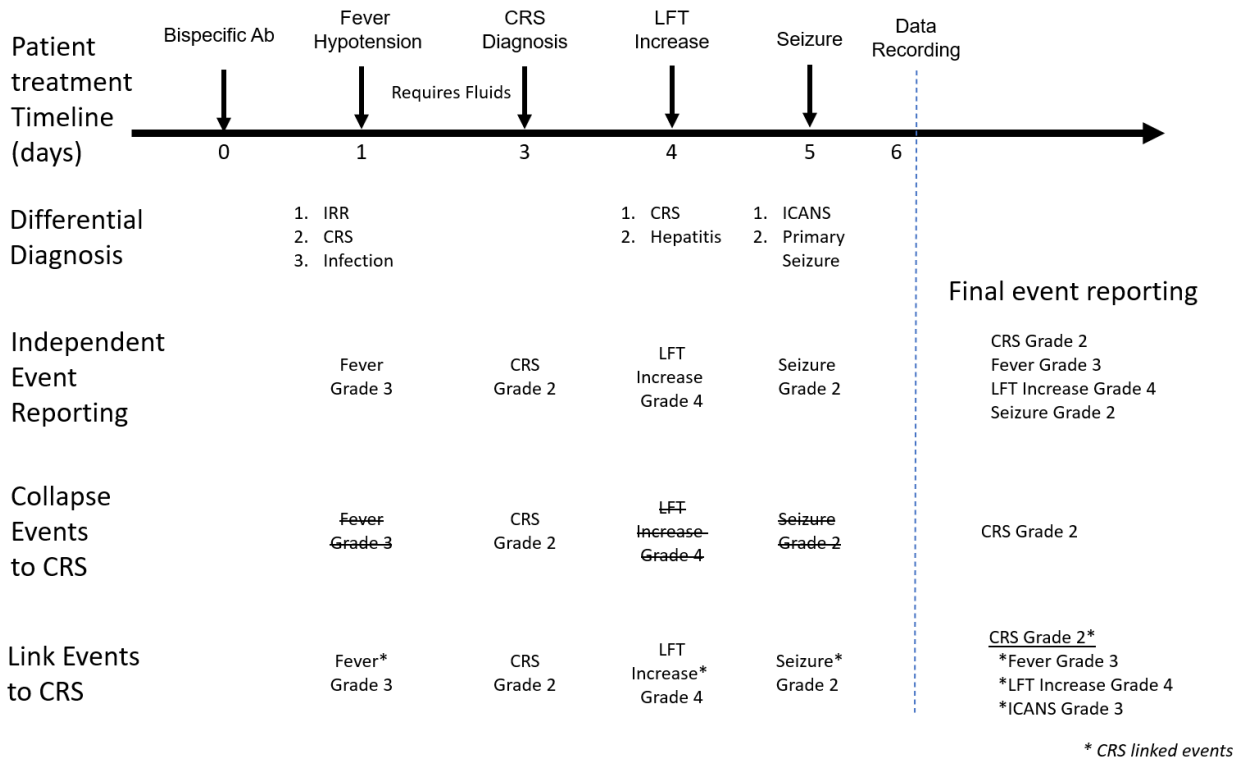
With CAR T-cell therapy, routine CRS assessment may range from daily CRS assessments immediately following infusion to two to three times a week for the first 30 days after infusion can help characterize the evolution of symptoms, development of additional toxicities, treatment, and response to treatment. The timing and frequency of CRS assessments for T-cell engagers may vary and be dependent on the pharmacokinetics and pharmacodynamics of the particular molecule and dosing schedule. Timing of sampling should be adapted to accommodate treatment cycles and protocol-defined scheduled visits.

### 4. Consistent Method for Recording and Reporting CRS Events

Identification and characterization of CRS can be challenging due the heterogeneity in presentation of signs and symptoms and similarity of these signs and symptoms of CRS to other adverse events, such as IRR or infection. A hypothetical case is shown in **Figure 2**, "Patient Timeline." A patient treated with a T-cell engager experiences several adverse events. Initially, the patient presents with a fever of 40.1 degrees Celsius lasting 6 hours and is accompanied by hypotension that is responsive to a one-liter fluid bolus. The fever and hypotension are CTCAE Grade 3. The next morning liver function test (LFT) increases are noted (Grade 4), and later that day, the patient has a brief generalized seizure that is self-limited, lasting less than a minute (Grade 2). CRS Grade 2 is diagnosed.[20] While all of these may precede the investigator diagnosing CRS, all these adverse events should be captured into the CRF and independently reported.

In our example case, the event of "fever" precedes the diagnosis of CRS and would be captured into the AE database independently and graded independently as the differential diagnosis for the fever could include not only CRS but other potential etiologies such as IRR and infection. Additional events such as the increase in LFTs and seizure are attributable to the CRS but could also be recorded as independent AEs into the database. Once CRS is diagnosed and recorded as an adverse event in the trial database, the symptoms of CRS should be linked together.

## Figure 2. Patient Treatment Timeline and Event Reporting Following Immunotherapy Administration




We propose a comprehensive method to capture all the events and link those AEs that are signs and symptoms of CRS to the CRS event. Such that CRS is the AE, but the symptoms (fever, LFT increase, seizure) that are AEs in themselves are attributable to CRS and are linked to the CRS event (**Figure 2** "Link Events to CRS"). For instance, one way is to flag each adverse event that is related to CRS and link it to the specific CRS event. This will allow a more qualitative analysis of CRS, as CRS can manifest in a variety of organ toxicities including hepatic, renal, and neuro-toxicity. This method would also allow the optionality of reporting all AEs, CRS, and the specific

organ toxicity, separately or allow collapsing of the CRS related events to a single adverse event. Given the importance of the central nervous system (CNS) related toxicity with T-cell therapies it is recommended that ICANS (immune effector cell-associated neurotoxicity syndrome) events be captured and scored separately. In the case described any seizure would be captured as a Grade 3 or greater ICANS.

However, without data collection standards several outcomes in terms of data capture may arise. For instance, one possible method is that all the signs and symptoms that are attributable to CRS could be collapsed into the AE preferred term of CRS. Once the investigator identifies CRS, as part of data cleaning, the fever, LFT increase and even seizure events could be accounted for by CRS and only the CRS event is reported (Figure 2 "Collapse Events to CRS"). However, this method would lead to the loss of actionable information for physicians and patients.

As recommended in **Table 3**, additional information should be captured including use of concomitant medications (i.e., tocilizumab or other cytokine-directed therapy, oxygen, vasopressors, corticosteroids) and specific interventions (i.e., method of oxygen delivery, mechanical intervention, IV fluids). Here in our example case, the use of IV fluids and not vasopressors defines a Grade 2 CRS event. Although these items may be collected in other parts of the electronic data capture record, it is important these events are easily linked to a specific CRS event as CRS grading is dependent on these interventions in most classification systems. In addition, some grading systems can lead to downgrading of events. As an example, liver function laboratory values may increase transiently and meet the criteria for CTCAE Grade 4 CRS based upon these laboratory changes; however, this increase will only meet the definition of a Grade 2 CRS by ASTCT criteria if it is not accompanied by clinically significant changes in blood pressure or oxygen requirement.

## Conclusions

Cytokine release syndrome is commonly seen with newer immunotherapies like T-cell engagers and CAR T-cells. All investigators should commit to a harmonized data collection approach using a dedicated CRS eCRF with data elements identified in Table 3 as a guide to ensure consistency in how data is collected and presented. This working group outlined several actionable proposals that can help incentivize more aligned strategies for deployment in early clinical development programs of emerging immunotherapies:

- Alignment on Defining CRS
- Strategy for Assessing CRS Over the Course of a Clinical Development Program
- Harmonized Data Elements for Characterizing CRS
- Consistent Method for Recording and Reporting CRS Events

As our clinical understanding of CRS and other clinical entities associated with the administration of these types of therapies evolves, a harmonized approach for defining, characterizing, and reporting CRS in patients receiving immunotherapies is necessary to support evidence-based monitoring and management of novel toxicities; facilitate the communication of risk-benefit profiles with regulatory agencies, the clinical community, and public; and improve patient care

and outcomes. Such an approach can further support retrospective analyses to facilitate new iterations of grading criteria and clinical guidelines to ensure the safe monitoring and administration of T-cell engaging immunotherapies.

## Appendix

An informal survey tool was conducted to provide a landscape assessment of the current approaches and efforts being used to harmonize definitions for CRS and align data collection strategies that can be analyzed retrospectively as definitions change and will maintain its relevance as the field evolves. This survey was circulated amongst participating drug sponsors and organizations and generated three key findings that guided this work:

First, survey responses indicated that, generally, there are not harmonized definitions for IRR and CRS in IO clinical trials. Often, a distinction between IRR and CRS is based on the temporality of the events, but this may be due to the absence of a better parameter. The lack of a standardized definition can be partially explained by the difficulty associated with applying a singular definition to a broad field of diverse agents such as monoclonal antibodies, T-cell engagers, and cell-based therapies. In addition to considering the impact of this context on CRS and IRR definitions, the development of core principles central to any definition of CRS (as opposed to a singular, rigid definition) should be considered. This approach would allow sufficient flexibility across contexts and as new data emerges.

Next, survey responses indicated that while the ASTCT 2019 CRS severity grading scale is most frequently used, other scales such as CTCAE and the Lee 2014 scales are also used for severity grading. With the evolution of severity grading scales in mind, it will be necessary to collect a core set of raw data elements for CRS events. This would enable retrospective analyses and comparison between therapies developed at different points in time and for which different severity scales were likely used. The collection of a core set of data elements may necessitate a CRS-specific case report form, which, as survey results indicated, is a practice already being implemented by most sponsors for the collection of elements such as grade, associated signs/symptoms, onset, and resolution.

Lastly, survey responses indicated that the uniform collection of data elements will be critical to enabling the mapping of CRS to different severity scales, comparison between drugs, and the future pooling of information. Common data elements such as the timing of events, lab findings, signs/symptoms, severity of events, and management of signs/symptoms should be collected. In thinking through proposed core data elements, it will be important to extend thinking past the current standard of care (SOC) and into the future of SOC for patients.

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