

Data Collection, Structuring, Analysis, and Reporting Considerations for CRS, ICANS, and IEC-HS in CAR-T Clinical Trials

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ABSTRACT

Cytokine Release Syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS) are key toxicities in CAR-T clinical trials and are critical to objective evaluation of product safety and risk-benefit. However, because CAR-T therapies are relatively novel and development experience remains limited, approaches to data collection, data structuring, analysis, and reporting for these events are not yet well standardized. This variability compromises the reliable assessment of these toxicities and limits the interpretability and comparability of safety findings across studies.

Drawing on practical project experience and broad literature review, this paper focuses on three key aspects of handling CRS, ICANS, and IEC-HS data: data collection, data mapping, and data analysis and reporting. Relevant information is often distributed across multiple sources, such as adverse event records, dedicated assessment forms, laboratory data, vital signs, neurologic assessments, concomitant medications, and intervention records. A clear and traceable framework is therefore needed to organize clinically related information and support consistent downstream analysis.

This paper proposes an end-to-end practical paradigm from data collection to data structure to analysis and reporting for CRS, ICANS, and IEC-HS in CAR-T studies. Key considerations include derivation and presentation of incidence, time to onset, maximum grade, duration, time to resolution, management, and outcome. This framework aims to improve standardization, traceability, and interpretability, thereby supporting more objective safety evaluation of CAR-T products.

INTRODUCTION

1. THE LANDSCAPE OF CAR-T CELL THERAPY

Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionized the treatment paradigm for hematologic malignancies. Since the historic first FDA approvals in 2017 for CD19-directed CAR-T therapies targeting relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) and large B-cell lymphoma (LBCL), the field has expanded rapidly. Today, the therapeutic landscape spans multiple targets—including B-cell maturation antigen (BCMA) and has extended into earlier lines of treatment for multiple myeloma and mantle cell lymphoma, with ongoing exploration into solid tumors and autoimmune diseases. However, the unique mechanism of action of CAR-T products—involving robust *in vivo* T-cell proliferation and immune activation—unleashes a distinct profile of toxicities that differs fundamentally from traditional chemotherapy or small-molecule targeted therapies.

2. UNIQUE TOXICITIES AND CRITICAL CLINICAL QUESTIONS

The most prominent and life-threatening class effects associated with CAR-T therapies are Cytokine Release Syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and the increasingly recognized Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS) (Lee et al. 2019, Hines et al., 2023). Mechanistically, CRS is driven by a systemic inflammatory response triggered by massive cytokine release (such as IL-6, IFN- γ , and TNF- α) from activated T cells and bystander myeloid cells. ICANS involves blood-brain barrier disruption and central nervous system inflammation, while IEC-HS represents a severe, hyperinflammatory hyperferritinemic state characterized by cytopenias and hemophagocytosis.

In clinical trials and product labeling, evaluating these toxicities requires answering six fundamental clinical questions to accurately characterize the safety profile and risk-benefit ratio of a CAR-T product:

Incidence: What proportion of patients will develop these toxicity events?

Severity: How severe are these toxicity events ?

Time to Onset: How soon do these toxicity events typically manifest?

Duration: How long do these toxicity events persist?

Management: What kind of interventions are needed?

Symptoms: What signs and symptoms do these toxicity events present with, and at what frequency?

3. THE DATA CHALLENGE AND PAPER OBJECTIVE

While these six clinical questions are explicitly reflected in product labels and often inform regulatory evaluation, translating them into analyzable data and robust statistical endpoints is not straightforward for data management, programming, and biostatistics teams. Because CAR-T therapies are still relatively new, industry-wide standards for collecting, structuring, deriving, and reporting CRS, ICANS, and IEC-HS data remain limited. As a result, each clinical question leads to a set of operational decisions that must be resolved before data can be handled consistently. These include how an event should be defined, which record should anchor onset and resolution, how severity should be represented, and how interventions and recurrences should be linked to an episode. The relationship between these clinical questions and the corresponding operational issues is summarized in Table 1.

Table 1. From clinical questions to open operational questions

Clinical question	Open operational question
Incidence	At what level is incidence counted — the syndrome-level event, or its individual signs and symptoms?
Severity	How is severity defined? Should signs/symptoms also be graded?
Time to onset	From which anchor (infusion date vs. randomization date)?
Duration	Driven by the syndromes or by its signs & symptoms — and how are recurrence, and ongoing events handled?
Management	What specific interventions to be captured?
Symptoms	How are signs and symptoms handled pre-specified checklist vs. collected as free-text + MedDRA, and reported as stand-alone AEs or only as components of the syndrome?
Other	Any special considerations regarding CRS/ICANS/IEC-HS?

This challenge is compounded by the fact that relevant information is scattered across multiple sources, including adverse event records, dedicated assessment forms, laboratory data, vital signs, neurologic assessments, concomitant medications, and intervention records. These data cannot be interpreted in isolation; their clinical meaning often depends on cross-domain integration and temporal context. For example, ferritin elevation may support identification of IEC-HS, but its relevance depends on accompanying findings such as cytopenias, coagulopathy, liver function abnormalities, persistent fever, and timing relative to CAR-T infusion. Likewise, fever, hypotension, and hypoxia may be recorded separately, but their co-occurrence and evolution define CRS. For ICANS, neurologic symptoms, structured neurologic assessments, and relevant treatments must be interpreted together to characterize the syndrome. Without a framework that links these interdependent observations, key endpoints such as incidence, maximum grade, time to onset, duration, time to resolution, and management may be derived inconsistently, reducing traceability and cross-study comparability.

Driven by these practical challenges, this paper proposes an end-to-end paradigm for the collection, structuring, analysis, and reporting of CRS, ICANS, and IEC-HS data in CAR-T clinical trials. Based on project experience, literature review, regulatory expectations, and CDISC implementation principles, the framework aims to bridge clinically relevant safety questions with the underlying data needed to answer them. By organizing fragmented but related information within a clear and traceable structure, this approach seeks to improve standardization, data traceability, and the overall interpretability of safety findings, thereby supporting a more objective evaluation of CAR-T product safety and risk-benefit.

DATA COLLECTION

OVERVIEW

Given that relevant information on CRS, ICANS, and IEC-HS is dispersed across multiple sources, a primary challenge in data collection is ensuring that the necessary information is appropriately captured in Case Report Forms (CRFs) to support consistent downstream analyses and address the clinical questions of interest. Based on practical project experience and a review of the literature, the following CRFs are proposed for this purpose.

CRS, ICANS, and IEC-HS events are captured in the “Adverse Events (AE)” form. Event severity, including the overall event grade according to ASTCT criteria and the CTCAE grade for individual signs and symptoms, as well as event onset and resolution times, are recorded in the “CRS ASTCT Criteria (CRASTCT)” and “CRS Signs and Symptoms (CRSSS)” forms for CRS; the “ICANS ASTCT Criteria (ICASTCT)” and “ICANS Signs and Symptoms (ICANSSS)” forms for ICANS; and the “HLH/MAS IEC-HS Grading (IEC_HS)” form for IEC-HS. Treatment and management of CRS, ICANS, and IEC-HS are captured in the “Prior and Concomitant Medications (CM)” and “Prior and Concomitant Procedures (PR)” forms. Other supplementary CRFs, such as the “Laboratory Test Result (LB)”, “Vital Signs (VS)”, and “ICE Tool Assessment (NEUAS)” forms, may also be collected to support comprehensive safety monitoring and analysis for CRS, ICANS, and IEC-HS.

INDIVIDUAL CRF

The data elements collected in each CRF and the rationale for their inclusion are presented below.

Note: The annotations in the CRFs shown below are based on the raw data.

Adverse Events (AE)

The AE form captures all adverse events occurring during the protocol-defined reporting period, including adverse events of special interest (AESIs). CRS, ICANS, and IEC-HS are key AESIs in CAR-T trials. Reporting a CRS, ICANS, or IEC-HS event in the AE form requires selection of the corresponding “AESI Category”, which in turn triggers completion of the relevant additional CRFs as summarized in table below.

Because grading for CRS, ICANS, and IEC-HS is based on ASTCT consensus criteria, the grading information for these events is not collected in the AE form, where CTCAE grade is normally captured. Instead, it is collected in the corresponding syndrome-specific CRFs when triggered.

The start and end dates and times of CRS/ICANS/IEC-HS are recorded in the AE form to support analyses of time to onset and event duration. Specifically, to avoid data inconsistency, these recorded dates and times must align with the initiation and resolution of their respective ASTCT grades in the corresponding CRFs triggered, rather than being subjectively determined.

CRS, ICANS, and IEC-HS are recorded in the AE form as syndrome-level adverse events, whereas

related signs and symptoms are captured in syndrome-specific CRFs as triggered to support diagnosis, grading, and clinical characterization. In general, such signs and symptoms are not reported separately as individual AEs in order to avoid duplicate data capture and potential double counting in downstream analyses. However, separate AE reporting may be appropriate when a sign or symptom is considered an independent clinical event.

Other variables, including seriousness, outcome, and causality, are also collected in the AE form but are not shown in the figure below.

AE No.	AENO	
Adverse event	AETERM	
Start date	AESTDAT	
Start time	AESTTIM	
End date	AEENDAT	
End Time	AEENTIM	
Is this event an AESI?	AECATOCC	No ☐ Yes ☐
AESI Category	AECAT	Cytokine Release Syndrome ☐ Neurological disorders, ICANS ☐ Neurological disorders, others ☐ Immune effector cell associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) ☐

AESI category	Trigger form
Cytokine Release Syndrome	- CRS (Cytokine Release Syndrome) ASTCT Criteria (CRASTCT) - CRS Signs and Symptoms (CRSSS)
Neurological disorders, ICANS	- ICANS ASTCT Criteria (ICASTCT) - ICANS (Immune Effector Cell Associated Cytotoxicity) Signs and Symptoms (ICANSSS)
Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)	IEC_HS (HLH/MAS IEC-HS Grading)

CRS ASTCT Criteria (CRASTCT)

The variables “AE No.” and “Adverse Event” are derived from the AE form. CRS grade according to ASTCT criteria, the grading criteria used, and the corresponding date and time are collected. Depending on the requirements for patient safety monitoring and the planned analyses, either the maximum ASTCT grade or each change in grade may be collected.

AE No.	AENO	
Adverse Event	AETERM	
Body temperature		☐ <38.0C (100.4F) ☐ ≥38.0C (100.4F)
Hypotension		☐ None ☐ Not requiring vasopressor ☐ Requiring vasopressor with or without vasopressin ☐ Requiring multiple vasopressors (excluding vasopressin)
Hypoxia		☐ None ☐ Requiring low flow nasal cannula or blow-by ☐ Requiring high flow nasal cannula, facemask, non-rebreather mask or venturi mask ☐ Requiring positive pressure (e.g. CPAP, BiPAP) ☐ Requiring intubation & mechanical ventilation
ASTCT CRS grade	CRSASTCT	☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5
Start date	ASTSTDAT	
Start time	ASTSTTIM	
End date	ASTENDAT	
End time	ASTENTIM	

CRS Signs and Symptoms (CRSSS)

The variables “AE No.” and “Adverse Event” are derived from the AE form. For CRS, related signs and symptoms, along with their corresponding MedDRA coding, CTCAE grade, and date and time of signs and symptoms, are collected. Depending on the patient's safety monitoring needs and analysis objectives, either the maximum CTCAE grade or each change in grade for each sign or symptom may be recorded.

Signs and symptoms related to CRS are captured as free-text entries to allow comprehensive documentation of clinically relevant manifestations, including atypical or unanticipated presentations that may not be fully represented by prespecified categories. These verbatim descriptions are subsequently coded using MedDRA to improve terminology standardization and facilitate data retrieval, aggregation, and cross-study comparison. Individual signs and symptoms are also graded using CTCAE to provide a standardized assessment of symptom severity, whereas overall CRS event grading is based on ASTCT consensus criteria. Together, this approach supports flexible capture of clinical presentation while enabling standardized terminology, structured severity assessment, and robust downstream analyses.

AE No.	AENO			
Adverse Event	AETERM			
Sign/symptom reported term	CRSTERM			
CTCAE grade	CRSTOXGR	Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5 ☐		
Sign/symptom start date	CRSSTDAT			
Sign/symptom start time	CRSSTIM			
Sign/symptom end date	CRSENDAT			
Sign/symptom end time	CRSENTIM			
Sign/symptom ongoing	CRSONGO	No ☐ Yes ☐		

ICANS ASTCT Criteria (ICASTCT)

The data collection approach for ICANS is broadly similar to that for CRS. The variables “AE No.” and “Adverse Event” are derived from the AE form, and ICANS grade according to ASTCT criteria, the grading criteria used, and the corresponding date and time are collected. Depending on the requirements for patient safety monitoring and the planned analyses, either the maximum ASTCT grade or each change in grade may be collected.

AE No.	AENO	
Adverse Event	AETERM	
ICE score		☐ 10 ☐ 7-9 ☐ 3-6 ☐ 0-2 ☐ 0 (Patient is Unarousable and Unable to Perform ICE) ☐ Not Applicable
Depressed level of consciousness		☐ Awakens spontaneously ☐ Awakens to voice ☐ Awakens only to tactile stimulus ☐ Unarousable or requires vigorous or repetitive tactile stimuli to arouse, stupor or coma
Seizure		☐ Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve w/ intervention ☐ Life threatening prolonged seizure (>5min), or repetitive clinical electrical seizures w/o return to baseline in between ☐ Not applicable
Motor findings		☐ Deep focal motor weakness ☐ Not applicable
Elevated ICP/cerebral edema		☐ Focal/local edema on neuroimaging ☐ Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad ☐ Not applicable
ASTCT ICANS grade	ICNASTCT	☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5
Start date	IASSTDAT	
Strat time		IASSTTIM
End date	IASENDAT	
End time		IASENTIM

ICANS Signs and Symptoms (ICANSSS)

The data collection approach for ICANS is broadly similar to that described for CRS, including variables "AE No." and "Adverse Event" are derived from the AE form, free-text capture of relevant signs and symptoms, MedDRA coding of verbatim descriptions, CTCAE grading and date and time of individual manifestations. Depending on the patient's safety monitoring and planned analysis, either the maximum CTCAE grade or each change in grade for each sign or symptom may be recorded.

AE No.	AENO		
Adverse Event	AETERM		
Sign/symptom reported term	ICNTERM		
CTCAE grade	ICNTOXGR	Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5 ☐	
Sign/symptom start date	ICNSTDAT		
Sign/symptom start time		ICNSTTIM	
Sign/symptom end date	ICNENDAT		
Sign/symptom end time		ICNENTIM	
Sign/symptom ongoing	ICNONGO	No ☐ Yes ☐	

HLH/MAS IEC-HS Grading (IEC_HS)

Similar to CRS and ICANS, the variables “AE Number” and “Adverse Event Reported Term” for IEC-HS are derived from the AE form, and IEC-HS grade according to ASTCT criteria, symptom and corresponding CTCAE grade are collected. Depending on the patient's safety monitoring and planned analysis, either the maximum ASTCT grade for the overall event and the maximum CTCAE grades for individual manifestations, or each change in grade, and corresponding date (and time) may be recorded.

One point worth emphasizing is that different from the CRSSS and ICANSSS forms, where signs and symptoms are collected as free-text with MedDRA coding, IEC-HS symptoms are collected using pre-specified categories (per Hines 2023 Table 1 IEC-HS: Definition and Identification), based on the considerations below:

Whereas CRS and ICANS are characterized by clinically recognizable but heterogeneous and sometimes unanticipated manifestations that warrant open-ended free-text capture, IEC-HS is fundamentally different. It is a syndrome newly defined by ASTCT in 2023, specific to the hemophagocytic lymphohistiocytosis (HLH)-like hyperinflammatory toxicity that occurs following CAR-T (immune effector cell, IEC) infusion: "The development of a pathological and biochemical hyperinflammatory syndrome independent from CRS and ICANS that (1) manifests with features of macrophage activation/HLH, (2) is attributable to IEC therapy, and (3) is associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis" (Hines et al., 2023). As a newly recognized syndrome with limited established understanding and because existing HLH diagnostic criteria (e.g., HLH-2004 and the HScore) are suboptimal following CAR-T cell therapy, the manifestations of IEC-HS were delineated by an ASTCT expert panel drawing on the HLH-2004 criteria, analyses of published case series, and unpublished expert experience (Hines et al., 2023). Because this framework yields a finite, predefined set of laboratory and organ-specific parameters rather than an open-ended clinical spectrum, IEC-HS manifestations are more appropriately captured using prespecified structured fields, for which MedDRA coding is generally not applied. This improves alignment with the syndrome definition, enhances consistency of data capture, and facilitates standardized grading and downstream analysis. Individual manifestations are graded using CTCAE, where applicable, to provide a standardized assessment of manifestation-level severity.

AE Number	AENO	
Adverse Event Reported Term	AETERM	
Initial ASTCT Grading	HMTXGR	Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5 ☐
Date Changed#1 ASTCT Grading	HM01DAT	Fixed Unit: yyyy mon dd
Changed#1 to ASTCT Grading	HM01TOX	Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5 ☐

IEC-HS symptom	HMSYMP	Elevated ferritin ($>2 \times$ ULN or baseline [at time of administration]) and/or rapidly rising (per clinical assessment) ☐ Onset with resolving/resolved CRS or worsening inflammatory response after initial improvement with CRS directed therapy ☐ Hepatic transaminase elevation ($>5 \times$ ULN [if baseline was normal] or $>5 \times$ baseline if baseline was abnormal) ☐ Hypofibrinogenemia (<150 mg/dL or $<LLN$) ☐ Hemophagocytosis in bone marrow or other tissue ☐ Cytopenias (new onset, worsening, or refractory) ☐ Lactate dehydrogenase elevations ($>ULN$) ☐ Other coagulation abnormalities (e.g., elevated PT/PTT) ☐ Direct hyperbilirubinemia ☐ New onset splenomegaly ☐ Fever (new or persistent) ☐ Neurotoxicity ☐ Pulmonary manifestations (e.g., hypoxia, pulmonary infiltrates, pulmonary edema) ☐ Renal insufficiency (new onset) ☐ Hypertriglyceridemia (fasting level, >265 mg/dL) ☐ Other ☐
IEC-HS symptom other, specify	HMSYMPOT	
CTCAE Grade	IECHSGR	Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5 ☐
IEC-HS Symptom Start Date	HMSTDAT	Fixed Unit: yyyy mon dd
Ongoing IEC-HS Symptom	HMONGO	No ☐ Yes ☐
IEC-HS Symptom End Date	HMENDAT	

Prior and Concomitant Medications (CM)

The CM form captures prior and concomitant medications used to treat adverse events, including CRS, ICANS, and IEC-HS, such as tocilizumab, anakinra, corticosteroids, and ruxolitinib. The variable “AE number(s) for which medication was taken” enables linkage of medication records to the corresponding CRS, ICANS, and IEC-HS events captured in the AE form and related triggered forms. In addition, “Time” may be collected in the CM form to document the timing of medication administration according to analysis needs.

Medication number	CMSPID	
Medication verbatim name	CMTRT	
Indication		
Therapy reason	CMTREAS	
		Adverse event ☐
		Medical history ☐
		Prophylaxis ☐
		Disease under study ☐
		Other ☐
If Other, specify		
AE number(s) for which medication taken	CMAENO	
Medical history condition(s) number for which medication taken		
Start date	CMSTDAT	
Ongoing	CMONGO	No ☐
		Yes ☐
End date	CMENDAT	

Prior and Concomitant Procedures (PR)

Similar to the CM form, the PR form captures prior and concomitant procedures used in the management of adverse events, including CRS, ICANS, and IEC-HS, such as nasal cannula oxygen and high-flow oxygen therapy. The variable “Adverse event number” enables linkage of procedure records to the corresponding CRS, ICANS, and IEC-HS events captured in the AE form and the associated triggered forms.

PR number	PRSPID	
Procedure Name	PRTRT	
Start date	PRSTDAT	
End date	PRENDAT	
Ongoing	PRONGO	Yes ☐
Indication	PRINDC	
		Adverse event ☐
		Medical history ☐
		Disease Under Study ☐
		Other ☐
Other Procedure Indication, Specify		
Adverse event number	PRAENO	

Supplementary CRFs:

Additional CRFs, such as those listed below, may be collected to support comprehensive safety monitoring and analysis of CRS, ICANS, and IEC-HS.

- The “Laboratory Test Results (LB)” form, including ferritin, hepatic transaminases, coagulation parameters, total and direct bilirubin, and lactate dehydrogenase, may contribute to the assessment of IEC-HS by capturing key laboratory abnormalities relevant to syndrome identification and clinical characterization.
- The “Vital Signs (VS)” form, including temperature and peripheral oxygen saturation, may contribute to the assessment of CRS and IEC-HS by providing objective physiological measures relevant to syndrome recognition and severity evaluation.
- The “ICE Tool Assessment (NEUAS)” form, including the ICE score, may contribute to the assessment of ICANS by providing a structured measure of neurocognitive function that supports event identification and grading.

DATA MAPPING AND TRACEABILITY CONSIDERATIONS

OVERVIEW

CRS, ICANS, and IEC-HS should be mapped as traceable clinical episodes rather than isolated AE terms. One episode may include the diagnosis, repeated ASTCT assessments, signs and symptoms, laboratory or vital-sign evidence, neurologic findings, and event-directed treatments. If these pieces are not connected, downstream analysis can lose the event course needed for onset, maximum grade, duration, resolution, recurrence, and management summaries.

Prior industry materials describe ADCRSNT as a CRS and neurotoxicity analysis dataset requested in FDA oncology review, with metadata discussed through the PHUSE Working Group materials for FDA Oncology Full Consolidated Comments - ADCRSNT. It is intended to support reviewer-oriented analyses of timing, severity, and management. Although those materials focus on CRS and neurotoxicity/ICANS and do not explicitly cover IEC-HS, the same episode-based structure is applicable to IEC-HS because it is another immune effector cell-associated toxicity requiring linked diagnosis, grading evidence, laboratory findings, and event-directed management.

At SDTM level, each episode is anchored in AE and supported by CE, FA, LB, VS, CM, PR, and other study-specific records linked through RELREC. This traceability then flows into the ADaM layer along two paths: CE maps to ADCE for symptom-level analysis and AE maps to ADAE for event-level analysis, while the combined SDTM evidence across all domains integrates into ADCRSNT. ADCRSNT should therefore not be viewed as sourced only from AE; it is an integrated analysis layer built on the full linked episode.

SDTM-to-ADaM Traceability for CRS, ICANS, and IEC-HS

AE anchors the SDTM episode; CE→ADCE and AE→ADAE carry it into ADaM, and the combined SDTM evidence integrates into ADCRSNT.

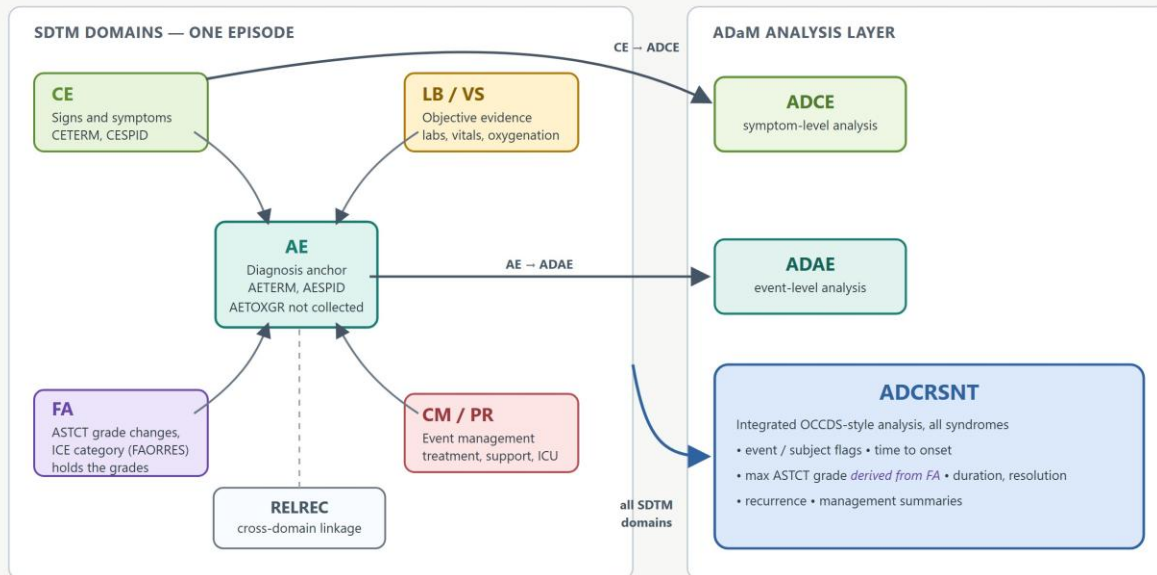


Figure 1. SDTM-to-ADaM traceability for CRS, ICANS, and IEC-HS. AE anchors the SDTM episode with supporting CE, FA, LB, VS, CM, and PR records linked through RELREC; CE maps to ADCE and AE maps to ADAE, and the combined SDTM evidence integrates into ADCRSNT.

SOURCE AND SDTM STRUCTURE

The unit of mapping should be the toxicity episode, identified by subject, toxicity term, start date/time, and a stable sponsor event identifier such as an AE number. That identifier should be carried into related eCRF modules so that RELREC can link the diagnosis, symptoms, assessments, and management records without relying only on text matching.

Source component	SDTM target	Role in mapping
AE page (AE)	AE	CRS, ICANS, or IEC-HS diagnosis; start/end; seriousness; outcome
Signs and symptoms (CRSSS, ICANSSS, IEC_HS)	CE	Symptom-level detail linked to the syndrome-level event
ASTCT or grade-change assessments (ICASTCT, CRAFTCT)	FA	Longitudinal grade-defining criteria, ICE score categories, and grade changes
Laboratory and vital-sign evidence (LB, VS)	LB, VS	Ferritin, cytopenias, coagulation markers, temperature, oxygenation, and other objective evidence
Neurologic assessment and ICE score (NEUAS)	QS or study standard domain	Original ICE score and neurologic trajectory, with derived grade-defining categories traceable to FA
Event-directed management	CM, PR	Tocilizumab, corticosteroids, anakinra, oxygen support, vasopressors, ventilation, transfusions, ICU care

Cross-domain relationship	RELREC	Explicit linkage across records belonging to the same episode
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Key mapping rules.

Mapping area	Recommendation
AE diagnosis anchor	Keep one diagnosis-level AE record per event. Store the diagnosis term in AEDECOD/AETERM namely, 'CRS', 'ICANS', etc. AETOXGR will be left as blank for CRS, ICANS and IEC-HS.
CE symptoms	Map separately collected signs and symptoms to CE and link them to AE using CESPID or the sponsor event identifier. Store symptom terms in CETERM, use CECAT/CECAT to distinguish CRS, ICANS, or IEC-HS symptom modules, and retain symptom CTCAE grade in CETOXGR when collected.
FA grade trajectory	Map ASTCT criteria, ICE score category, and all grade changes to FA with assessment date/time in FADTC, event grouping in FAGRPID, object/test detail in FAOBJ, FATEST, and FATESTCD, and grade or category results in FAORRES/FASTRESC. The original ICE score should remain in QS or a study-standard neurologic assessment domain, with the FA record carrying the grade-defining ICE category or range used for ICANS grading. Criteria versions can be retained in SUPPFA variables such as CRSASTCV or ICNASTCV.
Supporting evidence	Keep laboratory values, vital signs, neurologic findings, oxygen/vasopressor support, and procedures in their appropriate domains rather than forcing them into AE. Link relevant LB, VS, QS, or study-standard records to the episode through the common event identifier, visit/date-time alignment, and RELREC where applicable.
Event-directed treatment	Preserve tocilizumab, corticosteroids, anakinra, oxygen support, ventilation, vasopressors, transfusions, and other management records in CM/PR or study-standard domains. Retain episode identifiers such as CMSPID or study-specific procedure identifiers.
RELREC	Link AE, CE, FA, CM, PR, and other related records using a common RELID. The relationship should be driven by stable identifiers such as AE.AESPID/AENO, CE.CESPID, FA.FAGRPID or FASPID, and CM.CMSPID/CMAENO, not by text matching alone.

ADAM DERIVATION CONSIDERATIONS

The linked SDTM episode feeds three complementary ADaM datasets. ADAE supports the general adverse-event summaries, where CRS, ICANS, and IEC-HS appear as standard reported terms. ADCE supports the signs-and-symptoms summaries. ADCRSNT is the integrated OCCDS-style dataset that derives the syndrome-specific endpoints — incidence, timing, maximum grade, duration, resolution, and

management — across CRS, ICANS, and IEC-HS. The table below summarizes the key ADCRSNT derivations.

ADCRSNT concept	Derivation consideration
Event and subject flags	Record-level and subject-level flags for CRS, ICANS/neurotoxicity, and IEC-HS as applicable
Treatment-emergent status	Anchor to cell infusion when specified by protocol
Time to onset	Derive from infusion date/time to event start date/time
Maximum grade	Use all relevant ASTCT records from FA
Time to maximum grade	Use the first date/time the maximum grade is reached
Duration and resolution	Derive duration directly from the event start and end date/time recorded in AE. If the SAP instead considers factors such as grade changes or the end of related signs and symptoms, align the rule with the study team before implementation. Handle same-day onset/resolution, partial date/time, ongoing events, and recurrence with explicit SAP rules, and retain the most granular date/time so the FA trajectory is not collapsed before derivation.
Management	Derive timing and frequency of event-directed treatments and supportive care

For CAR-T studies, we recommend all safety-endpoint study-day variables (DY, ADY, and related timing) be anchored to the cell-infusion date rather than to randomization or first study treatment, so that onset, duration, and other time-to-event derivations are expressed relative to infusion across CRS, ICANS, and IEC-HS. This approach translates time-to-event metrics into a biologically meaningful timeline, enabling clinicians to predict exactly how many days post-infusion toxicities like CRS, ICANS, or IEC-HS are expected to manifest

REPORTING

In the overall summary adverse events, we recommend that CRS, ICANS, and IEC-HS be presented as ordinary AE terms sourced from ADAE, with incidence counted at the syndrome level — one event per episode — rather than by their constituent signs and symptoms.

Besides the overall AE analysis, we recommend a syndrome-level summary in Table 2, based on the integrated ADCRSNT dataset. It summarizes the severity of the CRS/ICANS/IEC-HS syndromes by ASTCT grade, together with time to onset, duration, and the event-directed medications, to give a whole picture of the CRS/ICANS/IEC-HS profile.

We recommend that the duration of a CRS, ICANS, or IEC-HS event be defined at the level of the overall syndrome — from the onset to the resolution of its overall ASTCT grade — rather than from the resolution of all its signs and symptoms. This is because, for CRS and ICANS, whose signs and symptoms are numerous and heterogeneous, the ASTCT grade is anchored on the core defining features (fever, hypotension, hypoxia), so a syndrome-level duration reflects the clinically meaningful course rather than the resolution of every incidental symptom; whereas for IEC-HS, whose manifestations are largely laboratory findings with limited standalone clinical relevance, the ASTCT grade reflects the overall clinical consequence, making the syndrome level the more meaningful anchor. Two additional considerations

warrant attention:

1. Ongoing events are excluded from the duration analysis, as their duration cannot be determined.
2. Recurrent events — two approaches exist. In this paper we recommend summarizing the duration of the first occurrence, consistent with the Breyanzi studies (Breyanzi r/r FL FDA review package 2023, Breyanzi r/r MCL FDA review package 2024, Breyanzi r/r MZL FDA review package 2025); other studies instead use the total duration, defined as (latest event end date – earliest event start date + 1) (ZUMA-1 FDA review package). Both have been used in FDA submissions.

Table 2. Summary of [[CRS|ICANS|IEC-HS]] events (Safety set)

		<<Dose level 1>>	<<Dose level 2>>	...	Total
	Statistic	N=xxx	N=xxx	N=xxx	N=xxx
[[CRS ICANS IEC-HS <<Other>>]] event					
Any	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 4	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 5	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to onset (<<unit>>)					
	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Duration (<<unit>>)					
	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Medications					
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Tocilizumab	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 dose	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>1 dose	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Glucocorticoid	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oxygen	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

We recommend that the individual signs and symptoms of these events not be reported as stand-alone AEs. Because CRS/ICANS/IEC-HS are typically AESIs whose signs and symptoms are already summarized in the label's Warnings and Precautions section. And the FDA review in the ABECMA review package also stated that duplicating them as stand-alone AEs would not be informative to prescribers (ABECMA FDA review package, 2021). Thus, we recommend signs and symptoms of these events to be

captured in a dedicated events domain (CE) and summarized separately by system organ class (SOC) and preferred term (PT), based on ADCE (Table 2).

For CRS and ICANS, we recommend these signs and symptoms be further summarized by CTCAE grade. First, because syndrome-specific signs and symptoms are excluded from the general AE analysis to avoid duplicate counting, omitting a dedicated CTCAE-graded summary would discard granular safety information and risk understating the true adverse-event burden, as clinically relevant manifestations would not appear in the primary AE tables. Second, while ASTCT grading is the standard for defining overall CRS/ICANS severity, it is anchored on only three cardinal signs (fever, hypotension, hypoxia); the overall ASTCT grade alone is therefore insufficient to characterize the broader clinical severity and systemic impact of an event. Summarizing all underlying signs and symptoms by CTCAE grade captures the full spectrum of the syndrome and yields a more complete and accurate safety profile.

For IEC-HS, as the syndrome lacks the clear clinical cardinal-sign phenotype of CRS/ICANS and is instead defined by a pre-specified set of laboratory- and organ-level features; its manifestations are therefore not summarized by SOC/PT but by the corresponding pre-specified CRF categories. CTCAE grading of the individual features may still be applied as an optional summary.

Table 3. [[CRS|ICANS]] signs and symptoms (Safety set)

System organ class		<<Dose level 1>>		<<Dose level 2>>		Total	
Preferred term	Statistic	N=xxx		N=xxx		N=xxx	
(MedDRA version xx.x)		All Grades	Grade>=3	All Grades	Grade>=3	All Grades	Grade>=3
<<CRS ICANS >> signs and symptoms		xx (xx.x)	xx (xx.x)		xx (xx.x)		xx (xx.x)
<<System organ class A>>	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred term 1>>	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred term 2>>	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...							
<<System organ class B>>	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred term 1>>	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred term 2>>	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...							

CONCLUSION

This paper presented an end-to-end paradigm for handling CRS, ICANS, and IEC-HS data in CAR-T trials, spanning CRF collection, SDTM mapping and traceability, and ADaM derivation and reporting. It resolves the two challenges raised at the outset: the operational decisions hidden behind each clinical question, and the fragmentation of relevant information across adverse-event, findings, laboratory, vital-sign, and medication records. The unifying principle is to treat each toxicity as a single traceable clinical episode — anchored in AE and linked across CE, FA, LB, VS, CM, and PR — so that syndrome-level endpoints (incidence, time to onset, maximum grade, duration, resolution, and management) can be derived consistently and reproducibly.

Event-Specific Considerations

Although the three syndromes share this common framework, they differ in ways that directly shape how their data should be collected, structured, and reported:

CRS. CRS presents through a clear cardinal-sign phenotype — fever, hypotension, and hypoxia — and its ASTCT grade is driven by the intensity of intervention required. For reporting, this means the overall ASTCT grade alone under-describes the true clinical burden: it should be complemented by a CTCAE-graded summary of the underlying signs and symptoms and by the event-directed treatments, rather than reported in isolation.

ICANS. ICANS is closely linked to CRS but is a clinically distinct, neurologic entity that is typically later in onset. For data handling, it should be assessed and graded independently from CRS even when concurrent; its severity is anchored on the objective ICE score together with other neurologic parameters, and it otherwise parallels CRS (free-text signs and symptoms with MedDRA coding and CTCAE grading, overall event graded by ASTCT).

IEC-HS. IEC-HS is fundamentally different: a macrophage-activation / HLH-like process defined by laboratory- and organ-level features rather than a cardinal-sign phenotype. This drives two considerations unique to IEC-HS. First, its manifestations are captured against a pre-specified set of clinical and laboratory criteria rather than as open-ended, free-text symptoms. Second, because these features do not map directly onto clinical severity, it is graded on overall clinical consequence (CTCAE-based) rather than against cardinal signs.

Table 4 consolidates these recommendations into a single roadmap, tracing each clinical question through its underlying operational question, the CRF forms that capture the data, the SDTM and ADaM mapping, and the corresponding reporting output.

Table 4. Roadmap from clinical questions to CRF collection, mapping, and reporting for CRS, ICANS, and IEC-HS

Clinical question	Open operational question and our considerations	CRF collection	Mapping	Reporting
Incidence	Q: At what level is incidence counted? A: We recommend incidence counted at the syndrome level rather than by their constituent signs and symptoms. (see REPORTING)	Adverse Events (AE)	SDTM: one syndrome-level AE record per episode (AETERM). ADaM: ADAE for the AE summary; syndrome flags in ADCRSNT.	Overall summary of adverse events
Severity	Q: How is severity defined? Should signs/symptoms also be graded? A: We recommend to summarize the severity of each syndromes by ASTCT grading plus summarize the signs and symptoms by CTCAE if applicable (See REPORTING)	CRS: CRS ASTCT Criteria (CRASTCT) and CRS Signs and Symptoms (CRSSS) ICANS: ICANS ASTCT Criteria (ICASTCT) and ICANS Signs and Symptoms (ICANSSS) IEC-HS: HLH/MAS IEC-HS Grading (IEC_HS)	SDTM: ASTCT grade trajectory in FA; symptom CTCAE grade in CE (CETOXGR). ADaM: max ASTCT grade reconciled in ADCRSNT; symptoms CTCAE grade in ADCE.	Syndrome by ASTCT grade (Table 2 Summary of [[CRS ICANS IEC-HS]] events); Signs/symptoms by CTCAE grade, SOC/PT (Table 3 [[CRS ICANS]] signs and symptoms (Safety set))
Time to onset	Q: From which anchor (infusion vs. randomization) ? A: We recommend to anchor to the cell-infusion date (See DATA MAPPING AND TRACEABILITY CONSIDERATION ADAM DERIVATION CONSIDERATIONS)	Adverse Events (AE)	SDTM: event start in AE (AESTDTC), anchored to infusion. ADaM: time to onset (infusion → event start) in ADCRSNT.	Table 2 Summary of [[CRS ICANS IEC-HS]] events
Duration	Q: Driven by the event or by its signs and symptoms — and how	Adverse Events (AE)	SDTM: event start/end in AE	Table 2 Summary of [[CRS ICANS IEC-HS]] events

Clinical question	Open operational question and our considerations	CRF collection	Mapping	Reporting
	are recurrence, and ongoing events handled? A: We recommend defining at the overall-syndrome level (by the ASTCT grade), not by individual signs and symptoms; ongoing events excluded and recurrence summarized by first occurrence. (See REPORTING)		(AESTDTC/AEENDTC) ADaM: duration and resolution in ADCRSNT.	
Management	Q: What specific interventions to be captured? A: Anti-cytokine therapy, corticosteroids, and other immunosuppressants (CM); supportive procedures such as oxygen support, vasopressors, and ventilation (PR) — which may influence severity grading. (See DATA COLLECTION – CM/PR).	Prior and Concomitant Medications (CM) Prior and Concomitant Procedures (PR)	SDTM: treatments/procedures in CM/PR linked to the episode via RELREC. ADaM: management endpoints in ADCRSNT.	Table 2 Summary of [[CRS ICANS IEC-HS]] events
Symptoms	Q: Collected as free-text + MedDRA or a pre-specified checklist — and reported as separate AEs or only as manifestation of the syndrome? A: We recommend CRS/ICANS — free-text + MedDRA, CTCAE-graded. IEC-HS — pre-specified categories, no MedDRA, CTCAE where applicable. Neither reported as stand-alone AEs, only as components of the syndrome. (See DATA COLLECTION, REPORTING)	CRS: CRS Signs and Symptoms (CRSSS) ICANS: ICANS Signs and Symptoms (ICANSSS) IEC-HS: HLH/MAS IEC-HS Grading (IEC_HS)	SDTM: signs and symptoms in CE (CETERM, CESPID) linked to AE. ADaM: symptom-level summary in ADCE.	Table 3 [[CRS ICANS]] signs and symptoms (Safety set)

Taken together, these considerations translate the clinical questions of CAR-T toxicity into a structured, traceable, and regulatory-aligned data workflow. Although the specific variables and derivations will vary by study, the episode-based framework offers a reusable reference for data managers, statistical programmers, and biostatisticians working on CRS, ICANS, and IEC-HS, supporting more standardized, interpretable, and comparable safety evaluation of CAR-T products. As experience with these toxicities continues to grow, we expect the framework to evolve further, with particular attention to the emerging and still less-standardized IEC-HS.

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