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Cytokine Release Syndrome (CRS) - Data Collection, Clinical Database Integration and Analyses in a Dose Escalation Cell Therapy Trial

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ABSTRACT

Cell therapy is a promising new therapeutic option in treating cancer. It has the potential to treat patients in other therapeutic areas such as autoimmune diseases. However, Cytokine Release Syndrome (CRS) remains a significant safety concern in these clinical trials. This presentation details the integration of CRS data into clinical study databases and subsequent analyses. We emphasize the process from data collection to CDISC-compliant data sets. CRS data is collected via electronic Case Report Forms (eCRFs) and integrated into Study Data Tabulation Model (SDTM) data sets. We will focus on SDTM.AE/SUPPAE for adverse events, SDTM.CE/SUPPCE for CRS signs and symptoms, and SDTM.CM/SUPPCM for treating CRS with drugs like tocilizumab. The relationships between these data sets are mapped using SDTM.RELREC to ensure accurate linkage of CRS events, treatments, and symptoms.

We then discuss the creation of Analysis Data Model (ADaM) data sets, specifically ADaM.ADAE, ADaM.ADCE and ADaM.ADCESUM, which facilitate detailed CRS analyses. Key variables such as Time to CRS onset since last treatment infusion, Time to resolution of CRS and Last dosing date/time before CRS onset are derived to support comprehensive analysis. These variables enable the examination of the timing, duration, and severity of CRS events hence the safety of interventions.

By showcasing this structured pathway from data integration to analysis, we highlight the critical role of robust statistical programming in enhancing the understanding and treatment of CRS in cell therapy trials. This methodology ensures data integrity and compliance while providing valuable insights for monitoring patient safety.

INTRODUCTION

Cell therapy is a groundbreaking treatment for cancer and holds promise for other conditions such as autoimmune diseases. However, managing Cytokine Release Syndrome (CRS) remains a significant safety concern. This presentation details the integration of CRS data into clinical study databases, emphasizing the process from data collection via electronic Case Report Forms (eCRFs) to the creation of Study Data Tabulation Model (SDTM) data sets. Key data sets like SDTM.AE/SUPPAE for adverse events and SDTM.CE/SUPPCE for CRS signs and symptoms are interconnected using SDTM.RELREC, ensuring precise linkage of events, treatments, and symptoms.

We also focus on the creation of Analysis Data Model (ADaM) data sets, specifically ADaM.ADAE, ADaM.ADCE and ADaM.ADCESUM, to facilitate detailed CRS analyses. Derived variables such as Time to CRS onset and Time to resolution of CRS are essential for evaluating the timing, duration, and severity of CRS events. By demonstrating this structured pathway from data integration to analysis, we highlight the critical role of robust statistical programming in enhancing the understanding and safety of CRS in cell therapy trials.

CRS IN CELL THERAPY STUDIES

- Cell therapy is a promising new therapeutic option in the field of cancer immunotherapy, as well as in other therapeutic areas such as autoimmune diseases.
- Cytokine release syndrome (CRS) or cytokine storm happens when your immune system responds to infection (e.g. COVID) or therapies more aggressively than it should and is a commonly observed AE in patients treated with cell therapy (or any immunotherapies that involve the activation of T cells).

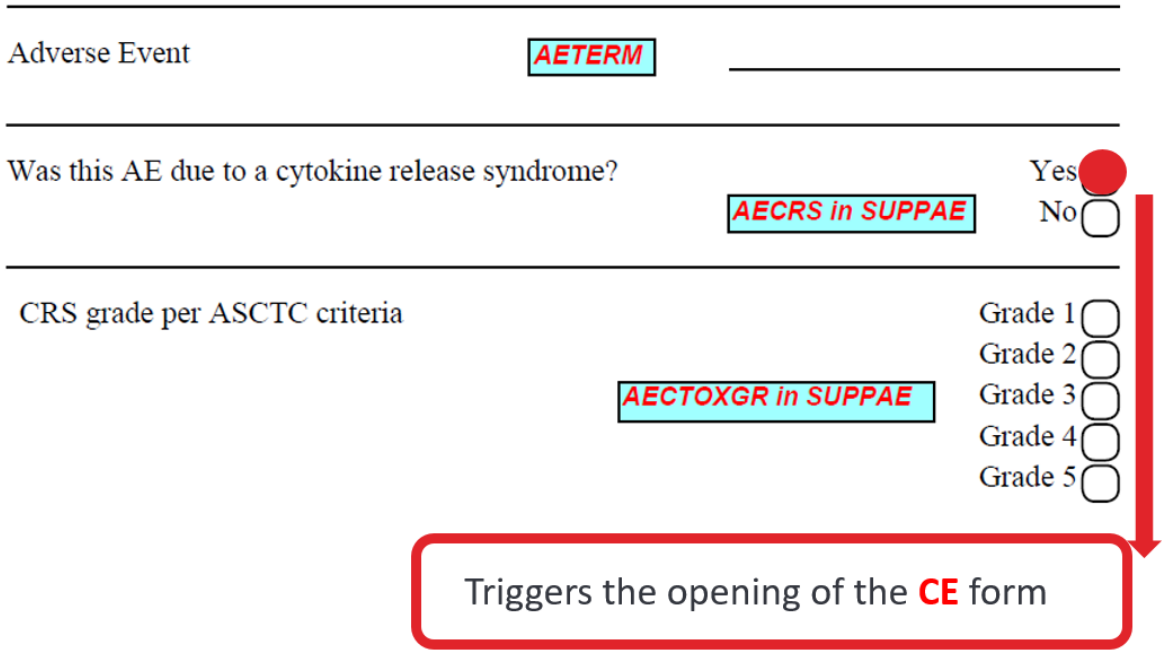
- CRS signs and symptoms include fever, nausea, fatigue and body aches. There could be many more symptoms depending on the organ system affected.
- CRS could be a safety concern in severe cases as it can cause organ failure and even death hence the importance to monitor accurately patient safety in these clinical trials.
- CRS occurrence can play a key role in study design involving dose escalation phase:
    - dose escalation decision based on dose limiting toxicities (DLT) occurrence, and grade ≥ 3 CRS (according to ASTCT/Lee grading) is one of the DLT criteria.
    - implementation of a Lead-in Dose (LiD) strategy if grade ≥ 2 CRS occurs in a dose escalation cohort. A LiD is then defined and used as the initial dose in each subsequent dose escalation cohort.
    - Grade ≥ 3 CRS is also one criterion for discontinuation of study treatment.
- FDA requested related analyses to be presented in all reports from DSUR/IB to CSR especially timing/grading of CRS and associated cytokine inhibitor use e.g. tocilizumab.

CRS DATA INTEGRATION IN DATABASE

ECRF PAGES

eCRF page AE

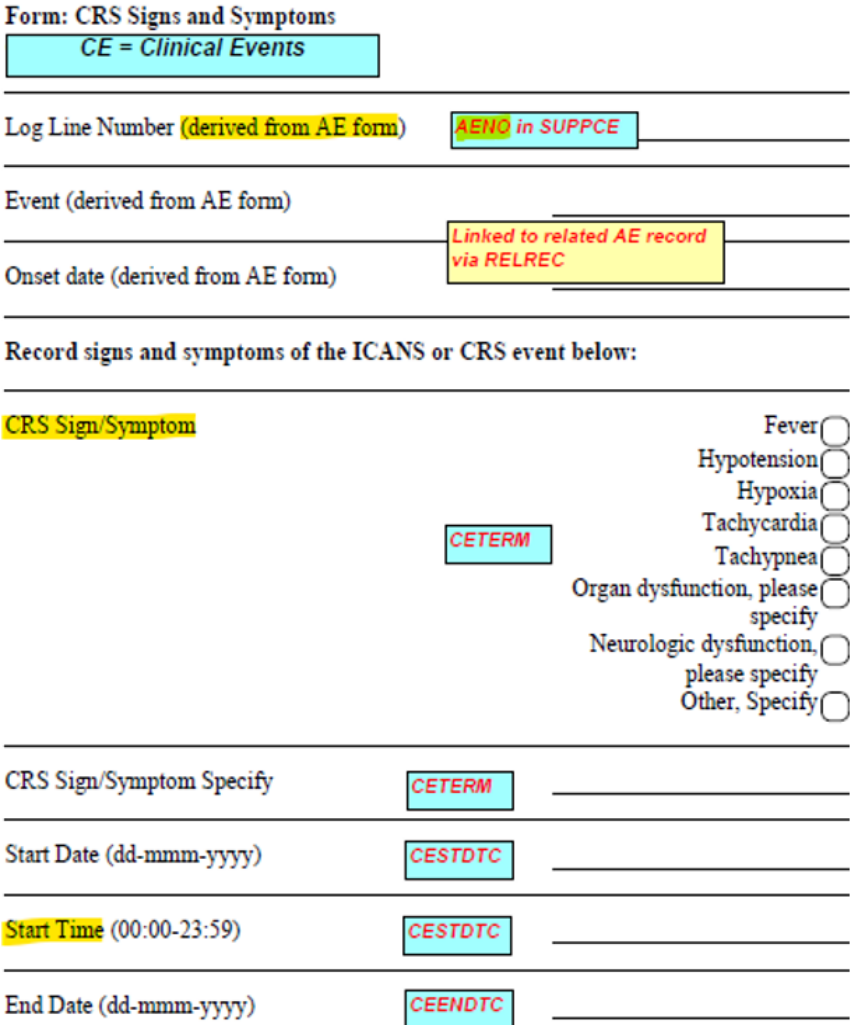
AE form collects usual AE data plus specific CRS data e.g. AETERM as “CYTOKINE RELEASE SYNDROME”, CRS flag, CRS grade (ASTCT/Lee grade) and dates. Notes: CRS graded using ASTCT system as opposed to CTCAE and captured in SUPPAE as AECTOXGR. Time is not collected in AE form.



Display 1. Sample from eCRF page AE

eCRF page CE

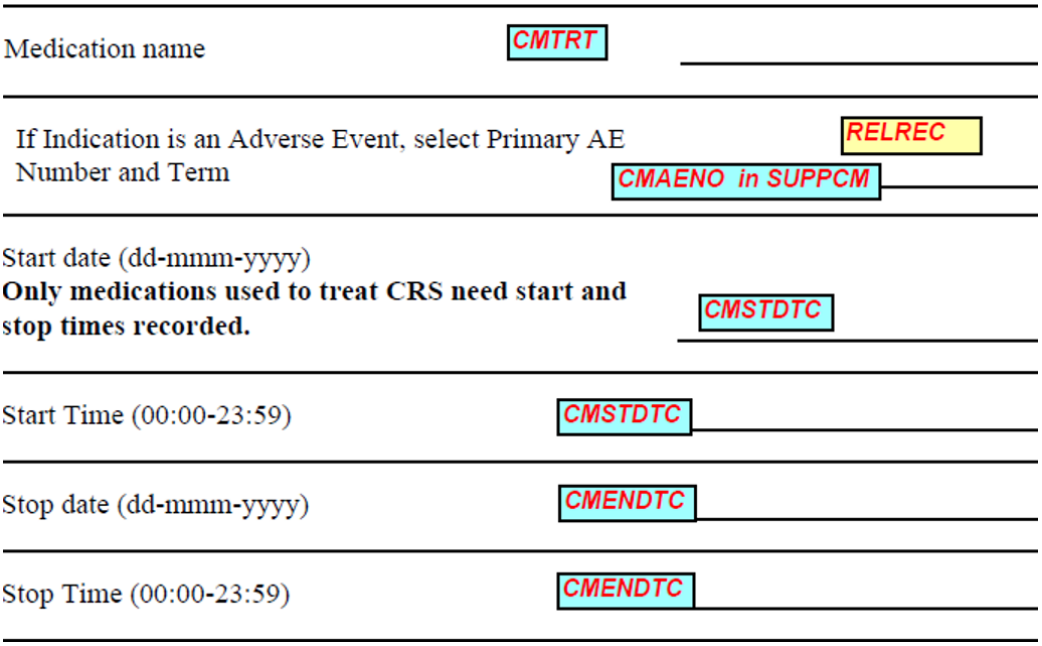
CRS Signs and Symptoms (S&S) form captures individual S&S, dates/times and AE identifier (AENO in SUPPCE) so multiple entries in CE can be associated to one CRS collected in AE form. Notes: Each CRS S&S is CTCAE graded in CETOXGR but in analyses, the corresponding ASTCT grade from AE is of interest. Time is required in CE form to derive timing of CRS.



Display 2. Sample from eCRF page CE

eCRF page CM

CM form collects usual concomitant medications plus cytokine inhibitor used to treat CRS (e.g. tocilizumab), dates/times and linking AE identifier (CMAENO in SUPPCM) so multiple entries can be associated to one CRS collected in AE form. Note: Time needs to be collected in CM form to capture timing of tocilizumab use.



Display 3. Sample from eCRF page CM

SDTM DATA SETS

SDTM.AE/SUPPAE (AE level)

In SDTM mapping specs, SDTM.AE.AESPID identifies one unique CRS with associated CRS flag (SUPPAE.QNAM=AECRS) and ASTCT grade (SUPPAE.QNAM=AECTOXGR) ≠ SDTM.AE.AETOXGR (CTCAE grade).

Dataset/Table Name:	**AE**			**Dataset/Table Label:**		Adverse Events		
Sort Order:	**STUDYID,USUBJID,AEDECOD,AESTDTC,AEENDTC,AESPID**			**Dataset Class:**		Events		
Dataset Structure:	**One record per adverse event per subject**							
Programmers Notes:	Exclude records with AEYN='No'							
OutName	**OutLabel**	**OutType**	**OutLeng**	**OutFormat**	**Flag**	**Calculation**	**Origin**	**Core**
AESPID	Sponsor-Defined Identifier	Char	6			Set to RECORDPOSITION. Format to a three character sequence number padded with zeros. (use z3. format so 0s are filled to the left of the data value)		Perm
AETERM	Reported Term for the Adverse Event	Char	200			*Add alert if AETERM is >200 characters	CRF	Req
AETOXGR	Standard Toxicity Grade	Char	20	CT:TOXGRV4		set to AESEV		Perm
AESTDTC	Start Date/Time of Adverse Event	char:datetime	20			Set to AESTDAT_DTC		Exp
AECRS	Cytokine Due to AE	char	10		S		CRF	
AECTOXGR	CRS Toxicity Grade	char	20		S		CRF	

Display 4. SDTM data sets AE/SUPPAE sample mapping specs

SDTM.CE/SUPPCE (Signs and symptoms for a CRS)

SUPPCE.QNAM=AENO (abbreviated CE.AENO) enables matching CRS Signs and Symptoms (S&S) with unique CRS record from SDTM data set AE. If several CRS S&S for a CRS then AENO is equal for all corresponding CRS S&S records. Note: Each CRS S&S is CTCAE graded in CETOXGR but in analyses, corresponding ASTCT grade from AE is of interest.

Dataset/Table Name:	**CE**			**Dataset/Table Label:**	Clinical Events			
Sort Order:	**STUDYID,USUBJID,CEDECOD, CESTDTC, CEENDTC, CESPID**			**Dataset Class:**	Events			
Dataset Structure:	**One record per event per subject**							
Programmers Notes:								
OutName	**OutLabel**	**OutType**	**OutLeng**	**OutFormat**	**Flag**	**Calculation**	**Origin**	**Core**
CESPID	Sponsor-Defined Identifier	Char	6			Set to RECORDPOSITION. Format to a three character sequence number padded with zeros. (use z3. format so 0s are filled to the left of the data value)		Perm
CETERM	Reported Term for the Clinical Event	Char	200			See Mapping Notes below		Req
CEDECOD	Dictionary-Derived Term	Char	200			See Mapping Notes below		Perm
CECAT	Category for Clinical Event	Char	50			See Mapping Notes below		Perm
CEBODSYS	Body System or Organ Class	Char	200			See Mapping Notes below		Perm
CEOUT	Outcome of Event	char	200			See Mapping Notes below	CRF	Perm
CETOXGR	Toxicity Grade	char	50			See Mapping Notes below	CRF	Perm
CESTDTC	Start Date/Time of Clinical Event	char:datetime	20			See Mapping Notes below		Perm
CEENDTC	End Date/Time of Clinical Event	char:datetime	20			See Mapping Notes below		Perm
AENO	Log Line Number (derived from AE form)	num	8		S		CRF	
INDATA	**CETERM**	**CEDECOD**	**CEBODSYS**	**CECAT**	**CESTDTC**	**CEENDTC**		
If index(datapagename,'CRS Signs	Set to upcase(CETERM_CRS). If CETERM='ORGAN DYSFUNCTION, PLEASE SPECIFY' or 'NEUROLOGIC DYSFUNCTION, PLEASE SPECIFY'or 'OTHER, SPECIFY' then set to upcase(CETERMSP_CRS) if non-missing	Set to PT_NAME	Set to SOC_	Assign as "CYTOKINE RELE	Set to CEST	Set to CEENDAT_DTC		

Display 5. SDTM data sets CE/SUPPCE sample mapping specs

SDTM.CM/SUPPCM (Tocilizumab used to treat CRS with ASTCT grade ≥ 2)

SUPPCM.QNAM=CMAENO (abbreviated CM.CMAENO) enables matching tocilizumab use from CM with unique CRS from SDTM data set AE. If several tocilizumab use for a CRS, then CMAENO is equal for all corresponding records.

Dataset/Table Name:	**CM**			**Dataset/Table Label:**	Concomitant/Prior Medications			
Sort Order:	**STUDYID,USUBJID,CMCAT,CMTRT,CMSTDTC,CMSPID**			**Dataset Class:**	Interventions			
Dataset Structure:	**One record per recorded intervention occurrence or constant-dosing interval per subject**							
Programmers Notes:								
OutName	**OutLabel**	**OutType**	**OutLeng**	**OutFormat**	**Flag**	**Calculation**	**Origin**	**Core**
CMTRT	Reported Name of Drug, Med, or Therapy	Char	200			a) If DATAPAGE = 'Prior and Concomitant Medications' then set to source data CMTRT b) If DATAPAGE = 'Prior Systemic Cancer Therapy' then set to PSTAGENT	CRF	Req
CMDECOD	Standardized Medication Name	Char	200	CT:WHODD		Set to PFBAS.		Perm
CMCAT	Category for Medication	Char	50	CT:CMCAT		Assign values as below: a) If DATAPAGE = 'Prior and Concomitant Medications' then assign as 'PRIOR		Perm
CMSTDTC	Start Date/Time of Medication	char:datetime	20			Set to values as below: a) If DATAPAGE = 'Prior and Concomitant Medications' then set to		Perm
CMENDTC	End Date/Time of Medication	char:datetime	20			Set to values as below: a) If DATAPAGE = 'Prior and Concomitant Medications' then set to		Perm
CMAENO	Primary AE	char	200		S		CRF	

Display 6. SDTM data sets CM/SUPPCM sample mapping specs

CRS data collection and organization example

Below is an example of a CRS (AESPID=2) captured in SDTM data set AE with ASTCT grade of 2 in SUPPAE, and 4 associated S&S in CE, that happened on the same day at different times, with CTCAE grade of 2: hypoxia, fever, etc. AE identifier (AENO=2) is captured in SUPPCE. Several concomitant medications used to treat this CRS are captured in CM (with associated time for dexamethasone), and SUPPCM captures AE identifier (CMAENO).

AE

DOM...	AESPID	AETERM	AETOXGR	AESTDTC
AE	002	CYTOKINE RELEASE SYNDROME		2021-04-22

SUPPAE

QNAM	QLABEL	QVAL
AECTOXGR	CRS Toxicity Grade	Grade 2

CE

DOMAIN	CESEQ	CESPID	CETERM	CETOXGR	CESTDTC
CE	1	003	HYPOXIA	Grade 2	2021-04-22T05:00
CE	2	002	FEVER	Grade 2	2021-04-22T05:00
CE	3	004	SINUS BRADYCARDIA	Grade 2	2021-04-22T05:00
CE	4	001	VOMITING	Grade 2	2021-04-22T03:15

SUPPCE

IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
CESEQ	1	AENO	Log Line Number (derived from AE form)	2
CESEQ	2	AENO	Log Line Number (derived from AE form)	2
CESEQ	3	AENO	Log Line Number (derived from AE form)	2
CESEQ	4	AENO	Log Line Number (derived from AE form)	2

CM

CMSEQ	CMSPID	CMTRT	CMINDC	CMSTDTC	CMENDTC
2	012	DEXAMETHASONE	ADVERSE EVENT	2021-04-22T09:06	2021-04-22
17	008	IBUPROFEN	ADVERSE EVENT	2021-04-22	2021-04-22
25	037	METOCLOPRAMIDE	ADVERSE EVENT	2021-04-22	2021-04-22
35	022	SLOW K	ADVERSE EVENT	2021-04-28	2021-05-12

SUPPCM

IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
CMSEQ	17	CMAENO	Primary AE	2-CYTOKINE RELEASE SYNDROME-22APR2021
CMSEQ	2	CMAENO	Primary AE	2-CYTOKINE RELEASE SYNDROME-22APR2021
CMSEQ	25	CMAENO	Primary AE	2-CYTOKINE RELEASE SYNDROME-22APR2021
CMSEQ	35	CMAENO	Primary AE	6-HYPOKALAEMIA-23APR2021

Display 7. Example of CRS data in SDTM data sets

SDTM.RELREC (AE/CE and AE/CM relationship for CRS)

SDTM data set RELREC captures all relationships between SDTMs:

- For AE/CE relationship, for each subject link is established using AE.AESPID and CE.AENO then RELID is derived with the same value for related records of IDVAR variables: AE.AESPID/CE.CESPID i.e. IDVARVAL values. Note: make sure that a CRS in AE has at least one CRS S&S captured in CE and a CRS S&S has a corresponding CRS in AE.
- For AE/CM relationship, for each subject link is established using AE.AESPID and CM.CMAENO then RELID is derived with the same value for related records of IDVAR variables: AE.AESPID/CE.CMSPID i.e. IDVARVAL values. Note: make sure that a CRS with ASTCT grade ≥ 2 in AE has at least one tocilizumab record captured in CM.

Dataset/Table Name:		**RELREC**	**Dataset/Table Label:**	Related Records	
Sort Order:	**STUDYID,USUBJID,RDOMAIN,IDVAR,IDVARVAL,RELID**		**Dataset Class:**	Relationships	
Dataset Structure:		**One record per related record, group of records or dataset**			
Programmers Notes:					

OutName	OutLabel	OutType	OutLength	OutForm	Flag	Calculation	Core
STUDYID	Study Identifier	Char	20			Set to source data	Req
RDOMAIN	Related Domain Abbreviation	Char	20	CT:DOMAIN			Req
USUBJID	Unique Subject Identifier	Char	30			Set to source data.	Exp
IDVAR	Identifying Variable	Char	8			See Mapping Notes below	Req
IDVARVAL	Identifying Variable Value	Char	25			See Mapping Notes below	Exp
RELTYPE	Relationship Type	Char	20	CT:RELTYPE		See Mapping Notes below	Exp
RELID	Relationship Identifier	Char	25			See Mapping Notes below	Req

RDOMAIN	IDVAR	IDVARVAL	Link Rules	RELTYPE	RELID	Comments
Set to 'AE' for rows from sdtmpr.AE.		Set to value of AESPID for rows from sdtmpr.AE.	Link AE and CE by USUBJID, AE.AESPID=(CE.AENO),		Derived Populate with a whole number unique to the association.	In order to link AE with CE the following is required. AE: Keep USUBJID AESPID AETERM AESTDTC.
Set to 'CE' for rows from sdtmpr.CE.	Set to 'AESPID' for rows from sdtmpr.AE. Set to 'CESPID' for rows from sdtmpr.CE.	Set to value of CESPID for rows from sdtmpr.CE.	AE.AETERM=(CE.AETERM) and AE.AESTDTC/(CE.AESTDTC).	null	SDTM RELREC.RELID should be the same across all associated records within the	CE: Keep USUBJID CESPID AETERM AESTDTC. Only keeping records where CE.AENO is non missing.
Set to 'AE' for rows from sdtmpr.AE.		Set to value of AESPID for rows from sdtmpr.AE.	Link AE and CM by USUBJID, AE.AESPID/(first part of CM.CMAENO), AE.AETERM/(second part of CM.CMAENO) and		Derived Populate with a whole number unique to the association. SDTM RELREC.RELID should	In order to link AE with CM the following is required. AE: Keep USUBJID AESPID AETERM AESTDTC.
Set to 'CM' for rows from sdtmpr.CM.	Set to 'AESPID' for rows from sdtmpr.AE. Set to 'CMSPID' for rows from sdtmpr.CM.	Set to value of CMSPID for rows from sdtmpr.CM.	AE.AESTDTC/(third part of CM.CMAENO).	null	be the same across all associated records within the USUBJID.	CM: Keep USUBJID CMSPID CMAENO. Only keeping records where CMAENO is non missing.

Display 8. SDTM data set RELREC sample mapping specs

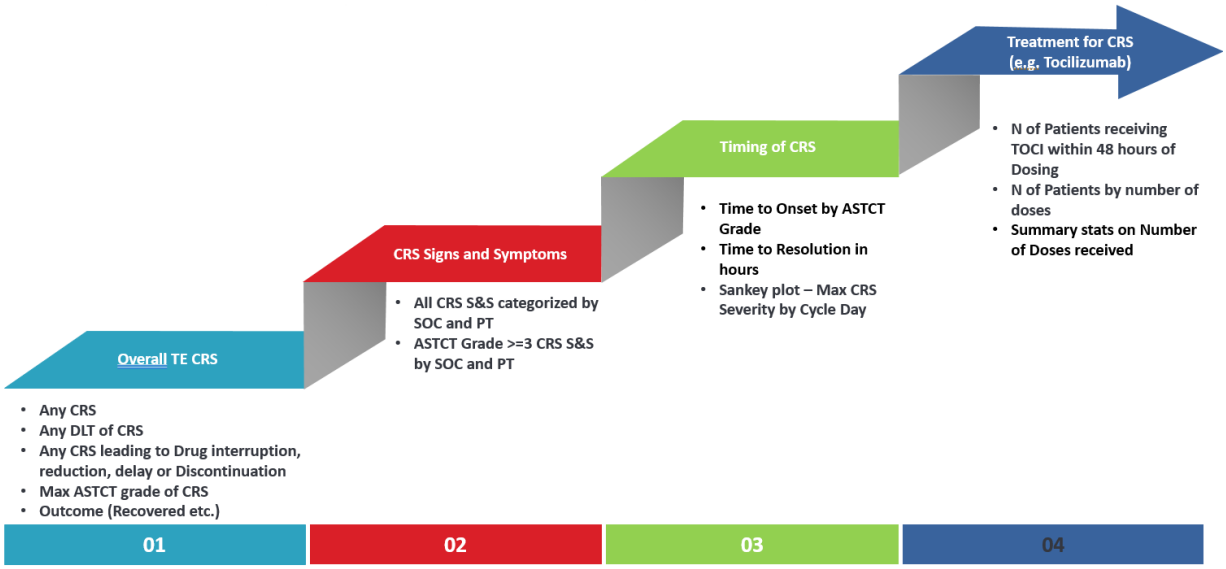
Below in red is an example of a CRS (AESPID=2) captured in SDTM data set AE linked with 4 associated S&S in CE as RELID=2 (similarly in blue, for AE and CM data sets relationship with RELID values 3 and 4).

IDVAR	IDVARVAL	RELID
AESPID	002	2
AESPID	002	3
AESPID	006	4
CESPID	001	2
CESPID	002	2
CESPID	003	2
CESPID	004	2
CMSPID	008	3
CMSPID	012	3
CMSPID	022	4
CMSPID	037	3

Display 9. Example of CRS data relationships in SDTM data set RELREC

ADAM DATA SETS

To describe CRS, we need to present various results, not only AE data type of analyses (e.g. any CRS, any DLT of CRS, or any CRS leading to…), but summaries for timing and treatment for CRS too.



Display 10. CRS reporting needs

The following ADaM data sets capture the corresponding data:

Reporting Need	ADAE	ADCE	ADCESUM
Any CRS, Any DLT of CRS	x		
Leading to Drug interruption, reduction, delay or Discontinuation	x		
Max ASTCT grade of CRS Outcome (Recovered etc.)	x		
CRS Signs and Symptoms - SOC and PT		x	
Grade >=3 Signs and Symptoms by SOC and PT		x	
Time to Onset and Resolution of CRS			x
Sankey plot – Max CRS Severity by Cycle Day			x
TOCI within 48 hours of Dosing			x
Patients by number of TOCI doses, Stats on Doses			x

Display 11. Required ADaM data sets

ADaM.ADAE (AE level)

ADAE contains all data from SDTM data set AE including CRS variables: AESPID that makes the link with ADCE, CRS flag and ASTCT grade.

Dataset	Variable Name	Variable Label	Type	Expected Length	CDISC Core	Controlled Terms / Format	Origin	Derivation / Method
ADAE	AETERM	Reported Term for the Adverse Event	Char	200	Req		Predecessor	AE.AETERM
ADAE	AECRS	Cytokine Due to AE	Char	1		(NY_YONLY)	Predecessor	SUPPAE.QVAL where SUPPAE.QNAM='AECRS'
ADAE	AECTOXGR	CRS Toxicity Grade	Char	20		(ATOXGR)	Predecessor	SUPPAE.QVAL where SUPPAE.QNAM = "AECTOXGR"
ADAE	AECTOXGN	CRS Toxicity Grade (N)	Num	8		(ATOXGRN)	Assigned	Extract substr(AE.AECTOXGR,7,1)
ADAE	AESPID	Sponsor-Defined Identifier	Char	6			Predecessor	AE.AESPID

Display 12. ADaM data set ADAE sample mapping specs

ADaM.ADCE (CRS Signs and symptoms level)

Occurrence data set including all data related to CRS Signs and symptoms copied from SDTM data set CE: AESPID will make the link with ADAE. Note: Importance of date/timing to check time to onset of CRS following previous treatment infusion hence imputation of date/time required e.g. if start time of CRS S&S is missing and date part is the same as date part of one of the infusions then impute with start time of that infusion.

ADaM.ADCESUM (AE CRS level) – CRS timing

Basic Data Structure (BDS) data set including parameters derived at the AE CRS level (different from the CRS S&S level). Each subject has potentially several CRS, each specific CRS within a subject is identified by AESPID (usual visit or date variables e.g. AVISIT or ADT not required per CDISC).

For readability in annotated mockup shells, parameters will be referred to as e.g. ADCESUM.TTRCRS for ADCESUM.AVAL (where PARAMCD=TTRCRS).

Display 13. ADCESUM CRS timing parameters

PARAMCD	PARAM	AVAL derivation description
TTRCRS	Time to Resolution of CRS (Hr)	Duration between earliest S&S start datetime and latest S&S stop datetime for a resolved CRS. If the CRS event has any S&S that is not resolved, TTRCRS is considered missing (for Table 2. Summary table presenting time to CRS onset and time to resolution of CRS)
LSTDSDTC	Last Trt Infusion Date/Time Before CRS	Merge SDTM.CE and SDTM.EX (Exposure) by USUBJID then select the last stop datetime infusion on or before first S&S start datetime for a CRS
TTONSIN	Time to Ons of CRS Since Lst Infu (Hr)	Duration between LSTDSDTC and first S&S start datetime for a CRS (for Table 2. Summary table presenting time to CRS onset and time to resolution of CRS)
NBINFUS	Number of Infusions Before CRS	Count number of infusions (using SDTM.EX) on or before first S&S for a CRS (for Table 3. Summary table presenting tocilizumab usage for a CRS)
INFUVIS	Visit Number of Infusion Before CRS	Visit number (EX.VISITNUM) of the infusion on or before first S&S for a CRS (for **Error! Reference s ource not found.**)

ADaM.ADCESUM (AE CRS level) – Toci use and timing

Data from SDTM data set CM included for Tocilizumab used to treat CRS with ASTCT grade ≥ 2.

Display 14. ADCESUM Toci use and timing parameters

PARAMCD	PARAM	AVAL derivation description
TOCIFL	Received Toci Flag	=Y if CRS event received Toci i.e. check if CRS treated with Toci by merging SDTM.AE with SDTM.CM (CMDECOD=”TOCILIZUMAB”) by USUBJID AESPID/CMAENO then with SDTM.CE by USUBJID AESPID/AENO
TOCIDTC	Date/Time of First Toci Administration	Select TOCIFL=Y records, TOCIDTC=CM.CMSTDTC for earliest record for a CRS
NBTOCI	Number of Toci Doses Received	Select TOCIFL=Y records, count number of Toci doses received for a CRS at subject level (for Table 3. Summary table presenting tocilizumab usage for a CRS)
TTONSTO	Time to First Toci Since Last Infus (Hr)	Select TOCIFL=Y records, duration between stop datetime of last infusion on or before receiving first Toci for a CRS (TOCIDTC)

CRS ANALYSES

LISTING

Treatment-emergent CRS listing including AE level data (dates, outcome, severity grade, and action taken), individual S&S preferred terms concatenated, CRS treated with tocilizumab flag, time to CRS onset from last treatment infusion and time to resolution of CRS.

Listing 16.2.7.6 ADAE.TRTEMFL=Y and ADAE.AECRS=Y
Treatment Emergent Cytokine Release Syndrome (CRS) Adverse Events
Safety Population

Study Phase: XXXXXXXXXXX
Dose Cohort: XXXXXXXXXXX

Patient ID	Age (yrs)/ Sex/ Race/ Ethnicity	Baseline Weight (kg)	ADAE.AEDECOD Preferred Term	ADAE.ASTDT/ASTDY Start Date (Day)/ ADAE.AENDT/AENDY Stop Date (Day)	ADAE.AEOUT Outcome	ADAE.AECTOXGR ASTCT Grade	ADCE.CEDECOD Signs and Symptoms of CRS Preferred Term	ADAE.AEACN ADAE.AEREL Action Taken/ Relationship to Study Treatment	ADAE.AESER SAE?	ADCESUM.TOCIFL Treated with Tociliz umab?	ADCESUM.TTONSIN Time to Onset of CRS (Hour) [a]	ADCESUM.TTRCRS Time to Resolution of CRS (Hour)
XXXXXX	XX/X/X /X	xx	Cytokine release syndrome	YYYY-MM-DD (XX)/ YYYY-MM-DD (XX)	XXXXXXX	X	XXXXXXXX/ XXXXXXXXX/ XXXXXXXXX	XXXXXXXX/ XXXXXX	X	X	XX	XX

Listing 1. Listing displaying CRS signs and symptoms data

FIGURE

The figure below is a Sankey plot with the X axis presenting Cycle Days. The Y axis presents the percentage of patients with their maximum CRS grades ranging from No CRS to Grade 3 and above. Further, the Y axis also separately presents the proportion of patients who were administered Tocilizumab as treatment from those not administered Tocilizumab. This is done for each grade level presented in the plot.

The Sankey plot also shows the flow of patients from one severity level to another over time. They could move to a higher grade or move to a lower grade. This is the area between any two cycle days. The colors in between any two cycle days have been deliberately made lighter to show the flow. The thickness of a band represents the proportion of subjects involved in a particular transition. A simple illustration is

between Cycle 1 Day 15 (C1D15) and C1D22, the negative slope of the light orange band shows the flow of subjects from Grade 2 to “No CRS”.

Figure 15.3.1.1
Sankey Plot of CRS Events by Dose Day for Each Dosing Regimen
Safety Population

Dose level: Total (N=XX)

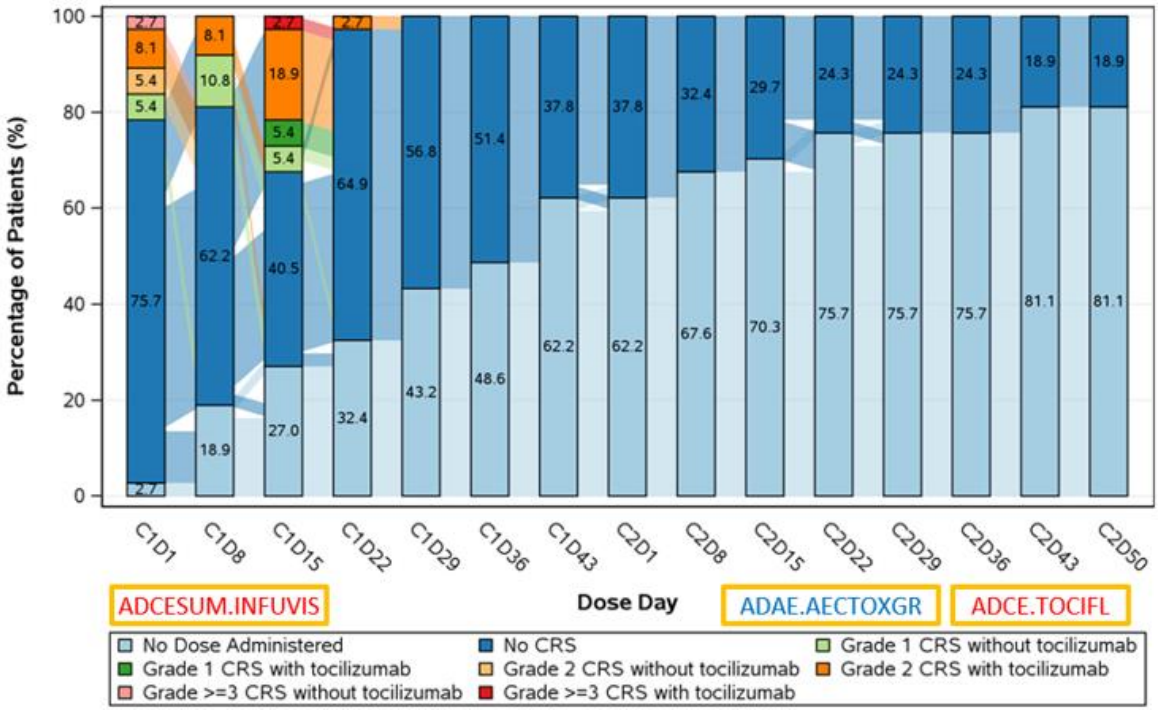


Figure 1. Sankey plot presenting CRS severity over time

SUMMARY TABLES

A summary of treatment-emergent CRS Signs and symptoms by grade, SOC and PT is presented below in Table 1.

Table 15.3.1.14.1
Treatment-Emergent Cytokine Release Syndrome (CRS) Signs and Symptoms by ASTCT grade, System Organ Class and Preferred Term
ADAE.TRTEMFL
Safety Population

	Dose Escalation Phase	
	Dose 1, 2, ... (N=xxx)	Total (N=xxx)
Cytokine Release Syndrome Signs/Symptoms [n (%)]		
System Organ Class 1 ADCE.CEBODSYS	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2 ADCE.CEDECOD	xx (xx.x)	xx (xx.x)
<continue>		
System Organ Class 2	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
<continue>		
ADAE.AECTOXGR	xx (xx.x)	xx (xx.x)
Grade 3 or above Cytokine Release Syndrome Signs/Symptoms [n (%)]		
System Organ Class 1	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
<continue>		
<continue>		

ASTCT = American Society for Transplantation and Cellular Therapy, CRS = Cytokine Release Syndrome, n = number of subjects;
Treatment-emergent Adverse Events (TEAEs) are defined as AEs that occur at or after first dose of study drug and until 30 days after the last dose of study drug. Events that existed before the first administration of study drug and then increased in severity during or after the first administration of study drug are also considered treatment-emergent.
MedDRA dictionary version XX.X was used.

Table 1. Summary table presenting CRS S&S by grade, SOC and PT

A summary of Time to onset of CRS from last treatment infusion by grade and time to resolution of CRS is presented below in Table 2.

Table 15.3.1.14.2
Treatment-Emergent Cytokine Release Syndrome (CRS) Adverse Events – Time to Onset and to Resolution of CRS Event
ADAE.TRTEMFL
Safety Population

	Dose Escalation Phase	
	Dose 1, 2, ... (N=xxx)	Total (N=xxx)
Time to Onset of CRS Event with Respect to Each Lead-in Dose and Full Dose(hours)[a]		
All Grades ADCESUM.TTONSIN		
m	xx	xx
Median	xx.x	xx.x
Min,Max	xx, xx	xx, xx
Grade 1 ADAE.AECTOXGR		
m	xx	xx
Median	xx.x	xx.x
Min,Max	xx, xx	xx, xx
Grade 2		
m	xx	xx
Median	xx.x	xx.x
Min,Max	xx, xx	xx, xx
Grade 3 or Above		
m	xx	xx
Median	xx.x	xx.x
Min,Max	xx, xx	xx, xx
Time to Resolution of CRS Event (hours) [b]		
m ADCESUM.TTRCRS	xx	xx
Median	xx.x	xx.x
Min,Max	xx, xx	xx, xx

ASTCT = American Society for Transplantation and Cellular Therapy, CRS = Cytokine Release Syndrome, n = number of subjects; m= number of events.
Treatment-emergent Adverse Events (TEAEs) are defined as AEs that occur at or after first dose of study drug and until 30 days after the last dose of study drug. Events that existed before the first administration of study drug and then increased in severity during or after the first administration of study drug are also considered treatment-emergent.
MedDRA dictionary version XX.X was used.
[a] Time to Onset of CRS with Respect to Each Lead-in Dose and Full Dose: Start time of the earliest signs and symptoms of CRS onset - stop time of each infusion immediately before each CRS event
[b] Time to Resolution of CRS: Stop time of the latest signs and symptoms of CRS resolution - start time of the earliest signs and symptoms of CRS onset

Table 2. Summary table presenting time to CRS onset and time to resolution of CRS

The summary table 3 below presents the number of patients with CRS receiving tocilizumab and categorized by grade, number of doses of toci received, and number of CRS events treated with toci in total/after x treatment infusion and categorized by grade.

Table 15.3.1.14.3
Tocilizumab Usage
ADAE.TRTEMFL=Y and ADAE.AECRS=Y
Patients in Safety Population with any Treatment-Emergent Cytokine Release Syndrome (CRS) Adverse Events

	Dose Escalation Phase	
	Dose 1, 2, ... (N=xxx)	Total (N=xxx)
Number of Patients with CRS received tocilizumab [n (%)] ADCESUM.TOCIFL	xx (xx.x)	xx (xx.x)
Number of Patients with Grade 1 CRS received tocilizumab [n (%)]	xx (xx.x)	xx (xx.x)
Number of Patients with Grade 2 CRS received tocilizumab [n (%)]	xx (xx.x)	xx (xx.x)
Number of Patients with Grade 3 or above CRS received tocilizumab [n (%)]	xx (xx.x)	xx (xx.x)
ADAE.AECTOXGR		
Number of Patients with CRS received one dose of tocilizumab [n (%)]		
Number of Patients with CRS received two doses of tocilizumab [n (%)]	xx (xx.x)	xx (xx.x)
Number of Patients with CRS received three or more doses of tocilizumab [n (%)]	xx (xx.x)	xx (xx.x)
ADCESUM.NBTOCI		
Number of Doses of tocilizumb Received for patients with CRS		
n	xx	xx
Mean (SD)	xx (xx.x)	xx (xx.x)
Median	xx (xx.x)	xx (xx.x)
Min, Max	Xx, xx	Xx, xx
Number of CRS events treated with tocilizumab [m/M (%)]	Xx/xx (xx.x)	Xx/xx (xx.x)
Immediately after First Infusion [m/M (%)] ADCESUM.NBINFUS	Xx/xx (xx.x)	Xx/xx (xx.x)
Immediately after Second Infusion [m/M (%)]	Xx/xx (xx.x)	Xx/xx (xx.x)
Immediately after Third Infusion [m/M (%)]	Xx/xx (xx.x)	Xx/xx (xx.x)
Immediately after Fourth Infusion [m/M (%)]	Xx/xx (xx.x)	Xx/xx (xx.x)
Immediately after Fifth or beyond Infusion [m/M (%)]	Xx/xx (xx.x)	Xx/xx (xx.x)
Number of Grade 1 CRS events treated with tocilizumab [m/M (%)]	Xx/xx (xx.x)	Xx/xx (xx.x)
Immediately after First Infusion [m/M (%)]	Xx/xx (xx.x)	Xx/xx (xx.x)
<continue>		
Number of Grade 3 or above CRS events treated with tocilizumab [m/M (%)]	Xx/xx (xx.x)	Xx/xx (xx.x)
<continue>		

n = number of subjects; m = number of events; M = Total number of CRS events.
Treatment-emergent Adverse Events (TEAEs) are defined as AEs that occur at or after first dose of study drug and until 30 days after the last dose of study drug. Events that existed before the first administration of study drug and then increased in severity during or after the first administration of study drug are also considered treatment-emergent.

Table 3. Summary table presenting tocilizumab usage for a CRS

CONCLUSION

In conclusion, the integration of CRS data into clinical study databases and the subsequent detailed analyses are paramount to advancing the safety and efficacy of cell therapy trials. By systematically collecting and organizing CRS data through CDISC-compliant data sets and employing robust statistical programming, we ensure precise linkage and comprehensive analysis of adverse events, symptoms, and treatments. This structured approach not only maintains data integrity and compliance but also provides critical insights into the timing, duration, and severity of CRS events. Ultimately, these efforts contribute significantly to enhancing patient safety and advancing therapeutic strategies in the field of cell therapy.

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