

COLLECTION, STANDARDIZATION, AND REPORTING OF ADVERSE EVENTS WITH TOXICITY CHANGES USING CDISC STANDARDS IN ONCOLOGY CLINICAL TRIALS

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INTRODUCTION AND PURPOSE

- Treatment-emergent adverse events (TEAE) tables are routinely produced in clinical trials
- TEAEs are the events that occur after treatment or worsen in toxicity after administration of study treatment
- The current data collection practices for adverse events, particularly collection of toxicity changes to an adverse event do vary across the industry. Different practices exist for the collection of toxicity changes for an adverse event (AE).
- However, there are two common approaches for data entry.

The first approach creates new records for the worsening of an AE (increase in toxicity grade), but no new records either for the adverse events that are improved (decrease in toxicity grade) or not changed in toxicity.

The second approach records all toxicity changes of an adverse event as new records. The newly entered records are considered as distinct adverse events.

- Both approaches have gaps at the data entry level, particularly assuming the toxicity changes as new adverse events, thus delinking an adverse event and its toxicity changes.

INTRODUCTION AND PURPOSE-CONTINUED

- In the context of treatment emergence, the first approach facilitates straightforward flagging of treatment-emergent adverse events. Whereas the second approach leads any toxicity changes after treatment start date being flagged as treatment-emergent adverse events.
- These inconsistent data collections not only impact the treatment-emergent definition and statistical programming but put an additional burden on sites to understand the sponsor's unique requirements before they enter the data. These variations also impact regulatory review and limit the ability to compare the safety profiles of the various drugs across the industry.
- To address these challenges, an industry-wide standardization of adverse event data entry and harmonization of the collected data to SDTM and ADaMs needs to be developed
- While it is impossible to address all unique study designs and the study needs, the current paper provides examples for the data collection, data harmonization to SDTM and ADaMs for the most common adverse event situations, and their treatment emergence

THE ORGANIZATION OF THE PAPER

- **COLLECTION OF AN ADVERSE EVENT AND ITS TOXICITY CHANGES IN CRF**
- **MAPPING THE CRF DATA TO SDTM DOMAINS: ADVERSE EVENTS (AE) AND FINDINGS ABOUT (FA) AND ESTABLISHING THE RELATIONSHIP BETWEEN TWO DATASETS USING THE RELREC DOMAIN**
- **DEVELOPING ADAM DATASETS: ANALYSIS DATASET FOR AE TOXICITY (ADAETOX) AND ANALYSIS DATASET FOR ADVERSE EVENTS (ADAE) AND DEFINING THE TREATMENT-EMERGENT FLAG (TRTEMFL)**
- **DATA FLOW AND DATA DEPENDENCIES**

COLLECTION OF AN ADVERSE EVENT AND ITS TOXICITY CHANGES IN CRF

Fig 1. Adverse Events and Adverse Event Toxicity Grade Change CRF

Adverse Events	
1.	Sequence Number
2.	AE Term
3.	Onset Date and Time
4.	End Date and Time
5.	Overall Toxicity

Adverse Event Toxicity Grade Change	
28.	Associated AE Sequence Number (from top of AE form)
	Toxicity Grade Onset Date
	Toxicity Grade Stop Date
	Toxicity Grade ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

ADVERSE EVENTS:

This section of CRF captures each unique adverse event and the fields of the section are described below.

- **Sequence Number:** This is auto-populated at the entry for each entry of adverse event with a new sequence number within a subject.
- **AE Term:** The adverse event name
- **Onset Date and Time:** Adverse event start date and Time
- **End Date and Time:** Adverse event end date and Time
- **Overall Toxicity:** When the toxicity changes, the 'Adverse Event Toxicity Grade Section' would be collected. In this case, the overall toxicity will be auto-populated by the EDC system based on the responses entered in questions in the Adverse Event Toxicity Grade Change Entry section

ADVERSE EVENT TOXICITY GRADE CHANGE ENTRY:

This section of CRF captures initial toxicity entry and any further changes to toxicity throughout the study and the fields of the section are described below.

- **Associated AE Sequence Number (from top of AE form):** auto-populated by EDC system from Sequence Number of Adverse Events sections.
- **Toxicity Grade Onset Date:** Start date of toxicity
- **Toxicity Grade Stop Date:** Stop date of toxicity
- **Toxicity Grade:** Toxicity Grade Value

MAPPING THE CRF DATA TO SDTM DOMAINS: ADVERSE EVENTS (AE) AND FINDINGS ABOUT (FA) AND ESTABLISHING THE RELATIONSHIP BETWEEN TWO DATASETS USING THE RELREC DOMAIN

AE = Adverse Events

Adverse Events		
1.	Sequence Number	AESPID
2.	AE Term	AETERM
3.	Onset Date and Time	AESTDTC
4.	End Date and Time	AEENDTC
5.	Overall Toxicity	AETOXGR

Adverse Event Toxicity Grade Change			FA = Findings About Events or Interventions			
28.	Associated AE Sequence Number (from top of AE form)	FASPID				
	Toxicity Grade Onset Date	FADTC				
	Toxicity Grade Stop Date			FAENDTC		
	Toxicity Grade	FATEST	FAORRES when FATESTCD = 'TOXGR'	FASTRESC	FASTRESN	

MAPPING THE CRF DATA TO SDTM DOMAINS: ADVERSE EVENTS (AE) AND FINDINGS ABOUT (FA) AND ESTABLISHING THE RELATIONSHIP BETWEEN TWO DATASETS USING THE RELREC DOMAIN-CONTINUED

Table 1. AE Metadata

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Origin//Method/Comment
STUDYID	Study Identifier	Char		Unique identifier for a study
DOMAIN	Domain Abbreviation	Char	AE	Derived. Concatenation of STUDYID and SUBJID
USUBJID	Unique Subject Identifier	Char		Unique Subject Identifier
AESQ	Sequence Number	Num		Derived. Sequence Number given to ensure uniqueness of subject records within a domain. May be any valid number.
AESPID	Sponsor-Defined Identifier Char	Numeric		CRF Page yy
AETERM	Reported Term for the Adverse Event	Num		CRF Page yy
AEDECOD	Dictionary-Derived Term	Char	MedDRA	Dictionary-derived text description of AETERM. Equivalent to the Preferred Term (PT in MedDRA).
AESER	Serious Event		NY	CRF Page yy
AETOXGR	Standard Toxicity Grade	Char		CRF Page yy
AESTDTC	Start Date/Time of Adverse Event	Char	ISO 8601	CRF Page yy
AEENDTC	End Date/Time of Adverse Event	Char	ISO 8601	CRF Page yy

Table 2. AE Data

STUDYID	DOMAIN	USUBJID	AESQ	AESPID	AETERM	AEDECOD	AESER	AETOXGR	AESTDTC	AEENDTC
XYZ	AE	001	5.4034E14	3	Thrombocytopenia	Thrombocytopenia	N	4	2018-01-16	2018-01-23
XYZ	AE	001	5.4034E14	5	Anemia	Anaemia	N	2	2018-01-18	2018-03-26
XYZ	AE	002	5.5175E14	19	Abscess L Flank	Abscess	Y	4	2018-06-25T22:30	2018-09-13

MAPPING THE CRF DATA TO SDTM DOMAINS: ADVERSE EVENTS (AE) AND FINDINGS ABOUT (FA) AND ESTABLISHING THE RELATIONSHIP BETWEEN TWO DATASETS USING THE RELREC DOMAIN-CONTINUED

Table 3. FA Metadata

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Origin//Method/Comment
STUDYID	Study Identifier	Char		Unique identifier for a study
DOMAIN	Domain Abbreviation	Char	FA	Two-character abbreviation for the domain.
USUBJID	Unique Subject Identifier	Char		Unique Subject Identifier
FASEQ	Sequence Number	Num		Derived. Sequence Number given to ensure uniqueness of subject records within a domain. May be any valid number.
FASPID	Sponsor-Defined Identifier Char	Numeric		CRF Page yy
FATESTCD	Findings About Test Short Name	Char		CRF Page yy
FATEST	Findings About Test	Char		CRF Page yy
FAOBJ	The object of the Observation	Char		Used to describe the object or focal point of the findings observation that is represented by –TEST. In this, an adverse event is a focal point for which toxicity grades are represented by FATEST.
FAORRES	Result or Finding in Original Units	Char		CRF Page yy
FASTRESC	Character Result/Finding in Std Format	Char		CRF Page yy
FASTRESN	Numeric Result/Finding in Standard Units	Num		CRF Page yy
FADTC	Date/Time of Collection	Char	ISO 8601	CRF Page yy. The start date of the record is stored in the –DTC variable.
FAENDTC	End Date/Time of Observation	Char	ISO 8601	CRF Page yy

Table 4. FA Data

STUDYID	DOMAIN	USUBJID	FASEQ	FASPID	FATESTCD	FATEST	FAOBJ
XYZ	FA	001	5.403426E14	3	TOXGR	Standard Toxicity Grade	Thrombocytopenia
XYZ	FA	001	5.403427E14	3	TOXGR	Standard Toxicity Grade	Thrombocytopenia
XYZ	FA	001	5.494205E14	3	TOXGR	Standard Toxicity Grade	Thrombocytopenia
XYZ	FA	001	5.40343E14	5	TOXGR	Standard Toxicity Grade	Anaemia
XYZ	FA	002	5.517488E14	19	TOXGR	Standard Toxicity Grade	Abscess
XYZ	FA	002	5.632284E14	19	TOXGR	Standard Toxicity Grade	Abscess
XYZ	FA	002	5.632285E14	19	TOXGR	Standard Toxicity Grade	Abscess
XYZ	FA	002	5.632288E14	19	TOXGR	Standard Toxicity Grade	Abscess

FAORRES	FASTRESC	FASTRESN	FADTC	FAENDTC
3	3		3 2018-01-16	2018-01-17
4	4		4 2018-01-18	2018-01-21
1	1		1 2018-01-22	2018-01-23
2	2		2 2018-01-18	2018-03-26
1	1		1 2018-06-25	2018-06-26
3	3		3 2018-06-27	2018-07-02
4	4		4 2018-07-03	2018-07-03
3	3		3 2018-07-04	2018-09-13

Table 5. RELREC Domain

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
XYZ	AE		AESPID		ONE	1
XYZ	FA		FASPID		MANY	1

DEVELOPING ADAM DATASETS: ANALYSIS DATASET FOR AE TOXICITY (ADAETOX) AND ANALYSIS DATASET FOR ADVERSE EVENTS (ADAE) AND DEFINING TREATMENT-EMERGENT FLAG

Table 6. ADAETOX metadata

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Source/Derivation
STUDYID	Study Identifier	Char		FA.STUDYID
USUBJID	Unique Subject Identifier	Char		FA.USUBJID
FASPID	Sponsor-Defined Identifier	Char		FA.FASPID
AESPID	Sponsor-Defined Identifier	Char		AE.AESPID
FASEQ	Sequence Number	Num		FA.FASEQ
AEDECOD	Dictionary-Derived Term	Char		AE.AEDECOD
FAOBJ	Object of the Observation	Num		FA.FAOBJ
ATERM	Analysis Term	Num		FA.FAOBJ or AE.AEDECOD
TOXSTD	Toxicity Grade Start Date	Num	YYMMDD10.	Numeric Version of FA.FADTC
TOXENDT	Toxicity Grade End Date	Num	YYMMDD10.	Numeric Version of FA.FAENDTC
ATOXGR	Analysis Toxicity Grade	Num	1,2,3,4,5	FA.FAORRES where FA.FATEST=" Standard Toxicity Grade"
ATOXGRN	Analysis Toxicity Grade (N)	Char		FA.FASTRESN where FA.FATEST=" Standard Toxicity Grade"
BTOXGR	Baseline Toxicity Grade	Num		The subject's baseline toxicity grade, ATOXGR of the baseline record identified by ABLFL.
BTOXGRN	Baseline Toxicity Grade (N)	Num		Numeric version of BTOXGR.
ABLFL	Baseline Record Flag	Char	Y	Set ABLFL=" Y" for the record within USUBJID and FA.FASPID for non-missing last record before TRTSDT.
POSTBLFL	Post Baseline Record Flag	Char	Y	Set POSTBLFL=" Y" for the record within USUBJID and FA.FASPID for the records that have TOXSTD on after TRTSDT and (either a. on/before (TRTEDT+30 days) for non-serious AEs or b. on/before (TRTEDT+90 days) for serious AEs)
AOC01FL	1 st worsening of AE post-baseline	Char	Y	1st Occurrence of the worsening of toxicity grade compared to its baseline toxicity grade within-the subject for AE.AESPID.
TRTSDT	Date of First Exposure to Treatment	Num	YYMMDD10.	ADSL.TRTSDT
TRTEDT	Date of Last Exposure to Treatment	Num	YYMMDD10.	ADSL.TRTEDE
SAFFL	Safety Population Flag	Char	Y	ADSL.SAFFL

Table 7. ADAETOX Data

STUDYID	USUBJID	AESPID	FASPID	FASEQ	AEDECOD	FAOBJ	ATERM	TOXSTD	TOXENDT	AESTDTC	AEENDTC
XYZ	001	3	3	5.40343E14	Thrombocytopenia	Thrombocytopenia	Thrombocytopenia	2018-01-16	2018-01-17	2018-01-16	2018-01-23
XYZ	001	3	3	5.40343E14	Thrombocytopenia	Thrombocytopenia	Thrombocytopenia	2018-01-18	2018-01-21	2018-01-16	2018-01-23
XYZ	001	3	3	5.4942E14	Thrombocytopenia	Thrombocytopenia	Thrombocytopenia	2018-01-22	2018-01-23	2018-01-16	2018-01-23
XYZ	001	5	5	5.40343E14	Anaemia	Anaemia	Anaemia	2018-01-18	2018-03-26	2018-01-18	2018-03-26
XYZ	002	19	19	5.51749E14	Abscess	Abscess	Abscess	2018-06-25	2018-06-26	2018-06-25T22.30	2018-09-13
XYZ	002	19	19	5.63228E14	Abscess	Abscess	Abscess	2018-06-27	2018-07-02	2018-06-25T22.30	2018-09-13
XYZ	002	19	19	5.63228E14	Abscess	Abscess	Abscess	2018-07-03	2018-07-03	2018-06-25T22.30	2018-09-13
XYZ	002	19	19	5.63229E14	Abscess	Abscess	Abscess	2018-07-04	2018-09-13	2018-06-25T22.30	2018-09-13

ATOXGR	ATOXGRN	BTOXGR	BTOXGRN	AESER	ABLFL	POSTBLFL	AOC01FL	TRTSDT	TRTEDT	SAFFL
3	3	3	3	N	Y			2018-01-17	2018-05-29	Y
4	4	3		N		Y	Y	2018-01-17	2018-05-29	Y
1	1	3		N	Y			2018-01-17	2018-05-29	Y
2	2			N	Y			2018-01-17	2018-05-29	Y
1	1	1		Y	Y			2018-06-27	2018-05-02	Y
3	3	1		Y	Y	Y		2018-06-27	2018-05-02	Y
4	4	1		Y	Y			2018-06-27	2018-05-02	Y
3	3	1		Y	Y	Y		2018-06-27	2018-05-02	Y

ANALYSIS DATASET FOR ADVERSE EVENTS (ADAE)

Table 8. ADAE metadata

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Notes
STUDYID	Study Identifier	Char		AE.STUDYID
USUBJID	Unique Subject Identifier	Char		AE.USUBJID
AESPID	Sponsor-Defined Identifier	Char		AE.AESPID
AESEQ	Sequence Number	Num		AE.AESEQ
AETERM	Reported Term for the Adverse Event	Char		AE.AETERM
AEDECOD	Dictionary-Derived Term	Char	MedDRA	AE.AEDECOD
AESTDTC	Start Date/Time of Adverse Event	Char	ISO 8601	AE.AESTDTC
ASTDT	Analysis Start Date	Num	YYMMDD10.	Numeric date corresponding to AE.AESTDTC
AEENDTC	Start Date/Time of Adverse Event	Char	ISO 8601	AE.AEENDTC
AENDT	Analysis End Date	Num	YYMMDD10.	Numeric date corresponding to AE.AEENDTC
AESER	Serious Event	Char	Y, N	AE.AESER
WORTOXDT	Worsening Toxicity Date	Char	YYMMDD10.	Populate with the values of ADAETOX.TOXSDT where ADAETOX.AOCC01FL="Y".
TRTEMFL	Treatment-Emergent Flag	Char	Y	Set TRTEMFL= "Y" For the records of ADSL.ASTDT is on /after TRTSDT and (either a. on/before (TRTEDT+30 days) for non-serious AEs or b. on/before (TRTEDT+90 days) for serious AEs) OR For the records where ADAE.WORTOXDT is on /after TRTSDT.
TRTSDT	Date of First Exposure to Treatment	Num	YYMMDD10.	ADSL.TRTSDT
TRTEDT	Date of First Exposure to Treatment	Num	YYMMDD10.	ADSL.TRTSDT
SAFFL	Safety Population Flag	Char	Y	ADSL.SAFFL

Table 9. ADAE Data

USUBJID	AESPID	AESEQ	AETERM	AEDECOD	AESTDTC	ASTDT
001	3	5.4034233E14	Thrombocytopenia	Thrombocytopenia	2018-01-16	2018-01-16
001	5	5.4034289E14	Anemia	Anaemia	2018-01-18	2018-01-18
002	19	5.5174881E14	Abscess L Flank	Abscess	2018-06-25T22:30	2018-06-25

AEENDTC	AENDT	AESER	WORTOXDT	TRTEMFL	TRTSDT	TRTEDT	SAFFL
2018-01-23	2018-01-23	N	2018-01-18	Y	2018-01-17	2018-05-29	Y
2018-03-26	2018-03-26	N		Y	2018-01-17	2018-05-29	Y
2018-09-13	2018-09-13	Y	2018-06-27	Y	2018-06-27	2018-05-02	Y

Conclusion

- This paper presents a practical example of Adverse event data with toxicity changes
- The step-by-step examples presented in this paper begin with data collection and provide data mapping strategies to SDTM and ADaM datasets using CDSIC standards
- The relationship between SDTM: FA and AE domains is presented using the RELREC domain. The creation of Analysis datasets: ADAETOX and ADAE is comprehensively presented using metadata, and SAS programs to provide traceability to SDTM domains
- The creation of Analysis datasets: ADAETOX and ADAE is comprehensively presented using metadata, and SAS programs to provide traceability to SDTM domains.
- Though the examples presented in the paper may not cover all the variabilities associated with study designs and study needs but represent the most common situations.
- These examples can be used as reference or the best practice for the adverse event data collection, standardization, and treatment emergence definitions.

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CONTACT INFORMATION

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Thank You!

