Paper DS03

Collection, Standardization, and Reporting of Adverse Events with Toxicity Changes Using CDISC Standards in Oncology Clinical Trials

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ABSTRACT:

Understanding the temporal changes of toxicity is crucial for accurate comparison of safety profiles between the treatments or even multiple toxicities within a treatment. The National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) is a widely used standard for reporting adverse event toxicity grades in oncology studies. Adverse events are evaluated against the NCI CTCAE guidelines and assigned toxicity grades. In this paper, we will carefully review the collection of adverse events and toxicity changes over time within-the study and rendering of the collected data in the SDTM Adverse Events (AE) and Finding About (FA) domains. Further evaluation includes using AE and FA domains to define treatment-emergent flags in the Analysis Dataset for Adverse Events (ADAE) for the events that are worsening in toxicity after treatment.

INTRODUCTION:

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. On the other hand, 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. For example, a study may be interested to display how a particular AE changes its toxicity over time. 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. In this paper, an adverse event is followed for its toxicity changes, and the relationship of an adverse event and its toxicity changes are captured at data entry and presented in standardized data structures (SDTM: AE, FA domains) establishing the traceability to case report form (CRF). Further ADaM datasets are designed to present toxicity changes of an adverse event and how the onset date of an AE or the date of the first worsening of AE post-baseline is used to flag the records with a treatment-emergent flag (TRTEMFL). The paper is organized as follows.

1. **COLLECTION OF AN ADVERSE EVENT AND ITS TOXICITY CHANGES IN CRF**
2. **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**
3. **DEVELOPING ADAM DATASETS: ANALYSIS DATASET FOR AE TOXICITY (ADAETOX) AND ANALYSIS DATASET FOR ADVERSE EVENTS (ADAE) AND DEFINING THE TREATMENT-EMERGENT FLAG (TRTEMFL)**
4. **DATA FLOW AND DATA DEPENDENCIES**

1. COLLECTION OF AN ADVERSE EVENT AND ITS TOXICITY CHANGES IN CASE REPORT FORM (CRF):

Collection of adverse event data with the toxicity changes requires inter-departmental collaboration and requires the involvement of statisticians, programmers, and data management personnel. It is critical to have clear data entry

guidelines/instructions for completing the AE CRF form. Presented below is how an adverse event and its toxicity changes are captured on CRF.
Here an adverse event is collected with two section headers: Adverse Events and Adverse Event Toxicity Change (Fig. 1).

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	O 1 O 2 O 3 O 4 O 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

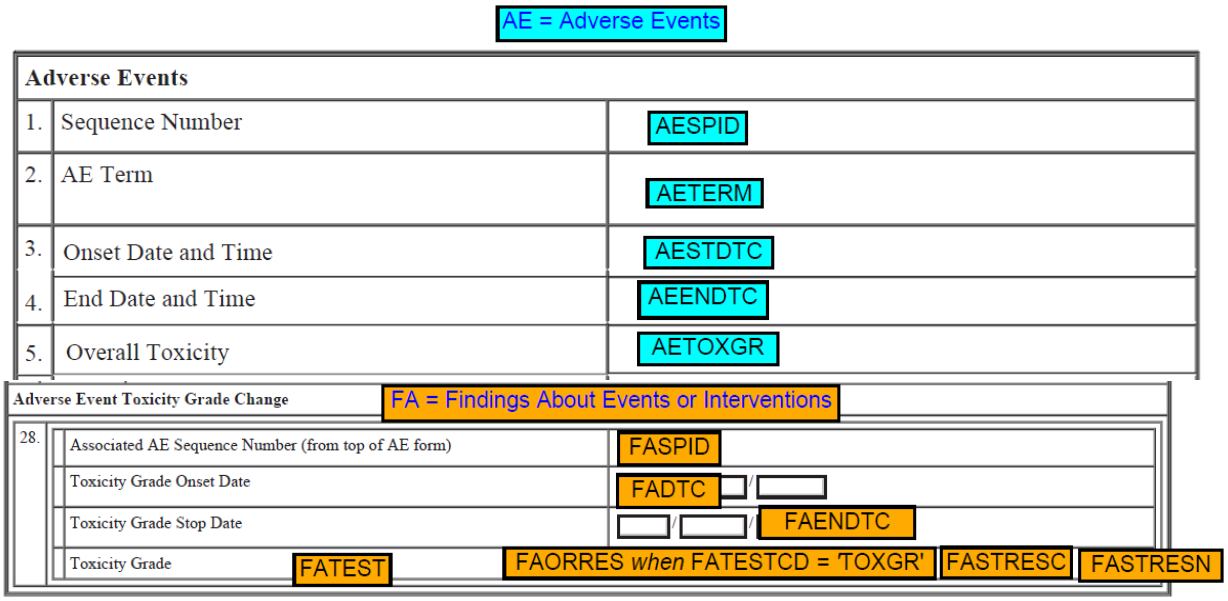
ADVERSE EVENT TOXICITY GRADE CHANGE ENTRY: This section of CRF captures initial toxicity entry and any further changes to toxicity throughout the study and the fields of the section are described below.

- **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

2. 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:

The annotated CRF (aCRF) is one of the components of the esubmission deliverables and maps the CRF fields to corresponding SDTM domains and variables**.** Here we present how the data fields within Adverse Events and Adverse Event Toxicity Grade Change sections of CRF are mapped to SDTM domains: AE and FA domains (Fig 2).

Fig 2. Annotated Adverse Events and Adverse Event Toxicity Grade Change CRF



After annotation, the metadata for AE and FA needs to be prepared to describe the mapping of CRF fields and any additional variables presented in these SDTM domains as per the SDTM implementation guidelines. Please see metadata for AE (Table 1) and FA domains (Table 3) along with sample data (Table 2 for AE and Table 4 for FA).

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
AESEQ	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	AESEQ	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

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

The AE domain captures one record for each new adverse event within USUBJID. AETOXGR has the value of the highest toxicity grade collected on CRF for each of the adverse events. Whereas the FA domain captures each toxicity change within an adverse event using FATEST/FATESTCD and FAORRES/ FASTRESC/FASTRESN. The start and end dates of the toxicity changes are presented with FADTC and FAENDTC respectively. It is interesting to note that FASTDTC is not allowed in the FA domain as it is Findings Domain and FADTC is creatively used to capture the toxicity change start date. Please note the link between records in the AE domain and FA domain is established through AESPID/FASPID. FAOBJ is populated with AEDECOD values. The FATEST/FATESTCD and FAOBJ are both needed to describe the topic of the record.

The RELREC domain presents a one-to-many dataset-level relationship between AE and FA domains (Table 5). The example below presents the relationship between a single record in AE domain and multiple records in FA domain using a sponsor ID (-- SPID) value:

> The --SPID variable within USUBJID is used to merge these datasets. It is a system-generated identifier is unique to each adverse event within each subject. Please note that all records in the AE domain are being related to all the records in the FA domain, so both USUBJID and IDVARVAL are null.

Table 5. RELREC Domain:

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

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

Two ADaM datasets are created: ADAETOX and ADAE.

ANALYSIS DATASET FOR AE TOXICITY (ADAETOX):

Input datasets AE, FA, and ADSL are used to present the toxicity changes of an AE using the ADaM dataset ADAETOX. AE and FA domains are brought together first by merging with --SPID variable and then merged with ADSL. The SDTM variable FAOBJ was mapped to the ADaM variable ATERM (Analysis Term), and variable FAORRES was mapped to ADaM variable ATOXGR. Each Toxicity change start/end dates: FADTC/FAENDTC are mapped to TOXSTDT/TOXENDT. The records qualifying the baseline definition are flagged with ABLFL= " Y " and the corresponding toxicity value is presented as BTOXGR for all records for a unique AE within USUBJID. Similarly, the post-baseline records are flagged with POSTBLFL= "Y", if the post-baseline toxicity start date is on after the treatment start date, but on/before the 30th day after the treatment end date (TRTEDT+30 days) for non-serious AEs. Whereas for the serious AEs that POSTBLFL= "Y" is extended up to the 90th day after treatment end date (TRTEDT+90 days). The occurrence flag AOCC01FL is used to flag the first worsening of an AE post-baseline within each subject and adverse event.

Note that the ADAETOX dataset brings back the relationships of AE and FA and provides transparencies regarding baseline and post-baseline toxicities. Importantly, metadata traceability is provided for analysis variables such as ABLFL, POSTBLFL, and AOCC01FL. The toxicity start date (TOXSTDT) corresponding to AOCC01FL=" Y" is critical for programming TRTEMFL in ADAE. For further details, please refer to ADAETOX metadata (Table 6), program, and data below (Table 7).

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

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Source/Derivation
AEDECOD	Dictionary-Derived Term	Char		AE.AEDECOD
FAOBJ	Object of the Observation	Num		FA.FAOBJ
ATERM	Analysis Term	Num		FA.FAOBJ or AE.AEDECOD
TOXSTDT	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 TOXSTDT on after TRTSDT and (either a. on/before (TRTEDT+30 days) for non-serious AEs or b. on/before (TRTEDT+90 days) for serous AEs)
AOCC01FL	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.TRTEDT
SAFFL	Safety Population Flag	Char	Y	ADSL.SAFFL

ADAETOX SAS Program:

```
*-------------------------------------------------------------------------------
                            ADAETOX -PROGRAMMING-SNIPPET
*-------------------------------------------------------------------------------

/*Assign values of  aespid to temporary variable spid*/
data ae;
 set sdtm.ae ;
   spid=input(aespid, best.);
run;

proc sort data=ae;
 by usubjid spid ;
run;
data fa;
 set sdtm.fa ;
   spid=input(aespid, best.);
run;

/*Merge Ae domain and FA domain by spid and create new variables */

data aefa;
 merge ae(in=a) fa;
       by usubjid spid;
       if a ;
       aterm=aedecod;
       toxstdt=input(strip(fadtc), yymmdd10.);
       toxendt=input(strip(faendtc),  yymmdd10.);
       atoxgr=faorres;
       atoxgrn=fastresn;

format toxstdt toxendt  yymmdd10.;
run;


 proc sort data=adam.adsl out=adsl;
       by usubjid;
 run;

 proc sort data= aefa;
       by usubjid;
 run;

data aefa_1;
 merge aefa(in=a) adsl;
       by usubjid;
       if a;
run;

/*Flag the baseline toxicity grades with baseline flag and */
/*Create new variable btoxgr with baseline toxicity values */
 /* Flag the post-baseline records*/

data aefa_2;
  set aefa_1;
  if (toxstdt ne  . and trtsdt ne . and toxstdt <trtsdt);
run;

proc sort data= aefa_2;
       by usubjid aespid toxstdt ;
 run;
```

```
data aefa_bl (keep=usubjid faseq aespid ablfl btoxgr  btoxgrn );
  set aefa_2;
       by usubjid aespid toxstdt;
       if last.aespid;
       ablfl="Y";
       btoxgr=atoxgr;
       btoxgrn=atoxgrn;
run;

proc sort data=aefa_bl;
  by usubjid faseq;
run;

proc sort data=aefa_1;
  by usubjid faseq;
run;

data aefa_3;
  merge aefa_1 (in=a) aefa_bl (keep=usubjid faseq ablfl);
  by usubjid faseq;
  if a;
run;

proc sort data=aefa_bl  ;
  by usubjid aespid;
run;

proc sort data=aefa_3 ;
  by usubjid aespid;
run;

data aefa_4;
  merge aefa_3(in=a) aefa_bl (keep=usubjid btoxgr aespid  btoxgrn);
  by usubjid aespid;
  if a;
             if (trtsdt<=toxstdt <=trtedt +30 and upcase(aeser) ="N") or (trtsdt<=toxstdt
             <=trtedt +90 and upcase(aeser) ="Y")
             then postblfl="Y";
  run;

/*Flag the record with AOCC01FL="Y for the first worsening of AE post-baseline */

proc sort data=aefa_4 out=aefa_5;
       where postblfl="Y" and (atoxgrn ne . and btoxgrn ne . and atoxgrn  >btoxgrn);
  by usubjid aespid toxstdt faseq;
run;

data aocc01fl  (keep=usubjid faseq aespid aocc01fl );
       set aefa_5;
       by usubjid aespid toxstdt faseq;
       if first.aespid;
       aocc01fl ='Y';
run;

proc sort data=aefa_4;
        by usubjid aespid faseq;
run;

proc sort data=aocc01fl;
       by usubjid aespid faseq;
run;
```

```
data aefa_5;
       merge aefa_4(in=a)  aocc01fl;
       by usubjid aespid faseq;
run;

/*Output final adaetox data*/
proc sort data=aefa_5 out=adam.adaetox;
       by usubjid aespid faseq;
run;
```

Table 7. ADAETOX Data

STUDYID	USUBJID	AESPID	FASPID	FASEQ	AEDECOD	FAOBJ	ATERM	TOXSTDT	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	POSTBLF	AOCC01FL	TRTSDT	TRTEDT	SAFFL
3	3	3	3	N	Y			2018-01-17	2018-05-29	Y
4	4	3	3	N		Y	Y	2018-01-17	2018-05-29	Y
1	1	3	3	N		Y		2018-01-17	2018-05-29	Y
2	2		.	N		Y		2018-01-17	2018-05-29	Y
1	1	1	1	Y	Y			2018-06-27	2018-05-02	Y
3	3	1	1	Y		Y	Y	2018-06-27	2018-05-02	Y
4	4	1	1	Y		Y		2018-06-27	2018-05-02	Y
3	3	1	1	Y		Y		2018-06-27	2018-05-02	Y

ANALYSIS DATASET FOR ADVERSE EVENTS (ADAE):

The ADAE dataset takes the records from SDTM AE, and importantly the first worsening of an AE post-baseline from ADAETOX. The AE and ADAETOX datasets are merged with USUBJID and –SPID followed by merging with ADSL by USUBJID. The numeric versions of AE onset/end dates are populated with new variables ASTDT/AENDT. The date of the first worsening of an AE post-baseline is populated with WORTOXDT. Finally, TRTEMFL is derived to "Y" for the records either using ASTDT or WORTOXDT compared to treatment start and end dates. In this specific example, adverse events are considered as treatment-emergent, if the AE start date is on or after the treatment start date(TRTSDT), and on or before the 30th day after the treatment end date (TRTEDT+30 days) for non-serious AEs. The window is further extended to the 90th day after treatment end date (TRTEDT+90 days) for serious AEs. Similarly, an AE is considered as treatment-emergent if the AE worsens from baseline and the worsening date (WORTOXDT) is on or after the treatment start date(TRTSDT), and on or before the 30th day after treatment end date (TRTEDT+30 days) for non-serious AEs. Again, this window is further extended to the 90th day after the treatment end date (TRTEDT+90 days) for serious AEs. Please note that while programming WORTOXDT in the ADAETOX dataset the above rule is considered. Please review the ADAE metadata (Table 8), program, and data (Table 9) for further details.

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

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Notes
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 serous 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

ADAE SAS Program:

```
*-------------------------------------------------------------------------------
                ADAE -PROGRAM-SNIPPET
*-------------------------------------------------------------------------------
proc sort data=sdtm.ae out=ae;
 by usubjid aespid;
run;
proc sort data= adam.adaetox out=worstoxdt (keep=usubjid toxstdt aespid
rename=(toxstdt=wortoxdt));
       by usubjid aespid ;
       where aocc01fl ="Y";
run;
data adae;
       merge ae worstoxdt;
       by usubjid aespid;

       astdt=input(strip(aestdtc), yymmdd10.);
```

```
        aeendt=input(strip(aeendtc),  yymmdd10.);

              if (trtsdt<=astdt <=trtedt +30 and upcase(aeser) ="N") or
                    (trtsdt<= astdt <=trtedt +90 and upcase(aeser) ="Y")or
                    (trtsdt<= wortoxdt )
              then trtemfl="Y";
run;
proc sort data=adae out= adam.adae;
       by usubjid aespid aeseq;
run;
```

Table 9. ADAE Data

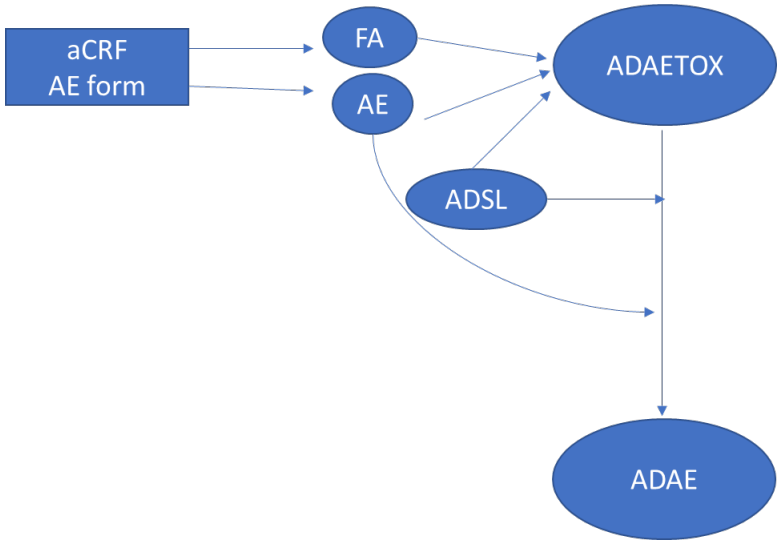
USUBJID	AESPID	AESEQ	AETERM	AEDECOD	AESTDTC	ASTDT
001	3	5.4034233E14	Thrombocytopenia	Thrombocytopenia	2018-01-16	2018-01-16
001	5	5.4034289E14	Anemia	Anaemia	2018-01-18	2018-01-18
002	19	5.5174881E14	Abscess L Flank	Abscess	2018-06-25T22:30	2018-06-25

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

4. DATA FLOW AND DATA DEPENDENCIES

The complex data flow in the creation of ADAETOX and ADAE can be presented at a high level using a data flow diagram as a part of the Analysis Data Reviewer Guide (ADRG). As you see in Fig.3, the CRF collected data for adverse events are mapped to AE and FA domains. The FA and AE domains are linked through –SPID within each USUBJID. The AE and FA SDTM domains are merged using USUBJID and --SPID and further merged with ADSL to create ADAETOX. The main intent of ADAETOX is to flag the first worsening of an AE post-baseline in addition to presenting all toxicity grades, timings, and baseline and post-baseline flags. ADAETOX is further subset for the records that have the first occurrence of worsening of AE post-baseline and merged with AE using --SPID followed by merging with ADSL. The onset dates of AE and the date corresponding to the first worsening of an AE post-baseline are used in conjunction with the treatment start date/end dates to flag the records with the treatment-emergent flag.

Figure 3. Data Flow Diagram of Adverse Events.



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. 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.

REFERENCES:

Please refer to https://www.cdisc.org/ for all CDISC documents discussed in this paper.

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