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How to Understand Therapeutic Area Data Standards User Guide for Reactogenicity Events in Vaccine Studies

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ABSTRACT

Vaccine clinical trial safety data submission should include reactogenicity events, unsolicited AEs, medically attended adverse events (MAAEs), and death.

Reactogenicity is a set of pre-defined adverse events collected within a prespecified time frame, typically collected on either diary cards or reactogenicity case report forms. Reactogenicity events can be classified as either administration site events (e.g., redness, itching, and pain) or systemic events (e.g., fever, fatigue, vomiting, and headache).

Reactogenicity data are required to be represented primarily in the SDTM Clinical Events (CE) with Findings About Clinical Events (FACE) domain and Vital Sign (VS) domain to provide the specific information for each event.

In this paper, I will discuss on how to understand Therapeutic Area Data Standards User Guide for Vaccines (TAUG-VAX) three model strategies "Flat Model", "Nested Model", and "Highly Nested Model" when mapping diary cards into FACE, VS, and CE domains. How to represent SDTM data when reactogenicity events continue beyond the planned assessment period.

INTRODUCTION

The purpose of the TAUG-VAX is to describe how to use CDISC standards to represent data pertaining to vaccines studies. Current version (1.1) of the TAUG-VAX focuses on safety data for reactogenicity events collected during vaccines trials and based on the CDISC SDTM v1.4 and the SDTMIG v3.2.

This paper will focus on two topics.

- The TAUG-VAX three model strategies.
- The reactogenicity events continue beyond the planned assessment period.

REACTOGENICITY SAFETY ASSESSEMENTS TRANSCRIPTION OF DIARY CARDS WITH THREE MODEL STRATEGIES

In order to explain the methods of mapping diary cards into SDTM based on the three model strategies, this paper will simplify the hypothetical trial design in TAUG-VAX by reducing the number of vaccines from four (two vaccines at the same occasion and both at two different time points) to two (one vaccine at two different time points) per subject. The paper also adds additional information of dummy Case Report Forms (CRF) and the definitions of the reactogenicity event occurrence and severity grading in a hypothetical protocol according to trial design.

Data are collected at four visits in the hypothetical trial.

- Visit 1: Screening and first administration of vaccine.
- Visit 2: Second administration of vaccine.
- Visit 3: Final assessments following the TREATMENT Epoch (e.g., blood sampling)
- Visit 4: At the end of a 90-day follow-up period.

The paper will focus on Visit 1, Visit 2.

For example, subject AB-1001 received two vaccines “VACCINE A”. The first administration of vaccine was on Study Day 1 (Visit 1, January 10, 2023); the second administration of vaccine was on Study Day 22 (Visit 2, January 31, 2023). Both visits fell within the "TREATMENT" Epoch. Based on CDISC SDTMv1.4 and the SDTMIGv3.2, SDTM Exposure (EX) domain is generated here.

EX.XPT

USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	VISITNUM	VISIT	EPOCH	EXDTC	EXSTDTC	EXENDTC	EXDY
ABC-1001	1	VACCINE A	0.5	mL	INJECTION	1	VISIT 1	TREATMENT	2023-01-10	2023-01-10	2023-01-10	1
ABC-1001	2	VACCINE A	0.5	mL	INJECTION	2	VISIT 2	TREATMENT	2023-01-31	2023-01-31	2023-01-31	22

After each vaccination, subjects self-monitor both systemic (fever and vomiting) and administration site (redness) reactogenicity events and record their findings on a daily diary form. Monitoring of symptoms starts immediately after vaccine administration. Monitoring continues through the end of the second calendar day after vaccination (Day 3), so the planned reactogenicity assessment period is from Day 1 to Day 3.

Dummy Diary Card Form

Date _____(mm/dd/yyyy)

Vomiting / Throwing up

[ ] 0 = None

[ ] 1 = Mild (1 - 2 times in 24 hours)

[ ] 2 = Moderate (3 - 5 times in 24 hours)

[ ] 3 = Severe (6 or more times in 24 hours)

Redness at the injection site - Measurement _____ (mm)

Temperature - Measurement _____ (°F)

The hypothetical protocol defined that a solicited reactogenicity event is considered to have occurred and severity grading if:

- **Fever**: The subject's maximum temperature is greater than 100.4°F and severity grading is Mild (≥100.4 -101.1°F); Moderate (≥101.1 – 102.0°F); Severe (≥102.0°F).
- **Vomiting**: The subject vomited at least once during the observation period and severity grading is Mild (1 - 2 times in 24 hours); Moderate (3 - 5 times in 24 hours); Severe (6 or more times in 24 hours).
- **Erythema**: The subject’s maximum longest diameter of the redness is greater than 25mm at the administration site and severity grading is Mild (≥25-50mm); Moderate (≥51-100 mm); Severe (≥100 mm).

In the examples shown in this TAUG-VAX, all daily assessments from diary cards are represented in the FA domain (vomiting and erythema) and VS domain (temperature). A global record for each visit is created to represent the event in the CE domain (vomiting, erythema, and fever) based on FA and VS.

There are three model strategies "Flat Model", "Nested Model", and "Highly Nested Model" to represent the diary card data into FA, VS, CE domains. The example below shows how.

The subject AB-1001 experienced all three events (fever, vomiting, and redness) at some point during the three-day evaluation period after the first vaccination. e.g., the subject experienced vomiting on the first day, and fever, redness on both the first and second day. After the second vaccinations, the subject did not experience any reactogenicity events during the three-day assessment interval.

1. FLAT MODEL

All the daily assessments are transcribed/loaded from the diary card into VS and FA domains; a global event record is created in CE domain, whether or not a reactogenicity event occurred during the assessment interval.

VS domain

Temperature for each day of two three-day observation periods are loaded into VS with value “SYSTEMIC” via variable VSSCAT and value “REACTOGENICITY” via variable VSCAT.

The variable VSLNKGRP has assigned values (”2”, "5") from each visit and can be used to link the records for two observation periods to the summary fever records in CE via CELNKGRP.

Individual dates from the daily diary collection are represented in the VS domain using the variable VSDTC.

VS.XPT

Row	STUDYID	DOMAIN	USUBJID	VSSEQ	VSLNKGRP	VSTESTCD	VSTEST	VSCAT	VSSCAT	VSORRES	VSORRESU
1	ABC	VS	ABC-1001	1	2	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	101.1	F
2	ABC	VS	ABC-1001	2	2	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	100.8	F
3	ABC	VS	ABC-1001	3	2	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	98.6	F
4	ABC	VS	ABC-1001	4	5	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	98.9	F
5	ABC	VS	ABC-1001	5	5	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	98.6	F
6	ABC	VS	ABC-1001	6	5	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	98.8	F

Row	VISITNUM	VISIT	EPOCH	VSDTC	VSDY	VSTPT	VSTPTNUM	VSTPTREF	VSRFTDTC	VSEVLINT	VSEVINTX
1	1	VISIT 1	TREATMENT	2023-01-10	1	END DAY 1	1	VACCINATION 1	2023-01-10		SINCE VACCINATION
2	1	VISIT 1	TREATMENT	2023-01-11	2	END DAY 2	2	VACCINATION 1	2023-01-10	-P1D	
3	1	VISIT 1	TREATMENT	2023-01-12	3	END DAY 3	3	VACCINATION 1	2023-01-10	-P1D	
4	2	VISIT 2	TREATMENT	2023-01-31	22	END DAY 1	1	VACCINATION 2	2023-01-31		SINCE VACCINATION
5	2	VISIT 2	TREATMENT	2023-02-01	23	END DAY 2	2	VACCINATION 2	2023-01-31	-P1D	
6	2	VISIT 2	TREATMENT	2023-02-02	24	END DAY 3	3	VACCINATION 2	2023-01-31	-P1D	

FA domain.

Daily assessments for redness and vomiting are represented using Clinical Events (FACE). The value in FAOBJ is the object of the assessment ("Erythema") instead of “Redness”.

The variable FALNKGRP has assigned values (”1”, "3", “4”, “6”) and can be used to link the records for two observation periods to the summary vomiting and Erythema records in CE via CELNKGRP.

Individual dates from the daily diary collection are represented in the FACE domain using the variable FADTC.

FACE.XPT

Row	STUDYID	DOMAIN	USUBJID	FASEQ	FALNKGRP	FATESTCD	FATEST	FAOBJ	FACAT	FASCAT	FAORRES	FAORRESU
1	ABC	FA	ABC-1001	1	1	EPSDNUM	Number of Episodes	Vomiting	REACTOGENICITY	SYSTEMIC	3	
2	ABC	FA	ABC-1001	2	1	EPSDNUM	Number of Episodes	Vomiting	REACTOGENICITY	SYSTEMIC	0	
3	ABC	FA	ABC-1001	3	1	EPSDNUM	Number of Episodes	Vomiting	REACTOGENICITY	SYSTEMIC	0	
4	ABC	FA	ABC-1001	4	3	LDIAM	Longest Diameter	Erythema	REACTOGENICITY	ADMINISTRATION SITE	35	mm
5	ABC	FA	ABC-1001	5	3	LDIAM	Longest Diameter	Erythema	REACTOGENICITY	ADMINISTRATION SITE	25	mm
6	ABC	FA	ABC-1001	6	3	LDIAM	Longest Diameter	Erythema	REACTOGENICITY	ADMINISTRATION SITE	15	mm
7	ABC	FA	ABC-1001	7	4	EPSDNUM	Number of Episodes	Vomiting	REACTOGENICITY	SYSTEMIC	0	
8	ABC	FA	ABC-1001	8	4	EPSDNUM	Number of Episodes	Vomiting	REACTOGENICITY	SYSTEMIC	0	
9	ABC	FA	ABC-1001	9	4	EPSDNUM	Number of Episodes	Vomiting	REACTOGENICITY	SYSTEMIC	0	
10	ABC	FA	ABC-1001	10	6	LDIAM	Longest Diameter	Erythema	REACTOGENICITY	ADMINISTRATION SITE	5	mm
11	ABC	FA	ABC-1001	11	6	LDIAM	Longest Diameter	Erythema	REACTOGENICITY	ADMINISTRATION SITE	0	mm
12	ABC	FA	ABC-1001	12	6	LDIAM	Longest Diameter	Erythema	REACTOGENICITY	ADMINISTRATION SITE	0	mm

Row	VISITNUM	VISIT	TAETORD	EPOCH	FADTC	FADY	FATPT	FATPTNUM	FATPTREF	FARFTDTC	FAEVLINT	FAEVINTX
1	1	VISIT 1	2	TREATMENT	2023-01-10	1	END DAY 1	1	VACCINATION 1	2023-01-10		SINCE VACCINATION
2	1	VISIT 1	2	TREATMENT	2023-01-11	2	END DAY 2	2	VACCINATION 1	2023-01-10	-P1D	
3	1	VISIT 1	2	TREATMENT	2023-01-12	3	END DAY 3	3	VACCINATION 1	2023-01-10	-P1D	
4	1	VISIT 1	2	TREATMENT	2023-01-10	1	END DAY 1	1	VACCINATION 1	2023-01-10		SINCE VACCINATION
5	1	VISIT 1	2	TREATMENT	2023-01-11	2	END DAY 2	2	VACCINATION 1	2023-01-10	-P1D	
6	1	VISIT 1	2	TREATMENT	2023-01-12	3	END DAY 3	3	VACCINATION 1	2023-01-10	-P1D	
7	2	VISIT 2	3	TREATMENT	2023-01-31	22	END DAY 1	1	VACCINATION 2	2023-01-31		SINCE VACCINATION
8	2	VISIT 2	3	TREATMENT	2023-02-01	23	END DAY 2	2	VACCINATION 2	2023-01-31	-P1D	
9	2	VISIT 2	3	TREATMENT	2023-02-02	24	END DAY 3	3	VACCINATION 2	2023-01-31	-P1D	
10	2	VISIT 2	3	TREATMENT	2023-01-31	22	END DAY 1	1	VACCINATION 2	2023-01-31		SINCE VACCINATION
11	2	VISIT 2	3	TREATMENT	2023-02-01	23	END DAY 2	2	VACCINATION 2	2023-01-31	-P1D	
12	2	VISIT 2	3	TREATMENT	2023-02-02	24	END DAY 3	3	VACCINATION 2	2023-01-31	-P1D	

CE domain.

The variable CELNKGRP has assigned values (”1”, “2”, "3", “4”, “5”, “6”) and can be used to link back all the records in FA via FALNKGRP (”1”, "3", “4”, “6”) and VS via VSLNKGRP (”2”, "5")

The overall start and end dates of the event are represented in the CE domain using the variables CESTDTC and CEENDTC respectively.

CE domain shows that the subject experienced fever, vomiting, and erythema after the first vaccination.

CE.XPT

Row	STUDYID	DOMAIN	USUBJID	CESEQ	CELNKGRP	CETERM	CEDECOD	CECAT	CESCAT	CEPRESP	CEOCCUR	CESEV
1	ABC	CE	ABC-1001	1	1	Vomiting	Vomiting	REACTOGENICITY	SYSTEMIC	Y	Y	SEVERE
2	ABC	CE	ABC-1001	2	2	Fever	Fever	REACTOGENICITY	SYSTEMIC	Y	Y	MILD
3	ABC	CE	ABC-1001	3	3	Redness	Erythema	REACTOGENICITY	ADMINISTRATION SITE	Y	Y	MILD
4	ABC	CE	ABC-1001	4	4	Vomiting	Vomiting	REACTOGENICITY	SYSTEMIC	Y	N	
5	ABC	CE	ABC-1001	5	5	Fever	Fever	REACTOGENICITY	SYSTEMIC	Y	N	
6	ABC	CE	ABC-1001	6	6	Redness	Erythema	REACTOGENICITY	ADMINISTRATION SITE	Y	N	

Row	TAETORD	EPOCH	CEDTC	CESTDTC	CEENDTC	CEDY	CETPT	CETPTNUM	CETPTREF	CERFTDTC	CEEVINTX
1	2	TREATMENT	2023-01-12	2023-01-10	2023-01-10	3	END DAY 3	3	VACCINATION 1	2023-01-10	SINCE VACCINATION
2	2	TREATMENT	2023-01-12	2023-01-10	2023-01-11	3	END DAY 3	3	VACCINATION 1	2023-01-10	SINCE VACCINATION
3	2	TREATMENT	2023-01-12	2023-01-10	2023-01-11	3	END DAY 3	3	VACCINATION 1	2023-01-10	SINCE VACCINATION
4	3	TREATMENT	2023-02-02			24	END DAY 3	3	VACCINATION 2	2023-01-31	SINCE VACCINATION
5	3	TREATMENT	2023-02-02			24	END DAY 3	3	VACCINATION 2	2023-01-31	SINCE VACCINATION
6	3	TREATMENT	2023-02-02			24	END DAY 3	3	VACCINATION 2	2023-01-31	SINCE VACCINATION

RELREC domain.

The Related Records (RELREC) domain shows that CE and FA can be linked via variables CELNKGRP, FALNKGRP and that CE and VS can be linked via variables CELNKGRP, VSLNKGRP.

RELREC.XPT

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
ABC	CE		CELNKGRP		ONE	1
ABC	FACE		FALNKGRP		MANY	1
ABC	CE		CELNKGRP		ONE	2
ABC	VS		VSLNKGRP		MANY	2

2. NESTED MODEL

Global record is created in CE domain for each reactogenicity event that is assessed; and the daily assessment records for an event are created in FACE and/or VS domain only if the event occurred during the assessment interval.

In nested model, an indicator question is asked first regarding whether or not a specific reactogenicity events (fever, vomiting, or redness) have occurred during the three-day assessment period.

- If the specific event does not occur during the three-day assessment interval, a global occurrence record where CETERM is the event name and CEOCCUR="N" is represented in CE; in this case, the three-day daily assessment records are ***not*** represented in FACE and VS.

- If the event does occur, a global occurrence record where CETERM is the event name and CEOCCUR="Y" is represented in CE; in this case, the each of the three days of records are also represented in FA or VS.

VS domain

The variable VSLNKID is populated with a value by which to link the records to the daily fever record in FACE. Daily temperature measurements in the VS domain are linked to the daily fever occurrence in FA.

The record of Day 3 still includes in VS even the subject did not have a fever on the last day of observation.

VS.XPT

Row	STUDYID	DOMAIN	USUBJID	VSSEQ	VSLNKID	VSTESTCD	VSTEST	VSCAT	VSSCAT	VSORRES	VSORRESU
1	ABC	VS	ABC-1001	1	1	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	101.1	F
2	ABC	VS	ABC-1001	2	2	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	100.8	F
3	ABC	VS	ABC-1001	3	3	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	98.6	F

Row	VISITNUM	VISIT	EPOCH	VSDTC	VSDY	VSTPT	VSTPTNUM	VSTPTREF	VSRFTDTC	VSEVLINT	VSEVINTX
1	1	VISIT 1	TREATMENT	2023-01-10	1	END DAY 1	1	VACCINATION 1	2023-01-10		SINCE VACCINATION
2	1	VISIT 1	TREATMENT	2023-01-11	2	END DAY 2	2	VACCINATION 1	2023-01-10	-P1D	
3	1	VISIT 1	TREATMENT	2023-01-12	3	END DAY 3	3	VACCINATION 1	2023-01-10	-P1D	

FA domain.

FALNKID connects the daily fever records to the daily temperature records in VS via VSLNKID.

The variable FALNKGRP has values (”1”, "2", “3”) and can be used to link the records to the summary vomiting, Fever, and Erythema records in CE via CELNKGRP.

FACE.XPT

Row	STUDYID	DOMAIN	USUBJID	FASEQ	FALNKID	FALNKGRP	FATESTCD	FATEST	FAOBJ	FASCAT	FAORRES	FAORRESU
1	ABC	FA	ABC-1001	1		1	EPSDNUM	Number of Episodes	Vomiting	SYSTEMIC	3	
2	ABC	FA	ABC-1001	2		1	EPSDNUM	Number of Episodes	Vomiting	SYSTEMIC	0	
3	ABC	FA	ABC-1001	3		1	EPSDNUM	Number of Episodes	Vomiting	SYSTEMIC	0	
4	ABC	FA	ABC-1001	4	1	2	OCCUR	Occurrence Indicator	Fever	SYSTEMIC	Y	
5	ABC	FA	ABC-1001	5	2	2	OCCUR	Occurrence Indicator	Fever	SYSTEMIC	Y	
6	ABC	FA	ABC-1001	6	3	2	OCCUR	Occurrence Indicator	Fever	SYSTEMIC	N	
10	ABC	FA	ABC-1001	7		3	LDIAM	Longest Diameter	Erythema	ADMINISTRATION SITE	35	mm
11	ABC	FA	ABC-1001	8		3	LDIAM	Longest Diameter	Erythema	ADMINISTRATION SITE	25	mm
12	ABC	FA	ABC-1001	9		3	LDIAM	Longest Diameter	Erythema	ADMINISTRATION SITE	15	mm

CE domain.

The variable CELNKGRP has values (”1”, “2”, "3”) and can be used to link back all the records in FA via FALNKGRP.

After the second vaccinations, the subject did not experience any reactogenicity events during the three-day assessment interval. the daily assessment records are ***not*** represented in FACE and VS, so Value of CELNKGRP is blank in CE domain,

CE.XPT

Row	STUDYID	DOMAIN	USUBJID	CESEQ	CELNKGRP	CETERM	CEDECOD	CECAT	CESCAT	CEPRESP	CEOCCUR	CESEV
1	ABC	CE	ABC-1001	1	1	Vomiting	Vomiting	REACTOGENICITY	SYSTEMIC	Y	Y	SEVERE
2	ABC	CE	ABC-1001	2	2	Fever	Fever	REACTOGENICITY	SYSTEMIC	Y	Y	MILD
3	ABC	CE	ABC-1001	3	3	Redness	Erythema	REACTOGENICITY	ADMINISTRATION SITE	Y	Y	MILD
4	ABC	CE	ABC-1001	4		Vomiting	Vomiting	REACTOGENICITY	SYSTEMIC	Y	N	
5	ABC	CE	ABC-1001	5		Fever	Fever	REACTOGENICITY	SYSTEMIC	Y	N	
6	ABC	CE	ABC-1001	6		Redness	Erythema	REACTOGENICITY	ADMINISTRATION SITE	Y	N	

RELREC domain.

The Related Records (RELREC) domain shows that VS and FA are one to one linked via variables VSLNKID, FALNKID and that CE and FA can be linked via variables CELNKGRP, FALNKGRP.

RELREC.XPT

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
ABC	CE		CELNKGRP		ONE	1
ABC	FACE		FALNKGRP		MANY	1
ABC	FACE		FALNKID		ONE	2
ABC	VS		VSLNKID		ONE	2

3. HIGHLY NESTED MODEL

A global record is created for each type of reactogenicity category that is assessed (i.e., systemic and site administration events). If an event occurred in one the categories, additional global records for all the events in that category are created. Daily assessment records for an event are created only if the event occurred during the three-day assessment interval.

CE domain.

The event category record (Systemic event, Administration site event) is connected to the individual reactogenicity event records via variable CEGRPID when CEOCCUR=”Y”.

CELNKGRP connects the global records in CE to the daily records in FA.

CE.XPT

Row	STUDYID	DOMAIN	USUBJID	CESEQ	CELNKGRP	CEGRPID	CETERM	CEDECOD	CECAT	CESCAT	CEPRESP	CEOCCUR	CESEV
1	ABC	CE	ABC-1001	1		1	Systemic event		REACTOGENICITY		Y	Y	
2	ABC	CE	ABC-1001	2	1	1	Vomiting	Vomiting	REACTOGENICITY	SYSTEMIC	Y	Y	SEVERE
3	ABC	CE	ABC-1001	3	2	1	Fever	Fever	REACTOGENICITY	SYSTEMIC	Y	Y	MILD
4	ABC	CE	ABC-1001	4		2	Administration site event		REACTOGENICITY		Y	Y	
5	ABC	CE	ABC-1001	5	3	2	Redness	Erythema	REACTOGENICITY	ADMINISTRATION SITE	Y	Y	MILD
6	ABC	CE	ABC-1001	6			Systemic event		REACTOGENICITY		Y	N	
7	ABC	CE	ABC-1001	7			Administration site event		REACTOGENICITY		Y	N	

Row	TAETORD	EPOCH	CEDTC	CESTDTC	CEENDTC	CEDY	CETPT	CETPTNUM	CETPTREF	CERFTDTC	CEEVINTX
1	2	TREATMENT	2023-01-12			3	END DAY 3	3	VACCINATION 1	2023-01-10	SINCE VACCINATION
2	2	TREATMENT	2023-01-12	2023-01-10	2023-01-10	3	END DAY 3	3	VACCINATION 1	2023-01-10	SINCE VACCINATION
3	2	TREATMENT	2023-01-12	2023-01-10	2023-01-11	3	END DAY 3	3	VACCINATION 1	2023-01-10	SINCE VACCINATION
4	2	TREATMENT	2023-01-12			3	END DAY 3	3	VACCINATION 1	2023-01-10	SINCE VACCINATION
5	2	TREATMENT	2023-01-12	2023-01-10	2023-01-11	3	END DAY 3	3	VACCINATION 1	2023-01-10	SINCE VACCINATION
6	3	TREATMENT	2023-02-02			24	END DAY 3	3	VACCINATION 2	2023-01-31	SINCE VACCINATION
7	3	TREATMENT	2023-02-02			24	END DAY 3	3	VACCINATION 2	2023-01-31	SINCE VACCINATION

VS, FACE, and RELREC domains in highly Nested Model are same as in Nested Model.

Summary of three model strategies

Model Strategy	VS & FACE domains	CE domain
Flat	All the daily assessments are transcribed from the diary card into VS (Temperature) and FACE (other reactogenicity evets) domains.	A global record is created in CE domain for each reactogenicity event that is assessed.
Nested	The daily assessment records for an event are created in FACE and/or VS domain only if the event occurred during the assessment interval.	Same as Flat. The value of CELNKGRP will be blank when the subject did not experience any reactogenicity events during the assessment interval.
Highly Nested	Same as Nested	A global record is created for each type of reactogenicity category. If an event occurred in one the categories, additional global records for all the events in that category are created.

REPRESENTATION OF EVENTS THAT CONTINUE BEYOND THE PLANNED ASSESSMENT PERIOD

When reactogenicity event continue beyond the planned assessment period (ongoing after Day 3 in the examples shown in this guide), the event will be represented in the unsolicited event (SDTM domain AE) and the entire event is represented in FAAE, Meanwhile, in CE domain, the variables Clinical Event End Reference Time Point (CEENTPT= Day 3) and Clinical Event End Relative to Reference Time Point (CEENRTPT= Ongoing) will be listed.

In AE domain, for the event happens to continue beyond day 3, the event will be categorized in the Adverse Event Category (AECAT) variable as “REACTOGENICITY”.

The start day/date (AESTDY/AESTDTC, CESTDY/CESTDTC) and the end day/date (AEENDY/AEENDTC, CEENDY/CEENDTC) of the reactogenicity event will be identical in both the CE and AE domain.

The examples here explain details.

If events end within Day 1 to Day 3 – as we discussed in three model strategies, summary events to CE only from FACE and VS, events won't be carried into AE;

If events are ongoing after day 3 – for example event start date=Day 2; end date=Day 12, both CE and AE start date= Day 3 and end date=Day 12; CEENTPT= Day 3; CEENRTPT=Ongoing; AECAT= REACTOGENICITY.

A trick of the situation may cause confusion and often be asked, how to map SDTM if reactogenicity events start after planned assessment period, for this situation, the events will be collected in the adverse events collection form and be mapped into AE directly. The variable AECAT won't be assigned "REACTOGENICITY" in AE domain and the events won't be carried into FA, VS, or CE.

We also need to face data inconsistent issues, for example, subjects marked events that continued beyond the planned assessment period in Diary Card, however, investigators confirmed later that the events ended by the last day of assessment period or early. Vice versa. Because we cannot query Diary Card, to handle the issues, one solution is to carry both records in FACE or VS; add footnotes in the listings and/or tables as an explanation; document in SDTM Reviewer's Guide.

CONCLUSION

Both CDISC and FDA prefer that "Flat Model" be utilized since electronic diary has been used widely. All of the diary information is easily loaded into database, and data for each day be included in FA and VS, even if a subject never experienced a particular event. "Nested Model" may be necessary for large trials with significant amounts of data.

There are two ways to link temperature measurement to fever occurrence.

- For example, in the Flat Model case, daily temperature measurements are represented in the VS domain, then be linked to summarized fever occurrence record in CE. CE and VS are linked to each other via the variables CELNKGRP and VSLNKGRP.
- Another way is in Nested Model case, both a VS and an FA record are created where daily temperature measurements are represented in the VS domain and can be linked to the daily fever occurrence in FA via the variables VSLNKID and FALNKID. The variable --LNKGRP is used to relate the daily assessments in FA to the global record in CE.

The reactogenicity events continue beyond the planned assessment period will be represented in both the Unsolicited Event (AE) and Clinical Event (CE).

REFERENCES

- CDICS "Therapeutic Area Data Standards User Guide for Vaccines" Version 1.1 (Provisional)
- FDA "Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review Guidance for Industry Technical Specifications Document" Version 2.1 (December 2019)

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RECOMMENDED READING

- CDISC SDTM v1.4
- CDISC SDTMIG v3.2 / *V3.4*

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