Paper DS05

Implementation of a flat model for reactogenicity events in vaccine studies

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ABSTRACT

Vaccines can protect us from infectious diseases by preparing the immune system to elicit antibody- and/or cell-mediated responses, which are specific against the pathogen. The safety and usability of an experimental vaccine is evaluated by assessments of reactogenicity. Reactogenicity describes immediate short-term reactions to vaccines, not long-term sequelae. In clinical trials, reactogenicity is measured by collecting sets of injection site and systemic signs and symptoms that are solicited from study participants over a specified time after vaccination. The CDISC Vaccine TAUG allows for three different strategies for mapping reactogenicity data in SDTM; known as the flat model, the nested model, and the highly nested model. The FDA has stated preference for the flat model in the guidance 'Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review'. In this paper, we discuss the nuances of standardizing the reactogenicity data by the 'Flat Model' Strategy.

INTRODUCTION

As the proverb states – "Prevention is better cure", this pandemic has shown vaccines has become an important form of defense against the fight of infectious disease. Also there is need for new vaccines production as we deal with new form of the virus/bacrteria strain spreading the infection.

This paper elaborates the implementation of the important safety aspect of the vaccines approval – reactogenicity events for agency submission. The step by step approach of the implementation of flat model for reactogenicity events is main agenda of this paper.

LITERARY REVIEW

VACCINE - DEFINITION

A vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine typically contains a biological preparation from disease-causing microorganism or made synthetically that resembles it. This preparation is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as a threat, destroy it, and to further recognize and destroy any of the microorganisms associated with that agent that it may encounter in the future.

REACTOGENICITY - DEFINITION

In clinical trials, the term reactogenicity refers to the property of a vaccine of being able to produce common, "expected" adverse reactions, especially excessive immunological responses and associated signs and symptoms, including fever and sore arm at the injection site. Other manifestations of reactogenicity typically identified in such trials include bruising, redness, induration, and swelling.

Reactogenicity is assessed in studies by monitoring a pre-defined set of adverse events over a pre-defined observation period. Pre-defined means identified prior to the start of the trial to support reactogenicity assessments of one or more investigational products in the study protocol.

REACTOGENICITY EVENTS

Reactogenicity events are adverse events that are common and known to occur for the intervention/investigational product being studied and should be collected in a standard, systematic format using a graded scale based on functional assessment or magnitude of reaction.

In clinical trials, reactogenicity is measured by collecting sets of injection site and systemic signs and symptoms that are solicited from study participants over a specified time after vaccination. The types of symptoms collected and the period for which they are collected depend on the vaccine being investigated and the objectives of individual studies. Reactions that are solicited (in which participants are actively questioned about the occurrence of each symptom) are usually reported at higher frequencies than the same symptoms when participants are asked to report them spontaneously (unsolicited symptoms).

While some signs can be objectively measured (body temperature, redness, swelling, heart rate), other symptoms are non-specific and subjective, and are perceived differently depending on a range of factors occurring at the time. These factors can include mood, presence of other medical conditions or symptoms, climate, individual perceptions of pain, etc. Effects of symptoms on an individual's physical functioning and quality of life, reduced work efficiency or use of healthcare resources or medications are also difficult to assess quantitatively. Furthermore, many illnesses and general conditions cause the same signs and symptoms (for example, fever, headache, fatigue), making it challenging to determine what is, and what is not caused by vaccination.

Reactogenicity events can be classified as either **administration site** or **systemic** events.

- ✓ Administration site events are those occurring at or around the vaccine's administration site. The term local is also commonly used to refer to events at or around the administration site.
- ✓ Systemic reactogenicity events are those affecting an entire system or body. These reactogenicity events can be non-localized (e.g., fatigue or fever).

The CDISC Vaccine TAUG (Therapeutic Area Data Standards User Guide for Vaccines – Version 1.1) allows for three different strategies for mapping reactogenicity data in SDTM: the flat model, the nested model, and the highly nested model. In this paper, we will be discussing on the FLAT MODEL implementation.

FLAT MODEL

All the daily assessments are transcribed/loaded from the diary card and a global event record is created, whether a reactogenicity event occurred during the assessment.

Safety data submitted for vaccine clinical trials should include reactogenicity data (i.e., a set of prespecified AEs collected within a prespecified time frame, often referred to as solicited AEs or reactions), unsolicited AEs, medically attended adverse events (MAAEs), and death.

The current vaccine studies focus on daily assessments performed by the subject and reported on a daily diary card. These subject assessments are complemented by global assessments performed by the investigator at the end of the daily assessments period and reported in a case report form.

In the flat model, daily assessments of the solicited symptoms are mapped to FACE and VS domains, and a global event record is created in the CE domain for each symptom, whether a reactogenicity event occurred during the assessment interval.

INPUTS FOR THE FLAT MODEL

The following data will be mapped into reactogenicity SDTM domains:

- Vaccines Symptom Diary - Data on reactogenicity events were collected via a reactogenicity collection form (e.g., a subject diary) for a pre-defined observation period starting on the day of each vaccine's administration.
- Vaccination Symptoms - Symptom resolved dates - Investigator-recorded data about reactogenicity events included action taken, resolution, causal relationship to vaccination, and start and end date of the event.
- unplanned assessment of local/systemic reaction

TIMEFRAME of the data collected

Vaccination
- Exposure to the IP
- Collected in CRF

Diary (Paper/Electronic)
- Period Based on the Protocol
- Filled by Study Subject

Vaccination Symptoms Resolved Dates
- The corresponding Clinical Visit
- Collected in CRF

Unplanned Assessments can happen anytime. Unplanned assessments happened within Diary Period or between end of diary period and Symptoms Resolved Dates-Clinical Visit is considered.

SDTM OUTPUTS

The following domains are mapped in SDTM:

FACE
FACE contains assessment of individual symptoms for each day of the assessment interval from the e-Diary, with exception of temperature, with FACAT = “REACTOGENICITY”. Additionally, any unplanned assessments performed by the investigator (typically when a severe reaction has been reported in the e-Diary) are mapped. Symptoms are further subcategorized as “ADMINISTRATION SITE” or “SYSTEMIC” in FASCAT. FAEVAL is used to identify who reported the data (STUDY SUBJECT or INVESTIGATOR).

VS
VS contains daily temperature measurements from the e-Diary along with any unplanned measurements recorded in the CRFs, with VSCAT = “REACTOGENICITY” and “REACTOGENICITY - UNPLANNED TEMPERATURE” respectively. Temperature is further subcategorized as “SYSTEMIC” in VSSCAT. VSEVAL is used to identify who reported the data (STUDY SUBJECT or INVESTIGATOR).

As the highest temperature is to be reported for each day, SUPPVS.VSCOLRST should be set to “MAXIMUM” for values from the e-Diary.

CE
CE contains one global “summary” record per subject per vaccination/site per symptom, with CECAT = “REACTOGENICITY”. Symptoms are further subcategorized as “ADMINISTRATION SITE” or “SYSTEMIC” in CESCAT. The global record will indicate whether the symptom occurred or not (CEOCCUR) and provide start and stop date (CESTDTC, CEENDTC) for those which did occur.

AE
AE has any clinical events which continue past the pre-assigned assessment interval will additionally be mapped to AE with AECAT = “REACTOGENICITY”.

RELREC
RELREC has relationships will be included to link data across FACE/CE, VS/CE, and CE/AE.

FLAT MODEL IMPLEMENTATION STEPS

NOT DONE Creation

In FACE and VS domains, for any missed diary days (no diary data for a given day which was expected based on the defined assessment interval following vaccination and subject still participating in study), a set of records will be derived for that day with xxSTAT = “NOT DONE” and xxREASND = “SUBJECT DID NOT COMPLETE ELECTRONIC DIARY”. In these cases where the entire record was derived, we will set xxDRVFL = “Y” (derived flag). For ongoing studies, we should only generate records up through the date of program execution (do not create records with future dates).

Create "NOT DONE" records for missed days as follows:

i. Get the subjects vaccinated from exposure data SDTM.EX.
ii. Create n Days for each vaccination (xxTPTREF) a subject received (n=no. of days diary is supposed to be captured). Number of diary days may be different for systemic and administration site events.
iii. Merge with existing diary data dataset FACE, VS by USUBJID, xxTPTREF.
iv. Create "NOT DONE" for the events with missing daily diary days (for all applicable systemic and administration site events) with FATESTCD=OCCUR.
v. If a subject has withdrawn from study during diary period, only create records up through the date of withdrawal.

SAS code for creating dataset having all symptoms and all diary days

```
data _ex_;
length TEST $80.;
set ex_ds; (INPUT SDTM EX in work library)
by subjectnumberstr _tptref_;
%do i=1 %to &test_sys_cnt;(FOT SYSTEMIC EVENTS)
TEST = "%scan(&test_sys, &i, '^')";
if first._tptref_ and not missing(vacdt) then do;
%do j = 1 %to &g_systemic_day.;
X_VSDSDAY = &j.;
if &j = 1 then diadt = vacdt;
```

```
else diadt +1;
output;
%end;
end;
%end;
%do i=1 %to &test_adm_cnt;(FOR ADMINISTRATIVE SITE EVENTS)
TEST = "%scan(&test_adm, &i, '^')";
if first._tptref_ and not missing(vacdt) then do;
%do j = 1 %to &g_admin_day.;
X_VSDSDAY = &j.;
if &j = 1 then diadt = vacdt;
else diadt +1;
output;
%end;
end;
%end;
run;
```

Sample calculation for FACE records

No. of vaccinated subjects with non-missing EXSTDTC	10
No. of Reactogenicity events (local and systemic events)	10
No. of diary days	7
No. of records in FACE per subject per vaccination for all reactogenicity events	70
No. of records in FACE per subject per vaccination for each reactogenicity events	7
Total no. of FACE Records for all vaccinated subjects all reactogenicity events	700

SDTM.EX

USUBJID	EXLNKID	EXLNKGRP	EXSTDTC	EXTPTREF
12345678	VACCINATION 1-DELTOID MUSCLE-LEFT	VACCINATION 1	2020-08-06T08:32:00	VACCINATION 1
12345678	VACCINATION 2-DELTOID MUSCLE-LEFT	VACCINATION 2	2020-08-27T07:36:00	VACCINATION 2

DIARY DATA FOR VAX1

SUBJECTNUMBERSTR	SYSTEMIC EVENT	VISIT	DIARY DAY	FADTC	FAORRES
12345678	Headache Occurrence	VAX1	5	2020-08-10T19:12:28	N
12345678	Headache Occurrence	VAX1	6	2020-08-11T18:25:43	N
12345678	Headache Occurrence	VAX1	7	2020-08-12T18:03:39	N
12345678	Headache Occurrence	VAX2	1	2020-08-27T19:10:42	N
12345678	Headache Occurrence	VAX2	2	2020-08-28T18:07:57	N
12345678	Headache Occurrence	VAX2	3	2020-08-29T18:24:00	N
12345678	Headache Occurrence	VAX2	4	2020-08-30T18:43:05	N
12345678	Headache Occurrence	VAX2	5	2020-08-31T18:16:03	N
12345678	Headache Occurrence	VAX2	6	2020-09-01T19:05:01	N

12345678	Headache Occurrence	VAX2	7	2020-09-02T22:08:18	N

SDTM.FACE

USUBJID	FATESTCD	FAOBJ	FATPTREF	VAX DATE	DIARY DATE	DIARY DAYS	FAORRES	FASTAT
12345678	OCCUR	HEADACHE	VAX1	06/08/2020	06/08/2020	1		NOT DONE
12345678	OCCUR	HEADACHE	VAX1	06/08/2020	07/08/2020	2		NOT DONE
12345678	OCCUR	HEADACHE	VAX1	06/08/2020	08/08/2020	3		NOT DONE
12345678	OCCUR	HEADACHE	VAX1	06/08/2020	09/08/2020	4		NOT DONE
12345678	OCCUR	HEADACHE	VAX1	06/08/2020	10/08/2020	5	N	
12345678	OCCUR	HEADACHE	VAX1	06/08/2020	11/08/2020	6	N	
12345678	OCCUR	HEADACHE	VAX1	06/08/2020	12/08/2020	7	N	

CE GLOBAL RECORD CREATION

CE will have the global records, summarizing whether each symptom occurred for each subject following each vaccination. Global records are creating using the diary data, Symptom Resolved Dates CRF, and Unplanned Assessment CRF. If the entire diary was not completed, then a set of global summary records will additionally be created in the CE domain with CESTAT = “NOT DONE” and CEREASND = “SUBJECT DID NOT COMPLETE ELECTRONIC DIARY”.

CEOCCUR, will be assigned as Y, when at least one dairy day has the occurrence of the event. It will be assigned as N when no event occurred and CESTAT not equal to NOT DONE.

The Start date of the event (CESTDTC) will be the diary date of first occurrence of the event - FACE.FADTC (date portion) when FATESTCD=OCCUR and FAORRES=Y and FADTC is within the diary assessment period (EXSTDTC <= FADTC <= EXSTDTC + x - 1) x – diary days as per protocol.

Stop date of the event (CEENDTC) in the global summary record in the CE domain will be based on the last date reported for that event (latest diary date where symptom occurred or stop date from Symptom Resolved Dates CRF). In a multi-dose vaccine study (> 1 vaccination, administered at different visits), if an event is continuing past the next vaccination date, then the event stop date will be set to the next vaccination date and a new event record will begin with the next vaccination.

Duration of event in the CE domain (CEDUR) will be based on the number of days that the event occurred during the assessment interval/diary period, even if the stop date is after the assessment interval. Any gaps are ignored.

If an event continues past the assessment interval, then CEENRTPT should be set to “ONGOING”.

CASE 1:

SDTM.FACE

USUBJID	FAOBJ	FAORRES	FASTAT	FAREASND	FADTC	FATPT	FATPTREF
12345678	HEADACHE		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	06/08/2020	DAY 1	VACCINATION 1
12345678	HEADACHE		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	07/08/2020	DAY 2	VACCINATION 1
12345678	HEADACHE		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	08/08/2020	DAY 3	VACCINATION 1
12345678	HEADACHE		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	09/08/2020	DAY 4	VACCINATION 1
12345678	HEADACHE	N			2020-08-10T19:12:28	DAY 5	VACCINATION 1
12345678	HEADACHE	N			2020-08-11T18:25:43	DAY 6	VACCINATION 1
12345678	HEADACHE	N			2020-08-12T18:03:39	DAY 7	VACCINATION 1
12345678	HEADACHE	N			2020-08-27T19:10:42	DAY 1	VACCINATION 2
12345678	HEADACHE	N			2020-08-28T18:07:57	DAY 2	VACCINATION 2
12345678	HEADACHE	N			2020-08-29T18:24:00	DAY 3	VACCINATION 2
12345678	HEADACHE	N			2020-08-30T18:43:05	DAY 4	VACCINATION 2
12345678	HEADACHE	N			2020-08-31T18:16:03	DAY 5	VACCINATION 2
12345678	HEADACHE	N			2020-09-01T19:05:01	DAY 6	VACCINATION 2
12345678	HEADACHE	N			2020-09-02T22:08:18	DAY 7	VACCINATION 2

SDTM.CE

USUBJID	CELNKGRP	CETERM	CEOCCUR	CESTDTC	CEENDTC	CETPTREF	CERFTDTC	CEENRTPT
12345678	VACCINATION 1	HEADACHE	N			VACCINATION 1	06/08/2020	
12345678	VACCINATION 2	HEADACHE	N			VACCINATION 2	27/08/2020	

CASE 2:

SDTM.FACE

USUBJID	FALNKID	FATEST	FAOBJ	FAORRES	FADTC	FATPT	FATPTREF
99999999	VACCINATION 1-HEADACHE-DAY 1	Occurrence Indicator	HEADACHE	N	2020-08-15T22:05:49	DAY 1	VACCINATION 1
99999999	VACCINATION 1-HEADACHE-DAY 2	Occurrence Indicator	HEADACHE	Y	2020-08-16T22:02:38	DAY 2	VACCINATION 1
99999999	VACCINATION 1-HEADACHE-DAY 3	Occurrence Indicator	HEADACHE	N	2020-08-17T22:08:08	DAY 3	VACCINATION 1
99999999	VACCINATION 1-HEADACHE-DAY 4	Occurrence Indicator	HEADACHE	N	2020-08-18T22:03:04	DAY 4	VACCINATION 1
99999999	VACCINATION 1-HEADACHE-DAY 5	Occurrence Indicator	HEADACHE	N	2020-08-19T22:03:22	DAY 5	VACCINATION 1
99999999	VACCINATION 1-HEADACHE-DAY 6	Occurrence Indicator	HEADACHE	N	2020-08-20T23:35:48	DAY 6	VACCINATION 1
99999999	VACCINATION 1-HEADACHE-DAY 7	Occurrence Indicator	HEADACHE	N	2020-08-21T21:51:41	DAY 7	VACCINATION 1
99999999	VACCINATION 2-HEADACHE-DAY 1	Occurrence Indicator	HEADACHE	Y	2020-09-04T23:58:23	DAY 1	VACCINATION 2
99999999	VACCINATION 2-HEADACHE-DAY 2	Occurrence Indicator	HEADACHE	Y	2020-09-05T21:10:38	DAY 2	VACCINATION 2
99999999	VACCINATION 2-HEADACHE-DAY 3	Occurrence Indicator	HEADACHE	N	2020-09-06T20:25:27	DAY 3	VACCINATION 2
99999999	VACCINATION 2-HEADACHE-DAY 4	Occurrence Indicator	HEADACHE	N	2020-09-07T22:03:12	DAY 4	VACCINATION 2
99999999	VACCINATION 2-HEADACHE-DAY 5	Occurrence Indicator	HEADACHE	N	2020-09-08T22:07:18	DAY 5	VACCINATION 2
99999999	VACCINATION 2-HEADACHE-DAY 6	Occurrence Indicator	HEADACHE	N	2020-09-09T20:37:51	DAY 6	VACCINATION 2
99999999	VACCINATION 2-HEADACHE-DAY 7	Occurrence Indicator	HEADACHE	N	2020-09-10T22:45:08	DAY 7	VACCINATION 2
99999999	VACCINATION 1-HEADACHE-DAY 2	Severity/Intensity	HEADACHE	MILD	2020-08-16T22:02:38	DAY 2	VACCINATION 1
99999999	VACCINATION 2-HEADACHE-DAY 1	Severity/Intensity	HEADACHE	MILD	2020-09-04T23:58:23	DAY 1	VACCINATION 2
99999999	VACCINATION 2-HEADACHE-DAY 2	Severity/Intensity	HEADACHE	MILD	2020-09-05T21:10:38	DAY 2	VACCINATION 2

SDTM.CE

USUBJID	CELNKGRP	CETERM	CEOCCUR	CESEV	CESTDTC	CEENDTC	CETPTREF	CERFTDTC	CEENRTPT
99999999	VACCINATION 1-HEADACHE	HEADACHE	Y	MILD	16/08/2020	16/08/2020	VACCINATION 1	15/08/2020	
99999999	VACCINATION 2-HEADACHE	HEADACHE	Y	MILD	04/09/2020	05/09/2020	VACCINATION 2	04/09/2020	

AE RECORD CREATION

When CEENRTPT = “ONGOING” then a similar event record should be created and added to the AE domain, with same start and stop date, however the AEDUR will only include days during which the symptom was present after the diary period,

e.g. if an event occurred during Days 2 – 9 and there was a 7-day diary, then CEDUR = “P6D” and AEDUR = “P2D”.

SDTM.CE

USUBJID	CELNKGRP	CETERM	CEOCCUR	CESEV	CESTDTC	CEENDTC	CETPTREF	CERFTDTC	CEENRTPT	CEENTPT
99999999	VACCINATION 1-DELTOID MUSCLE-LEFT-PAIN AT INJECTION SITE	PAIN AT INJECTION SITE	Y	MODERATE	13/08/2020	14/08/2020	VACCINATION 1	12/08/2020		
99999999	VACCINATION 1-DELTOID MUSCLE-LEFT-REDNESS	REDNESS	N				VACCINATION 1	12/08/2020		
99999999	VACCINATION 1-DELTOID MUSCLE-LEFT-SWELLING	SWELLING	N				VACCINATION 1	12/08/2020		
99999999	VACCINATION 2-DELTOID MUSCLE-LEFT-PAIN AT INJECTION SITE	PAIN AT INJECTION SITE	Y	MODERATE	01/09/2020	03/09/2020	VACCINATION 2	01/09/2020		
99999999	VACCINATION 2-DELTOID MUSCLE-LEFT-REDNESS	REDNESS	N				VACCINATION 2	01/09/2020		
99999999	VACCINATION 2-DELTOID MUSCLE-LEFT-SWELLING	SWELLING	N				VACCINATION 2	01/09/2020		
99999999	VACCINATION 1-CHILLS	CHILLS	Y	MODERATE	13/08/2020	13/08/2020	VACCINATION 1	12/08/2020		
99999999	VACCINATION 1-DIARRHEA	DIARRHEA	N				VACCINATION 1	12/08/2020		
99999999	VACCINATION 1-FATIGUE	FATIGUE	Y	MODERATE	13/08/2020	14/08/2020	VACCINATION 1	12/08/2020		
99999999	VACCINATION 1-FEVER	FEVER	N				VACCINATION 1	12/08/2020		
99999999	VACCINATION 1-HEADACHE	HEADACHE	Y	MILD	13/08/2020	14/08/2020	VACCINATION 1	12/08/2020		
99999999	VACCINATION 1-JOINT PAIN	JOINT PAIN	Y	MODERATE	13/08/2020	01/09/2020	VACCINATION 1	12/08/2020	ONGOING	DAY 7
99999999	VACCINATION 1-MUSCLE PAIN	MUSCLE PAIN	Y	MILD	14/08/2020	14/08/2020	VACCINATION 1	12/08/2020		
99999999	VACCINATION 1-VOMITING	VOMITING	N				VACCINATION 1	12/08/2020		
99999999	VACCINATION 2-CHILLS	CHILLS	N				VACCINATION 2	01/09/2020		
99999999	VACCINATION 2-DIARRHEA	DIARRHEA	N				VACCINATION 2	01/09/2020		
99999999	VACCINATION 2-FATIGUE	FATIGUE	Y	MILD	02/09/2020	08/09/2020	VACCINATION 2	01/09/2020	ONGOING	DAY 7
99999999	VACCINATION 2-FEVER	FEVER	N				VACCINATION 2	01/09/2020		
99999999	VACCINATION 2-HEADACHE	HEADACHE	N				VACCINATION 2	01/09/2020		
99999999	VACCINATION 2-JOINT PAIN	JOINT PAIN	Y	MODERATE	01/09/2020		VACCINATION 2	01/09/2020	ONGOING	DAY 7
99999999	VACCINATION 2-MUSCLE PAIN	MUSCLE PAIN	Y	MODERATE	03/09/2020	05/09/2020	VACCINATION 2	01/09/2020		
99999999	VACCINATION 2-VOMITING	VOMITING	N				VACCINATION 2	01/09/2020		

SDTM.AE

USUBJID	AELNKGRP	AETERM	AESTDTC	AEENDTC	AEENRTPT	AEENTPT
99999999	VACCINATION 1-JOINT PAIN	JOINT PAIN	13/08/2020	01/09/2020		
99999999	VACCINATION 2-JOINT PAIN	JOINT PAIN	01/09/2020		ONGOING	POSTVAX2
99999999	VACCINATION 2-FATIGUE	FATIGUE	02/09/2020	08/09/2020		

CONCLUSION

This paper is the initiative work of explaining the flat model implementation for reactogenicity events. It details the basic assumptions and working logic for implementing the flat model logic.

REFERENCES

CDISC Vaccine Therapeutic Area User Guide (TAUG) version 1.1: https://www.cdisc.org/standards/therapeutic-areas/vaccines/vaccines-therapeutic-area-user-guide-v11/html

CBER OVRR Technical Specifications Document version Dec. 2019:https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-study-datasets-vaccines-office-vaccines-research-and-review

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