Standardization of Reactogenicity Data into Findings

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ABSTRACT

Reactogenicity event(s) is the key safety assessment of the vaccines TA. It refers to a particular expected or generic reaction following vaccine administration. The term reaction usually implies that the adverse event has a causal relationship with the vaccination, or at least there exists a distinct possibility. Reactogenicity is evaluated by observing a pre-specified set of adverse events over a pre-defined observation period. Standardizing the reactogenicity data in the SDTM datasets implements the 'FLAT MODEL' strategy prescribed by the Vaccines TAUG. This paper will be discussing on standardizing the diary data from study subjects into finding domains as applicable rolling it into 'Flat Model' strategy.

INTRODUCTION

Vaccination, the revolutionary prophylactic immunotherapy developed in the eighteenth century, has become the most successful and cost-effective of medical remedies available to modern society. Current pandemic taught us 'Prevention is better than cure'. With this principle in mind, vaccines clinical trials are moving forward with more purpose of the work. This paper discusses on the vaccination reactogenicity.

Immunogenicity is the ability to induce a humoral and/or cell mediated immune response while reactogenicity is the property of a vaccine of being able to produce excessive immunological responses and associated signs and symptoms.

Both immunogenicity and reactogenicity are sustained by inflammatory reactions (innate immunity). The difference will be at the level (probably nature) of inflammatory reactions involved in both cases. A certain level of inflammatory reactions is needed to sustain a good adaptive immune response, but the excess of these inflammatory reactions will instead impair the same adaptive immune response by creating in some cases serious inflammatory and/or oxidative conditions on basis of immune cell and tissue destruction and associated signs and symptoms (Side effects).

The current attitude regarding the benefits versus the risks of vaccination puts a large emphasis on safety, because vaccines are usually given to healthy populations who may receive no immediate health benefit, particularly when the incidence of the target infectious disease is low. Vaccine reactogenicity and safety is assessed at all points of the vaccine development process, from preclinical toxicology studies using cell cultures and animal models, to rigorous assessment in clinical studies and post-licensure pharmacovigilance. Following licensure, safety remains of prime concern; ongoing surveillance evaluates vaccine safety in large populations under real-world settings.

REACTOGENICITY

Reactogenicity refers to a subset of immediate short-term reactions of a system to vaccines administered. Vaccine reactogenicity characterizes the physical manifestation of the inflammatory response to a vaccine and can result in injection site and systemic symptoms.

It is a common belief that adverse reactions after vaccination are predictive signs of a good immune response. In clinical trials, information on these expected signs and symptoms after vaccination is actively sought (or 'solicited') for the following.

- ✓ Pain and distress at the time of vaccination

- ✓ To promote the benefits of vaccination

- ✓ Setting expectations for vaccinees about what might occur post vaccination.

- ✓ Reducing anxiety by managing the vaccination setting

✓ An important mechanism by which the healthcare professionals contribute to the continuous monitoring of vaccine safety.

WHAT CAUSES REACTOGENICITY?

Vaccine antigens and immune enhancers (as adjuvants) injected into the muscle are recognized by the body as potential pathogens and/or danger signals. This recognition leads to the stimulation of local cells, followed by the recruitment of blood immune cells to the local site and the production of different soluble factors including vasodilators and cytokines, which may trigger the development of signs and symptoms of local inflammation (pain, redness and swelling). The passage of some of those factors in the bloodstream, as well as the production of other systemic factors by immune blood cells or distant organs (e.g., liver), may contribute to the development of general symptoms (fever, myalgia, headache etc) in the vaccinee.

REACTOGENICITY EVENTS

Reactogenicity events are adverse events/symptoms 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.

While some symptoms can be objectively measured (body temperature, redness, swelling), other symptoms are non-specific and subjective, and are perceived differently depending on a range of factors occurring at the time. 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.

These events are further sub-categorized as –

➢ Administrative Site reactions or local reactions – The inflammatory reactions on the administrated site causing local reactions.

➢ Systemic Reactions - The mediators and products of inflammation at a localized site in the body spilling into the circulation and can affect other body systems causing systemic reactions.

DATA COLLECTION FOR REACTOGENICITY

The reactogenicity data is collected through diary card (paper based)/ electronic diary(through an app) completed by participant. The electronic diary (e-diary) will be installed on a provisioned device or on the personal device of the participant or participant's parent(s)/legal guardian (in case of pediatric studies).

Participants will be advised to complete a diary for specific time interval after each vaccination to record solicited local (induration, itch, pain, redness, swelling, tenderness, and warmth at the injection site) and systemic (chills, fatigue, fever of ≥38°C, feverish, headache, joint pain, malaise, muscle ache, and nausea) reactogenicity events. Participants will be reporting the severity of their reactogenicity events as mild, moderate, severe, or life threatening as per definitions provided. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically. Stored in an centralized location for review by investigators and the clinicians via an internet-based portal.

The following data collected for reactogenicity events:

➢ 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
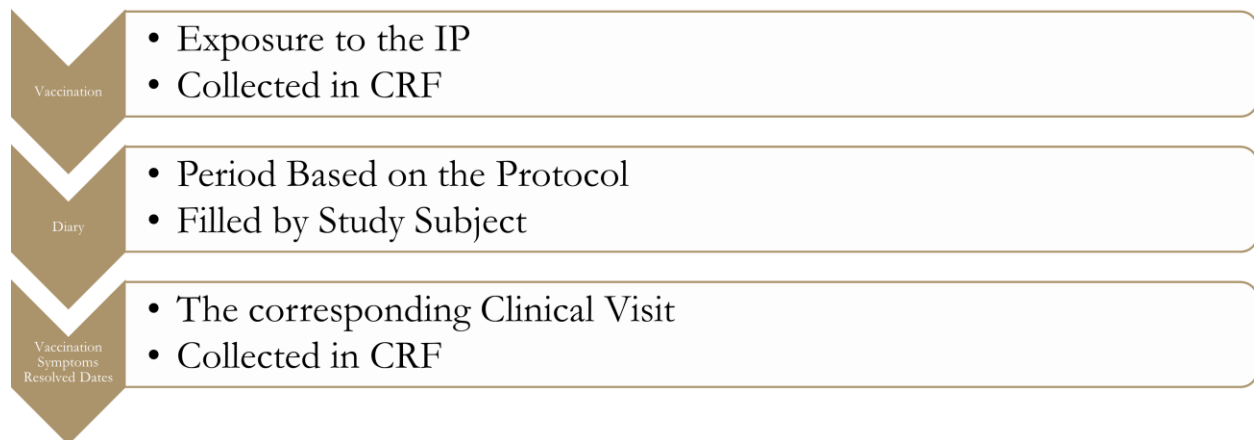
TIMEFRAME OF THE DATA COLLECTION

Fig1. Timeframe of the Data Collection

REACTOGENICITY DATA INTO SDTM

Reactogenicity data will be represented primarily in the CE domain with the Findings About Clinical Event (FACE) domain and VS domain to provide the specific information for each event. FDA recommends the usage of Vaccine TAUG "FLAT MODEL" for reporting these reactogenicity events in SDTM, i.e., that data for each day be included, even if a subject never experienced a particular event.

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.

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.

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.

RELREC

A dataset-level relationship in Related Records (RELREC) should be used to represent relationships between CE and FACE and between VS and assessments of fever in CE.

This paper will focus on the SDTM domains mapping – FACE and VS.

FLAT MODEL IMPLEMENTATION STEPS

CREATION OF NOT DONE RECORDS

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).

STEPS

- ➢ Obtain the subjects vaccinated from exposure data SDTM.EX.
- ➢ 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.
- ➢ Merge with existing diary data dataset FACE, VS by USUBJID, xxTPTREF.
- ➢ Create "NOT DONE" for the events with missing daily diary days (for all applicable systemic and administration site events) with FATESTCD=OCCUR.

Consider a vaccine trial, where the subjects are vaccinated twice and diary about solicited adverse events will be collected for 7 days following administration. The following set of local reactions and systemic events are collected in the electronic diary through an app installed in the participant mobile device.

LOCAL REACTIONS/ ADMINISTRATION SITE EVENTS	SYSTEMIC EVENTS
PAIN AT INJECTION SITE REDNESS SWELLING	HEADACHE FATIGUE CHILLS FEVER (Temperature Measurements)

Table 1. Local Reaction and Systemic Events Collected

The participants will be providing the occurrence of the events and severity of these events when occurred during pre-defined diary period. The below tables are the sample diary data filled up by the participant for a systemic event.

SUBJECTID	EVENT	DAIRY DAY	DIARY DATE	RESULT
123456789	Headache Occurrence	5	10-Aug-20	NO
123456789	Headache Occurrence	6	11-Aug-20	NO
123456789	Headache Occurrence	7	12-Aug-20	NO

Table 2. Diary Data for First Vaccination Administration

SUBJECTID	EVENT	DAIRY DAY	DIARY DATE	RESULT
123456789	Headache Occurrence	1	27-Aug-20	NO
123456789	Headache Occurrence	2	28-Aug-20	NO
123456789	Headache Occurrence	3	29-Aug-20	NO
123456789	Headache Occurrence	4	30-Aug-20	YES
123456789	Headache Severity	4	30-Aug-20	MILD
123456789	Headache Occurrence	5	31-Aug-20	NO
123456789	Headache Occurrence	6	01-Sep-20	NO
123456789	Headache Occurrence	7	02-Sep-20	NO

Table 3. Diary Data for Second Vaccination Administration

Number of vaccinated subjects with non-missing EXSTDTC	10
Number of reactogenicity events as per protocol	10
Number of Diary Days as per protocol	7
Number of records in FACE per subject per vaccination for each reactogenicity events	7
Number of records in FACE per subject per vaccination for all reactogenicity events	70
Total number of FACE Records for all vaccinated subjects all reactogenicity events	700

Table 4. Sample Calculation for Expected Observation Numbers in SDTM FACE Dataset

The above sample calculation shows the general idea on the SDTM records expected in FACE for reactogenicity events.

USUBJID	EXLNKID	EXLNKGRP	EXTRT	EXSTDTC	EXTPTREF
123456789	VACCINATION 1 - DELTOID MUSCLE - LEFT	VACCINATION 1	VAX	2020-08- 06T08:32:00	VACCINATION 1
123456789	VACCINATION 2 - DELTOID MUSCLE - LEFT	VACCINATION 2	VAX	2020-08- 27T07:36:00	VACCINATION 2

Table 5. SDTM Exposure SAS® Dataset

Based on the above exposure details of the participant, we will be expecting diary to be completed twice for both vaccinations and for all days of diary period pre-defined. The table shows the SDTM FACE observations for the subject vaccinated with above details.

USUBJID	FATESTCD	FAOBJ	FAORRES	FADRVFL	FADTC	FATPT	FATPTREF	FARFTDTC
123456789	OCCUR	HEADACHE		Y	2020 08 06	DAY 1	VACCINATION 1	2020 08 06T08:32:00
123456789	OCCUR	HEADACHE		Y	2020-08-07	DAY 2	VACCINATION 1	2020-08- 06T08:32:00
123456789	OCCUR	HEADACHE		Y	2020-08-08	DAY 3	VACCINATION 1	2020-08- 06T08:32:00
123456789	OCCUR	HEADACHE		Y	2020-08-09	DAY 4	VACCINATION 1	2020-08- 06T08:32:00
123456789	OCCUR	HEADACHE	N		2020-08-10	DAY 5	VACCINATION 1	2020-08- 06T08:32:00
123456789	OCCUR	HEADACHE	N		2020-08-11	DAY 6	VACCINATION 1	2020-08- 06T08:32:00
123456789	OCCUR	HEADACHE	N		2020-08-12	DAY 7	VACCINATION 1	2020-08- 06T08:32:00
123456789	OCCUR	HEADACHE	N		2020-08-27	DAY 1	VACCINATION 2	2020-08- 27T07:36:00
123456789	OCCUR	HEADACHE	N		2020-08-28	DAY 2	VACCINATION 2	2020-08- 27T07:36:00
123456789	OCCUR	HEADACHE	N		2020-08-29	DAY 3	VACCINATION 2	2020-08- 27T07:36:00
123456789	OCCUR	HEADACHE	Y		2020-08-30	DAY 4	VACCINATION 2	2020-08- 27T07:36:00
123456789	SEV	HEADACHE	MILD		2020-08-30	DAY 4	VACCINATION 2	2020-08- 27T07:36:00
123456789	OCCUR	HEADACHE	N		2020-08-31	DAY 5	VACCINATION 2	2020-08- 27T07:36:00
123456789	OCCUR	HEADACHE	N		2020-09-01	DAY 6	VACCINATION 2	2020-08- 27T07:36:00
123456789	OCCUR	HEADACHE	N		2020-09-02	DAY 7	VACCINATION 2	2020-08- 27T07:36:00

Table 6. SDTM Findings About SAS® Dataset

In the above table, we can deduce that for second vaccination, the participant has completed all days of diary, but for the first vaccination its partially filled. The missing diary days information is shown as FASTAT=NOT DONE and FADRVFL is set to Y as these are derived records for the missing days. For these derived records the following assumptions are made.

- ➢ The day of vaccination is the DAY 1 of diary.
- ➢ The missing diary days/date are populated based on the exposure date.
- ➢ The time part (if collected) of exposure will not be considered for deriving missing diary dates.
- ➢ FAREASND= "SUBJECT DID NOT COMPLETE ELECTRONIC DIARY" will be assigned.
- ➢ The derived records will be upto the diary period only.

LIMITATIONS IN THE DERIVATION OF MISSING DIARY RECORDS

ONGOING DIARY PERIOD

The derived NOT DONE records should not be created for future dates. If the current data is available only for partial diary days and the remaining diary days are in future dates, then no derived records will be

created. The same is applicable when a deliverable made with cut off date and/or specific snapshot of diary data.

For example, if a study is submitted with a particular cutoff date, which is falling in between the diary period, then derived NOT DONE records will not be created after the cut off date, even though it might be part of the diary period.

WITHDRAWAL DURING DIARY PERIOD

When the participant is discontinued/withdrawn from the study during the diary period and diary is not/partially filled, then the derived NOT DONE records will be created up through (including) the date of discontinuation (DSSTDTC). E.g., If a subject completed only 2 days of 7-day diary, but withdrew on 3rd day after vaccination, then we would only add records for day 3.

MISMATCH IN AGE GROUP

When the reactogenicity events is different for different age groups in a particular study, then the derived NOT DONE records will be created for missing diary days only when the reactogenicity event and the age group of the participant matches as per the protocol. For example, for pediatric studies, the systemic events change between different age groups. If a participant enters response for the mismatched reactogenicity event, it will be moved as such in the SDTM and DM will be communicated on the mismatch entry. If there are any missing diary days in these scenarios, the derived NOT DONE records will not be created.

Also, if a subject responds in a wrong reactogenicity event, not matching the age profile provided in the protocol, the correct reactogenicity events will be populated completely with the derived NOT DONE records, assuming no response provided for that correct reactogenicity events.

REACTOGENICITY SUBSET POPULATION

When a vaccine trial has huge number of participant, the subset of population is recommended for the analysis. In these scenarios, the participants who are part of the reactogenicity subsets will be considered to be displayed in the SDTM datasets and derived NOT DONE records will be created for those subjects only.

MULTIPLE LOCATION/LATERALITY/DIRECTIONALITY

When a vaccine trial includes multiple administration in the same exposure visit, then possibility of multiple locations/laterality/directionality arises. In these scenarios, the reactogenicity local events should be collected for multiple locations/laterality/directionality depending on the requirement by the study design. For example, if two vaccines are administered in deltoid muscle with left and right laterality, the local reactions should be collected for both left and right laterality.

Also, when a study has multiple administration in a single exposure visit, but protocol specifies analysis of a single administration for reactogenicity events, then the other administration should be ignored for any/all reactogenicity events.

This limitation is applicable for local reactions or administrative site events.

USUBJID	FATESTCD	FAOBJ	FASCAT	FAORRES	FASTAT	FALOC	FALAT	FADTC	FATPT	FATPTREF
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE		NOT DONE	DELTOID MUSCLE	RIGHT	2021-05-24	DAY 1	VACCINATION 1
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE		NOT DONE	DELTOID MUSCLE	LEFT	2021-05-24	DAY 1	VACCINATION 1
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE	N		DELTOID MUSCLE	RIGHT	2021-05-25T19:47:11	DAY 2	VACCINATION 1
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE	N		DELTOID MUSCLE	LEFT	2021-05-25T19:47:11	DAY 2	VACCINATION 1
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE		NOT DONE	DELTOID MUSCLE	LEFT	2021-05-26	DAY 3	VACCINATION 1
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE		NOT DONE	DELTOID MUSCLE	RIGHT	2021-05-26	DAY 3	VACCINATION 1
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE	N		DELTOID MUSCLE	RIGHT	2021-05-27T19:46:44	DAY 4	VACCINATION 1
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE	N		DELTOID MUSCLE	LEFT	2021-05-27T19:46:44	DAY 4	VACCINATION 1
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE	N		DELTOID MUSCLE	LEFT	2021-05-28T18:59:27	DAY 5	VACCINATION 1
123456789	OCCUR	PAIN AT INJECTION SITE	ADMINISTRATION SITE	N		DELTOID MUSCLE	RIGHT	2021-05-28T18:59:27	DAY 5	VACCINATION 1

Table 7. SDTM Findings About SAS® Dataset showing Multiple Laterality Diary Records

The systemic event – FEVER – will be determined based on the temperature measurements. The below table shows the flat model implementation of the temperature measurements. When the VSSTRESN>=38, then the FEVER is assumed as occurred. The participant are advised to respond with maximum body temperature of the day, therefore, collection result is assigned as MAXIMUM in SUPPVS.

USUBJID	VSTESTCD	VSORRES	VSORRESU	VSSTRESN	VSSTRESU	VSSTAT	VSDRVFL	VSDTC	VSTPT
123456789	TEMP	98.3	F	36.83	C			2022-08-30T19:01:38	DAY 1
123456789	TEMP	98.1	F	36.72	C			2022-08-31T19:17:55	DAY 2
123456789	TEMP	98.7	F	37.06	C			2022-09-01T20:51:19	DAY 3
123456789	TEMP			.		NOT DONE	Y	2022-09-02	DAY 4
123456789	TEMP	98.4	F	36.89	C			2022-09-03T21:32:26	DAY 5
123456789	TEMP			.		NOT DONE	Y	2022-09-04	DAY 6
123456789	TEMP	98	F	36.67	C			2022-09-05T21:20:39	DAY 7

Table 8. SDTM Vital Signs SAS® Dataset showing Temperature Measurements from Diary

CONCLUSION

The diary observations transcribed from the participants are completely embedded into finding for each day of the diary. Each day of the diary days are accounted in these finding domains – FACE and VS (Temperature Measurements). The partially filled and/or completely not filled diary entries are included as the derived NOT DONE records with –REASND as "SUBJECT DID NOT COMPLETE ELECTRONIC DIARY".

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