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Handling of Vaccine SDTM Data for FDA CBER/OVRR Submission Compliance

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ABSTRACT

SDTM (Study Data Tabulation Model) is one of the required standards for data submission to the FDA, and following SDTM-IG is the conventional practice. However, submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review (OVRR) in FDA/CBER division has specific rules. They are often ignored in practice, which may result in compliance issues and even rejection of vaccine study submissions.

In this paper, we will cover the rectification work for a vaccine study to address SDTM compliance with FDA CBER/OVRR rules, which includes re-mapping reactogenicity data, recording solicited AEs to CE and FACE; mapping unsolicited AEs, MAAE (PIMMC, NOCD) and death to AE and FAAE domains; relocating rule-specified information into domains where they belong, and covering the unique mapping of biological assay data, immunogenicity, and efficacy data.

INTRODUCTION

An important safety aspect of vaccine development is the assessment of the vaccine's reactogenicity. Reactogenicity refers to the property of a substance to produce an expected or common adverse reaction when introduced into the body. Another aspect that comes under efficacy is the vaccine's immunogenicity. Immunogenicity is the ability of a foreign substance, such as an antigen, to provoke an immune response in the body of a human or other animal.

In this paper, the following will be discussed in detail:

i) Inspect reactogenicity data and map solicited adverse events to the CE domain, the additional data should go to FACE (Findings About Clinical Event), VS, CM, and other related domains.
ii) Record unsolicited adverse events, MAAE (PIMMC, NOCD), death information to the AE domain, the additional data should go to FAAE (Findings About Adverse Event), VS, CM, MH, DD, and other related domains when applicable.
iii) Move the information into the standard domains where they belong, and then create a dataset-level relationship in RELREC.
iv) Abnormal lab should be recorded into the AE domain.
v) Reactogenicity data beyond the assessment period, ongoing, or become serious, record these AEs in both CE and AE domains, and set the attributes as per guidelines.
vi) Inspect Biological assay data in the IS or LB, other finding domains, and map the test results for microbes of interest (e.g., PCR, ELISA, or cell culture) to Microbiology Specimen (MB) domain.
vii) Inspect Immunogenicity data and map to the Immunogenicity Specimen (IS) domain.
viii) Efficacy data primarily report into the CE domain with specific data in the MB, VS, HO, and PE (if applicable).
ix) If multiple vaccines are administered over time, the DS domain should include the TAETORD (Order of Element within Arm) variable.

HANDLING OF REACTOGENECITY DATA

Reactogenicity data can be of two types, which are systemic (e.g., fever, vomiting, and headache) and administration site (e.g., redness, tenderness, and pain) events usually monitored after the vaccination. These solicited adverse events are often mapped to the Adverse Events (AE) domain. But for vaccine studies, these events should be mapped to the Clinical Events (CE) domain with CECAT as

“Reactogenicity” and CESCAT as either “Administration Site” or “Systemic”. However, a study protocol may specify conditions under which a reactogenicity event should also be reported as an adverse event. Those conditions may include seriousness (as defined for adverse events), duration, or other factors.

For reactogenicity data mapping, we used the “Flat Model” strategy as mentioned in the “Therapeutic Area Data Standards User Guide for Vaccines (TAUG-Vax)”. There are “Nested Model”, and “Highly Nested Model” strategies available too (please refer to TAUG-Vax which is noted in the references section of this paper). According to flat model strategy, the daily assessments of the solicited symptoms are mapped to FACE (daily records for the solicited event), and VS (daily temperature measurements), and a global event record is created in the CE domain for each symptom. CETERM is the event name and CEOCCUR is ‘Y’ when the event occurs or ‘N’ if the solicited event did not occur. The overall start and end dates of the event are represented in the CE domain using the variables CESTDTC and CEENDTC respectively when the start and end dates of the reactogenicity event were collected on the CRF (Case Report Form) in addition to the individual dates from the daily diary collection. Individual dates from the daily diary collection are represented in the FACE domain using the variable FADTC. If only the daily diary collection dates were collected, CESTDTC and CEENDTC would not be populated in CE. RELREC domain should be created to represent the relationship between 1. CE and FACE, and 2. CE and VS.

In the below example, the CE domain shows a subject’s clinical events. The third row from Table 1 shows the induration event which did not occur. The daily details of this Induration are stored in the FACE domain (Table 2). The last row in Table 1 shows that the subject is experiencing “Fever” as a reactogenicity event. The daily temperature measurements for this event are shown in the VS domain (Table 3). And these relationships are shown in RELREC domain (Table 4).

USUBJID	CELNKGRP	CETERM	CECAT	CESCAT	CEPRESP	CEOCCUR	CESTDTC	CEENDTC
12345	V1-REACTO-DIAR	DIARRHEA	REACTOGENICITY	SYSTEMIC	Y	N		
12345	V1-REACTO-ECCH	ECCHYMOSIS	REACTOGENICITY	ADMINISTRATION SITE	Y	N		
12345	V1-REACTO-INDU	INDURATION	REACTOGENICITY	ADMINISTRATION SITE	Y	N		
12345	V1-REACTO-TEMP	FEVER	REACTOGENICITY	SYSTEMIC	Y	Y	12/19/2020	12/25/2020

Table 1 SDTM.CE

USUBJID	FALNKGRP	FATESTCD	FAOBJ	FACAT	FASCAT	FAORRES	FAORRESU	FADTC
12345	V1-REACTO-INDU	SIZE	Hardness of skin size at injection site	REACTOGENICITY	ADMINISTRATION SITE	0	mm	12/19/2023
12345	V1-REACTO-INDU	SIZE	Hardness of skin size at injection site	REACTOGENICITY	ADMINISTRATION SITE	0	mm	12/20/2023
12345	V1-REACTO-INDU	SIZE	Hardness of skin size at injection site	REACTOGENICITY	ADMINISTRATION SITE	0	mm	12/21/2023

Table 2 SDTM.FACE

USUBJID	VSLNKGRP	VSTEST	VSCAT	VSSCAT	VSORRES	VSDTC
12345	V1-REACTO-TEMP	Temperature	REACTOGENICITY	SYSTEMIC	37.5	12/19/2020
12345	V1-REACTO-TEMP	Temperature	REACTOGENICITY	SYSTEMIC	38.1	12/20/2020
12345	V1-REACTO-TEMP	Temperature	REACTOGENICITY	SYSTEMIC	37.1	12/21/2020
12345	V1-REACTO-TEMP	Temperature	REACTOGENICITY	SYSTEMIC	37.5	12/22/2020
12345	V1-REACTO-TEMP	Temperature	REACTOGENICITY	SYSTEMIC	37.4	12/23/2020
12345	V1-REACTO-TEMP	Temperature	REACTOGENICITY	SYSTEMIC	37.1	12/24/2020
12345	V1-REACTO-TEMP	Temperature	REACTOGENICITY	SYSTEMIC	36.7	12/25/2020

Table 3 SDTM.VS

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

Table 4 SDTM.RELREC

If a reactogenicity event extends beyond the assessment interval, then it should also be mapped into the AE domain with AECAT as 'Reactogenicity'. In both AE and CE, the start day/date (--STDY/--STDTC) and the end day/date (-- ENDY/--ENDTC) should be identical (please refer Table 1's last record CESTDTC/CEENDTC and Table 5's last record AESTDTC/AEENDTC). Duration (--DUR), if collected on CRF, should capture the time that the event occurred as part of the assessment interval and as part of the continuance separately – e.g., an event that lasted for 5 days in the assessment interval and 2 days beyond the assessment would be CEDUR= 5 days and AEDUR = 2 days (Table 5 highlighted record). And this relationship should be entered into RELREC.

USUBJID	AESEQ	AETERM	AECAT	AESTDTC	AEENDTC	AEDUR	AESHOSP
12345	1	Pneumonia	Unsolicited Adverse Event	12/28/2020	12/31/2020		Y
12345	2	cough	Unsolicited Adverse Event	12/20/2020	12/20/2020		N
12345	3	Fever	Reactogenicity	12/19/2020	12/25/2020	P2D	N

Table 5 SDTM.AE

HANDLING OF UNSOLICITED ADVERSE EVENTS DATA

Unsolicited adverse events should be represented in the AE domain. AE domain should have one record per adverse event per subject. If there are other medically attended adverse events, map them to AE with AECAT as "PIMMC" (Potential immune-mediated medical conditions) and AECAT as "NOCD" (New onset of a chronic disease). Day-to-day details about these AEs are captured in FAAE and if necessary, in VS domain. Other domains like CM/PR (AECONTRT), HO (AESHOSP), and/or DD (AESDTH) should be utilized if the corresponding variables in AE are marked as yes, and related information is present.

Below (Table 6) is an example that subject# 12345 has an adverse event of Pneumonia (Table 5) and is hospitalized, this event is represented in HO (Healthcare Encounters) domain with HOTERM as “HOSPITAL” .

USUBJID	HOSEQ	HOTERM	HOSTDTC	HOENDTC
12345	1	HOSPITAL	12/28/2020	12/31/2020

Table 6 SDTM.HO

If a chronic disease (from medical history MH) is worsen following the vaccination, AE domain should contain data about the disease, following vaccination with disease information captured in AECAT/AESCAT. If a laboratory result (from LB) for a particular assessment of a subject is outside the normal range (abnormal), it should additionally be captured in the AE domain with the highest level noted. RELREC should be used for all these dataset-level relationships.

HANDLING OF EFFICACY DATA

Vaccine immunogenicity data provide proof of the type, magnitude, and duration of specific immune responses being induced by the study vaccine. Accurate representation of vaccine-induced immune response is one of the main objectives in vaccine development and clinical studies. Data related to the assessment of immunogenicity should be mapped to IS (Immunogenicity Specimen Assessments) findings domain. An example of IS domain is shown in Table 7. Specimen-based, (typically) systemic, immune response data should be modeled in the IS domain instead of the LB domain. Examples include but are not limited to, assessments of anti-allergen antibodies and vaccine-induced antibodies.

USUBJID	ISTEST	ISORRES	ISORRESU	VISIT
12345	RSV IgG Antibody	10	titer	Baseline
12345	RSV IgG Antibody	50	titer	Visit 1
12345	RSV IgG Antibody	60	titer	Visit 2

Table 7 SDTM.IS

In vaccine studies, with disease as the primary endpoint, the definition of trial endpoints with respect to efficacy depends on characteristics of the disease and the candidate vaccine. This efficacy data maps to CE domain with CECAT as ‘Efficacy’. Since efficacy is pre-specified (CEPRESP=’Y’), the variables CEOCCUR, Clinical Event Completion Status (CESTAT), and Clinical Event Reason Not Collected (CEREASND) should be included. CETERM should be indicative of the disease. If hospitalization occurs or concomitant medication was taken to alleviate symptoms, then CESHOSP and CECONTRT variables are utilized.

Test results from assays conducted to confirm the presence of the microbe of interest (e.g., polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), cell culture, etc.) should be reported in the MB (Microbiology Specimen)/MS (Microbiology Susceptibility) domains. According to SDTM IG, MB domain is designed to store microbiology findings that include organisms found, gram stain results, and organism growth status. The MS domain is designed to store any findings related to the organisms found and submitted in MB. This domain is intended to be used in conjunction with the MB domain.

DISPOSITION (DS) DOMAIN

Disposition domain holds one record per disposition status or protocol milestone per subject. When multiple doses of vaccine are administered over time then DS should include the use of the TAETORD (Planned Order of Element within Arm) timing variable along with DSDECOD, DSTERM, DSCAT, and DSSTDTC variables (Table 8).

USUBJID	DSSEQ	DSTERM	DSCAT	TAETORD	DSSTDTC
12345	1	INFORMED CONSENT OBTAINED	PROTOCOL MILESTONE	1	12/19/2020
12345	2	RANDOMIZED	PROTOCOL MILESTONE	1	12/19/2020
12345	3	VACCINE DISPENSATION	PROTOCOL MILESTONE	2	12/19/2020
12345	4	VACCINE DISPENSATION	PROTOCOL MILESTONE	3	1/19/2021
12345	5	COMPLETED	DISPOSITION EVENT	4	2/4/2021

Table 8 SDTM.DS

CONCLUSION

This paper briefly discussed on how to apply CDISC standards to represent data in vaccine studies in compliance with FDA CBER/OVRR submission. In a nutshell, reactogenicity data should be mapped to CE and FACE but not to AE or custom domains. Immunogenicity data should be mapped to IS and MB but not to the LB domain. Disease endpoint efficacy data should be mapped to the CE domain. We hope these insights on mapping the vaccine study data to SDTM domains will help you in higher-quality SDTM production and submission.

REFERENCES

Therapeutic Area Data Standards User Guide for Vaccines (TAUG-Vax) version 1.1: https://www.cdisc.org/standards/therapeutic-areas/vaccines/vaccines-therapeutic-area-user-guide-v11/html

Optimizing Your Study Data Submissions to FDA: OVRR Data Submission: https://sbiaevents.com/files/OVRR-Webinar-May-2018.pdf

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