Paper SA07

Clinical Disease Endpoint Flag Implementation for Vaccine Studies

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ABSTRACT

Before being approved for use in people, every novel vaccine(s) must undergo stringent safety, immunogenicity, and protective efficacy evaluations. Assessment of a vaccine's reactogenicity—its ability to suggest that a drug has the potential to elicit a typical unfavorable response when ingested—is a critical safety step in the development of vaccines. Another aspect that comes under viability is the antibody's immunogenicity. The ability of a foreign substance, like an antigen, to cause an immune response in a human body is known as immunogenicity. The degree to which vaccination protects recipients from adverse health outcomes, including infection, serious illness, hospitalization, and death, in the actual world. The clinical disease endpoint flag is recommended by the regulatory bodies as an approach for evaluating the efficacy of treatment. This paper discusses the regulatory agencies' guidance to include these CDECASE flags to SDTM datasets as well as how they impact further analysis.

INTRODUCTION

The candidate vaccine for human usage goes through multiple levels of evaluations and assessments. The pivotal role for the approval goes to the effectiveness of the vaccines administrated. The main point to be noted here is that majority of the vaccines are administrated to healthy populations and getting adverse effects and/or less effectiveness of the vaccines led to rejection of the candidate vaccine. Also, pediatric population is a major critical population where vaccines are administrated, utmost care to be taken in these scenarios.

This paper elaborates the clinical disease endpoint implementation in SDTM data based on the protocol specified procedure. Also, CBER guidance “Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review” requests that a “clinical disease endpoint case flag” (CDECASE) be included in the SUPPDM domain in SDTM to flag confirmed cases of the disease of interest which are used to determine efficacy.

DEVELOPMENT OF VACCINE

Prior to regulatory approval, a vaccine candidate usually undergoes three phases of development in humans, which, for the most part, progress sequentially: Phase I, Phase II, and Phase III. After successful completion of Phase III trials and following licensure of the product, Phase IV studies, also referred to as post marketing: surveillance studies PMS are used to continue to monitor the vaccine for safety and effectiveness.

PHASE I

The first-in-human studies refer to the first administration of a vaccine candidate to healthy humans. The primary objective is to evaluate the safety and reactogenicity, while the secondary objective is collection of immune response.

PHASE II

A candidate vaccine should proceed to Phase II clinical evaluation after achieving a satisfactory outcome in Phase I studies in terms of both safety and immunogenicity. The transition from a controlled clinical setting to field evaluation incurs much greater monetary investment, hence stringent go/no-go criteria are observed by the developers.

Phase II is to identify the vaccine preparation, optimal dose, and schedule to be taken up for confirmatory Phase III trials. These studies have the desired statistical power and a defined sample size, and hence are expected to provide a clinically meaningful outcome on the safety, immunogenicity, and efficacy end points. It also assesses the impact of multiple variables on immune response, such as age, ethnicity, gender, and presence of maternal or pre-existing antibodies (in infants), and evaluate the following:

- ✓ Age of first administration of Vaccine
- ✓ Number of Vaccine Doses
- ✓ Sequence or interval between vaccine doses, route of administration, duration of immunity,
- ✓ potential need for booster immunizations, and qualitative aspects of the immune response.

PHASE III

Pivotal Phase III trials, essential for registration and approval to market of a vaccine, assess the effect of the final formulation. These trials are typically designed to evaluate efficacy and safety.

In Phase III studies of vaccines against infectious diseases, the end point chosen should be of importance to public health and should also be clinically important. Often the evaluation of protective efficacy focuses on the ability of the vaccine to prevent clinical disease. However, if an organism causes a range of infections (e.g., from mild infection to clinical disease to severe disease), then the primary end point can be carefully selected in accordance with the proposed indication. The various vaccine effects of interest that can be evaluated are:

- ✓ Vaccine efficacy for susceptibility, colonization, progression, and pathogenicity and infectiousness.
- ✓ Total vaccine efficacy.
- ✓ Indirect effects of vaccination in those not vaccinated.
- ✓ Total effects of vaccination in those vaccinated.
- ✓ Overall population-level effects.

CLINICAL DISEASE ENDPOINT

A clinical endpoint is a measurable outcome or event in a clinical trial that determines the safety and efficacy of a treatment. Endpoints are objective tools that help guide clinical decision making. They are usually included in the study objectives and can vary depending on the nature of the trial. Clinical Endpoints are very crucial for determining the efficacy of vaccine candidates.

Vaccine efficacy is one of the major clinical endpoints for the vaccine trials. The US FDA proposed that laboratory-confirmed disease infection be adopted as the primary endpoint in vaccine effectiveness studies. Infection, severity, or transmission might be prevented with an effective vaccine.

Vaccine efficacy is measured using a range of outcomes that differ based on the pathogens, infection repercussion, and kinetics of transference. Since immunogenicity is an important consideration when developing a vaccine, the intensity of the immune response necessary to safeguard against disease infection is unpredictable. Vaccine Efficacy (VE) is defined as the percent reduction in incidence (of disease or infection) among the vaccinated.

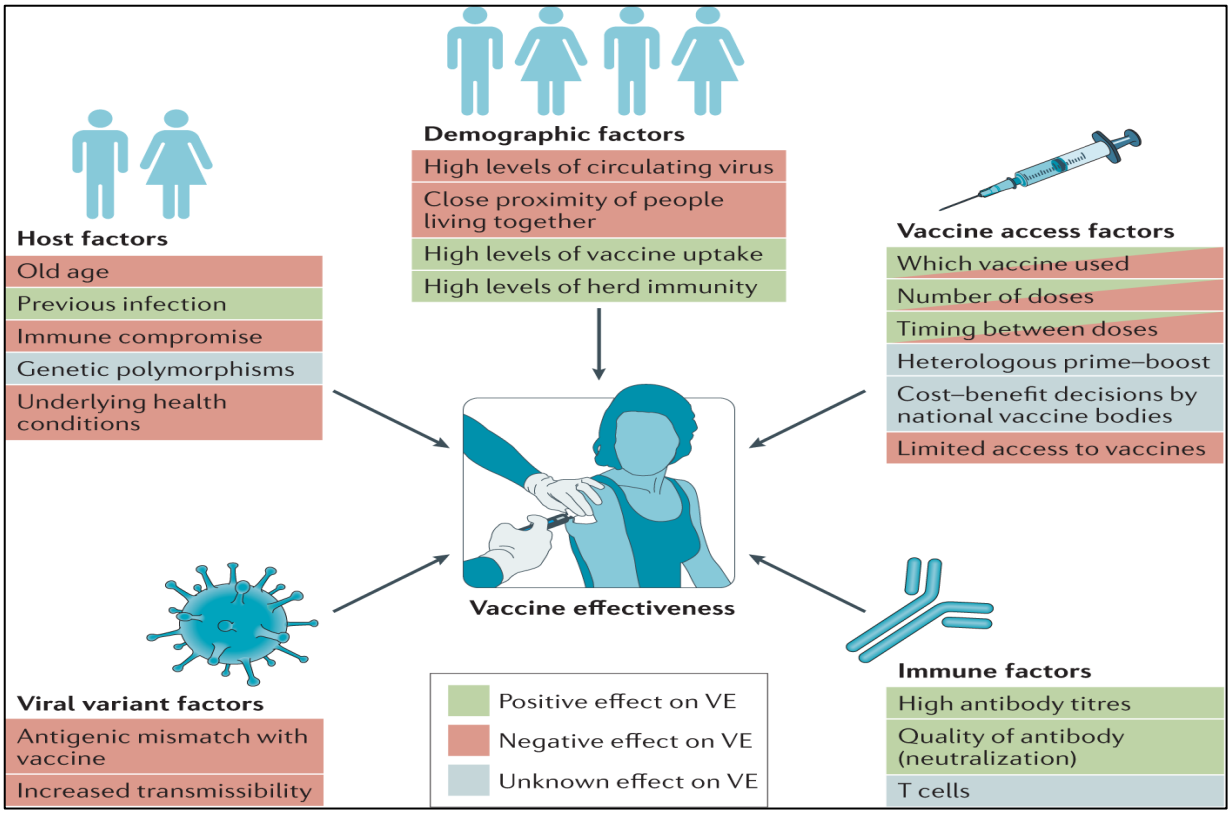

Figure 1. VACCINE EFFECTIVENESS

The CBER guidance “Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review” requests that a “clinical disease endpoint case flag” (CDECASE) be included in SDTM to flag confirmed cases of the disease of interest which are used to determine efficacy. 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.

SDTM DOMAINS – CDECASE IMPLEMENTATION

SUPPDM

When the study is not submitted to showcase the effectiveness of the vaccines, CDECASE variable is created in the supplemental DM with QNAM = ”CDECASE”, QLABEL = “Clinical Endpoint Case Flag” and QVAL = “TBD”.

When the study is submitted for the evaluation of the effectiveness of the vaccines, if the disease of interest is confirmed, either by Clinical investigator or adjudication committee or using the information from a clinical assessment and the results of confirmatory tests, it should be flagged in a supplemental DM domain with QNAM = “CDECASE,” (QLABEL) = “Clinical Endpoint Case Flag” and QVAL = “Y”. If the disease of interest is not confirmed by either the clinical investigator or by an adjudication committee or the results of assessments it should be flagged in a supplemental DM domain with QNAM = “CDECASE” QLABEL = “Clinical Endpoint Case Flag” and QVAL = “N”.

FACE

The signs and symptoms for the confirmation of the disease will be collected in the FACE with FACAT=EFFICACY.

MB

The MB domain will be collection of details on the assessments for the confirmation of the disease, through methods defined in the protocol. 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 domain.

CE

The efficacy data will be primarily collected/reported in CE domain. To differentiate an efficacy clinical event (i.e., case of the disease of interest) from other clinical events, the variable CECAT should be utilized, and “efficacy” should be stated. Since efficacy is pre-specified, the variables CEOCCUR, Clinical Event Completion Status (CESTAT), and Clinical Event Reason Not Collected (CEREASND) should be included. The CETERM for the efficacy clinical event should be indicative of the disease, e.g., for an influenza vaccine, “influenza-like illness or ILI;” or for a human papillomavirus vaccine, “cervical intraepithelial neoplasia or CIN”.

If hospitalization occurs during the clinical trial because of occurrence of the “disease of interest,” the CE domain variable Clinical Event Requires or Prolongs Hospitalization (CESHOSP) should be marked with “Y.” Additional data regarding the hospitalization and/or other healthcare encounter should be provided in the HO domain.

Two case scenarios are briefed below showing the CDECASE implementation in SDTM.

SCENARIO-1

Consider a clinical trial for the COVID-19 vaccine. The CDECASE flag is mandated by the US FDA for showcasing the effectiveness of the vaccine, as per the OVRR guideline. The sign and symptoms of the disease, in this case, for COVID-19 symptoms will be collected in CRF. Based on the sign and symptoms occurrence, the clinical event data will be constructed.

Symptoms	Symptom Present*
FEVER	
NEW OR INCREASED COUGH	
NEW OR INCREASED SHORTNESS OF BREATH	
CHILLS	
NEW OR INCREASED MUSCLE PAIN	
NEW LOSS OF TASTE OR SMELL	
SORE THROAT	
DIARRHEA	
VOMITING	

Figure 2. CRF PAGE SHOWING THE SYMPTOMS OF THE COVID DISEASE

USUBJID	FATESTCD	FATEST	FAOBJ	FAORRES	VISITNUM	VISIT
ABCD 123 12345678	FSYDATE	First Symptom Date	Potential COVID-19	2021-09-20	901	COVID ILLNESS A
ABCD 123 12345678	FSYDATE	First Symptom Date	Potential COVID-19	2021-12-10	902	COVID ILLNESS B
ABCD 123 12345678	LSYDATE	Last Symptom Date	Potential COVID-19	2021-09-25	901	COVID ILLNESS A
ABCD 123 12345678	LSYDATE	Last Symptom Date	Potential COVID-19	2021-12-20	902	COVID ILLNESS B
ABCD 123 12345678	OCCUR	Occurrence Indicator	CHILLS	N	901	COVID ILLNESS A
ABCD 123 12345678	OCCUR	Occurrence Indicator	CHILLS	Y	902	COVID ILLNESS B

Table 1. FACE DOMAIN SHOWING SIGNS AND SYMPTOMS OF THE DISEASE

A placeholder will be added in the supplemental DM with the following details.

QNAM = ‘CDECASE’

QLABEL = ‘Clinical Disease Endpoint Flag’

QVAl = ‘TBD’

STUDYID	RDOMAIN	USUBJID	QNAM	QLABEL	QVAL	QORIG	QEVAL
ABCD	DM	ABCD 123 12345678	CDECASE	Clinical Disease Endpoint Flag	TBD	DERIVED	CLINICAL STUDY SPONSOR
ABCD	DM	ABCD 567 12345678	CDECASE	Clinical Disease Endpoint Flag	TBD	DERIVED	CLINICAL STUDY SPONSOR

Table 2. SUPPDM SHOWING THE PLACEHOLDER

Similarly, a placeholder will be added to the Clinical Events domain with CECAT = ‘EFFICCAY’ and CETERM = ‘COVID Confirmed’, for each of the protocol specified illness VISITs, the occurrence variable will be left blank for these

placeholders. Also, CETERM = 'COVID like Illness' and CECAT = 'EFFICACY' will be added based on the data collected in the sign and symptoms CRF page, CEOCCUR will be 'Y' if at least one of the symptoms from the list has occurred for the subject.

DOMAIN	USUBJID	CETERM	CECAT	CEOCCUR	VISIT	CEDTC	CESTDTC	CEENDTC
CE	ABCD 123 12345678	COVID-19 like Illness	EFFICACY	N	COVID ILLNESS A			
CE	ABCD 123 12345678	COVID-19 Confirmed	EFFICACY					
CE	ABCD 123 12345678	COVID-19 like Illness	EFFICACY	Y	COVID ILLNESS B	2021-12-20	2021-12-10	2021-12-20
CE	ABCD 123 12345678	COVID-19 Confirmed	EFFICACY					

Table 3. CLINICAL EVENT DOMAIN WITH CDECASE DETAILS

When the disease is confirmed based on the protocol defined procedure, the Supplemental DM will be updated with QVAL as 'Y'.

STUDYID	RDOMAIN	USUBJID	QNAM	QLABEL	QVAL	QORIG	QEVAL
ABCD	DM	ABCD 123 12345678	CDECASE	Clinical Disease Endpoint Flag	Y	DERIVED	CLINICAL STUDY SPONSOR
ABCD	DM	ABCD 567 12345678	CDECASE	Clinical Disease Endpoint Flag	N	DERIVED	CLINICAL STUDY SPONSOR

Table 4. SUPPDM AFTER CONFIRMATION OF DISEASE

The Clinical Event domain will be updated for the CECOCCR Value for CETERM = 'COVID-19 Confirmed'. Additionally, the signs and symptoms will be listed for the COVID-19 disease confirmed scenarios.

DOMAIN	USUBJID	CETERM	CECAT	CEPRESP	CEOCCUR	VISIT	CEDTC	CESTDTC	CEENDTC
CE	ABCD 123 12345678	COVID-19 like Illness	EFFICACY		N	COVID ILLNESS A			
CE	ABCD 123 12345678	COVID-19 Confirmed	EFFICACY						
CE	ABCD 123 12345678	COVID-19 like Illness	EFFICACY		Y	COVID ILLNESS B	2021-12-20	2021-12-10	2021-12-20
CE	ABCD 123 12345678	COVID-19 Confirmed	EFFICACY		Y	COVID ILLNESS B	2021-12-20	2021-12-10	2021-12-20
CE	ABCD 123 12345678	CHILLS	EFFICACY	Y	Y	COVID ILLNESS B	2021-12-20		

Table 5. CE AFTER DISEASE CONFIRMATION

SCENARIO-2

Consider a vaccine clinical trial for the respiratory illness disease (RSV). The CDECASE was determined for multiple levels of the disease. CETERM is constructed based on the frequency of the symptoms occurred during the protocol specified illness visit.

USUBJID	FATESTCD	FATEST	FAOBJ	FAORRES	VISIT
ABC 1234 12345678	FSYMDATE	First Symptom Date	RESPIRATORY ILLNESS	2020-10-20	RI_1
ABC 1234 12345678	LSYMDATE	Last Symptom Resolved Date	RESPIRATORY ILLNESS	2021-11-11	RI_1
ABC 1234 12345678	OCCUR	Occurrence Indicator	NEW OR INCREASED COUGH	Y	RI_1
ABC 1234 12345678	OCCUR	Occurrence Indicator	NEW OR INCREASED NASAL CONGESTION	Y	RI_1
ABC 1234 12345678	OCCUR	Occurrence Indicator	NEW OR INCREASED NASAL DISCHARGE	Y	RI_1
ABC 1234 12345678	OCCUR	Occurrence Indicator	NEW OR INCREASED SHORTNESS OF BREATH	N	RI_1

Table 6. FACE DOMAIN

USUBJID	CETERM	CECAT	CEPRESP	CEOCCUR	VISIT	CEDTC	CESTDTC	CEENDTC
ABC 1234 12345678	ARI	EFFICACY	Y	Y	RI_1	2020-10-24	2020-10-20	2021-11-11
ABC 1234 12345678	ARI-RSV confirmed case	EFFICACY	Y	Y	RI_1	2020-10-24	2020-10-20	2021-11-11
ABC 1234 12345678	First evaluable LRTI-RSV with >=2 symptoms confirmed	EFFICACY	Y	Y	RI_1	2020-10-24	2020-10-20	2021-11-11
ABC 1234 12345678	First evaluable LRTI-RSV with >=3 symptoms confirmed	EFFICACY	Y	Y	RI_1	2020-10-24	2020-10-20	2021-11-11
ABC 1234 12345678	Exacerbation of Asthma	EFFICACY			RI_1	2020-10-21		
ABC 1234 12345678	NEW OR INCREASED COUGH	EFFICACY	Y	Y	RI_1	2020-10-24		
ABC 1234 12345678	NEW OR INCREASED NASAL CONGESTION	EFFICACY	Y	Y	RI_1	2020-10-24		
ABC 1234 12345678	NEW OR INCREASED NASAL DISCHARGE	EFFICACY	Y	Y	RI_1	2020-10-24		
ABC 1234 12345678	NEW OR INCREASED SHORTNESS OF BREATH	EFFICACY	Y	N	RI_1	2020-10-24		
ABC 1234 12345678	NEW OR INCREASED SORE THROAT	EFFICACY	Y	N	RI_1	2020-10-24		
ABC 1234 12345678	NEW OR INCREASED SPUTUM PRODUCTION	EFFICACY	Y	Y	RI_1	2020-10-24		
ABC 1234 12345678	NEW OR INCREASED WHEEZING	EFFICACY	Y	Y	RI_1	2020-10-24		
ABC 1234 12345678	TACHYPNEA	EFFICACY	Y	N	RI_1	2020-10-24		

Table 7. CLINICAL EVENT DOMAIN WITH MULTIPLE LEVEL DISEASE CONFIRMATION SCENARIOS

Any non-disease related illness identified by the assessments should be reported in Adverse Events (AE) with AECAT = 'NON-ENDPOINT CLINICAL DIAGNOSIS' and corresponding signs and symptoms for that event should be reported in FAAE domain.

CONCLUSION

The paper summarizes the implementation of the CDECASE flag in SDTM with the following domains usage – SUPPDM, FCAE and CE. Further analysis of these domains data will be used in determining the effectiveness and the vaccine efficacy, which will led to the vaccine's usage in the human population. Apart from the reactogenicity parameters, the clinical disease endpoint plays major role in vaccine approval.

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