

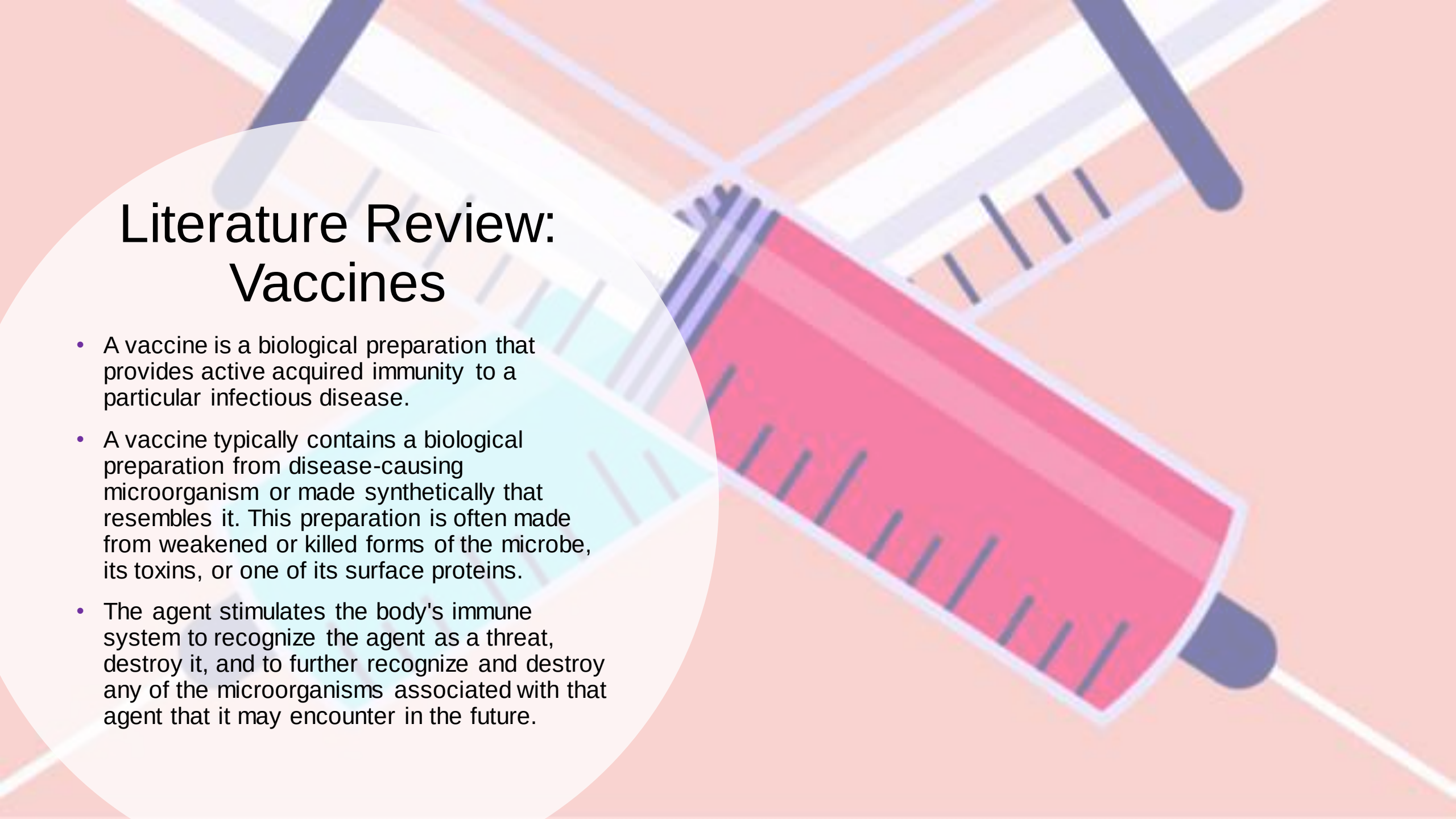


DS05-Implementation of a flat model for reactogenicity events in vaccine studies

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Topics covered

- Literature review
 - *Vaccines, Reactogenicity, Reactogenicity events*
- Flat model
- Raw data
- Timeframe
- Process flow
 - *Reacto, NOT DONE Records, Examples*
- Clinical Events reporting & syntax
- Adverse Events reporting



Literature Review: Vaccines

- 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.



Literature Review: Reactogenicity?

- 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.

The background of the slide is a composite image. On the left, a person wearing a brown lab coat is visible, with their hands near a white container. On the right, there is a close-up of several clear glass vials with blue caps, arranged in a row. A white diagonal line separates the two images.

Literature Review: 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.
- Typically, reactogenicity adverse events are solicited and collected on diary cards or a reactogenicity case report form.

Flat Model- Requirements

- 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.

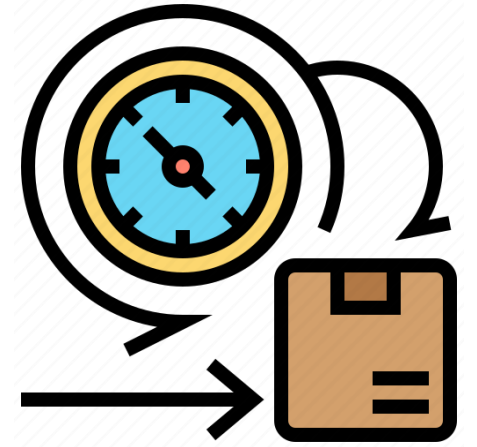


Raw data for Reactogenicity Events

- Vaccines Symptom Diary – External data – Filled by Study subject
- Unplanned Assessment Of Local Reaction – CRF data – Investigator Assessed
- Vaccination Symptoms Diary - Symptom Resolved Dates – CRF data – Investigator Assessed



Timeframe of the data captured



Vaccination	Diary	Vaccination Symptoms Resolved Dates
•Exposure to the IP •Collected in CRF	•Period Based on the Protocol •Filled by Study Subject	•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.

Process Flow



Process Flow – Creating *NOT DONE* Records

“NOT DONE” records are created for all missing diary days per subject, per vaccination, per event, per day.



Get 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.

CRF (CE, Create "NOT DONE" for the events with missing daily diary days (for all applicable systemic and administration site events) with FATESTCD=OCCUR. Create missing records only for the actual systemic and administration events only, and not for the related findings e.g. hospitalization.

FACE)

Diary (Merge with existing diary data dataset
FACE, VS by USUBJID, xxTPTREF.
(FACE)

Note:

If a subject has withdrawn from study during diary period, only create records up through the date of withdrawal.

If missing diary records are present for a subject, check for subject discontinuation from study (DS.DSDECOD ^= 'COMPLETED' where DSPHASE = 'FOLLOW-UP'). Target FACE and VS should have records for each planned diary day as long as the subject did not discontinue from the study. Only create missed diary days up through (including) the date of discontinuation (DS.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 a record for day 3.

Sample calculation for record numbers in FACE

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	

FACE Dataset

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

SYSTEMIC EVENT		VAX REFERENCE		DIARY DAY	DIARY DATE	
SUBJECTNUMBERSTR	R_VSDTEST_012	VISITID	VISITREFNAME	X_VSDSDAY	FADTC	FAORRES
12345678	Headache Occurrence	301	VAX1	5	2020-08-10T19:12:28	N
12345678	Headache Occurrence	301	VAX1	6	2020-08-11T18:25:43	N
12345678	Headache Occurrence	301	VAX1	7	2020-08-12T18:03:39	N
12345678	Headache Occurrence	302	VAX2	1	2020-08-27T19:10:42	N
12345678	Headache Occurrence	302	VAX2	2	2020-08-28T18:07:57	N
12345678	Headache Occurrence	302	VAX2	3	2020-08-29T18:24:00	N
12345678	Headache Occurrence	302	VAX2	4	2020-08-30T18:43:05	N
12345678	Headache Occurrence	302	VAX2	5	2020-08-31T18:16:03	N
12345678	Headache Occurrence	302	VAX2	6	2020-09-01T19:05:01	N
12345678	Headache Occurrence	302	VAX2	7	2020-09-02T22:08:18	N

FACE Dataset

USUBJID	FALNKID	FATEST	FAOBJ	FAORRES	FASTAT	FAREASND	VISITNUM	VISIT	FADTC	FATPT	FATPTREF
12345678	VACCINATION 1-HEADACHE-DAY 1	Occurrence Indicator	HEADACHE		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	60765	V1_DAY1_VAX1_L	06/08/2020	DAY 1	VACCINATION 1
12345678	VACCINATION 1-HEADACHE-DAY 2	Occurrence Indicator	HEADACHE		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	60765	V1_DAY1_VAX1_L	07/08/2020	DAY 2	VACCINATION 1
12345678	VACCINATION 1-HEADACHE-DAY 3	Occurrence Indicator	HEADACHE		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	60765	V1_DAY1_VAX1_L	08/08/2020	DAY 3	VACCINATION 1
12345678	VACCINATION 1-HEADACHE-DAY 4	Occurrence Indicator	HEADACHE		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	60765	V1_DAY1_VAX1_L	09/08/2020	DAY 4	VACCINATION 1
12345678	VACCINATION 1-HEADACHE-DAY 5	Occurrence Indicator	HEADACHE	N			60765	V1_DAY1_VAX1_L	2020-08-10T19:12:28	DAY 5	VACCINATION 1
12345678	VACCINATION 1-HEADACHE-DAY 6	Occurrence Indicator	HEADACHE	N			60765	V1_DAY1_VAX1_L	2020-08-11T18:25:43	DAY 6	VACCINATION 1
12345678	VACCINATION 1-HEADACHE-DAY 7	Occurrence Indicator	HEADACHE	N			60765	V1_DAY1_VAX1_L	2020-08-12T18:03:39	DAY 7	VACCINATION 1

Creating NOT DONE Records

- FACE
 - Will contain the daily diary (except temperature) records plus findings from Unplanned Assessment of Reactogenicity (CRF). “NOT DONE” records in FA (with FATESTCD=OCCUR) are created for all missing diary days per subject, per vaccination, per event, per day.
- VS
 - Will contain the temperature findings from the daily diary and any unplanned assessments of temperature from CRF data. “NOT DONE” records in VS are created for all missing diary days per subject, per vaccination, per day.



Clinical Events (CE)

- Global records, summarizing whether each symptom occurred for each subject following each vaccination is included in Clinical Events.
- Global records are created using the diary data, Symptom Resolved Dates CRF, and Unplanned Assessment CRF.
- If data is not available for subject/vaccination/symptom, then global NOT DONE record will be created in CE.



Clinical Events (CE) Syntax

- CEOCCUR

Assign 'Y' if any FAORRES = 'Y' when FATESTCD = 'OCCUR' (diary) or if [OCCUR = 'Y' (UNPL) and xxDTC within diary period]; else 'N'. When CESTAT = 'NOT DONE' then CEOCCUR will be null.

- CESTDTC

First FACE.FADTC (date portion) when FATESTCD=OCCUR and FAORRES=Y and FADTC is within the diary assessment period ($EXSTDTC \leq FADTC \leq EXSTDTC + x - 1$)



Clinical Events (CE) Syntax

- CEENDTC
 - If ONGOING = "NO/YES" and end date is available: if less than or equal to subsequent vaccination date then assign value of xxENDTC, else use next vaccination date
 - If ONGOING = "NO" and end date is missing, map the date when event last ended in daily diary or UNPL form (last.FADTC when FAORRES = Y - date portion only)
 - If ONGOING = "YES" and end date is missing then map the date of start of next vaccination (EX.EXSTDTC) to CEENDTC, else set to missing
 - If ONGOING is null, then take last diary date of symptom (last.FADTC when FAORRES = Y - date portion only)



CE Dataset

USUBJID	CELNKGRP	CETERM	CEOCCUR	CESTAT	CESEV	CETOXGR	CESTDTC	CEENDTC	CETPTREF	CERFTDTC
12345678	VACCINATION 1-HEADACHE	HEADACHE	N						VACCINATION 1	06/08/2020
12345678	VACCINATION 2-HEADACHE	HEADACHE	N						VACCINATION 2	27/08/2020

CETERM	CEOCCUR	CESTAT	CESEV	CETOXGR	CESTDTC	CEENDTC	CETPTREF	CERFTDTC
HEADACHE	Y		MILD		16/08/2020	16/08/2020	VACCINATION 1	15/08/2020
HEADACHE	Y		MILD		04/09/2020	05/09/2020	VACCINATION 2	04/09/2020

Adverse Events (AE)

Create records in AE when:

- Event end date is missing and is ongoing as per CRF page
- Event end date is after last day of diary period and is ongoing as per CRF page

If a reactogenicity event should happen to continue beyond the assessment interval, it should also be represented in the AE domain, with the CE domain record indicating that the event extended beyond the assessment interval



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Thank You

