Preparing Vaccine Studies for Regulatory Submissions

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PRESENTER – MICHAEL BEERS

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- More than 10 years experience at both Pharma and CROs
- SME on FDA projects for CDER and CBER

QUESTIONS

- Ask a question at any time during the webinar
- Questions will be answered at the end

AGENDA

- Introduction
- Relevant Industry Guidance
- Data Common to Vaccine Trials
  - How the data should be mapped
  - How the industry is mapping it
- Common Issues/Challenges/Inconsistencies
- Conclusion

DISCLAIMER

- This webinar discusses the key guidance necessary to be aware of when preparing data for submission. This is not the exhaustive list of guidance for vaccine trials in general, such as design of trials, etc.

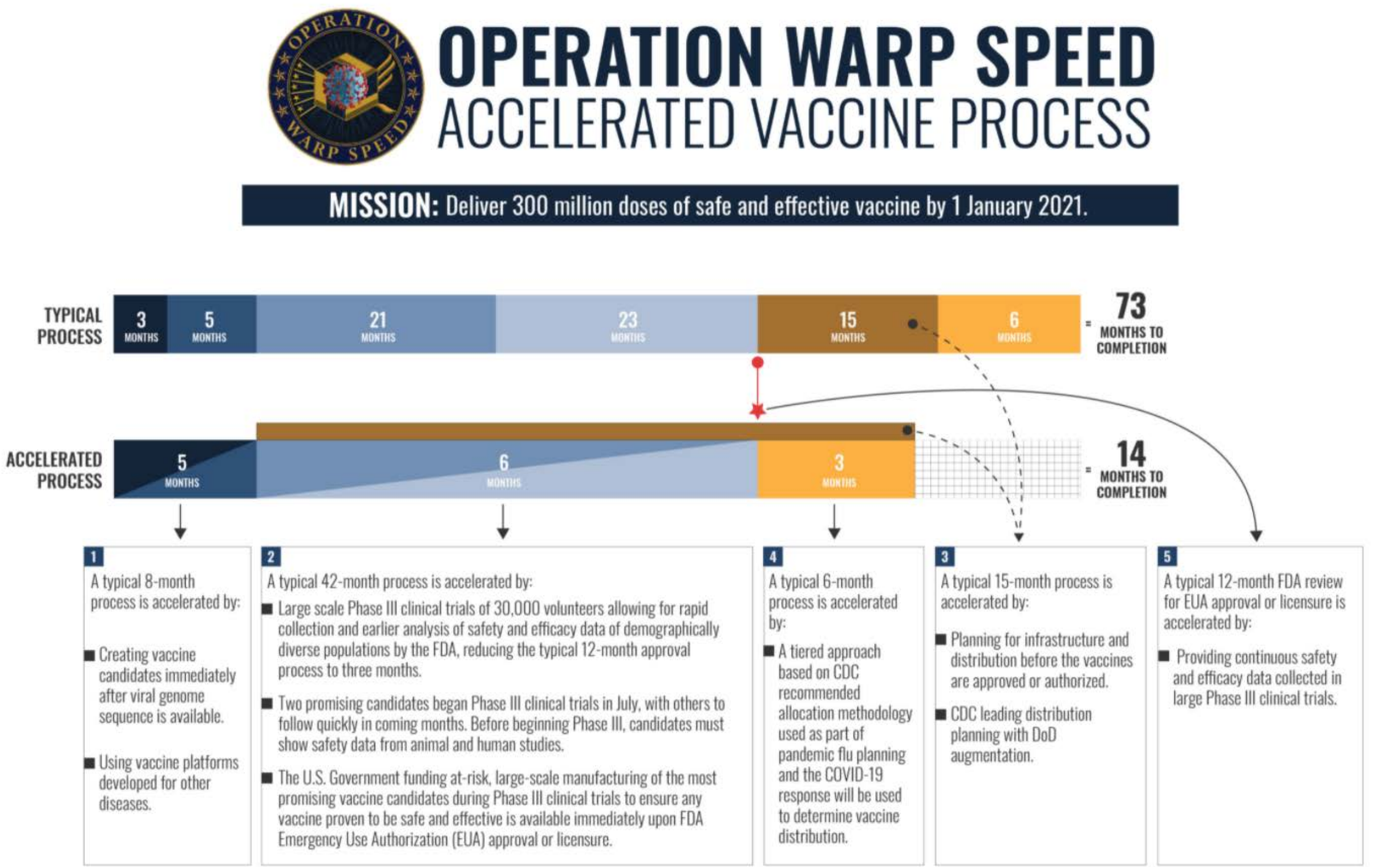
- I do not speak for the regulatory agencies or standards development organizations in any way

- Always consult with your review division to be sure you are submitting what they want

INTRODUCTION

INTRODUCTION

- The goal: reduce time to get drugs, biologics, vaccines on the market
  - Public health emergencies escalate this need for reduced review time/effort
  - COVID-19
    - Operation Warp Speed
    - Emergency Use Authorization



https://www.defense.gov/Explore/Spotlight/Coronavirus/Operation-Warp-Speed/

DATA STANDARDIZATION

- Data Standardization is one important way to help in reducing review time
- Increased automation is necessary to accomplish this goal
  - Manual processing and review is inefficient
  - Data quality evaluation is more difficult
- Automation relies on adherence to standards/guidance and high quality data
- The challenge is being aware of all the relevant guidance, and what to do when they contradict each other

GUIDANCE FOR INDUSTRY

GUIDANCE FOR INDUSTRY

REGULATORY AGENCIES

- FDA
  - Technical Conformance Guide
    - Current version is v4.7, March 2021
    - https://www.fda.gov/media/147233/download
  - Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review (Vaccines Technical Specifications Guidance v2.1)
    - CBER (Center of Biologics Evaluation and Research), OVRR (Office of Vaccines Research and Review)
    - https://www.fda.gov/media/112581/download
  - Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency
    - Includes Q&A section
    - https://www.fda.gov/media/136238/download

GUIDANCE FOR INDUSTRY

REGULATORY AGENCIES

- PMDA
  - PMDA's Efforts to Combat COVID-19
    - https://www.pmda.go.jp/english/about-pmda/0002.html
  - Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2
    - https://www.pmda.go.jp/files/000237021.pdf
    - More focused on study design/conduct
  - Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of vaccines against variants
    - https://www.pmda.go.jp/files/000240416.pdf

GUIDANCE FOR INDUSTRY

CDISC

- SDTMIG, ADaMIG
- Therapeutic Area User Guides
  - Guidance for Ongoing Studies Disrupted by COVID-19
    - Applies to all types of trials, nothing vaccine-specific
  - Interim User Guide for COVID-19 v1.0
    - Note that the final version is expected to be released soon
    - Section 13, page 31 - Vaccines
  - Vaccines TAUG v1.1
  - Influenza TAUG v1.1
  - Tuberculosis TAUG v2.0
  - Ebola TAUG v1.0
  - HIV TAUG v1.0, Virology TAUG v2.1
    - Just minor mention of vaccines, an example or two in each

GUIDANCE FOR INDUSTRY

NECESSARY TO CONSULT MULTIPLE GUIDANCE DOCUMENTS

- FDA's TCG, section 5.2.18 Vaccines Therapeutic Area User Guide v1.1

5.2.18 Vaccines Therapeutic Area User Guide v1.1

The Vaccine TAUG should be used in conjunction with the FDA Guidance for Industry "Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review." Investigator determined reactogenicity reporting should follow the "Interim User Guide for COVID-19" examples on page 32 with the following revisions:

- FDA's TCG, Appendix D: Additional Documents Evaluated By FDA

CDISC Document: Guidance for Ongoing Studies Disrupted by COVID-19 Pandemic

It is the current preference of the Agency that for all clinical studies, not limited to those impacted by COVID-19, subject visit data for scheduled (whether or not they occurred), and unscheduled visits be submitted in one single dataset structured as the current CDISC Subject Visits (SV) domain. It is also Agency preference that three non-standard variables (NSVs) for missed visits, --REASOC (Reason for Occur Value), --EPCHGI (Epi/Pandemic Related Change Indicator), and --CNTMOD (Contact Mode), outlined in the CDISC document "Guidance for Ongoing Studies Disrupted by COVID-19 Pandemic" be included within the SV domain and not within the supplemental SUPPSV domain or in other SDTM datasets. Submitting

DATA COMMON TO VACCINE STUDIES

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DATA COMMON TO VACCINE STUDIES

- Tests for disease being vaccinated against
  - Mostly routine mapping to MB or LB, depending on test, won't discuss in this webinar
- Details of disease being vaccinated against
  - Mostly routine mapping, depending timing information, won't discuss in this webinar
- Vaccine administration
  - Mostly routine mapping to EX, won't discuss in this webinar
- Antibody data
  - Mostly routine mapping not specific to vaccines, won't discuss in this webinar
- Risk factors for disease being vaccinated against
- Efficacy/Endpoints
- Reactogenicity data

RISK FACTORS FOR DISEASE BEING VACCINATED AGAINST

- What the CDISC TAUGs say
  - COVID-19 TAUG:
    - Pre-existing medical conditions mapped to MH, Smoking mapped to SU
    - PPE, travel, contacts, exposure to animals mapped new domain ER (Environmental and Social Factors)
  - Vaccines and Influenza TAUGs: Nothing specific
  - Ebola TAUG:
    - Epidemiological risk factors and contact mapped to ER domain
  - Tuberculosis TAUG:
    - Environmental risk factors, contact, and exposure to TB mapped to ER domain
    - Comorbid conditions, and conditions predisposing to TB mapped to MH

ER – Description/Overview

The Environmental and Social Factors (ER) domain represents data that was collected to assess the factors that might influence a subject's disease or medical condition via environmental contact or through participation in activities associated with increased or decreased risk.

⚠ The domain definition is draft. It is not yet included in the SDTM Domain Abbreviation controlled terminology.

RISK FACTORS FOR DISEASE BEING VACCINATED AGAINST

- What the OVRR Vaccines Technical Specifications Guidance v2.1 says
  - Nothing specific

- How the industry is currently handling it
  - Generally mapped to SC or SUPPDM
  - Apparent hesitancy to use this new (custom at the moment) domain
    - Discuss with your review division that this new domain will be used, as specified in the CDISC COVID-19 TAUG
    - Email CBER-edata@fda.hhs.gov

EFFICACY/ENDPOINTS

- What the OVRR Vaccines Technical Specifications Guidance v2.1 says
  - Section 4.0:

    For clinical trials in which efficacy against clinical disease is an objective, efficacy data will primarily be reported in the CE domain with specific information provided in the MB domain, FACE domain, VS domain, and PE domain (if necessary).

  - Section 4.0:

    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. 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. If the disease of interest is confirmed (e.g., by the clinical investigator or by an adjudication committee, using the information from a clinical assessment and the results of confirmatory tests), it should be reported in CE variable CEDECOD (e.g., Influenza), and flagged in a supplemental DM domain with QNAM = "CDECASE," (QLABEL) = "clinical disease endpoint case flag," and (QVAL) = "Y."

EFFICACY/ENDPOINTS

- What the CDISC Vaccines TAUG v1.1 says
  - Not covered, but states it will be covered in subsequent versions of this guide
- How the industry is currently handling it
  - Use of the clinical disease endpoint case flag (SUPPDM.CDECASE) seems to be somewhat limited
  - Likely because it is not listed in any CDISC guidance, you must be aware of the FDA guidance

REACTOGENICITY DATA

- What reactogenicity data is
  - The typical and expected adverse reactions related to administration of a vaccine, either local or systemic, and typically solicited for a certain period of time after the administration.
    - Common reactions:
      - Systemic: fever, myalgia, fatigue, headache, nausea, chills
      - Administration-site: redness/erythema, swelling/induration, pain/tenderness
- Why the mapping is complicated
  - The collected findings aren't just mapped to a single SDTM domain, they are also used to create corresponding event or findings records in other domains
    - Example: asked if they had fever that results in a FA record, results in a VS record for temperature, results in a CE record, potentially results in an AE record

REACTOGENICITY DATA

- What the CDISC Vaccines TAUG v1.1 says
  - Flat Model
    - Records from daily assessments (usually eDiary), whether it occurred or not, mapped to FACE/VS
    - Global event record created in CE

DOMAIN	USUBJID	CESEQ	CELNKGRP	CETERM	CEDECOD	CECAT	CESCAT	CEPRESP	CEOCCUR	CESEV	CEDTC	CESTDTC	CEENDTC	CETPT	CETPTNUM	CETPTREF	CERFTDTC
CE	ABC-001-001	1	VACC1-HEADACHE	HEADACHE	Headache	REACTOGENICITY	SYSTEMIC	Y	Y	MODERATE	2019-03-22	2019-03-20	2019-03-21	DAY 3	3	VACCINATION 1	2019-03-20
CE	ABC-001-001	2	VACC1-ERYTHEMA	ERYTHEMA	Erythema	REACTOGENICITY	ADMINISTRATION SITE	Y	N		2019-03-22			DAY 3	3	VACCINATION 1	2019-03-20
CE	ABC-001-001	3	VACC1-FEVER	FEVER	Fever	REACTOGENICITY	SYSTEMIC	Y	Y		2019-03-22	2019-03-20	2019-03-21	DAY 3	3	VACCINATION 1	2019-03-20

DOMAIN	USUBJID	FASEQ	FALNKGRP	FATESTCD	FATEST	FAOBJ	FACAT	FASCAT	FAORRES	FADTC	FADY	FATPT	FATPTNUM	FATPTREF	FARFTDTC
FA	ABC-001-001	1	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	Y	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	2	VACC1-HEADACHE	SEV	Severity/Intensity	HEADACHE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	3	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	Y	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	4	VACC1-HEADACHE	SEV	Severity/Intensity	HEADACHE	REACTOGENICITY	SYSTEMIC	MILD	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	5	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	N	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20
FA	ABC-001-001	6	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	7	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	8	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20

DOMAIN	USUBJID	VSSEQ	VSLNKGRP	VSTESTCD	VSTEST	VSCAT	VSSCAT	VSORRES	VSORRESU	VSDTC	VSDY	VSTPT	VSTPTNUM	VSTPTREF	VSRFTDTC
VS	ABC-001-001	1	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	102	F	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
VS	ABC-001-001	2	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	101.4	F	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
VS	ABC-001-001	3	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	98.3	F	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20

REACTOGENICITY DATA

- What the CDISC Vaccines TAUG v1.1 says
  - Nested Model
    - Records from daily assessments mapped to FACE/VS only if occurred (during assessment period)
    - Global record created in CE for each event

DOMAIN	USUBJID	CESEQ	CELNKGRP	CETERM	CEDECOD	CECAT	CESCAT	CEPRESP	CEOCCUR	CESEV	CEDTC	CESTDTC	CEENDTC	CETPT	CETPTNUM	CETPTREF	CERFTDTC
CE	ABC-001-001	1	VACC1-HEADACHE	HEADACHE	Headache	REACTOGENICITY	SYSTEMIC	Y	Y	MODERATE	2019-03-22	2019-03-20	2019-03-21	DAY 3	3	VACCINATION 1	2019-03-20
CE	ABC-001-001	2	VACC1-ERYTHEMA	ERYTHEMA	Erythema	REACTOGENICITY	ADMINISTRATION SITE	Y	N		2019-03-22			DAY 3	3	VACCINATION 1	2019-03-20
CE	ABC-001-001	3	VACC1-FEVER	FEVER	Fever	REACTOGENICITY	SYSTEMIC	Y	Y		2019-03-22	2019-03-20	2019-03-21	DAY 3	3	VACCINATION 1	2019-03-20

DOMAIN	USUBJID	FASEQ	FALNKGRP	FATESTCD	FATEST	FAOBJ	FACAT	FASCAT	FAORRES	FADTC	FADY	FATPT	FATPTNUM	FATPTREF	FARFTDTC
FA	ABC-001-001	1	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	Y	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	2	VACC1-HEADACHE	SEV	Severity/Intensity	HEADACHE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	3	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	Y	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	4	VACC1-HEADACHE	SEV	Severity/Intensity	HEADACHE	REACTOGENICITY	SYSTEMIC	MILD	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	5	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	N	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20
FA	ABC-001-001	6	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	7	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	8	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20

DOMAIN	USUBJID	VSSEQ	VSLNKGRP	VSTESTCD	VSTEST	VSCAT	VSSCAT	VSORRES	VSORRESU	VSDTC	VSDY	VSTPT	VSTPTNUM	VSTPTREF	VSRFTDTC
VS	ABC-001-001	1	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	102	F	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
VS	ABC-001-001	2	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	101.4	F	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
VS	ABC-001-001	3	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	98.3	F	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20

REACTOGENICITY DATA

- What the CDISC Vaccines TAUG v1.1 says
  - Highly Nested Model
    - Records from daily assessments mapped to FACE/VS only if occurred (during assessment period)
    - Global record created in CE for each category (systemic, site administration, etc.)

2 global category records added

Erythema record no longer in CE

DOMAIN	USUBJID	CESEQ	CELNKGRP	CETERM	CEDECOD	CECAT	CESCAT	CEPRESP	CEOCCUR	CESEV	CEDTC	CESTDTC	CEENDTC	CETPT	CETPTNUM	CETPTREF	CERFTDTC
CE	ABC-001-001	1		SYSTEMIC EVENT		REACTOGENICITY		Y	Y		2019-03-22			DAY 3	3	VACCINATION 1	2019-03-20
CE	ABC-001-001	2	VACC1-HEADACHE	HEADACHE	Headache	REACTOGENICITY	SYSTEMIC	Y	Y	MODERATE	2019-03-22	2019-03-20	2019-03-21	DAY 3	3	VACCINATION 1	2019-03-20
CE	ABC-001-001	3	VACC1-FEVER	FEVER	Fever	REACTOGENICITY	SYSTEMIC	Y	Y		2019-03-22	2019-03-20	2019-03-21	DAY 3	3	VACCINATION 1	2019-03-20
CE	ABC-001-001	4		ADMINISTRATION SITE EVENT		REACTOGENICITY		Y	N		2019-03-22			DAY 3	3	VACCINATION 1	2019-03-20

DOMAIN	USUBJID	FASEQ	FALNKGRP	FATESTCD	FATEST	FAOBJ	FACAT	FASCAT	FAORRES	FADTC	FADY	FATPT	FATPTNUM	FATPTREF	FARFTDTC
FA	ABC-001-001	1	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	Y	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	2	VACC1-HEADACHE	SEV	Severity/Intensity	HEADACHE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	3	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	Y	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	4	VACC1-HEADACHE	SEV	Severity/Intensity	HEADACHE	REACTOGENICITY	SYSTEMIC	MILD	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	5	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	N	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20
FA	ABC-001-001	6	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	7	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	8	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20

DOMAIN	USUBJID	VSSEQ	VSLNKGRP	VSTESTCD	VSTEST	VSCAT	VSSCAT	VSORRES	VSORRESU	VSDTC	VSDY	VSTPT	VSTPTNUM	VSTPTREF	VSRFTDTC
VS	ABC-001-001	1	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	102	F	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
VS	ABC-001-001	2	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	101.4	F	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
VS	ABC-001-001	3	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	98.3	F	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20

REACTOGENICITY DATA

- What the OVRR Vaccines Technical Specifications Guidance v2.1 says
  - Section 3.1

Reactogenicity data should 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. A more detailed description of how reactogenicity data should be collected is described in the Vaccine TAUG2. We prefer that the Vaccine TAUG "flat model" be utilized, i.e., that data for each day be included, even if a subject never experienced a particular event. However, the "nested model," which includes only a summary record for a particular event if a subject never experienced that event, may be necessary for large trials with significant amounts of data. Sponsors should discuss which model is appropriate with their review team prior to beginning their clinical trial.

- How the industry is currently handling it
  - Flat model: A record in CE for each solicited event for each treatment period (EPOCH) and records in FACE for each solicited event for each day (for a certain evaluation period) for each treatment period (EPOCH)

COMMON ISSUES/CHALLENGES/INCONSISTENCIES

REACTOGENICITY EVENTS MAPPED TO AE

- Reactogenicity events mapped to AE if last beyond assessment interval
  - CDISC COVID-19 TAUG, Section 13, page 31:

> One known issue is whether reactogenicity events that meet criteria for reporting as adverse events should be reported in both the Clinical Events (CE) and Adverse Events (AE) domains. The FDA technical specification[11] says (p. 3) that "if a reactogenicity event should happen to continue beyond the assessment interval, it should also be represented in the AE domain," which seems to answer this question for submissions to the FDA.

  - CDISC Vaccines TAUG:
    - Section 6, Example 2 could lead to confusion

Example 2

In this example, the subject experienced vomiting each day during the three-day assessment period (Rows 1-3) after the first set of vaccinations. The vomiting continued for two more days and ended on Study Day 5 (Row 4). The subject was told to record the date that the vomiting stopped and the maximum number of daily episodes that occurred since the observation period ended. When the reactogenicity event continues beyond the planned assessment interval and is still considered a clinical event as defined by the protocol (i.e., is not a protocol-defined adverse event), a new record can be created in FA. In the CE record that represents the vomiting event as a whole, the variable CEENDTC represents the day the event ended. In this example, if a reactogenicity event occurred anytime during the planned observation period, the overall start and end dates of the reactogenicity event were collected on the eCRF in addition to the individual dates from the daily diary collection. Individual dates from the daily diary collection are represented in the FA domain using the variable FADTC and the overall start and end dates of the event are represented in the CE domain using the variables CESTDTC and CEENDTC respectively. Please note that if only the daily diary collection dates were collected, CESTDTC and CEENDTC would not be populated.

    - Section 6, Example 3 does show an event that continues beyond the assessment period mapped to AE, but does not include the FDA's guidance on CEDUR/AEDUR

REACTOGENICITY EVENTS MAPPED TO AE

- Reactogenicity events mapped to AE if last beyond assessment interval
  - AESTDTC and AEENDTC should match CESTDTC and CEENDTC
    - CBER OVRR, Section 3.1:
      - *The start day/date (--STDY/--STDTC) and the end day/date (--ENDY/--ENDTC) of the reactogenicity event should be identical in both the CE and AE domain…*

  - CEDUR is used only for the assessment period. AEDUR is for after the assessment period.
    - CBER OVRR, Section 3.1:

> "reactogenicity." The start day/date (--STDY/--STDTC) and the end day/date (--ENDY/--ENDTC) of the reactogenicity event should be identical in both the CE and AE domain; whereas the duration (--DUR) should report 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 6 days in the assessment interval and 3 days beyond the assessment would be reported as Clinical Event Duration (CEDUR) = 6 days and Adverse Event Duration (AEDUR) = 3 days). We recommend one or more check boxes in the CRF, indicating the duration of

    - Therefore AEDUR will not necessarily be AESTDTC-AEENDTC. Same for CE

REACTOGENICITY EVENTS MAPPED TO AE

- Reactogenicity events mapped to AE if last beyond assessment interval
  - CEDUR vs AEDUR

DOMAIN	USUBJID	FASEQ	FALNKGRP	FATESTCD	FATEST	FAOBJ	FACAT	FASCAT	FAORRES	FADTC	FADY	FATPT	FATPTNUM	FATPTREF	FARFTDTC
FA	ABC-001-001	1	VACC1-FATIGUE	OCCUR	Occurrence Indicator	FATIGUE	REACTOGENICITY	SYSTEMIC	Y	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	2	VACC1-FATIGUE	SEV	Severity/Intensity	FATIGUE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	3	VACC1-FATIGUE	OCCUR	Occurrence Indicator	FATIGUE	REACTOGENICITY	SYSTEMIC	Y	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	4	VACC1-FATIGUE	SEV	Severity/Intensity	FATIGUE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	5	VACC1-FATIGUE	OCCUR	Occurrence Indicator	FATIGUE	REACTOGENICITY	SYSTEMIC	Y	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20
FA	ABC-001-001	6	VACC1-FATIGUE	SEV	Severity/Intensity	FATIGUE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20
FA	ABC-001-001	7	VACC1-FATIGUE	OCCUR	Occurrence Indicator	FATIGUE	REACTOGENICITY	SYSTEMIC	Y	2019-03-23	4	DAY 4	4	VACCINATION 1	2019-03-20
FA	ABC-001-001	8	VACC1-FATIGUE	SEV	Severity/Intensity	FATIGUE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-23	4	DAY 4	4	VACCINATION 1	2019-03-20
FA	ABC-001-001	9	VACC1-FATIGUE	OCCUR	Occurrence Indicator	FATIGUE	REACTOGENICITY	SYSTEMIC	Y	2019-03-24	5	DAY 5	5	VACCINATION 1	2019-03-20
FA	ABC-001-001	10	VACC1-FATIGUE	SEV	Severity/Intensity	FATIGUE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-24	5	DAY 5	5	VACCINATION 1	2019-03-20
FA	ABC-001-001	11	VACC1-FATIGUE	OCCUR	Occurrence Indicator	FATIGUE	REACTOGENICITY	SYSTEMIC	Y	2019-03-25	6	DAY 6	6	VACCINATION 1	2019-03-20
FA	ABC-001-001	12	VACC1-FATIGUE	SEV	Severity/Intensity	FATIGUE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-25	6	DAY 6	6	VACCINATION 1	2019-03-20
FA	ABC-001-001	13	VACC1-FATIGUE	OCCUR	Occurrence Indicator	FATIGUE	REACTOGENICITY	SYSTEMIC	Y	2019-03-26	7	DAY 7	7	VACCINATION 1	2019-03-20
FA	ABC-001-001	14	VACC1-FATIGUE	SEV	Severity/Intensity	FATIGUE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-26	7	DAY 7	7	VACCINATION 1	2019-03-20

Notice that CEENDTC is after last FADTC

DOMAIN	USUBJID	CESEQ	CELNKGRP	CETERM	CEDECOD	CECAT	CESCAT	CEPRESP	CEOCCUR	CESEV	CEDTC	CESTDTC	CEENDTC	CEDUR	CETPT	CETPTNUM	CETPTREF	CERFTDTC
CE	ABC-001-001	1	VACC1-FATIGUE	FATIGUE	Fatigue	REACTOGENICITY	SYSTEMIC	Y	Y	MODERATE	2019-03-26	2019-03-20	2019-03-28	P7D	DAY 7	7	VACCINATION 1	2019-03-20

Same Dates between CE and AE

Different Durations

DOMAIN	USUBJID	AESEQ	AELNKGRP	AETERM	AEDECOD	AECAT	AESCAT	AEPRESP	AEOCCUR	AESEV	AESTDTC	AEENDTC	AEDUR	AETPTREF	AERFTDTC
AE	ABC-001-001	1	VACC1-FATIGUE	FATIGUE	Fatigue	REACTOGENICITY	SYSTEMIC	Y	Y	MODERATE	2019-03-20	2019-03-28	P2D	VACCINATION 1	2019-03-20

REACTOGENICITY EVENTS MAPPED TO AE

- Reactogenicity events mapped to AE if last beyond assessment interval
  - What value to use in AETERM?
    - No real guidance stating what to use, but makes sense to use the exact same value as CETERM
  - How to differentiate these from other adverse events?
    - CBER OVRR specifies a category value to use: *The event should be categorized in the Adverse Event Category (AECAT) variable as "reactogenicity."*
  - These are then typically not mapped to ADAE, instead to a different ADaM dataset
    - Move reactogenicity events into SDTM AE domain, only to move them out again in ADaM?
    - Results in an ADAE vs. AE traceability validation rule sponsors are required to explain

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (issue Rate)	Explanation
AD0253	Record key from SDTM AE is not traceable to ADaM ADAE (not enough ADAE recs)	Error	AE	100 (5.00%)	AECAT=REACTOGENICITY records not kept in ADAE

CESTDTC AND CEENDTC COLLECTION

- CESTDTC and CEENDTC should be collected
  - CDISC COVID-19 TAUG, Section 13:

> One known issue discusses CESTDTC and CEENDTC in global Clinical Events (CE) reactogenicity records; examples in the TAUG-Vaccines assume that these dates are collected. The FDA technical specification (p. 2) says that "if an event occurred, the clinical event start day/date (CESTDY/CESTDTC) and end day/date (CEENDY/CEENDTC) of the reactogenicity event should be collected and included in the dataset."

  - CDISC Vaccines TAUG:
    - *Please note that if only the daily diary collection dates were collected, CESTDTC and CEENDTC would not be populated.*
  - Often, however, it seems that only the daily diary collection dates are collected
    - Sponsors use: min(FADTC) for CESTDTC and max(FADTC) for CEENDTC for an assessment period

Variable	Label / Description	Type	Role	Length or Display	Controlled Terms or ISO Format	Origin / Source / Method / Comment
CESTDTC	Start Date/Time of Clinical Event	date	Timing		ISO 8601	Derived Minimum FACE.FADTC per reaction per vaccination period <Algorithm to derive CESTDTC>
CEENDTC	End Date/Time of Clinical Event	date	Timing		ISO 8601	Derived Maximum FACE.FADTC per reaction per vaccination period <Algorithm to derive CEENDTC>

MIXING DATA WITHIN CE DOMAIN

- Mixing reactogenicity events with other clinical events in CE
  - Standard way to differentiate?
    - CBER OVRR:
      - *Reactogenicity events should be indicated by using "reactogenicity" in the variable Clinical Event Category (CECAT). It should be further subcategorized into "administration site" or "systemic," using the variable Clinical Event Subcategory (CESCAT).*
    - CBER OVRR:
      - *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.*
  - Reactogenicity event not measured on a certain day
    - Problems with mixing in other events that aren't prespecified
    - Be sure to use STAT/REASND when OCCUR is null

CONTROLLED TERMINOLOGY

- Controlled Terminology
  - There is some CDISC Controlled Terminology reactogenicity data, but not all
    - FATESTCD/FATEST

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)
C171443		Yes	COVID-19 Findings About Test Code	C19FATCD	COVID-19 Findings About Test Code
C171442		Yes	COVID-19 Findings About Test Name	C19FAT	COVID-19 Findings About Test Name
C132316		Yes	Ebola Virus Findings About Test Code	EBFATSCD	Ebola Virus Findings About Test Code
C132315		Yes	Ebola Virus Findings About Test Name	EBFATS	Ebola Virus Findings About Test Name
C127266		Yes	Tuberculosis Findings About Test Code	TBFATSCD	Tuberculosis Findings About Test Code
C127267		Yes	Tuberculosis Findings About Test Name	TBFATS	Tuberculosis Findings About Test Name
C142187		Yes	Vaccines Findings About Test Code	VNFATSCD	Vaccines Findings About Test Code
C142189		Yes	Vaccines Findings About Test Name	VNFATS	Vaccines Findings About Test Name

    - FACAT/FASCAT
      - None
    - CECAT/CESCAT/AECAT/AESCAT
      - None from CDISC, but CBER OVRR specifies some values to use:
        - For CECAT: “reactogenicity” or “efficacy”
        - For CESCAT: “administration site” or “systemic”
      - Recommendation: use these values specified by CBER OVRR guidance, but uppercase

OTHER ISSUES

- Sponsors might use FA, instead of FACE
  - If a study has no other findings about data, is it a requirement to use FACE over FA?
  - Recommendation is to use FACE

- Sponsors sometimes use variables such as EPOCH instead of --TPTREF to identify vaccine administration
  - It could be argued that VACCINATION 1, VACCINATION 2, etc possibly fits into EPOCH
  - Recommendation is to definitely use the --TPTREF variable

NO GUIDANCE FOR ANALYSIS DATA

- No guidance for analysis data
  - There is not much CDISC or FDA guidance on how to submit the analysis data
    - CDISC Interim User Guide for COVID-19: Nothing related to ADaM
    - CDISC Vaccines TAUG v1.1: *The scope of this version of the TAUG did not include CDASH and ADaM components. CDASH and ADaM components will be considered for development in either a supplement or subsequent version of the user guide.*
    - CDISC Ebola TAUG v1.0: *For the Analysis Data Model (ADaM), the form of guidance has not yet been established, but may be in future iterations of this document if resources become available.*
    - CDISC Influenza TAUG v1.1: *CDASH and ADaM are not included in version 1.1, but may be added in a later version.*
    - CDISC Tuberculosis TAUG v2.0: *CDASH and ADaM will be considered out of scope for v2.0*
    - CBER OVRR Vaccines Technical Specifications Guidance v2.1: nothing related to analysis data

NO GUIDANCE FOR ANALYSIS DATA

- No guidance for analysis data
  - Sponsors are free to use whatever ADaM dataset they want
  - This results in the same/similar data mapped in a completely different way across the industry
  - Results in reduced automation and increased manual effort

Application 1, Sponsor A

Dataset	Description	Class
ADSL	Subject-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET
ADAE	Adverse Event Analysis Dataset	OCCURRENCE DATA STRUCTURE
ADCE	Reactogenicity Events Analysis Dataset	BASIC DATA STRUCTURE
ADIMMUNO	Immunogenicity Analysis Dataset	BASIC DATA STRUCTURE
ADLB	Laboratory Test Result Analysis Dataset	BASIC DATA STRUCTURE
ADREACT	Reactogenecity Findings Analysis Dataset	BASIC DATA STRUCTURE
ADVS	Vital Sign Analysis Dataset	BASIC DATA STRUCTURE

Application 2, Sponsor B

Dataset	Description	Class
ADSL	Subject-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET
ADIS	Immunogenicity Analysis Dataset	BASIC DATA STRUCTURE
ADLB	Laboratory Analysis Dataset	BASIC DATA STRUCTURE
ADMB	Microbiology Specimen Analysis Dataset	BASIC DATA STRUCTURE
ADEX	Exposure Analysis Dataset	ADAM OTHER
ADAE	Adverse Event Analysis Dataset	OCCURRENCE DATA STRUCTURE
ADSR	Solicited Reactions Analysis Dataset	OCCURRENCE DATA STRUCTURE

Application 3, Sponsor C

Dataset	Description	Class
ADSL	Subject-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET
ADFACE	Reactogenicity Findings Analysis Dataset	BASIC DATA STRUCTURE
ADLB	Laboratory Analysis Dataset	BASIC DATA STRUCTURE
ADIM	Immunogenicity Analysis Dataset	BASIC DATA STRUCTURE
ADVS	Vital Signs Analysis Dataset	BASIC DATA STRUCTURE
ADAE	Adverse Events Analysis Dataset	OCCURRENCE DATA STRUCTURE
ADCE	Reactogenicity Analysis Dataset	OCCURRENCE DATA STRUCTURE

CONCLUSION

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- What should Sponsors/CROs do?
  - Be aware of all guidance available for mapping each type of data
  - When industry guidance contradicts each other, prioritize FDA guidance
- What should CDISC do?
  - Update guidance to remove highly nested model, as it is not listed as one preferred by FDA
  - Create controlled terminology for reactogenicity data, so preparers don't have to look through TAUGs
  - Incorporate other pieces of FDA guidance into new versions of TAUGs
  - Create guidance for analysis data
- What should Pinnacle 21 do?
  - Without enforcement, widespread implementation is less likely
    - Create validation rules extracted from the TAUGs and regulatory guidance


QUESTIONS?