A new data model to meet CBER guidance on submission of reactogenicity data for vaccine trials

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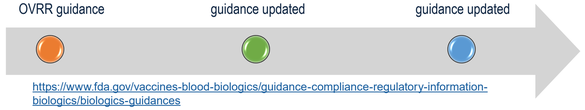
Abstract

The FDA Center for Biologics Evaluation and Research (CBER) published a guidance for industry in April 2018 (with updates in October and December 2019): Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review (OVRR). This guidance will aid clinical and statistical review of vaccine applications by submitting standardized datasets. Merck is designing a new data model to follow CBER's requirements.

This poster presents the next-generation data model with the focus on the submission of reactogenicity data for vaccine trials. Specifically, the poster (1) introduces the key OVRR requirements and the new data models; (2) elaborates the end-to-end process from electronic Vaccination Report Card (eVRC), electronic Case Report Form (eCRF), electronic data capture (EDC) system, to CDISC SDTM and ADaM data; (3) demonstrates the key features and impacts on statistical analysis and report; (4) evaluates the impacts on protocol design, data specifications, data entry guidelines, eVRC screenshot and electronic clinical outcome assessment (eCOA) database standards, data review and reconciliation, medical monitoring, site monitoring, and investigator training; and (5) presents challenges and conclusions.

BACKGROUND

FDA CBER guidance for industry on submitting study datasets for vaccines to the OVRR



https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

This technical specification document provides detailed information for how data for vaccine trials should be submitted to the OVRR moving forward. It specifically requires the submission of reactogenicity data:

- *"Safety data submitted for vaccine clinical trials should include **reactogenicity data** (i.e., a set of prespecified AEs collected within a prespecified timeframe, often referred to as **solicited AEs** or reactions)"*
- *"**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"*

KEY OVRR REQUIREMENTS ON REACTOGENICITY DATA

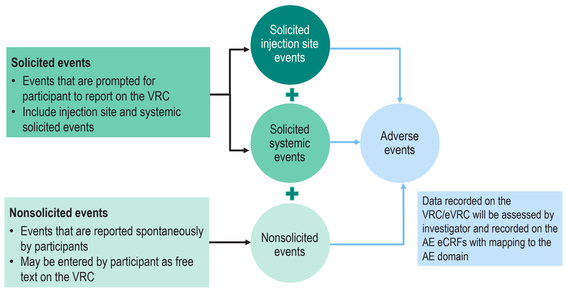
Untouched daily participant records of solicited complaints and temperatures should be represented in the FACE and VS domains.

The **reactogenicity data (solicited events)** should be represented primarily in the CE domain. This is a significant change. In the past, all adverse event data were represented in the AE domain.

A reactogenicity event should also be represented in the AE domain in the following cases

- If a reactogenicity event rises to the level of an Serious adverse event (SAE).
- If a reactogenicity event should happen to continue beyond the assessment period.
- If a reactogenicity event is assessed by the investigator as unrelated to the vaccine but instead related to another diagnosis, the definitive diagnosis would be recorded in the AE domain.
- If a reactogenicity event results in discontinuation of study medication (added by Merck, for multidose trials only).

PRE-OVRR DATA MODEL OF ADVERSE EVENTS



OBJECTIVE: To Build a Next Generation Data Model to Support Full Adoption of OVRR Guidance and Follow Vaccine TAUG.

NEXT-GENERATION OVRR DATA MODELS

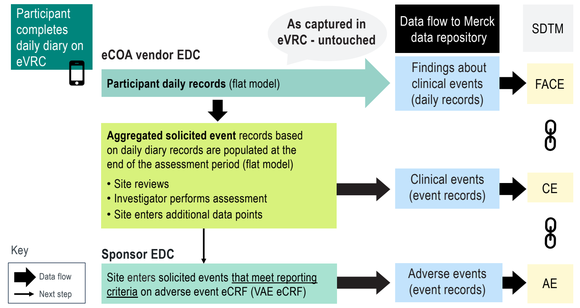
Version 1.0: auto-population of aggregated solicited AE data (based on participant reported daily diary records of solicited complaints) + entry of investigator's assessments in **eCOA vendor EDC**

- Pros: first full OVRR model, auto-pop, and evaluation of aggregated solicited event
- Cons: data entry and reconciliation in 2 EDC systems are burdensome, not scalable for global studies, requires eCOA vendor EDC capability

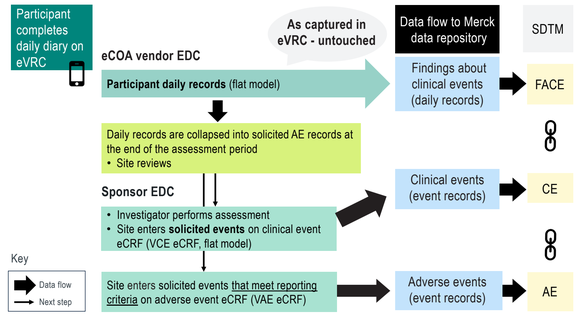
Version 2.x: entry of investigator's assessments of solicited events on clinical event eCRF in **sponsor EDC**

- Pros: streamlined data entry and reconciliation in one EDC system, can work with various eCOA vendors
- Cons: requires either manual entry (v2.1) or auto-transfer of aggregated solicited event data from eCOA vendor EDC to sponsor EDC (v2.2)

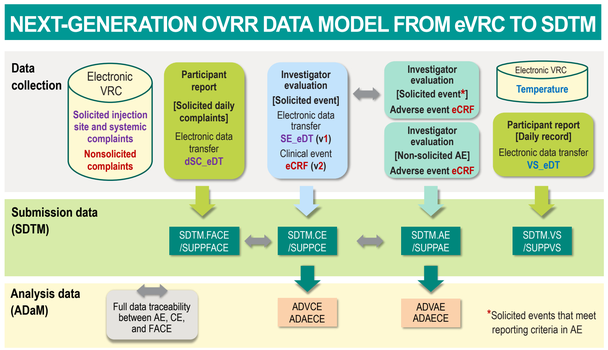
NEXT-GENERATION OVRR DATA MODEL (VERSION 1.0)



NEXT-GENERATION OVRR DATA MODEL (VERSION 2.X)



NEXT-GENERATION OVRR DATA MODEL FROM eVRC TO SDTM



KEY FEATURES

- **Untouched daily participant records** of solicited complaints represented in the FACE domain.
- **Separation of solicited and nonsolicited AEs**: solicited AEs represented in the CE domain; nonsolicited AEs represented in the AE domain, with the exception that solicited AEs or the related diagnosis should also be represented in the AE domain in the 4 scenarios:
  - If a reactogenicity event should happen to **continue beyond the assessment interval**.
  - If a reactogenicity event rises to the level of an **SAE** during the prespecified assessment interval.
  - If a reactogenicity event is assessed by the investigator as unrelated to the vaccine, but instead **related to another diagnosis**, the diagnosis would be recorded in the AE domain.
  - If a reactogenicity event results in study medication discontinuation (multidose trial only).
- **Linked data**: full linkage between CE, FACE, and AE. A dataset-level relationship in related records (RELREC) to represent relationships between CE and FACE and between CE and AE.
- A flat model with **full data traceability**: CE data include a record for each solicited event for each subject. CE data represent **investigator's assessment** based on **participant's daily diary records**. Full data traceability is provided to track **any discordance between investigator vs participant reporting** in terms of **occurrence** and **severity**.

DATA COLLECTION FOR SOLICITED EVENT IN EDC

Basic info (investigator assessments based on aggregated participant daily diary records of solicited complaints)	Safety assessments	OVRR requirements
• Time point (CETPT) • Event term (CETERM) • Location of injection site reaction (CELOC) • Occurrence (CEOCCUR) • Maximum size (SUPPCE.LDIAM/ LDIAMU) • Overall severity (CESEV) • Start date/time (CESTDTC) • End date/time (CEENDTC) • Pattern (CEPATT) (to be derived) • Outcome (CEOUT) • Duration (CEDUR)	• Relationship with vaccine (CEREL) • Seriousness (CESER) • Medical history (systemic only): if a systemic solicited event is "medical history worsening," "medical history not worsening," or "not medical history" (SUPPCE.CEMDHXAS)	• Ongoing: did the solicited event resolve by the end of the assessment period (CEENRTPT) • Last date of the assessment period (CEENTPT) • Symptom of other diagnosis indicator (systemic only) (SUPPCE. CESODIND) • Reconstructed: the recording of the solicited event is considered reconstructed data from subject recall (SUPPCE.CERECON) • Analgesic/antipyretic taken to prevent or treat pain associated with vaccine administration (SUPPCE.CECONTRT)

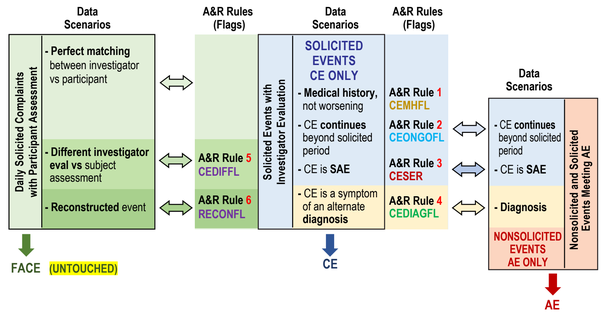
DATA TRACEABILITY: INVESTIGATOR VS PARTICIPANT

- The next-generation OVRR data model provides full data traceability between investigator vs participant assessments: the CE data (CEOCCUR, CESEV) represent investigator's assessment; SUPPCE data (CEOCCUR1, CESEV1) document participant's assessment if different from investigator's assessment.
- Reasons investigator changed assessment are collected and mapped to SUPPCE.
- Easier track of discordance between investigator vs participant in occurrence and severity.

	N	Occur=Y (participant	Occur=Y (investigator)	Difference in occurrence	From Y to N	From N to Y	From ND to Y
Solicited AE term	n	n1	n2	n1-n2	na	nb	nc

N=number of participants in the all-participants-as-treated population.
n2=n1-na+nb+nc.

A TWO-LAYER LINKED MODEL



ANALYSIS AND REPORT: BUSINESS RULES

- Main safety TLFs package will be based on investigator's assessments.
- ALL solicited and unsolicited events that represent in CE and/or AE will be included in the ADaM.ADAECE.
- Flags will be used to include/exclude records from safety analysis populations and TLFs.

Business rules for analysis and reporting	Flags
RULE 1: Part of a "medical history, not worsening": the solicited event will NOT contribute to the safety TLFs, because it does not meet the definition of AE.	CEMHFL
RULE 2: Continues beyond assessment period: the solicited event will contribute to the safety TLFs as a single, solicited adverse event. The complete duration will support reporting.	CEONGOFL
RULE 3: A solicited event that becomes SAE will contribute to the safety TLFs, and be reported as a single, solicited, and serious AE. The complete duration will support reporting.	CESER
RULE 4: Part of another diagnosis: the solicited event will NOT contribute to the safety TLFs for not meeting the AE definition. Only diagnosis will be included in the safety TLFs to avoid double reporting.	CEDIAGFL
RULE 5: Different investigator vs. participant assessment: investigator's evaluation will contribute to the main safety TLFs. Participant's assessment may be listed per agency request.	CEDIFFL
RULE 6: Reconstructed data reported during safety follow-up may contribute to the safety TLFs, per discussion with the agency prior to submission.	RECONFL

- Vaccine TA standard programs should be used to support A&R process.
- Pinnacle 21 validation: data issues should be fixed during the study and documented in csdrg.pdf.

IMPACTED STUDY PHASES AND DELIVERABLES

Planning phase	eVRC build	Data collection, review, and monitoring	Analysis and reporting
• Protocol • eCRFs – Clinical event eCRF – Adverse event eCRF – Concom. med eCRF • DTS for eDT data – dSC_eDT – SE_eDT • DEGs • Edit checks • SDSP	• eVRC screenshot standards • eCOA vendor database standards • Participant user guide • Site manual	• Sponsor EDC • Data review and reconciliation • Medical monitoring • Site monitoring • Investigator training	• SDTM specs and program – FACE/SUPPFACE – CE/SUPPCE – AE/SUPPAE • ADaM specs and standard program – ADVCE – ADVAE – ADAECE • A&R TLFs

AE=adverse event; CE=clinical event; DEG=data entry guideline; dSC=daily solicited complaint; DTS=data transfer specification; eCOA=electronic clinical outcome assessment; eCRF=electronic case report form; EDC=electronic data capture; eDT=electronic data transfer; eVRC=electronic vaccine report card; FACE=findings about clinical event; SDSP=study data standardization plan; SE=solicited event.

CHALLENGES

- **Global submission:** impact on ex-US health authority submissions
- **Industry:** sponsors may interpret and/or adopt OVRR guidance differently
- **Standard:** different interpretations in OVRR guidance vs CDISC vaccine TAUG
- **Resource:** inclusion of both investigator and participant assessments for the same solicited event requires more resources to support complex data collection and mapping
- **Operation**
  - Development of new eCRFs and data collection model from EDC to SDTM
  - Development of new safety data review and reconciliation rules and edit checks
  - Site acceptance: requires intensive site training and monitoring and allowance for learning curve
  - Development of business rules and standard programs to support analysis and reporting

Conclusions

This poster is an overview of the end-to-end process of the next-generation OVRR data model for reactogenicity data submission.

- All phase 2 and 3 trials moving forward will adopt full OVRR data model with a few exceptions.
- Trials within the same program may adopt different OVRR data models.
- If a trial does not adopt full OVRR data model, the team should consider submitting a waiver request to FDA.
- Best practice is to start OVRR discussion as early as possible to ensure adequate time for regulatory interactions and documentations.
- Close communication and collaboration between sponsor and agency, between sponsor and vendor, and across sponsor's internal functional areas are highly recommended to streamline adoption of OVRR requirements.

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