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Adapting and Evolving with OVRR Requirements

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Agenda

1. OVRR guidance
2. MSD response – challenges to implementing guidance
3. MSD response – adapting existing standards
4. MSD response – evolving new standards
5. Remaining challenges

OVRR Guidance

OVRR guidance

In April 2018 the Office of Vaccine Research and Review (OVRR) of the United States Food and Drug Administration (FDA) issued guidance document:

- Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review: Guidance for Industry
- With a corresponding Webinar in May 2018
- The guidance referenced CDISC's Therapeutic Area User Guide for Vaccines (TAUG-Vax) published in March 2018

OVRR guidance

Domains listed in the document that should be included:

- TS, DM, SV, CM, EX, DS, DV, MH
- PE if included in the protocol
- LB if safety labs present in the protocol

This is consistent with the SDTM standard

OVRR guidance

Additional requirements beyond the existing SDTMIG 3.2 standard for DS:

- Added DSDECOD and DSTERM, DSCAT and DSSTDTC are required
- Requires TAETORD for when multiple doses of vaccine are administered
  - Including the requirement that TAETORD to be used in other domains

OVRR guidance

Expectations are laid out for other domains and their use in safety, immunogenicity, and efficacy data.

- AE, CE, FA, VS, MB, IS
- Immunogenicity Specimen (IS) is to be used for immunogenicity data.
  - It should not be mapped to LB.
- A majority of the guidance covers safety data, providing a short section on efficacy
- The inclusion of RELREC is used throughout

OVRR guidance – safety data

Safety data includes:

- reactogenicity data
- unsolicited AEs
- medically attended adverse events (MAAEs)
- death

OVRR guidance – safety data

Death

- Reported in AE with details in DD
- Reported in DM using DTHDTC and DTHFL

Medically attended adverse events (MAAE)

- Reported in AE and HO
- Certain events need specific AECAT:
  - 'NOCD' for new onset of a chronic disease
  - 'PIMMC' for potential immune-mediated medical conditions
- Details are given about using AE and MH to represent chronic diseases that are exacerbated

OVRR guidance – safety data - reactogenicity

Reactogenicity

- A set of prespecified AEs collected within a prespecified time frame, often referred to as solicited AEs or complaints
- OVRR prefers the ‘flat model’ from the vaccine TAUG
  - Data for each day to be included, even if a subject never experienced a particular event
  - Records are mapped to CE, FACE and VS

OVRR guidance – safety data - reactogenicity

- Daily records are mapped to FACE
- Daily temperature records are mapped to VS
- One record per event per subject is additionally mapped to CE
  - Uses CETERM, CEOCCUR, CESTDTC, CEENDTC
  - The guidance gives detailed rules about:
    - Handling missing diary entries
    - Values for CECAT and CESCAT
  - This is unusual since most collected data is represented only once in SDTM data and is rarely derived

OVRR guidance – safety data - reactogenicity

- Events that continue beyond the assessment interval are also mapped to AE
  - The guidance gives detailed rules about:
    - Value for AECAT
    - Use of CEENRTPT and CEENTPT
    - How to assign CESTDTC, CEENDTC, AESTDTC, AESTDTC, CEDUR and AEDUR
- Serious events occur during the assessment interval are additionally mapped to AE
  - The guidance gives detailed rules about:
    - Value for AECAT
    - Use of AESER and CESER
    - The date the event became serious is mapped to SUPPAE

OVRR guidance – safety data - reactogenicity

- Reactogenicity events determined by the investigator to be unrelated to the vaccine are also mapped to AE
  - The guidance gives detailed rules in addition to the regular reactogenicity mapping
    - Creating an AE record with the diagnosis
    - Mapping the daily records to FAAE
    - Use of CEREL and AEREL

OVRR guidance – safety data

- Analgesic/antipyretic used for prevention or treatment of pain and/or fever associated with vaccine administration:
  - Mapped to CM
  - Values for CMCAT
  - Use of CECONTRT
- Unsolicited events
  - Mapped to AE
  - Use of AETPTREF and AEELTM in relations to dosing
  - AE should contain a collapsed record
  - FAAE is used for daily records

OVRR guidance – efficacy data

- Efficacy data is mapped to CE, MB and SUPPDM:
  - Values for CECAT
  - MB is used for test results from assays conducted to confirm the presence of the microbe of interest
  - A clinical endpoint case flag is added to SUPPDM

MSD Response

Challenges to implementing guidance

- The guidance included a great deal of extremely detailed instructions
- Touching many domains
- Requirements were added that were not covered by existing conformance rules
- Included new requirements for specific variables and controlled terms
- Guidance was expected to be immediately implemented

Challenges to implementing guidance

- MSD had decades of successful vaccine submissions
- Usage of end-to-end CDISC compliant standards
- Guidance affected protocols, data collection, SDTM and ADaM, end-to-end flow
- MSD had recently transitioned from paper vaccine report cards (VRC) to eVRC
- Had many ongoing studies and vaccine programs
- The new guidance required careful assessment of new requirements against existing standards

Adapting existing standards

MSD's response to this challenge:

- Formation of an internal OVRR cross-functional working group
  - The goal was to adapt the existing end-to-end process
- In January 2020 MSD met with other large pharmaceutical companies to discuss common challenges in adopting the guidance including:
  - Multiple systems to assess eDiary data versus eCRF collection is challenging for sites and Sponsors.
  - Changes impact Medical Monitoring Plan, SOPs, Data Entry Guidelines, eCRF design.
  - Changes required for data management standards from collection to reporting.
- The working group furthermore assessed feedback from the FDA in response to subsequent vaccine submissions.

Adapting existing standards

- The working group revised mature in-house standards to meet the new expectations.
- MSD already had proprietary, well-established end-to-end standards used across therapeutic areas for data collection and SDTM and ADaM dataset creation.
- In order not to disrupt ongoing work in other therapeutic areas MSD created several separate standards for vaccine trials.

Adapting existing standards

- MSD addressed ongoing trials via an FDA waiver request for these studies where compliance would be difficult.
- Some of these included partner studies beginning prior to the guidance.
  - Data was received at the end of study
  - Partners had differing levels of SDTM expertise.
- MSD complied where possible
  - Compliance was not possible when the data was not collected.
  - In several cases there were no entry of daily records.

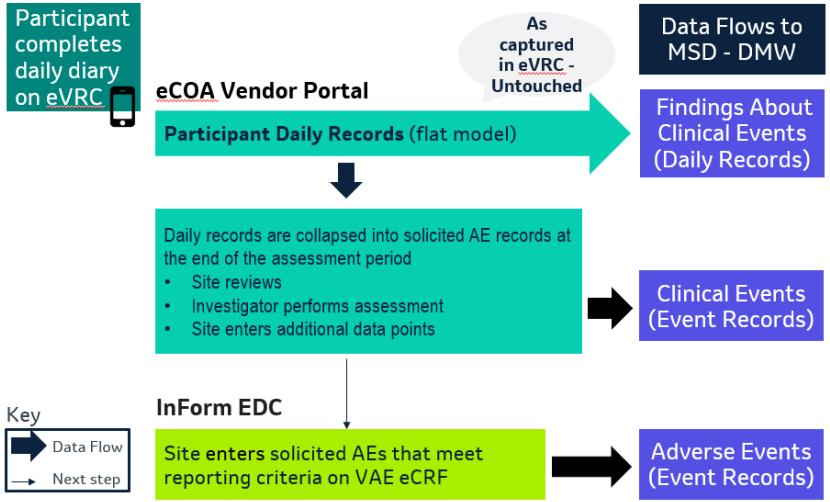
Adapting existing standards

- MSD used an iterative approach to adapting existing in-house standards
- We refer to these as Models 1, 2, and 3
- Our focus was on revising data collection rather than trying to programmatically address some of the issues

Adapting existing standards

Model 1

- Developed to address an immediate need for an early stage trial that enrolled quickly
- eVRC data was collected in eCOA
  - Collapsed into solicited event records in eCOA
  - The investigator reviewed the data and entered their assessment of events in eCOA
  - The eVRC data and the investigator assessment transferred to Data Management Warehouse (DMW)
- Solicited events Data collected in eCOA were manually entered into Inform EDC for events that meet AE reporting criteria
- Cleaning was done in both systems, causing additional burden on site and sponsor



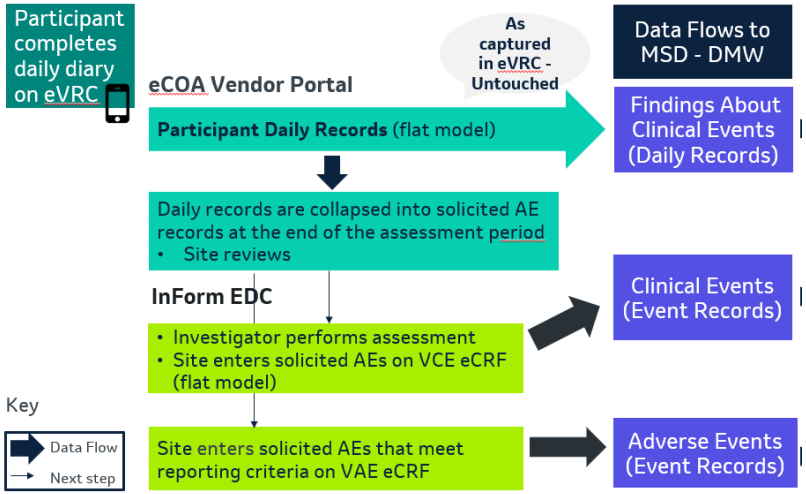
Evolving new standards

- Model 1 was evaluated, and shortcomings were noted
- Feedback from CBER after submissions and Study Data Submission Plans were also incorporated
- Leading to the development of Model 2
- Model 2 was intended to bridge Model 1 to Model 3
  - The team scoped out the future state but were unable to develop the ideal model due to the speed of drug development and time needed for the automated transfer component.

Evolving New Standards

Model 2

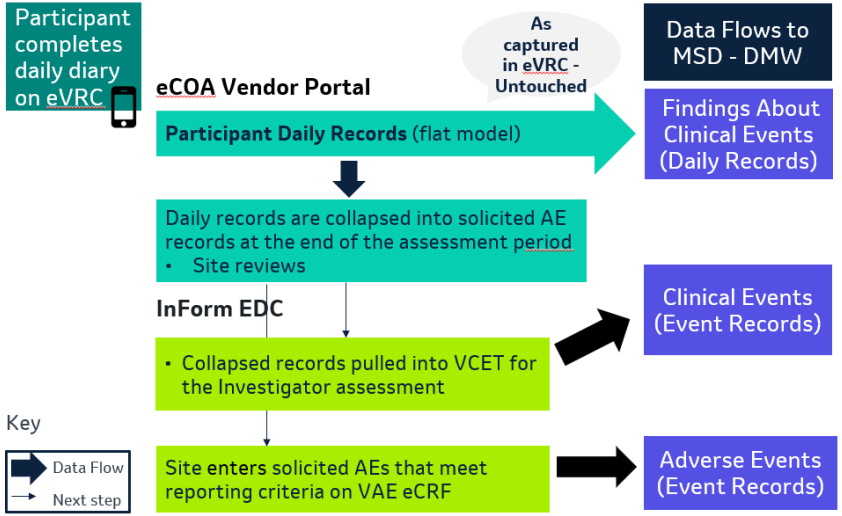
- eVRC data collected by eCOA Vendor
- Collapsed solicited events generated in eCOA at the assessment period, report created to allow manually entry by the investigator site into Vaccines Clinical Events in Inform
  - All records are entered whether it occurred or not.
  - Investigator enters if they agree or not and reason if they do not agree
- More manual work for the sites



Evolving New Standards

Model 3

- No manual transcription, VRC data is collected in eCOA by the participant
- Missing records incorporated from eCOA into Inform
- Collapsed CE data is generated in eCOA and pulled into Inform EDC
  - Investigator applies their medical judgement to the Inform records and enters if they agree if the event occurs along with any assessment that differs providing the reason in addition to their assessment.
- The site fills in any additional information required for Adverse Events.
- Complex post-processing implemented to generate SDTM datasets from the collected data to comply with the OVRR rules



Remaining challenges

Remaining challenges include:

- Supporting ongoing studies in both Model 2 and 3
- Implementation of efficacy rules
- MSD adoption of new systems along with the evolving OVRR requirements
- Incorporating additional feedback from OVRR
  - MSD is participating in a vaccine industry standards group addressing this issue

Overall, the OVRR team is pleased with their progress, and they feel they have arrived at successful solutions for the issues raised by the guidance

Thank You!

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