



Challenges Addressing CBER Guidance on Reactogenicity, from Collection to Analysis

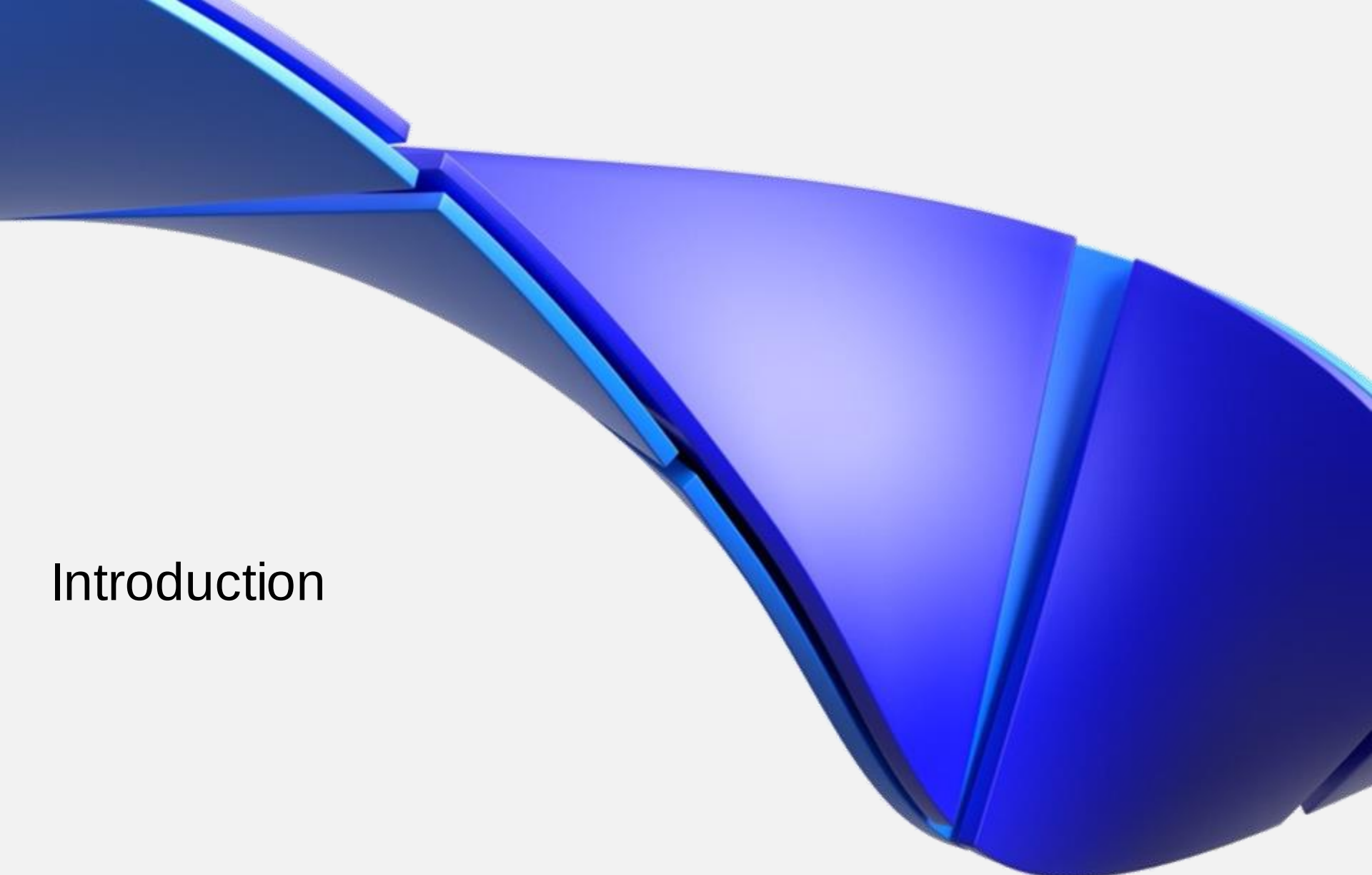
Sandra VanPelt Nguyen
Emily Bernstein-Hanlon

March 8, 2023

Agenda

- Introduction
- Events Continuing Beyond the Assessment Interval
- Missing Diary Data
- Participant Versus Investigator Assessments
- Reactogenicity Versus Adverse Events
- Conclusion



A large, abstract graphic on the right side of the slide. It consists of several overlapping, curved, and faceted planes in various shades of blue and purple, creating a sense of depth and movement. The shapes appear to be part of a larger, complex structure that is partially visible.

Introduction

Introduction

Reactogenicity

- Expected, common reactions typically caused by an inflammatory response to a vaccine
 - Administration site reactions
 - Systemic events
- Pre-specified in protocol
- Collected within a specified timeframe post-vaccination
 - Participant-filled daily diary
 - Investigator-filled case report forms (CRFs)

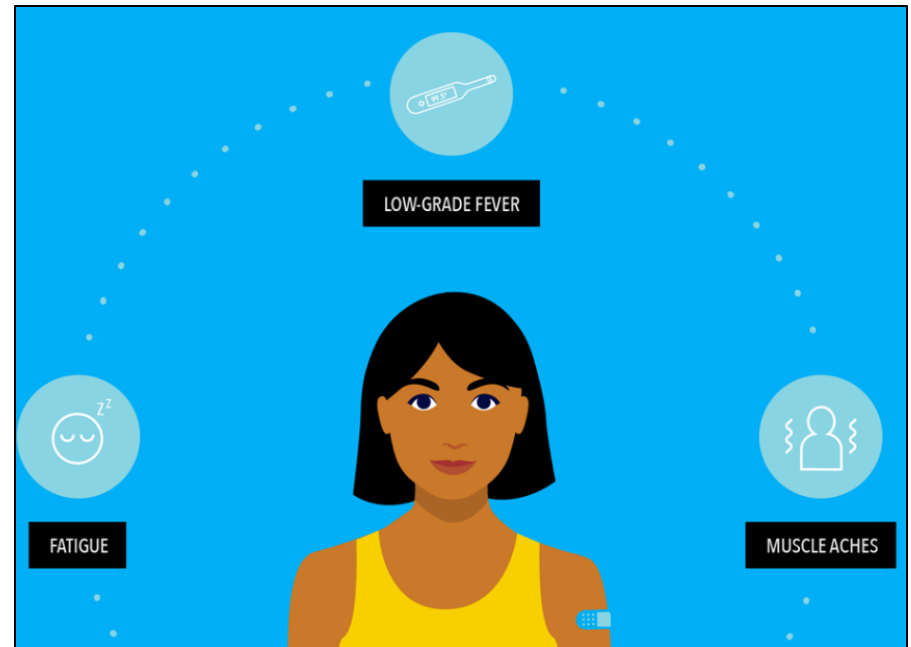


Image from
https://www.pfizer.com/news/articles/a_life_saving_education_the_body_s_response_to_a_vaccine

Introduction

Guidance

CDISC TAUG-Vax v1.1¹

- Focuses on safety data for reactogenicity events collected during vaccines trials and related exposure and trial design considerations
- Presents flat, nested, and highly nested Models

CBER OVRR Guidance v2.1²

- Detailed information and specifications for the content of tabulation datasets for submission to OVRR, including safety and efficacy data
- Preference for flat model

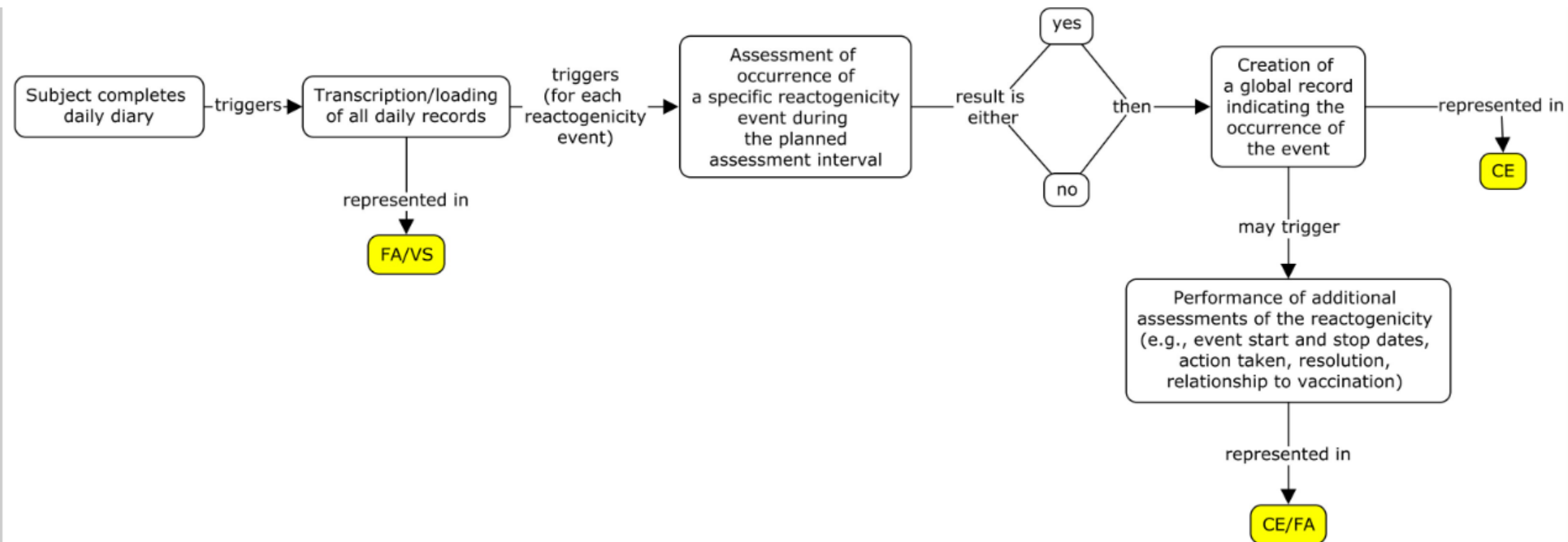
Neither document addresses analysis considerations for reactogenicity

¹ Clinical Data Interchange Standards Consortium (CDISC). Therapeutic Area Data Standards User Guide for Vaccines. Version 1.1(Provisional), April 2018. Available at: <https://www.cdisc.org/standards/therapeutic-areas/vaccines/vaccines-therapeutic-area-user-guide-v11/html>

² US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review: Guidance for Industry. Version 2.1, December 2019. Available at: <https://www.fda.gov/media/112581/download>.

Introduction

Flat Model



Reference: CDISC TAUG-Vax v1.1 Figure 3

Introduction

Summary Record Collection vs. Derivation

Collect summary event data in CRF

Pros

Cons

Sites are more familiar with participants' events	Additional time and cost for sites to enter the data
No need to derive summary records/simpler programming	Additional data review and cleaning
Complete traceability of SDTM to CRF	Need to query sites to address discrepancies in the data
	Determination of event duration and max severity may be challenging for sites

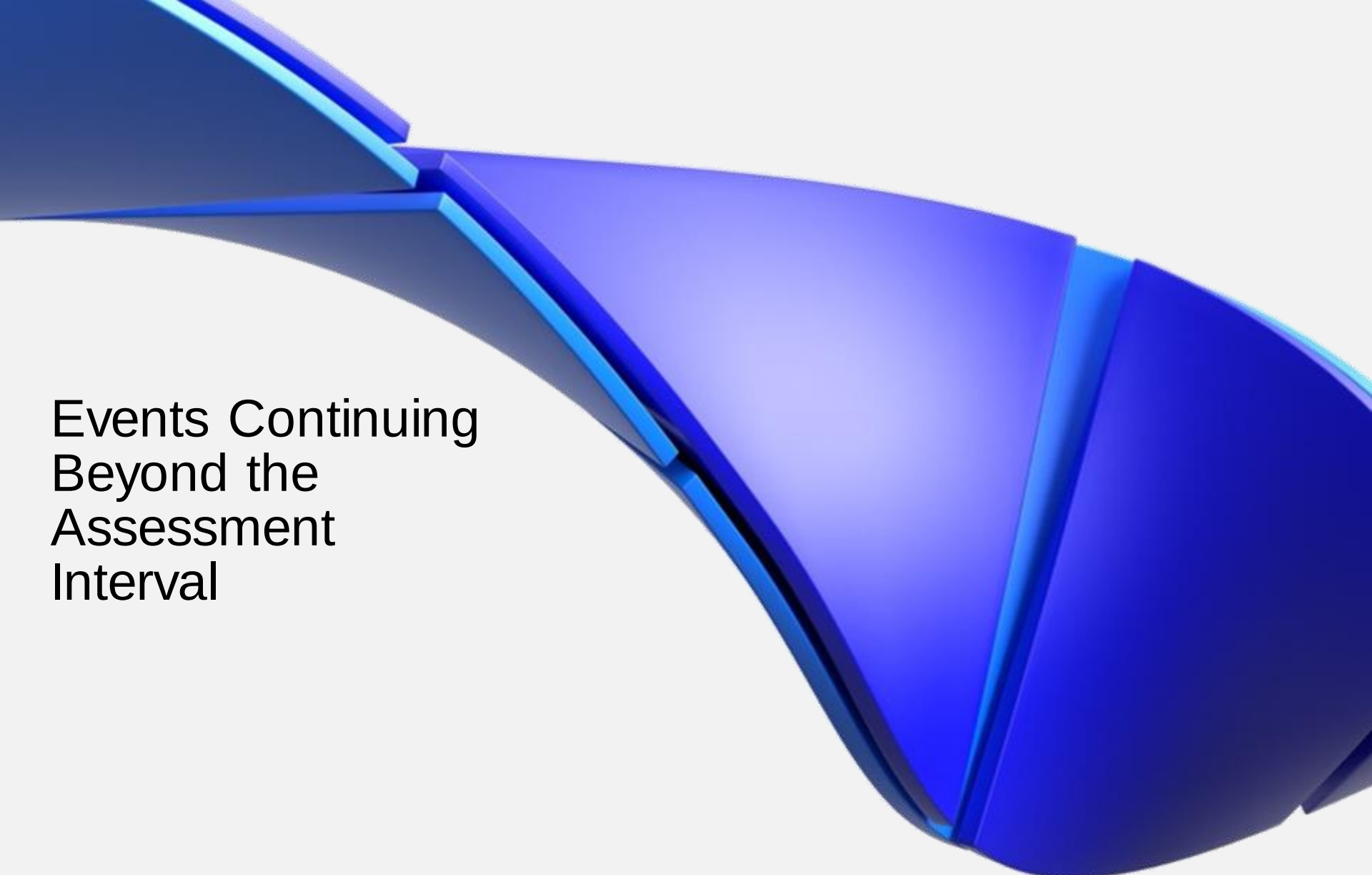
Derive summary event records programmatically

Pros

Cons

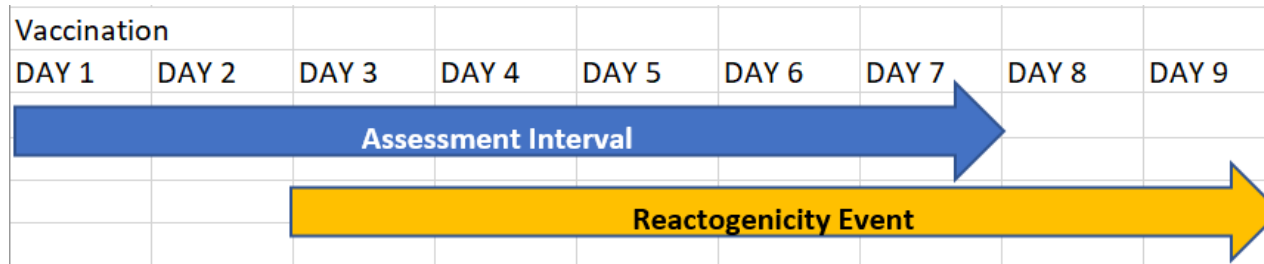
Reduces burden to sites	This level of derivation is not typically performed in SDTM
Reduces data cleaning and queries	Derivation logic is complex
Ensures correct calculation of event duration and max severity	Less traceability
	Source data may be incomplete or discrepant

Source placeholder

Abstract blue and purple geometric shapes, possibly representing a stylized DNA helix or a molecular structure, curving across the top and right side of the slide.

Events Continuing Beyond the Assessment Interval

Events Continuing Beyond the Assessment Interval



CBER Guidance v2.1

Should be represented in both CE and AE domains

- Start and end dates should be identical in AE and CE
- Duration in CE should be the duration during the assessment interval
- Duration in AE should be the duration past the assessment interval

Recent CBER Feedback

Pfizer was recently informed that ongoing reactogenicity events no longer need to be reported in the AE domain. Instead, the CE domain will summarize the entire duration of the event.

Events Continuing Beyond the Assessment Interval

Original guidance:

ce.xpt:

USUBJID	CESEQ	CEDECOD	CEOCCUR	CESTDTC	CEENDTC	CEDUR	CETPTREF	CEENTRTPT	CEENTPT
001-0001	9	Myalgia	Y	2023-01-03	2023-01-09	P5D	VACCINATION 1	ONGOING	DAY 7

ae.xpt:

USUBJID	AEDECOD	AESTDTC	AEENDTC	AEDUR	AETPTREF
001-0001	Myalgia	2023-01-03	2023-01-09	P2D	VACCINATION 1

****In both cases, CEENTRTPT/CEENTPT should be used to indicate that the event is ongoing past the assessment interval.**

New approach:

ce.xpt:

USUBJID	CEDECOD	CEOCCUR	CESEV	CESTDTC	CEENDTC	CEDUR	CETPTREF	CEENTRTPT	CEENTPT
001-0001	Myalgia	Y	MODERATE	2023-01-03	2023-01-09	P7D	VACCINATION 1	ONGOING	DAY 7

Events Continuing Beyond the Assessment Interval

Example - multi-vaccine trials

For events ongoing at the time of the next vaccination, Pfizer was instructed that end date should be assigned as the next vaccination date

ec.xpt:

USUBJID	ECTRT	ECDOSE	ECDOSU	ECDOSFRM	ECLOC	ECLAT	ECSTDTC	ECENDTC
001-0001	DummyVax	0.2	mL	INJECTION	ARM	LEFT	2023-01-01T10:00	2023-01-01T10:00
001-0001	DummyVax	0.2	mL	INJECTION	ARM	LEFT	2023-02-01T11:30	2023-02-01T11:30

VAX1

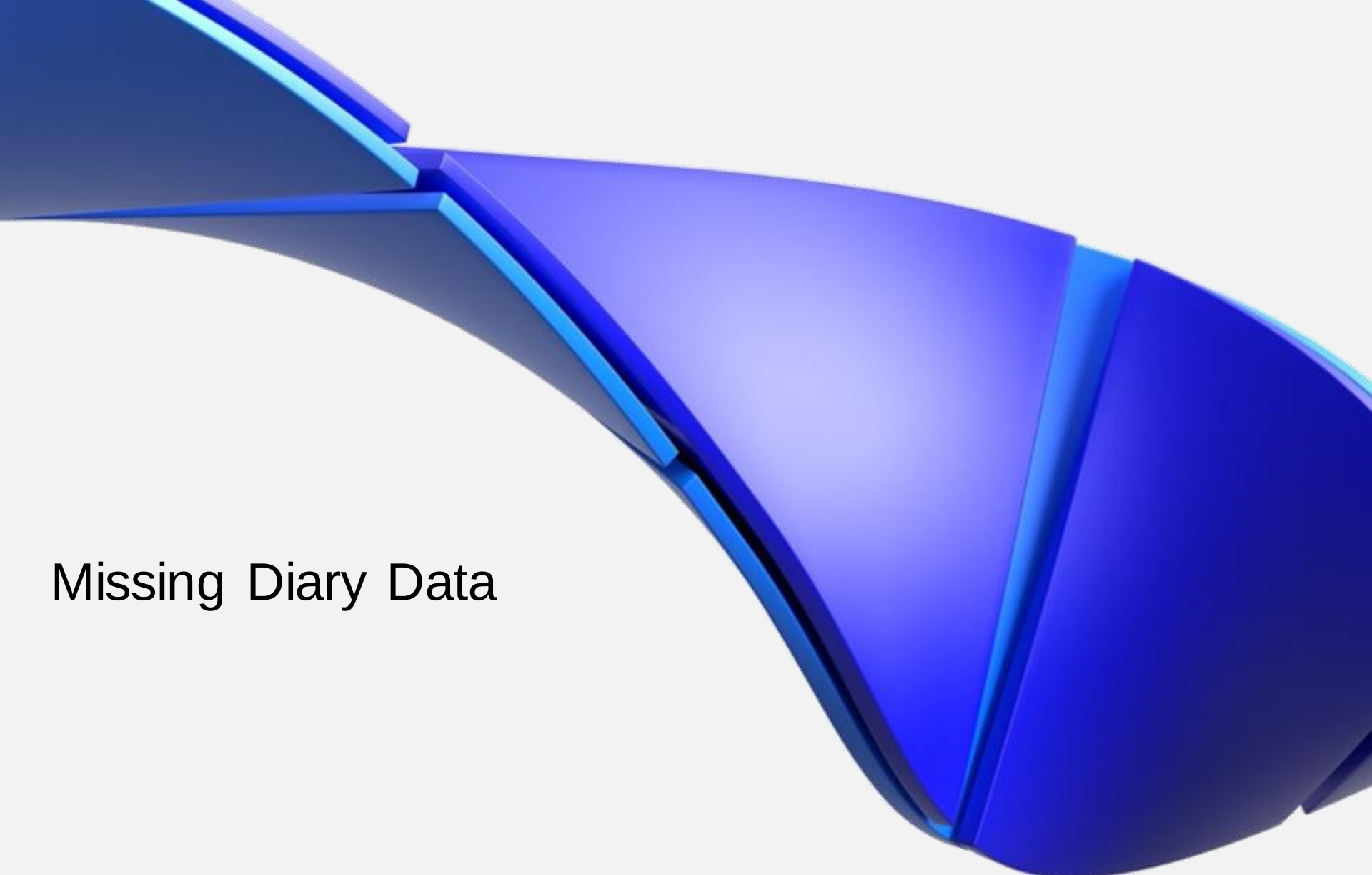
VAX2

ce.xpt:

USUBJID	CESEQ	CEDECOD	CEOCCUR	CESTDTC	CEENDTC	CEDUR	CETPTREF	CEENTRTPT	CEENTPT
001-0001	5	Myalgia	Y	2023-01-03	2023-02-01	P30D	VACCINATION 1	ONGOING	DAY 7

suppce.xpt:

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
CE	001-0001	CESEQ	5	DRVDTCL	Derived Date Flag	Y

An abstract, three-dimensional geometric shape composed of several blue, curved, and faceted planes. The shape is positioned on the right side of the slide, extending from the top right towards the bottom right. It has a complex, crystalline appearance with sharp edges and smooth curves, rendered in various shades of blue with highlights and shadows that give it a sense of depth and volume.

Missing Diary Data

Missing Diary Data



- Symptoms are expected to be assessed for each day of the assessment period.
- If a day is missed, then dataset should indicate data was not collected and the reason not done.
- Will need to decide how to handle missing records in analysis.

Missing Diary Data

Example of intermittent missing diary data

ec.xpt:

USUBJID	ECTRT	ECDOSE	ECDOSU	ECDOSFRM	ECLOC	ECLAT	ECSTDTC	ECENDTC
001-0001	DummyVax	0.2	mL	INJECTION	ARM	LEFT	2023-01-01T10:00	2023-01-01T10:00

vs.xpt:

USUBJID	VSTEST	VSORRES	VSORRESU	VSSTAT	VSREASND	VSDTC	VSTPT	VSTPTREF
001-0001	Temperature	98.0	F			2023-01-01	DAY 1	VACCINATION 1
001-0001	Temperature	99.1	F			2023-01-02	DAY 2	VACCINATION 1
001-0001	Temperature			NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	2023-01-03	DAY 3	VACCINATION 1
001-0001	Temperature	98.9	F			2023-01-04	DAY 4	VACCINATION 1
001-0001	Temperature	98.7	F			2023-01-05	DAY 5	VACCINATION 1
001-0001	Temperature	97.6	F			2023-01-06	DAY 6	VACCINATION 1
001-0001	Temperature	97.3	F			2023-01-07	DAY 7	VACCINATION 1

Missing Diary Data

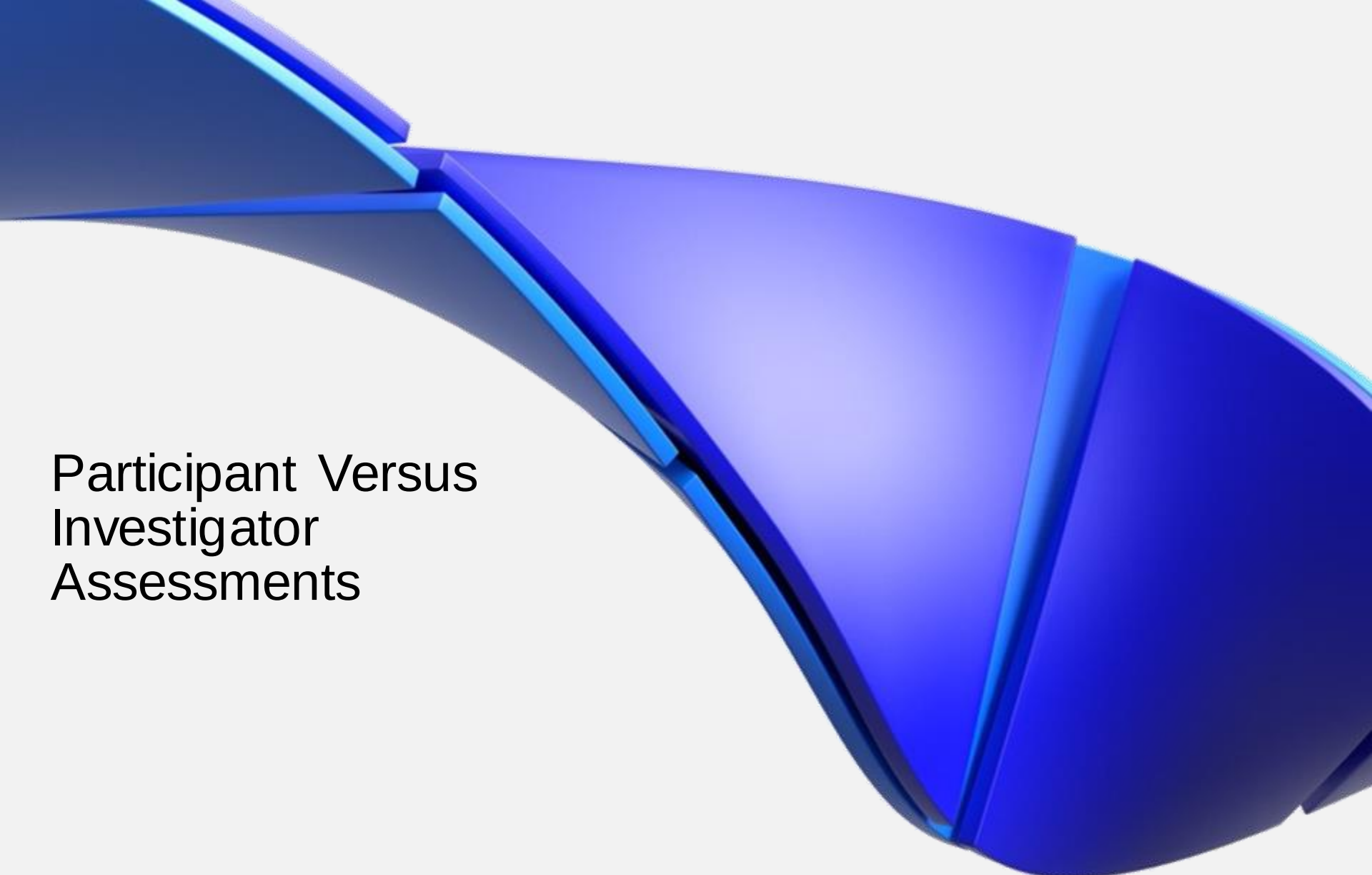
Example of all diary data missing

vs.xpt:

USUBJID	VSTEST	VSORRES	VSSTAT	VSREASND	VSDTC	VSTPT	VSTPTREF	VSFTDTC
001-0001	Temperature		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	2023-01-01	DAY 1	VACCINATION 1	2023-01-01
001-0001	Temperature		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	2023-01-02	DAY 2	VACCINATION 1	2023-01-01
001-0001	Temperature		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	2023-01-03	DAY 3	VACCINATION 1	2023-01-01
001-0001	Temperature		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	2023-01-04	DAY 4	VACCINATION 1	2023-01-01
001-0001	Temperature		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	2023-01-05	DAY 5	VACCINATION 1	2023-01-01
001-0001	Temperature		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	2023-01-06	DAY 6	VACCINATION 1	2023-01-01
001-0001	Temperature		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	2023-01-07	DAY 7	VACCINATION 1	2023-01-01

ce.xpt:

USUBJID	CEDECOD	CEPRESP	CEOCCUR	CESTAT	CEREASND	CETPTREF	CERFTDTC
001-0001	Fever	Y		NOT DONE	SUBJECT DID NOT COMPLETE ELECTRONIC DIARY	VACCINATION 1	2023-01-01

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Participant Versus Investigator Assessments

Participant Versus Investigator Assessments



Participant

- Planned assessments
- Assessed same day
- Subjective

Investigator

- Unplanned assessments
- Recall bias?
- Objective
- Qualified to determine Grade 4 reaction

*Assessments are distinguished by Category and Evaluator

Participant Versus Investigator Assessments

Example – investigator and participant report different severity

face.xpt:

USUBJID	FATEST	FAOBJ	FACAT	FAORRES	FAEVAL	FADTC	FATPT
001-0001	Occurrence Indicator	Diarrhea	REACTOGENICITY	N	STUDY SUBJECT	2023-01-01	DAY 1
001-0001	Occurrence Indicator	Diarrhea	REACTOGENICITY	Y	STUDY SUBJECT	2023-01-02	DAY 2
001-0001	Severity/Intensity	Diarrhea	REACTOGENICITY	MODERATE	STUDY SUBJECT	2023-01-02	DAY 2
001-0001	Occurrence Indicator	Diarrhea	REACTOGENICITY – UNPLANNED ASSESSMENT	Y	INVESTIGATOR	2023-01-02	DAY 2
001-0001	Severity/Intensity	Diarrhea	REACTOGENICITY – UNPLANNED ASSESSMENT	SEVERE	INVESTIGATOR	2023-01-02	DAY 2
001-0001	Occurrence Indicator	Diarrhea	REACTOGENICITY	N	STUDY SUBJECT	2023-01-03	DAY 3
001-0001	Occurrence Indicator	Diarrhea	REACTOGENICITY	N	STUDY SUBJECT	2023-01-04	DAY 4
001-0001	Occurrence Indicator	Diarrhea	REACTOGENICITY	N	STUDY SUBJECT	2023-01-05	DAY 5
001-0001	Occurrence Indicator	Diarrhea	REACTOGENICITY	N	STUDY SUBJECT	2023-01-06	DAY 6
001-0001	Occurrence Indicator	Diarrhea	REACTOGENICITY	N	STUDY SUBJECT	2023-01-07	DAY 7

Participant Versus Investigator Assessments

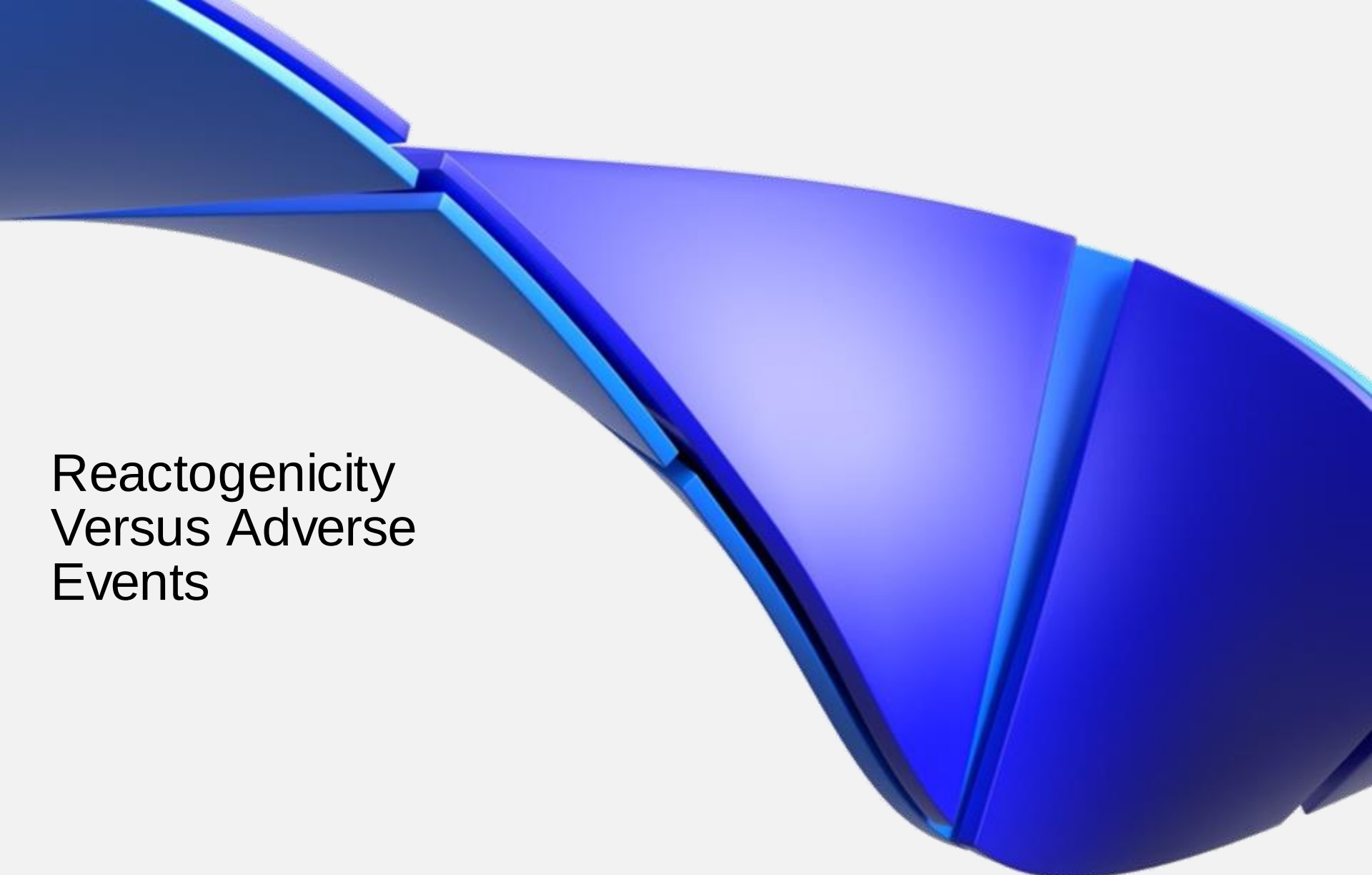
Example – investigator and participant report different severity, continued

ce.xpt:

USUBJID	CESEQ	CEDECOD	CESEV	CEOCCUR	CESTDTC	CEENDTC	CEDUR
001-0001	11	Diarrhea	SEVERE	Y	2023-01-02	2023-01-02	P1D

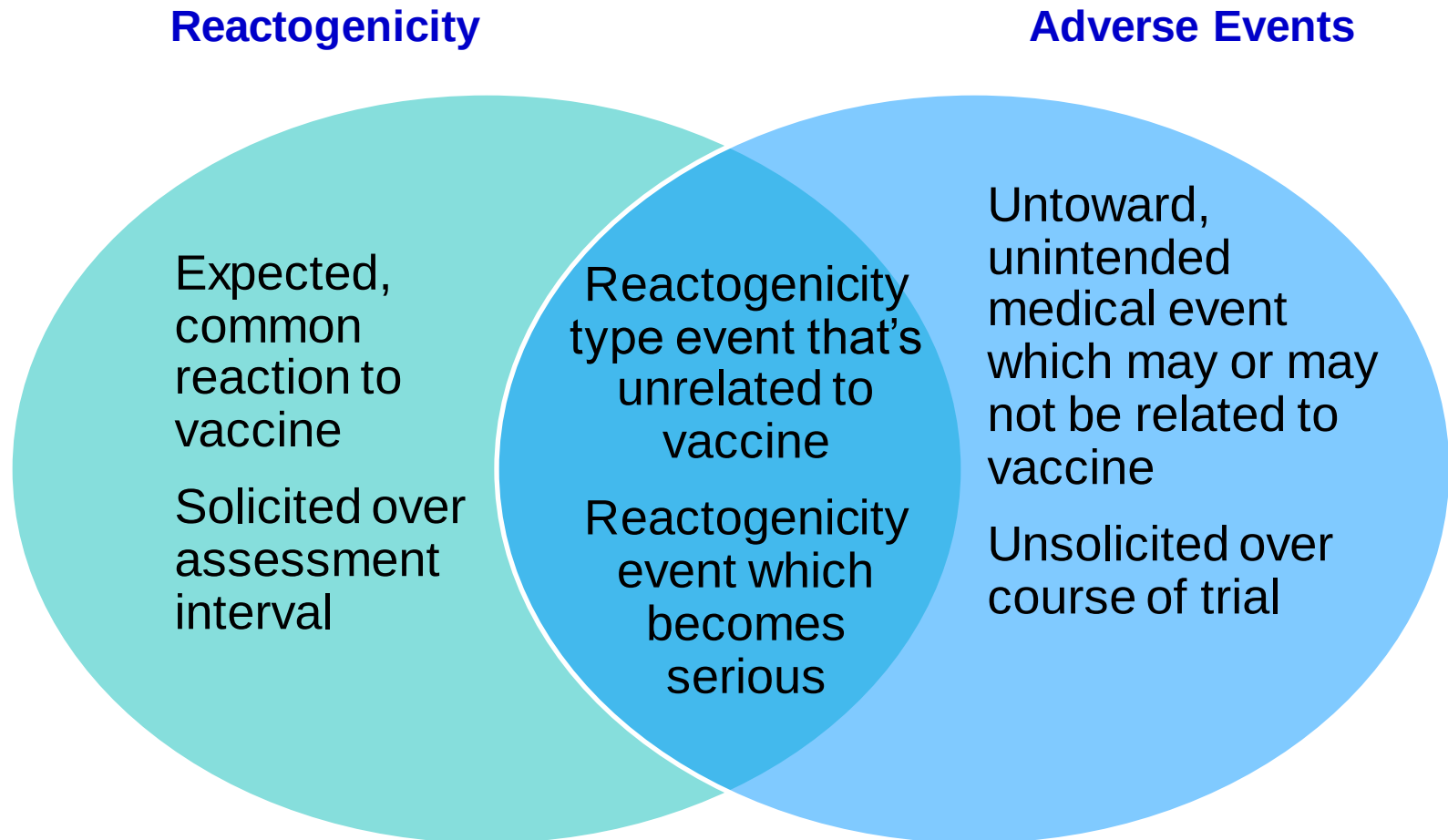
suppce.xpt:

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
CE	001-0001	CESEQ	11	CEEVAL	Evaluator	INVESTIGATOR
CE	001-0001	CESEQ	11	CESEV1	Severity/Intensity 1	MODERATE
CE	001-0001	CESEQ	11	CEDIFFRS	Reason Investigator Changed Assessment	INVESTIGATOR ASSESSED AS MORE SEVERE DURING UNPLANNED ASSESSMENT

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Reactogenicity Versus Adverse Events

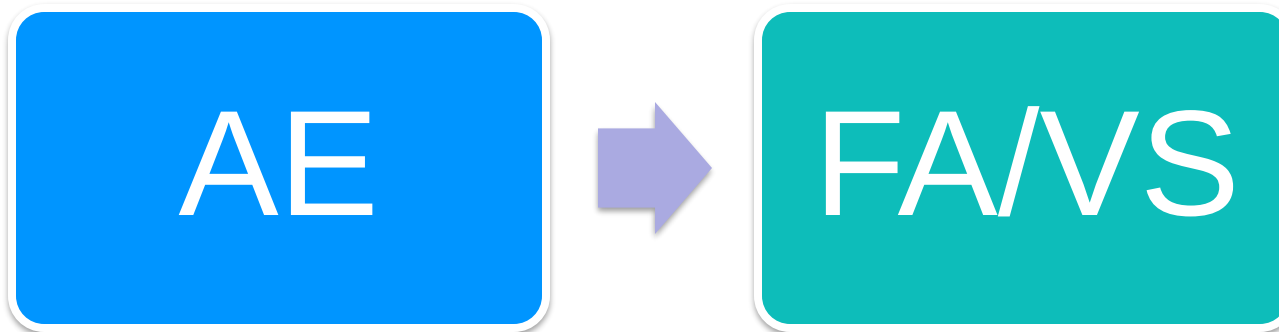
Reactogenicity Versus Adverse Events



Reactogenicity Versus Adverse Events

Adverse Events Meeting Reactogenicity Criteria

- The site may become aware of reactogenicity events which are not captured in the diary records and record them in the AE CRF
- These events need to be identified and moved from AE to FACE/VS if they occurred during the reactogenicity assessment interval
 - CRF categorization
 - Manual review
 - Programmatic selection



Reactogenicity Versus Adverse Events

Example – reactogenicity data entered in the AE CRF and moved to FACE

raw AE data:

USUBJID	AEDECOD	AEREL	AESV	AESTDTC	AEENDTC
001-0001	Diarrhea	RELATED	MODERATE	2023-01-02	2023-01-04

face.xpt:

USUBJID	FASEQ	FATEST	FAOBJ	FACAT	FAORRES	FASTAT	FAEVAL	FADTC	FATPT
001-0001	1	Occurrence Indicator	Diarrhea	REACTOGENICITY	N		STUDY SUBJECT	2023-01-01	DAY 1
001-0001	2	Occurrence Indicator	Diarrhea	REACTOGENICITY	Y		STUDY SUBJECT	2023-01-02	DAY 2
001-0001	3	Severity/Intensity	Diarrhea	REACTOGENICITY	MODERATE		STUDY SUBJECT	2023-01-02	DAY 2
001-0001	4	Occurrence Indicator	Diarrhea	REACTOGENICITY – UNPLANNED ASSESSMENT	Y		INVESTIGATOR	2023-01-02	DAY 2
001-0001	5	Severity/Intensity	Diarrhea	REACTOGENICITY – UNPLANNED ASSESSMENT	MODERATE		INVESTIGATOR	2023-01-02	DAY 2
001-0001	6	Occurrence Indicator	Diarrhea	REACTOGENICITY	Y		STUDY SUBJECT	2023-01-03	DAY 3
001-0001	7	Severity/Intensity	Diarrhea	REACTOGENICITY	MODERATE		STUDY SUBJECT	2023-01-03	DAY 3
001-0001	8	Occurrence Indicator	Diarrhea	REACTOGENICITY – UNPLANNED ASSESSMENT	Y		INVESTIGATOR	2023-01-03	DAY 3
001-0001	9	Severity/Intensity	Diarrhea	REACTOGENICITY – UNPLANNED ASSESSMENT	MODERATE		INVESTIGATOR	2023-01-03	DAY 3
001-0001	10	Occurrence Indicator	Diarrhea	REACTOGENICITY		NOT DONE	STUDY SUBJECT	2023-01-04	DAY 4
001-0001	11	Occurrence Indicator	Diarrhea	REACTOGENICITY – UNPLANNED ASSESSMENT	Y		INVESTIGATOR	2023-01-04	DAY 4
001-0001	12	Severity/Intensity	Diarrhea	REACTOGENICITY – UNPLANNED ASSESSMENT	MODERATE		INVESTIGATOR	2023-01-04	DAY 4
001-0001	13	Occurrence Indicator	Diarrhea	REACTOGENICITY	N		STUDY SUBJECT	2023-01-05	DAY 5
001-0001	14	Occurrence Indicator	Diarrhea	REACTOGENICITY	N		STUDY SUBJECT	2023-01-06	DAY 6
001-0001	15	Occurrence Indicator	Diarrhea	REACTOGENICITY	N		STUDY SUBJECT	2023-01-07	DAY 7

Reactogenicity Versus Adverse Events

Example – reactogenicity data entered in the AE CRF and moved to FACE, continued

suppface.xpt:

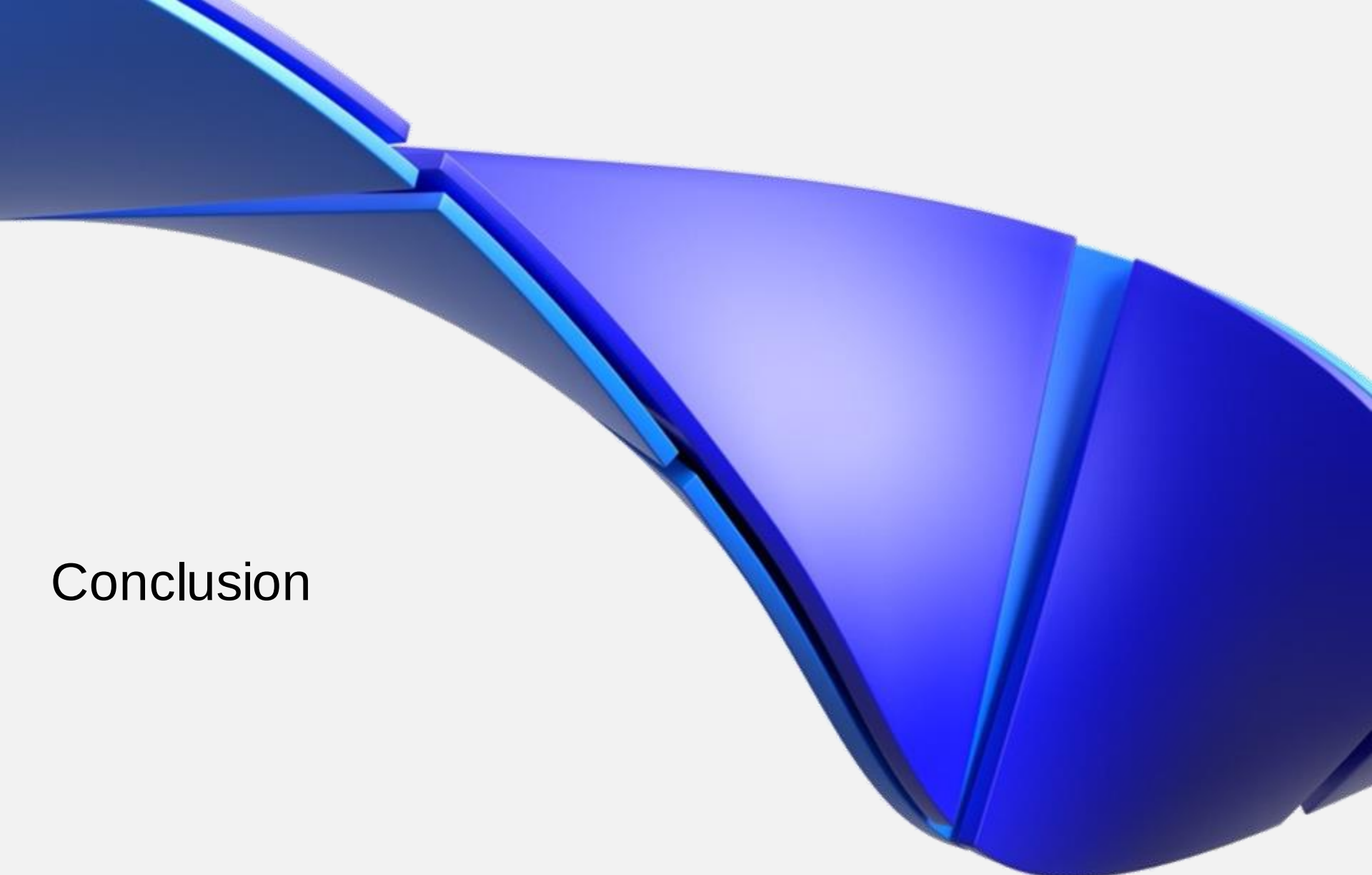
RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
FACE	001-0001	FASEQ	4	UNPLSRC	Source of Unplanned Assessment	AE
FACE	001-0001	FASEQ	5	UNPLSRC	Source of Unplanned Assessment	AE
FACE	001-0001	FASEQ	8	UNPLSRC	Source of Unplanned Assessment	AE
FACE	001-0001	FASEQ	9	UNPLSRC	Source of Unplanned Assessment	AE
FACE	001-0001	FASEQ	11	UNPLSRC	Source of Unplanned Assessment	AE
FACE	001-0001	FASEQ	12	UNPLSRC	Source of Unplanned Assessment	AE

ce.xpt:

USUBJID	CESEQ	CEDECOD	CESEV	CEOCCUR	CESTDTC	CEENDTC	CEDUR
001-0001	11	Diarrhea	MODERATE	Y	2023-01-02	2023-01-04	P3D

suppce.xpt:

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
CE	001-0001	CESEQ	11	CEEVAL	Evaluator	INVESTIGATOR
CE	001-0001	CESEQ	11	CEENDTC1	End Date/Time of Clinical Event 1	2023-01-03
CE	001-0001	CESEQ	11	UNPLSRC	Source of Unplanned Assessment	AE

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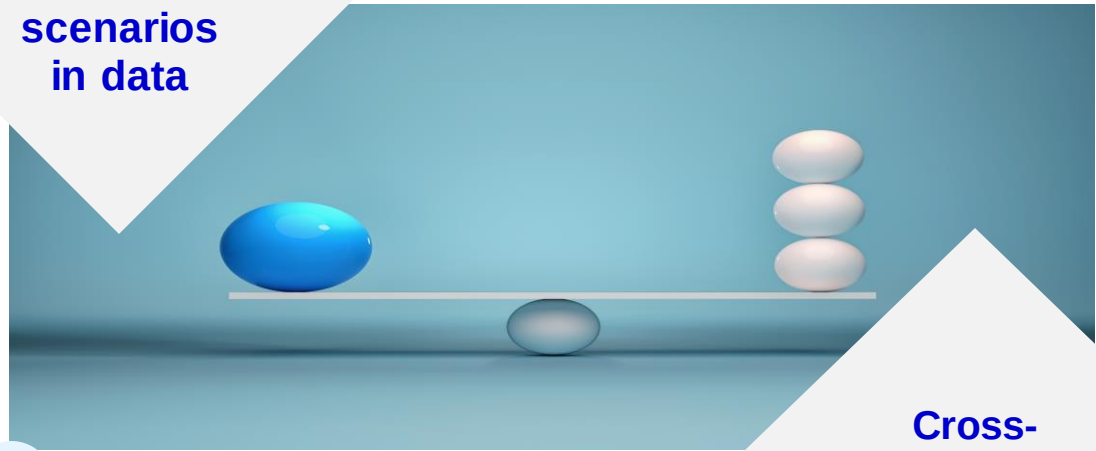
Conclusion

Conclusion

Changes

**Lack of/
out-of-date
guidance**

**New
scenarios
in data**



**Collect
or
derive?**

**How to
analyze?**



**Cross-
functional
collaboration**

Standards

Communication



Thank You

For more information, contact:

sandra.vanpeltnghuyen@pfizer.com

emily.bernstein-hanlon@pfizer.com