



USUBJID Challenges: Representing Multiple Participations for Analysis & Reporting

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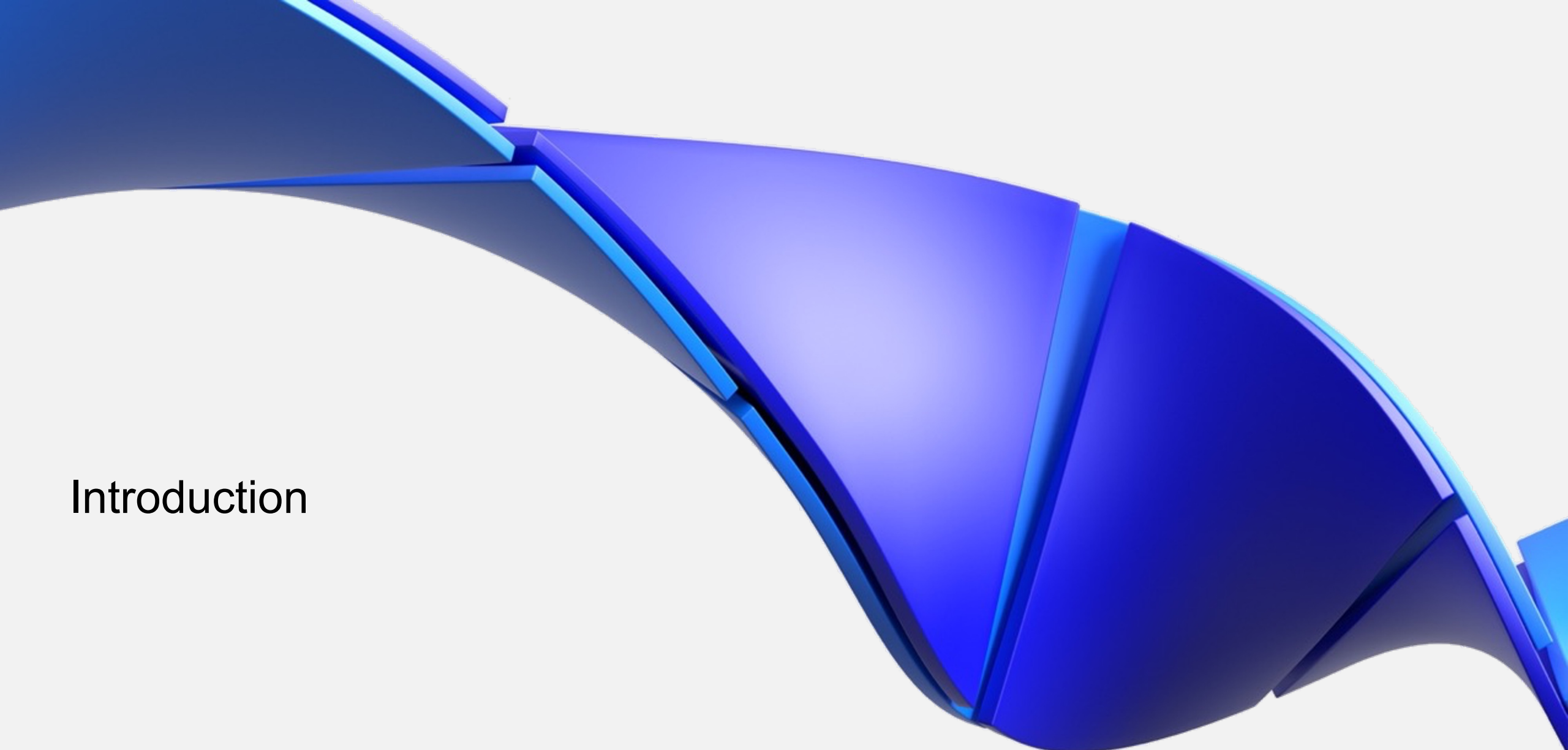
February 26, 2024



Agenda

- Introduction
- Data Collection
- Scenario One – One Participation Summarized
- Scenario Two – All Participations Summarized
- Submission Challenges
- Conclusion



An abstract, three-dimensional geometric shape composed of several blue, curved, and faceted planes. The shape is dynamic and angular, resembling a stylized wave or a modern architectural structure. It is rendered with soft shadows and highlights, giving it a sense of depth and volume. The color is a vibrant blue, with some areas appearing slightly lighter due to the lighting.

Introduction

Introduction

Multiple Participations

- Challenge our existing structures
- Occur due to re-enrollment or unplanned multiple enrollments
- SDTM mapping can be similar across scenarios while ADaM design depends on analysis needs



Image from <https://learnstore.cdisc.org/?category=20&keyword=on-demand&cond=advand&search=%EF%80%82>

Introduction

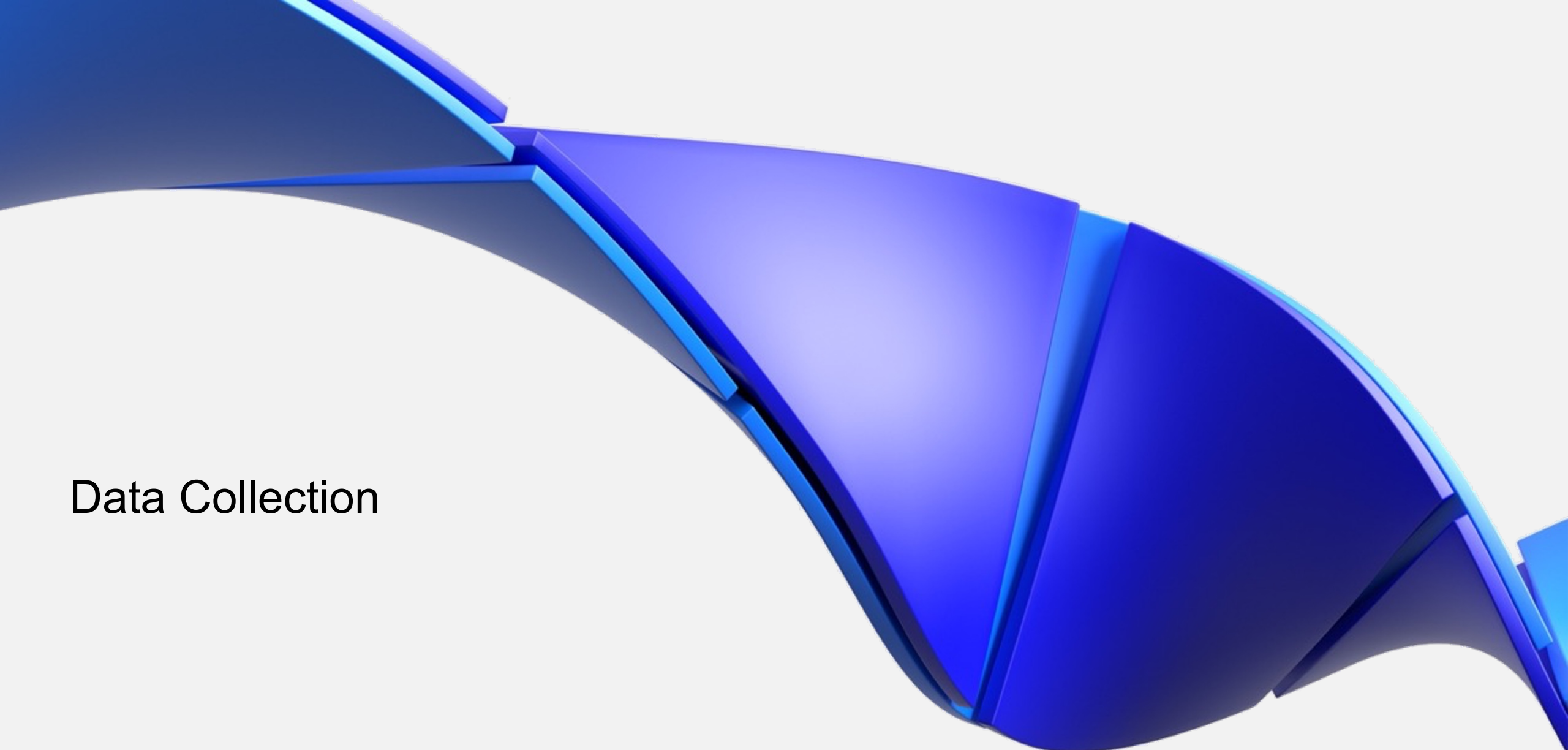
Multiple Participations – USUBJID

FDA Study Data Technical Conformance Guide (TCG)

- A unique SUBJID should be assigned for each participation
- SUBJID should be included in all related domains
- DM domain should contain the primary enrollment/screening
- Additional enrollments or screenings should be included in a custom domain structured like DM domain
- Add explanation in the data reviewer's guide along with a table showing all SUBJID for each USUBJID in the study

Clinical Data Interchange Standards Consortium (CDISC) SDTMIG v3.3

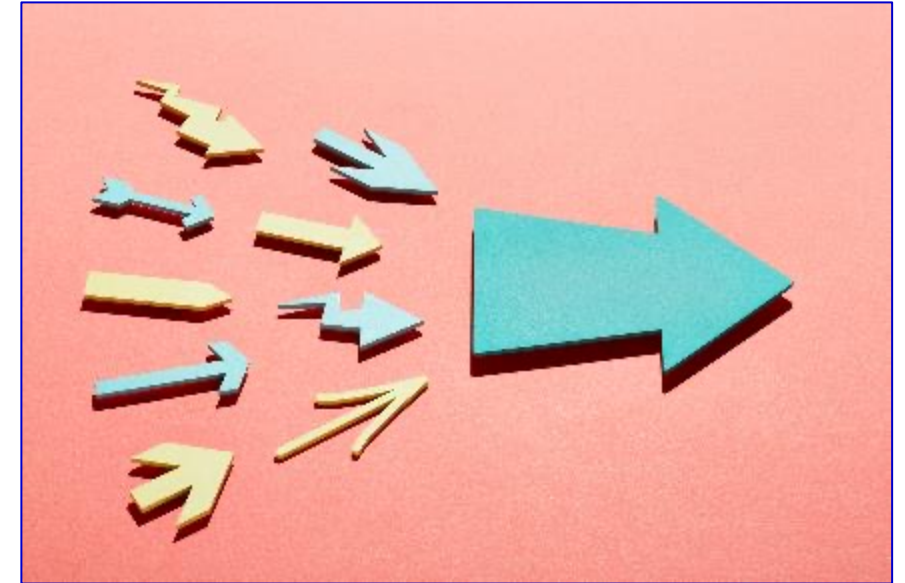
- USUBJID must uniquely identify a participant across all studies for all applications and submission involving the product
- USUBJID will remain the same throughout the study while SUBJID identifies each unique participation
- CDISC multiple subject instances team proposed a custom domain, Demographics for Multiple Participations (DC)

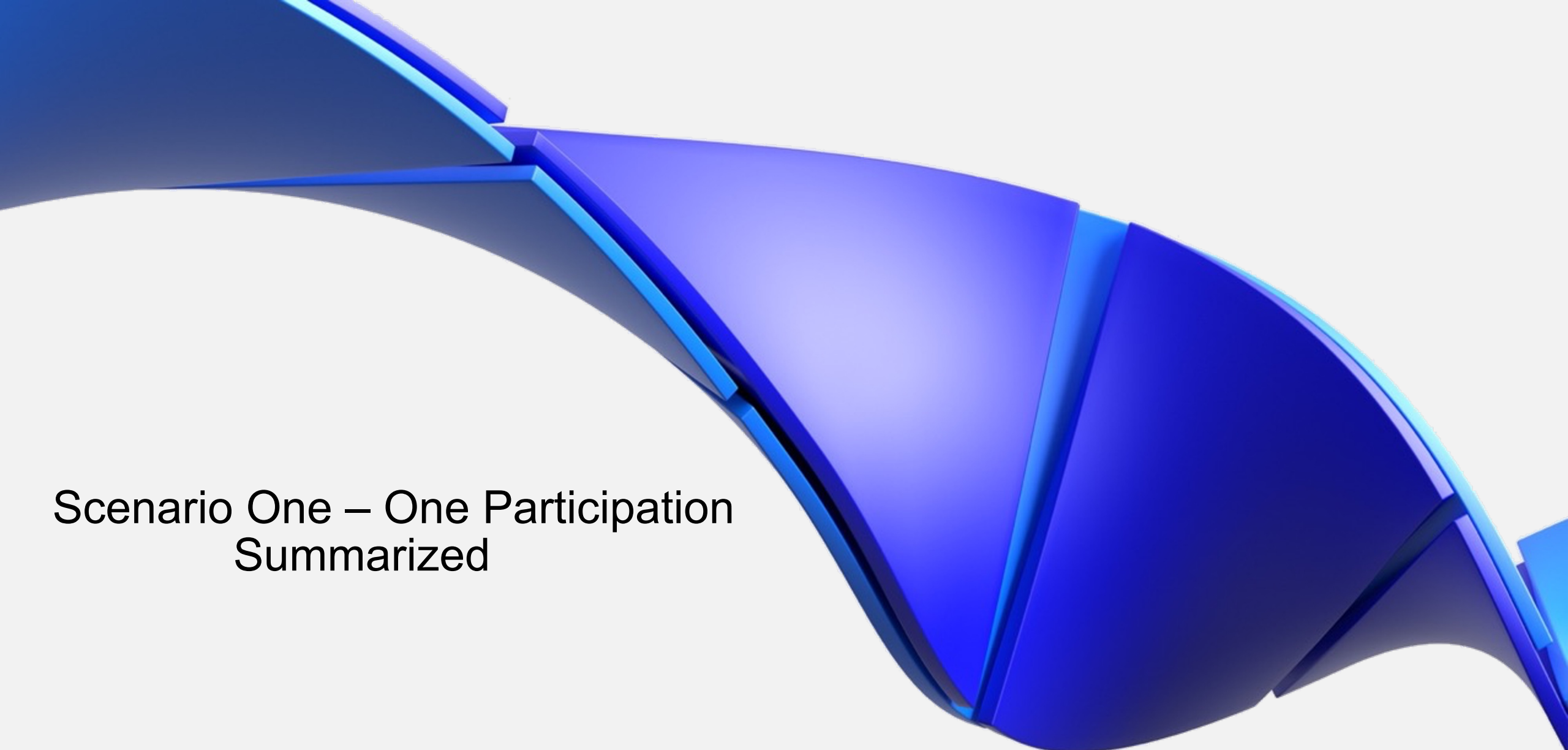
An abstract, three-dimensional blue geometric shape composed of several flat, triangular and quadrilateral facets. The shape is curved and dynamic, with a color gradient from a deep blue to a lighter, almost white blue at the edges. It appears to be a stylized representation of a molecular structure or a complex data visualization. The shape is positioned on the right side of the slide, with its left edge curving towards the center.

Data Collection

Data Collection

- First STUDYID, SITEID and SUBJID should be collected
- More complicated for multiple prior participations
- Difficulties arise resulting in incorrect USUBJID assignment when sites
 - Deviate from CRF completion guidelines
 - Enter the data late
 - Do not understand the criticality of collecting the required fields
- Unplanned multiple enrollments when sites are not aware are more challenging to track
- USUBJID changes between interim data cuts supporting submissions is a challenge

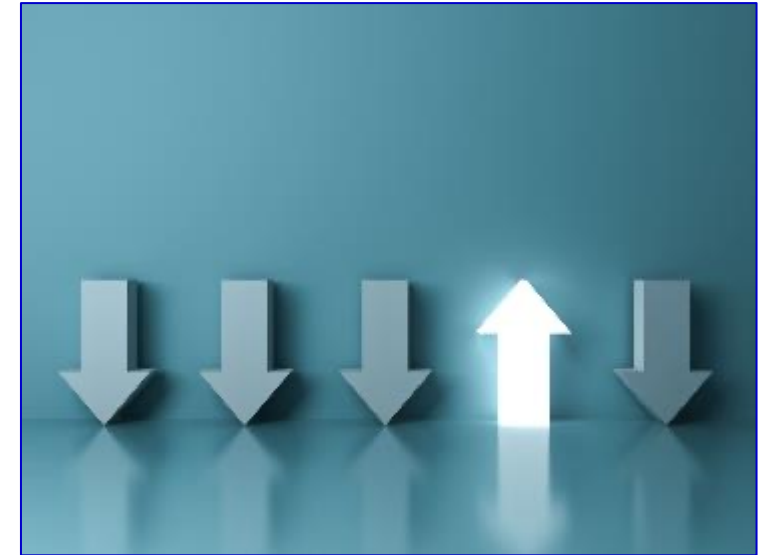


Abstract blue 3D geometric shapes, possibly representing a stylized DNA helix or a series of connected planes, in shades of blue and purple, set against a light gray background.

Scenario One – One Participation Summarized

Scenario One – One Participation

- Single enrollment is summarized
- Occurs when planned re-enrollment or un-planned multiple enrollment with one participation is analyzed
- Two approaches can be considered:
 - A subset can be applied to include the participation of interest
 - Cumulative domains can be created but will introduce additional challenges.
- Example: A participant enrolled first to the 10mg study drug, then returned and enrolled again in the 30mg study drug 8 months later.



Scenario One – One Participation

SDTM: Single Participation Approach

- DM domain examples if individual participation is summarized, repeated for each participation

dm.xpt for first participation

USUBJID	SUBJID	RFSTDTC	RFENDTC	RFICDTC	BRTHDTC	ARMCD	ARM
AAA 001 1001	1001	2023-01-01	2023-03-30	2022-12-03	1998-01-01	A	STUDY DRUG 10 mg

dm.xpt for second participation

USUBJID	SUBJID	RFSTDTC	RFENDTC	RFICDTC	BRTHDTC	ARMCD	ARM
AAA 001 1001	1003	2023-09-01	2023-11-30	2023-08-05	1998-01-01	C	STUDY DRUG 30 mg

- If second participation is analyzed
 - RFICDTC, RFSTDTC and RFENDTC will be from later SUBJID
 - USUBJID is mapped based on individual's initial participation
 - ARMCD = 'C' and ARM = 'STUDY DRUG 30 mg'



Scenario One – One Participation

SDTM: Cumulative Participation Approach

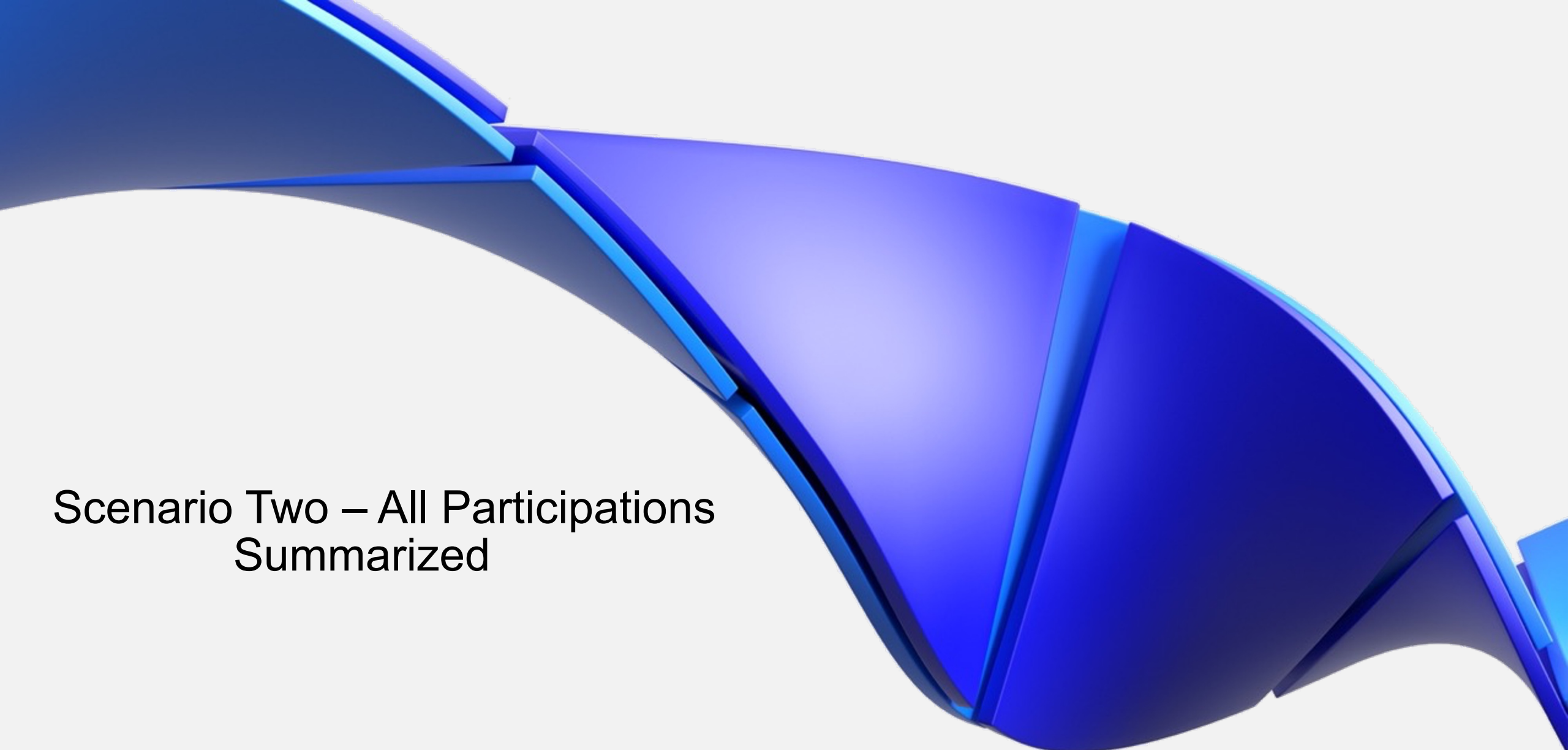
- Retain all participations creating cumulative SDTM domains, use ADaM datasets to flag analysis records
- Set DM.RFSTDTC from first participation and DM.RFENDTC from latest participation
 - Add alternative SUBJIDy* variable

dm.xpt

USUBJID	SUBJID	SUBJID2	RFSTDTC	RFENDTC	RFICDTC	BRTHDTC	ARMCD	ARM
AAA 001 1001	1003	1001	2023-01-01	2023-11-30	2022-12-03	1998-01-01	C	STUDY DRUG 30 mg

- Mapping prior participation for RFICDTC, RFSTDTC and ARM variables can be cumbersome
- Proposed DC domain will be useful to contain participation data for traceability

* Nonstandard Variable (NSV)

An abstract, three-dimensional blue geometric shape, resembling a stylized wave or a series of connected planes, dominates the right side of the slide. It has a gradient from light blue to dark blue and casts a shadow on the white background.

Scenario Two – All Participations Summarized

Scenario Two – All Participations Summarized

SDTM Approach – DC Domain

- Includes a record for each participation (SUBJID)
- DCSEQ provides the order of participations



dc.xpt

USUBJID	SUBJID	DCSEQ	RFSTDTC	RFENDTC	RFICDTC	BRTHDTC	ARMCD	ARM
AAA 001 1001	1001	1	2023-01-01	2023-03-30	2022-12-03	1998-01-01	A	STUDY DRUG 10 mg
AAA 001 1001	1003	2	2023-09-01	2023-11-30	2023-08-05	1998-01-01	C	STUDY DRUG 30 mg

Scenario Two – All Participations Summarized

SDTM Approach – DM Domain

- One record per USUBJID
- TCG: primary participation
- Considerations when selecting participation for DM domain:
 - Analysis focus
 - EPOCH and study day variables
 - Pinnacle 21 (P21) conformance issues (records before DM.RFSTDTC/RFICDTC or after DM.RFENDTC)
- Below example summarizes both participations into one record



dm.xpt

USUBJID	SUBJID	RFSTDTC	RFENDTC	RFICDTC	BRTHDTC	ARMCD	ARM
AAA 001 1001	1001	2023-01-01	2023-11-30	2022-12-03	1998-01-01	A	STUDY DRUG 10 mg

Scenario Two – All Participations Summarized

SDTM Approach – AE Domain

- All participations included, SUBJID required to distinguish
- Study day variables relative to DM.RFSTDTC (first participation)
- EPOCH and AETRTEM defined within each participation

ae.xpt

USUBJID	SUBJID	AEDECOD	AESTDTC	AEENDTC	AESTDY	AEENDY	EPOCH	SUPPAE. AETRTEM
AAA 001 1001	1001	Anaemia	2023-01-03	2023-01-05	3	5	TREATMENT	Y
AAA 001 1001	1001	Irritable bowel syndrome	2023-01-10	2023-01-15	10	15	TREATMENT	Y
AAA 001 1001	1003	Headache	2023-08-10	2023-08-12	222	224	SCREENING	
AAA 001 1001	1003	Cough	2023-10-10	2023-10-20	283	293	FOLLOW-UP	Y

Scenario Two – All Participations Summarized

SDTM Approach – VS Domain

- VSLOBXFL defined relative to DM.RFXSTDTC

vs.xpt

USUBJID	SUBJID	VSTESTCD	VSORRES	VSDTC	VSDY	VSLOBXFL	VISIT	EPOCH
AAA 001 1001	1001	DIABP	75	2022-12-03	-28		SCREENING	SCREENING
AAA 001 1001	1001	DIABP	72	2023-01-01	1	Y	DAY 1	TREATMENT
AAA 001 1001	1001	DIABP	78	2023-02-01	32		1 MONTH	FOLLOW-UP
AAA 001 1001	1001	DIABP	80	2023-03-30	89		3 MONTHS	FOLLOW-UP
AAA 001 1001	1003	DIABP	81	2023-08-05	217		SCREENING	SCREENING
AAA 001 1001	1003	DIABP	84	2023-09-01	244		DAY 1	TREATMENT
AAA 001 1001	1003	DIABP	83	2023-10-01	274		1 MONTH	FOLLOW-UP
AAA 001 1001	1003	DIABP	82	2023-11-30	334		3 MONTHS	FOLLOW-UP



Scenario Two – All Participations Summarized

ADaM Approach – ADPL Domain



- Participation-Level Analysis Dataset
- ORDER (NSV) identifies the order of the participations
- Can be used in place of ADSL to create other ADaM domains

adpl.xpt

USUBJID	SUBJID	ORDER	TRT01P	TRTSDT	TRTEDT	EOSDT	RFICDTC
AAA 001 1001	1001	1	STUDY DRUG 10 mg	01JAN2023	01FEB2023	30MAR2023	2022-12-03
AAA 001 1001	1003	2	STUDY DRUG 30 mg	01SEP2023	01OCT2023	20NOV2023	2023-08-05

Scenario Two – All Participations Summarized

ADaM Approach – ADSL Domain

- TRTxxP/TRTxxA/TRxxSDT/TRxxEDT can be used to represent each distinct treatment period
- MULENRFL (NSV) identifies participants with multiple participations
- SUBJIDy identifies each participation

adsl.xpt

Row	USUBJID	SUBJID	SUBJID2	TRTSDT	TRTEDT	TRT01P	TR01SDT
1	AAA 001 1001	1001	1003	01JAN2023	01OCT2023	STUDY DRUG 10 mg	01JAN2023

Row	TR01EDT	TRT02P	TR02SDT	TR02EDT	MULENRFL
1	01FEB2023	STUDY DRUG 30 mg	01SEP2023	01OCT2023	Y

Scenario Two – All Participations Summarized

ADaM Approach – ADAE Domain

- AE merged with ADPL to calculate variables within each participation
- TRTEMFL and ONTRTFL defined within each participation

adae.xpt

Row	USUBJID	SUBJID	AEDECOD	TRTSDT	TRTEDT	ASTDT	AENDT
1	AAA 001 1001	1001	Anaemia	01JAN2023	01FEB2023	03JAN2023	05JAN2023
2	AAA 001 1001	1001	Irritable bowel syndrome	01JAN2023	01FEB2023	10JAN2023	15JAN2023
3	AAA 001 1001	1003	Headache	01SEP2023	01OCT2023	10AUG2023	12AUG2023
4	AAA 001 1001	1003	Cough	01SEP2023	01OCT2023	10OCT2023	20OCT2023

Row	ASTDY	AENDY	APERIOD	TRTA	APHASE	TRTEMFL	ONTRTFL
1	3	5	1	STUDY DRUG 10 mg	FIRST TREATMENT	Y	Y
2	10	15	1	STUDY DRUG 10 mg	FIRST TREATMENT	Y	Y
3	-21	-19	2	STUDY DRUG 30 mg	SECOND SCREENING		
4	40	50	2	STUDY DRUG 30 mg	SECOND FOLLOW-UP	Y	

Scenario Two – All Participations Summarized

ADaM Approach – ADVS Domain

- ADY defined within each participation
- ABLFL defined within each participation, BASETYP distinguishes
- Having single ANL01FL across both participations provides flexibility

advs.xpt/

Row	USUBJID	SUBJID	TRTSDT	PARAMCD	AVAL	BASE	ADT	ADY	ABLFL
1	AAA 001 1001	1001	01JAN2023	DIABP	75	72	03DEC2022	-28	
2	AAA 001 1001	1001	01JAN2023	DIABP	72	72	01JAN2023	1	Y
3	AAA 001 1001	1001	01JAN2023	DIABP	78	72	01FEB2023	32	
4	AAA 001 1001	1001	01JAN2023	DIABP	80	72	30MAR2023	89	
5	AAA 001 1001	1003	01SEP2023	DIABP	81	84	05AUG2023	-26	
6	AAA 001 1001	1003	01SEP2023	DIABP	84	84	01SEP2023	1	Y
7	AAA 001 1001	1003	01SEP2023	DIABP	83	84	01OCT2023	31	
8	AAA 001 1001	1003	01SEP2023	DIABP	82	84	30NOV2023	91	

Row	BASETYP	AVISIT	ANL01FL	APERIOD	TRTA	APHASE
1	PERIOD 01	SCREENING		1	STUDY DRUG 10 mg	FIRST SCREENING
2	PERIOD 01	DAY 1	Y	1	STUDY DRUG 10 mg	FIRST TREATMENT
3	PERIOD 01	1 MONTH	Y	1	STUDY DRUG 10 mg	FIRST FOLLOW-UP
4	PERIOD 01	3 MONTHS	Y	1	STUDY DRUG 10 mg	FIRST FOLLOW-UP
5	PERIOD 02	SCREENING		2	STUDY DRUG 30 mg	SECOND SCREENING
6	PERIOD 02	DAY 1	Y	2	STUDY DRUG 30 mg	SECOND TREATMENT
7	PERIOD 02	1 MONTH	Y	2	STUDY DRUG 30 mg	SECOND FOLLOW-UP
8	PERIOD 02	3 MONTHS	Y	2	STUDY DRUG 30 mg	SECOND FOLLOW-UP

Scenario Two – All Participations Summarized

Tables, Figures and Listings

- Example of both participations summarized in the same table
- Frequency counts grouped by treatment arm

AE table double counting multiple participations with different treatment arms

System Organ Class Preferred Term	Study Drug 10 mg (N=10)	Study Drug 30 mg (N=10)
	n (%)	n (%)
Any adverse event	1 (10)	1 (10)
Blood and lymphatic system disorders	1 (10)	0
Anaemia	1 (10)	0
Respiratory, thoracic and mediastinal disorders	0	1 (10)
Cough	0	1 (10)

Scenario Two – All Participations Summarized

Tables, Figures and Listings

- Example of multiple participations within the same treatment arm summarized in the same table
- Frequency counts grouped by treatment arm and SUBJID get correct counts

adae.xpt

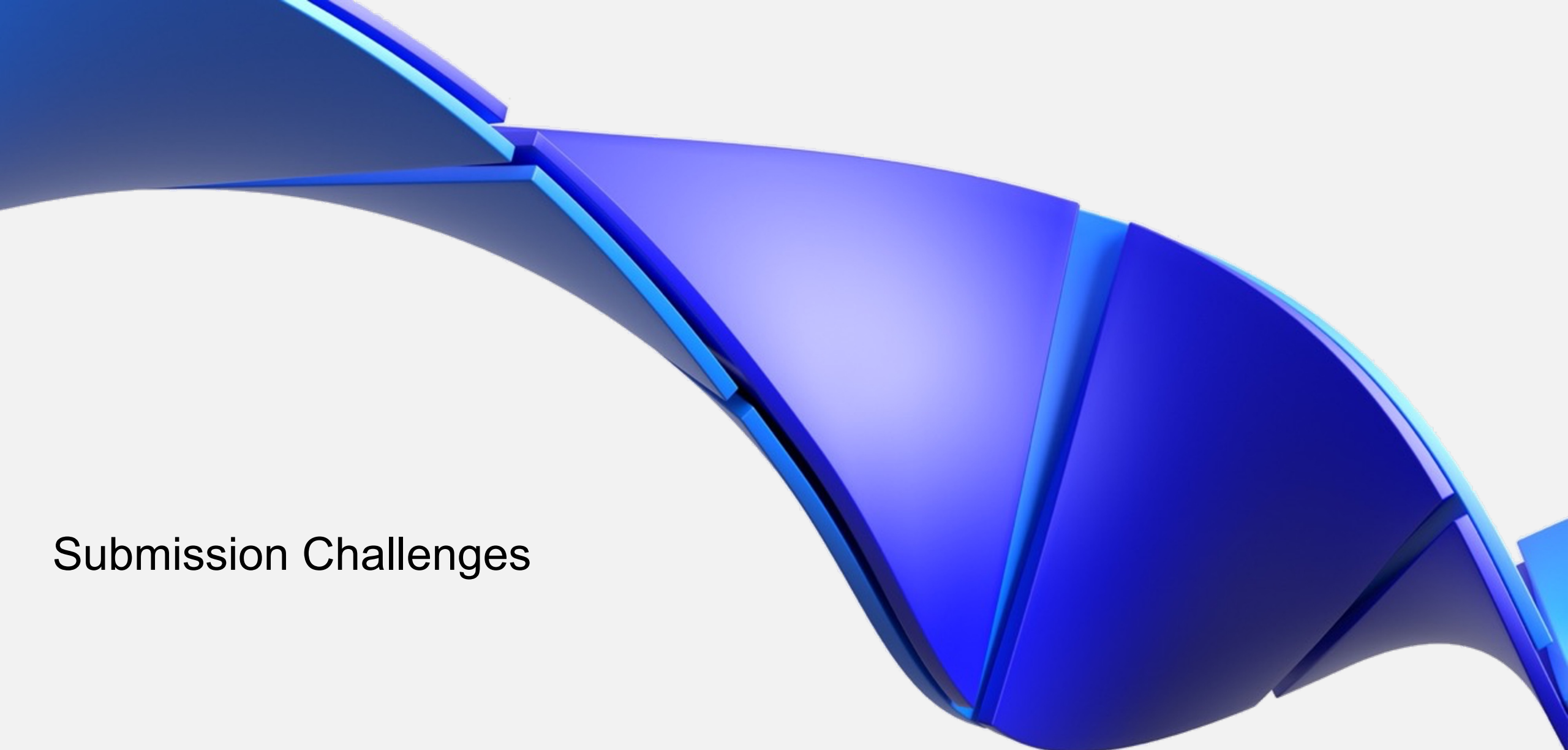
USUBJID	SUBJID	AEBODSYS	AEDECOD	APERIOD	TRTA	APHASE	TRTEMFL	ONTRTFL
AAA 001 1002	1002	Nervous system disorders	Headache	1	STUDY DRUG 10 mg	FIRST TREATMENT	Y	Y
AAA 001 1002	1005	Nervous system disorders	Headache	2	STUDY DRUG 10 mg	SECOND TREATMENT	Y	Y

AE table using USUBJID as unique key

System Organ Class Preferred Term	Study Drug 10 mg (N=10) n (%)
Any adverse event	1 (10)
Nervous system disorders	1 (10)
Headache	1 (10)

AE table using SUBJID as unique key

System Organ Class Preferred Term	Study Drug 10 mg (N=11) n (%)
Any adverse event	2 (18)
Nervous system disorders	2 (18)
Headache	2 (18)

An abstract graphic composed of several overlapping, curved, blue geometric shapes that create a sense of depth and movement, resembling a stylized wave or a series of connected planes. The shapes are rendered with gradients and shadows, giving them a three-dimensional appearance.

Submission Challenges

Submission Challenges

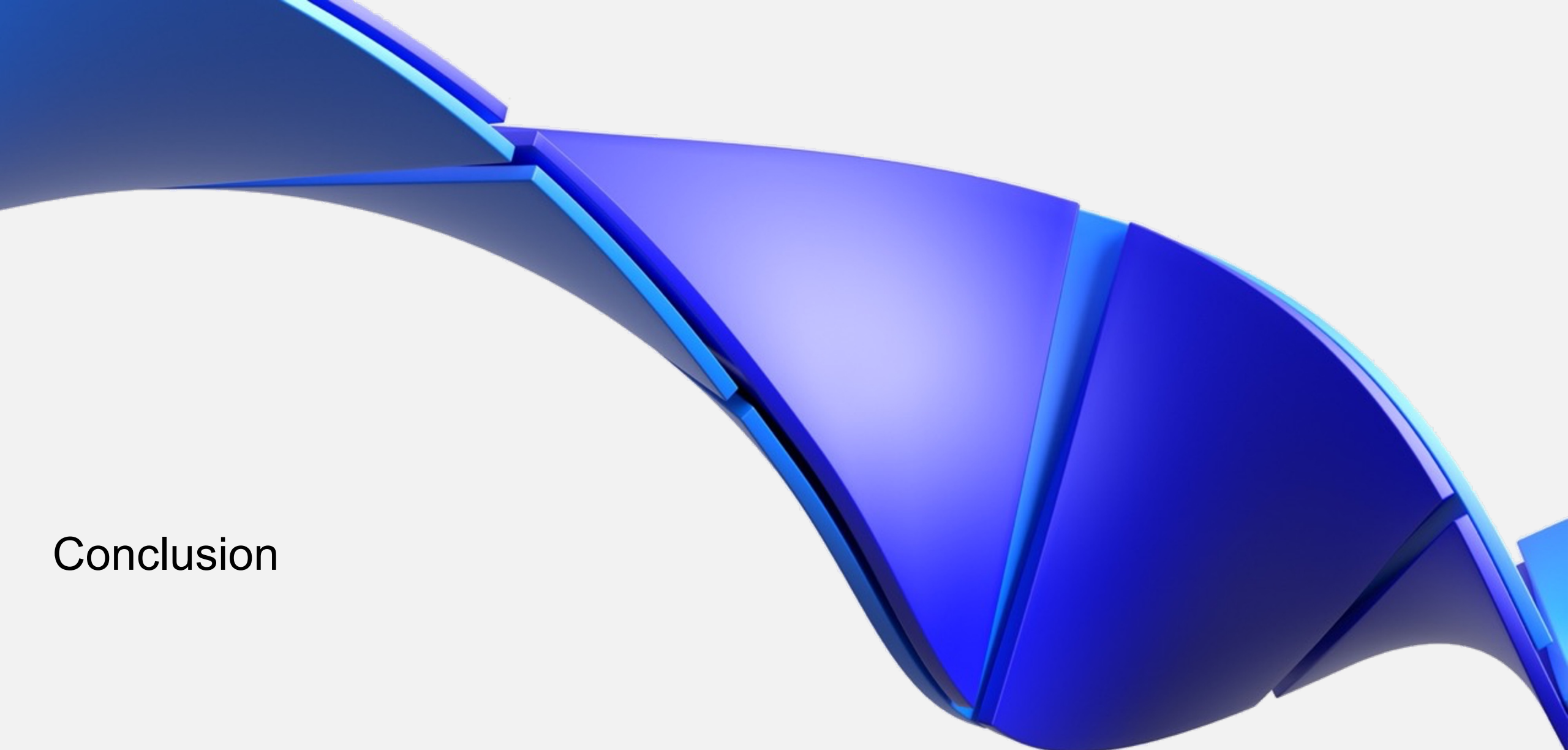
Scenario One – One Participation Summarized

- Trial Design Models include all participations while subject level SDTM domains contain a subset
- Prior participation traceability is not possible

Scenario Two – All Participations Summarized

- Proposed DC domain recommended but requires discussion with regulatory agencies
- SUBJID is essential in subject-level domains, needs to be explained in the cSDRG.
- ADPL dataset should be clearly described and explained in the ADRG.

- Care must be taken upfront to ensure USUBJID is unchanged between submissions
- If USUBJID does change, it's the sponsors responsibility to inform the regulatory agency

An abstract graphic composed of several overlapping, curved, blue geometric shapes that create a sense of depth and movement, resembling a stylized wave or a series of connected planes. The shapes are rendered with gradients and shadows, giving them a three-dimensional appearance.

Conclusion

Conclusion

- Multiple participations pose challenges
- Accurate data collection to assign the correct USUBJID is critical
- With more complex study designs evolving, updated standards are needed
- Proposed DC domain is recommended but requires downstream considerations
- Implementing the proposed DC and ADPL will give flexibility
 - Increased traceability
 - More complex to implement
 - Challenges our existing structures and standards
 - Requires discussion with regulatory agency ahead of time



Acknowledgments



- Thank you to our reviewers:
 - Helen Yang
 - Lisa Houterloot
 - Sandra VanPelt Nguyen
 - Liping Zhang
- And to the stream chairs



Thank You

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