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Your Guide to Successfully Upversioning CDISC Standards

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Co-Authored by David Neubauer, Standards Engineer, IQVIA and
Toral Patel, Standards Engineer, IQVIA

Meet the Speakers

Kapila Patel

Title: Senior Statistical Programmer

Organization: IQVIA

Kapila Patel has over 20 years of experience in the areas of Data Standards and providing technical support to clinical trial systems/data. Previous publications cover topics including metadata curation, data integration, and SDTM and ADaM implementation. Kapila is member of the CDISC SDS NSV subteam, Curator Forum, PHUSE SDTM ADAM Implementation FAQ team, and icSDRG team.

Soumya Rajesh

Title: Senior Standards Engineer

Organization: IQVIA

Soumya Rajesh has over 18 years of experience in the areas of SDTM Standards, Programming and Regulatory Operations, in various Therapeutic Areas and study phases. Previous publications cover topics such as Sound SDTM & ADaM, Clinical Classifications, Findings About, Disposition, SDTM IG vs. Model, and ISS & ISE Dataset Preparation, at various industry conferences since 2018. Soumya is also Current Lead for the CDISC SDS LT, Co-Lead of the SDS NSV sub-team, member of CDASH NSV Registry sub-team, PHUSE Working Groups and PharmaSUG Conference Committee.

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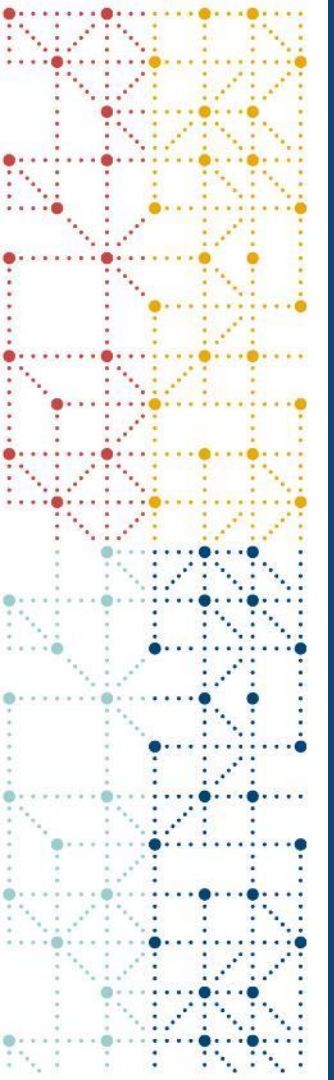
- *The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of CDISC.*

- *The authors have no real or apparent conflicts of interest to report.*



Introduction

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Background

Goals

In Scope

- SDTM
- Define-XML
- FDA
- PMDA

Out of Scope

- CDASH
- SEND
- ADaM

Agenda

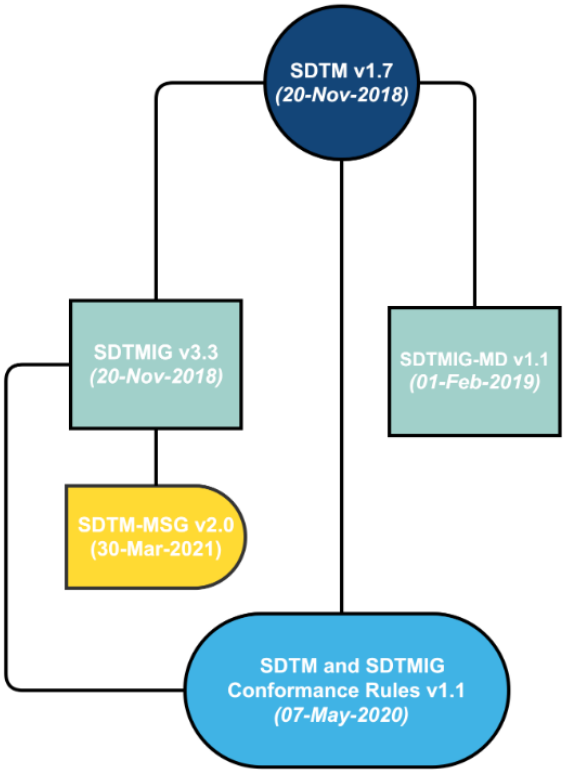
1. Alignment of CDISC Standards
2. When/Why of Upversioning
3. Changes in SDTMIG v3.3 at a Glance
4. Permissible Variables
5. Subject Visits (SV)
6. Physical Exams (PE)
7. MO vs. Morphology/Physiology Domains
8. Changes in Define-XML v2.1 at a Glance
9. VLM for Multiple Codelists/Use Cases
10. Conformance/Validation

Alignment of CDISC Standards

Alignment of CDISC Standards

SDTMIG v3.3 aligns with:

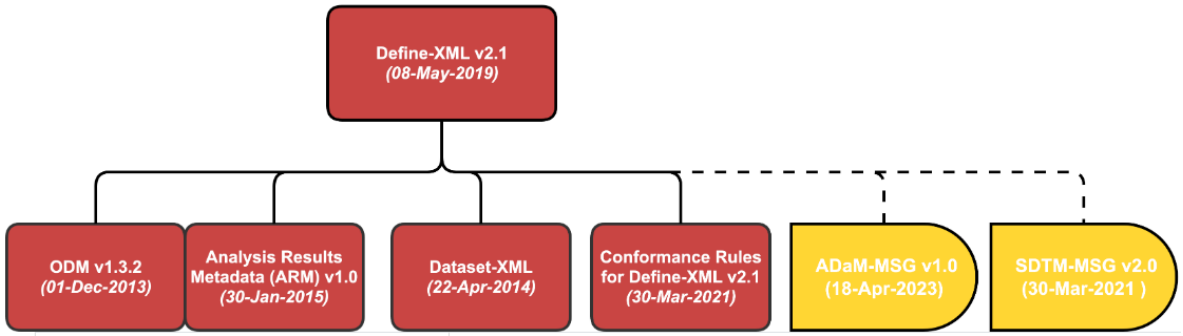
- SDTM v1.7
- SDTM IG MD v1.1
- SDTM MSG v2.0
- SDTM and SDTM IG Conformance Rules v1.1
- SDTM IG AP v1.0
- SDTM IG PGx v1.0 (Provisional)

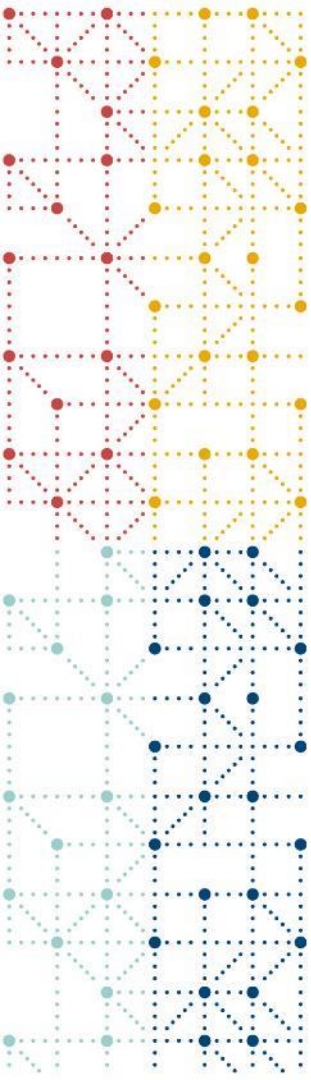


Alignment of CDISC Standards (Continued)

Define-XML 2.1 aligns with:

- ODM v1.3.2
- Analysis Results Metadata (ARM) v1.0
- Dataset-XML
- Conformance Rules for Define-XML v2.1
- ADaM MSG v1.0
- SDTM MSG v2.0





When/Why of Upversioning

Points To Consider While Up-versioning

1. Study Data Standardization Plan (SDSP)
2. Sponsor/Regulatory Agency agreement on versions of standards
3. Alignment with company's processes
4. Pooled analyses (ISS/ISE)
5. Statuses of the studies (startup/ongoing/legacy)
6. Evaluate metadata updates as needed (new/modification/deprecation)
7. Submission documents revisions (SDTM aCRF, SDRG, and define.xml)
8. Time/cost/benefit analysis
9. Traceability

Changes in SDTMIG v3.3 at a Glance

Changes in SDTMIG v3.3 at a Glance

New 'Study Reference' domain class:

- DI, OI, and PB domains described

12 newly modeled domains:

- 7 findings class (CV, FT, MK, NV, OE, RE, and UR)
- 2 interventions class (AG, ML)
- 1 relationship class (RELSUB)
- 1 special purpose class (SM)
- 1 trial design class (TM)

168 newly modeled variables:

- ARMNRS, ACTARMUD, FOCID, --LOBXFL, etc.

Changes in SDTMIG v3.3 at a Glance (Continued)

New handling of Permissible variables:

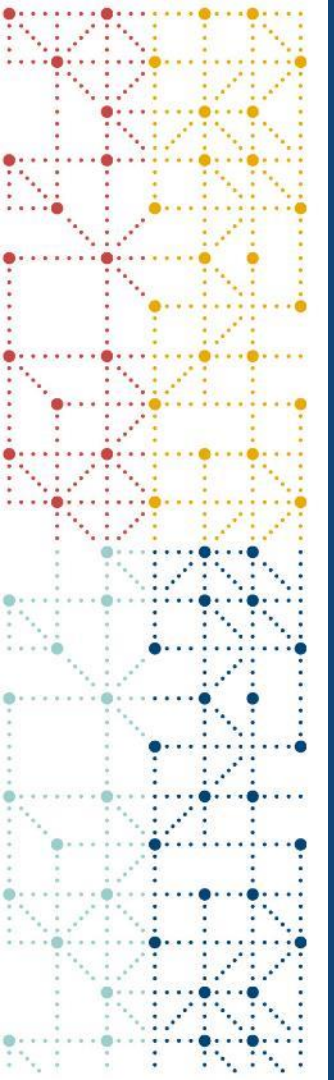
- More on that soon

Expanded use for established domains:

- RS, MB, and MS

For all items/sections added, removed, and revised see:

- Appendices in IG and model
- Diff reports for both in CDISC Library



Permissible Variables

Permissible Variables SDTMIG v3.2 vs SDTMIG v3.3

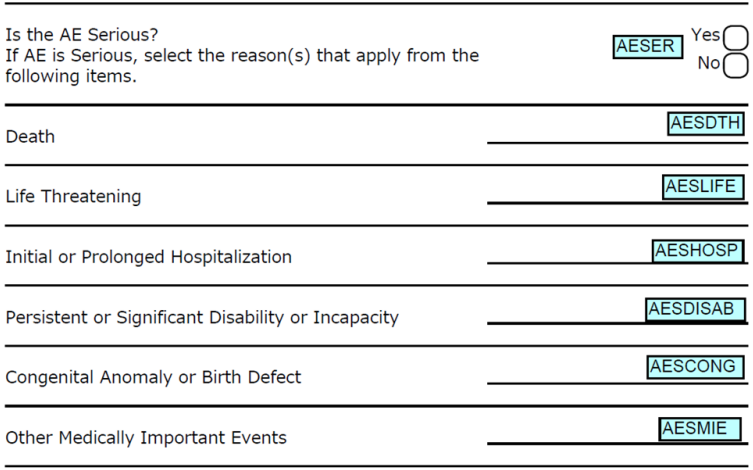
As per SDTMIG v3.2, section 2.5 The SDTM Standard Domain Models:

- As long as no data was collected for Permissible variables, a sponsor is free to drop them and the corresponding descriptions from the Define-XML.

As per SDTMIG v3.3, section 2.5 The SDTM Standard Domain Models:

- If a study includes a data item that would be represented in a Permissible variable, then that variable must be included in the SDTM dataset, even if null. Indicate no data were available for that variable in the Define-XML document.
- If a study did not include a data item that would be represented in a Permissible variable, then that variable should not be included in the SDTM dataset and should not be declared in the Define- XML document.

Permissible Variables Example AE SDTM v3.2

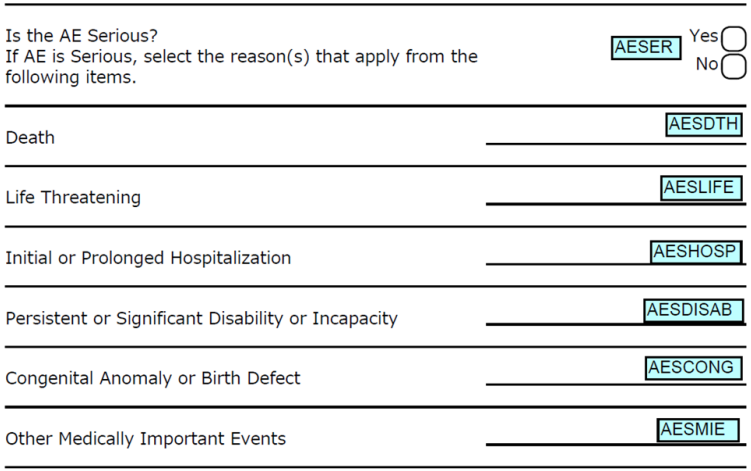


Is the AE Serious? If AE is Serious, select the reason(s) that apply from the following items.	AESER	Yes ☐ No ☐
Death	AESDTH	
Life Threatening	AESLIFE	
Initial or Prolonged Hospitalization	AESHOSP	
Persistent or Significant Disability or Incapacity	AESDISAB	
Congenital Anomaly or Birth Defect	AESCONG	
Other Medically Important Events	AESMIE	

ROW	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AESEV	AESER	AESTDTC
1	ABC123	AE	123101	1	HEADACHE	MODERATE	N	2023-01-21
2	ABC123	AE	123101	2	FEVER	MILD	N	2023-01-22
3	ABC123	AE	123101	3	BACK PAIN	MILD	N	2023-01-24

SDTMIG v3.2 ae.xpt

Permissible Variables Example AE SDTM v3.3



ROW	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AESEV	AESER	AESCONG	AESDISAB	AESDTH	AESHOSP	AESLIFE	AESMIE	AESTDTC
1	ABC123	AE	123101	1	HEADACHE	MODERATE	N							2023-01-21
2	ABC123	AE	123101	2	FEVER	MILD	N							2023-01-22
3	ABC123	AE	123101	3	BACK PAIN	MILD	N							2023-01-24

SDTMIG v3.3 ae.xpt

Permissible Variables Example AE Define-XML v2.1

AESCONG [No Data]		Congenital Anomaly or Birth Defect	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESDISAB [No Data]		Persist or Signif Disability/Incapacity	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESDTH [No Data]		Results in Death	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESHOSP [No Data]		Requires or Prolongs Hospitalization	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESLIFE [No Data]		Is Life Threatening	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESMIE [No Data]		Other Medically Important Serious Event	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]

Define-XML v2.1 ae.xpt HasNoData

Subject Visits (SV)

Subject Visits (SV)

- Guidance for Ongoing Studies Disrupted by COVID-19: Visit Events (VE) domain
- Limitations of SV domain in SDTMIG v3.3
- As per FDA TCG June 2023:
  - All clinical studies
  - Scheduled (occurring and those not) and unscheduled visits
  - Subject Visits (SV) domain.
  - --REASOC, --EPCHGI, and --CNTMOD within the SV domain
  - Not SUPPSV or in other SDTM datasets
- Advise SVREASOC, SVCNTMOD, SVEPCHGI as mentioned by FDA and SVPRESP and SVOCCUR
- Use def:IsNonStandard = "Yes"
- Explain the conformance warnings/errors in SDRG

Subject Visits (SV)

ROW	STUDYID	DOMAIN	USUBJID	VISITNUM	VISIT	SVPRESP	SVOCCUR	SVREASOC	SVCNTMOD	SVEPCHGI	SVSTDTC	SVENTDTC	SVUPDES
1	123456	SV	101	1	SCREEN	Y	Y		IN PERSON		2020-02-13	2020-02-18	
2	123456	SV	101	2	DAY 1	Y	Y		IN PERSON		2020-02-19	2020-02-19	
3	123456	SV	101	3	WEEK 1	Y	Y		IN PERSON		2020-02-25	2020-02-25	
4	123456	SV	101	4	WEEK 2	Y	N	CLINIC CLOSED DUE TO HOT WEATHER					
5	123456	SV	101	4.1	WEEK 2: UNSCHEDULED 1				REMOTE AUDIO VIDEO	Y	2020-03-07	2020-03-07	EVALUATION OF AE
6	123456	SV	101	5	FOLLOW-UP	Y	Y		TELEPHONE CALL	Y	2020-03-16	2020-03-16	

SDTMIG v3.3 sv.xpt

Physical Exams (PE)

Physical Exam (PE) prompts in SDTM

- Sponsors observed mapping trigger questions on PE forms to PEORRES as "Performed“.
- PE domain is not intended to be used this way.
- Per CDASH Best practices, when you don’t have actual results, but rather just a prompt for whether the Physical Exam was done, it should map to PR as the occurrence of a procedure.
- Refer to the CDISC Knowledge Base Article (KBA): “How should I represent whether a physical exam was performed in SDTM?”.
- See example annotations on the next 2 slides.

How Not to Map PE In SDTMIG v3.3

Form: Physical Examination (Y/N)

Generated On: 30 Aug 2023 14:21:45

Was the physical examination performed? PETESTCD = PEALL	PEORRES = PERFORMED	Yes ☐
	PESTAT = NOT DONE	No ☐
If No, Reason Not Done	PEREASND	Not collected ☐
		Not required at this visit ☐
		Measurement skipped at this visit ☐
		Subject refused ☐
		Equipment malfunction ☐
		Staff unavailable ☐
		No further information ☐
Date of examination (DD MMM YYYY)	_____	PEDTC

How to Map Prompt Questions to PR In SDTMIG v3.3

Form: Physical Examination (Y/N)

Generated On: 30 Aug 2023 14:21:45

Was the physical examination performed? PRTRT = PHYSICAL EXAMINATION PRPRESP = Y PROCCUR

- Yes ☐
- No ☐

If No, Reason Not Done PRREASOC in SUPPPR

- Not collected ☐
- Not required at this visit ☐
- Measurement skipped at this visit ☐
- Subject refused ☐
- Equipment malfunction ☐
- Staff unavailable ☐
- No further information ☐

Date of examination (DD MMM YYYY) _____ PRSTDTC

MO vs. Morphology/Physiology Domains

Morphology (MO) vs. Morphology/Physiology Domains

As per SDTMIG v3.2, section 6.3 Findings Morphology (MO):

- Represent morphological and physiological findings in separate domains.
- Separating morphological from physiological findings was difficult, and provided less value.

As per SDTMIG v3.3, section 6.3.9 Morphology:

- Morphology results in appropriate body system based on physiology/morphology domain (CV, NV, MK, OE, RE, RP, and UR).
- All body system domains share the same structure.
- MOTEST and MOTESTCD are removed from CT, based on the decision to decommission MO in future versions.
- TEST and TESTCD are included in CT for each body system-based domain.
- Although, v3.3 has MO domain, it has been deprecated in v3.4, hence it is recommended to not use MO where possible when submitting in v3.3.

Morphology (MO) Example in SDTMIG v3.2

ROW	STUDYID	DOMAIN	USUBJID	MOSEQ	MOTESTCD	MOTEST	MORRES	MORRESU	MOSTRESC	MOSTRESN	MOSTRESU	MOLOC
1	STUDY01	MO	232-P01	1	VOLUME	Volume	50	mL	50	50	mL	KIDNEY
2	STUDY01	MO	232-P01	2	VOLUME	Volume	100	mL	100	100	mL	LIVER
3	STUDY01	MO	232-P01	3	MASS	Mass	225	g	225	225	g	HEART, LEFT VENTRICLE

SDTMIG v3.2 mo.xpt

UR and CV Domain Examples in SDTMIG v3.3

ROW	STUDYID	DOMAIN	USUBJID	URSEQ	URTESTCD	URTEST	URORRES	URRRESU	URSTRESC	URSTRESN	URSTRESU	URLOC
1	STUDY01	UR	232-P01	1	VOLUME	Volume	50	mL	50	50	mL	KIDNEY
2	STUDY01	UR	232-P01	2	VOLUME	Volume	100	mL	100	100	mL	LIVER

SDTMIG v3.3 ur.xpt

ROW	STUDYID	DOMAIN	USUBJID	CVSEQ	CVTESTCD	CVTEST	CVORRES	CVRRESU	CVSTRESC	CVSTRESN	CVSTRESU	CVLOC
1	STUDY01	CV	232-P01	1	MASS	Mass	225	g	225	225	g	HEART, LEFT VENTRICLE

SDTMIG v3.3 cv.xpt

Changes in Define-XML v2.1 at a Glance

Changes in Define-XML v2.1 at a Glance

def:Origin Type and Source

- Type indicates how the data for the variable originated
- Source identifies the party responsible for the data's origin

Variable or Value Level Metadata

Cardinality is One or More

Define-XML Codelists

- ORIGINT - Origin Type
- ORIGINS - Origin Source

Variable	Where Condition	Label / Description	Type	Length or Display Format	Controlled Terms or ISO Format	Origin / Source / Method / Comment
LBORRES VLM		Result or Finding in Original Units	text	8		Origin specified at Value Level Metadata
	LBTESTCD = "HCT" (Hematocrit) and LBSPEC = "BLOOD" and LBNAM ≠ "LOCAL LAB"	Hematocrit	float	4		Collected (Source: Vendor) From Central lab (LB.LBNAM NE "LOCAL LAB")
	LBTESTCD = "HCT" (Hematocrit) and LBSPEC = "BLOOD" and LBNAM = "LOCAL LAB"	Hematocrit	float	4		Collected (Source: Investigator) From Local lab (LB.LBNAM="LOCAL LAB"). Note that the CRF page reference is given only for illustration purposes. The sample acrf.pdf does not include the local lab CRF page. Annotated CRF [1]

Changes in Define-XML v2.1 at a Glance (Continued)

def:HasNoData

- Dataset and variable level use
- Comment required when used

AESCONG [No Data]		Congenital Anomaly or Birth Defect	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESDISAB [No Data]		Persist or Signif Disability/Incapacity	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESDTH [No Data]		Results in Death	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESHOSP [No Data]		Requires or Prolongs Hospitalization	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESLIFE [No Data]		Is Life Threatening	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]
AESMIE [No Data]		Other Medically Important Serious Event	text	Record Qualifier	1	No Yes Response, subset for variables with only "Y" or null values • "Y" = "Yes"	Collected (Source: Investigator) Annotated CRF [22]

Changes in Define-XML v2.1 at a Glance (Continued)

def:IsNonStandard

- Used for datasets, variables, and codelists

Non-Standard Dataset

- Sponsor-defined
- Not in version of standard used for submission

Non-Standard Variable

- Not in version of standard used for submission
- Not for supplemental qualifier variables (QNAM, QVAL, etc.)

Non-Standard Codelist

- Sponsor-defined

Subcategory for Disposition Event [Non Standard]

Permitted Value (Code)	Display Value (Decode)
STUDY TREATMENT	Study Treatment
STUDY PARTICIPATION	Study Participation

VLM for Multiple Codelists/Use Cases

VLM for Multiple Codelists/Use Cases

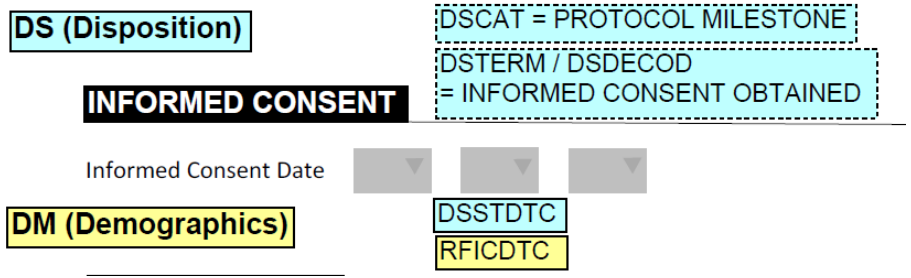
Multiple Codelists - Single Variable

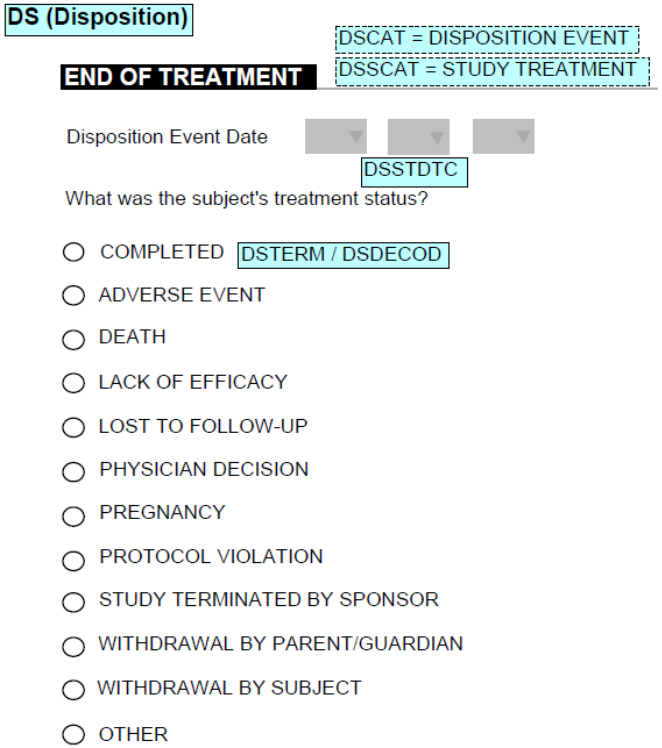
- DSDECOD using NCOMPLT and PROTMLST codelists

DSDECOD	Standardized Disposition Term	Char	(NCOMPLT)(PROTMLST)	Synonym Qualifier	Controlled terminology for the name of disposition event or protocol milestone. Examples of protocol milestones: "INFORMED CONSENT OBTAINED", "RANDOMIZED". There are separate codelists used for DSDECOD where the choice depends on the value of DSCAT. Codelist "NCOMPLT" is used for disposition events and codelist "PROTMLST" is used for protocol milestones. The variable may be	Req

VLM for Multiple Codelists/Use Cases (Continued)

Multiple Forms – Same Variable





VLM for Multiple Codelists/Use Cases (Continued)

Problem: Define-XML CodeListRef Element

- Cardinality = One
- Can't specify multiple codelists at variable level

Solution: VLM

- Multiple codelists specified at value level

DSDECOD VLM		Standardized Disposition Term	text	Synonym Qualifier	29		
	DSSCAT ≠ ""	Standardized Disposition Term	text		29	Completion/Reason for Non-Completion [13 Terms]	Collected (Source: Investigator) Annotated CRF [27 28]
	DSSCAT = ""	Standardized Disposition Term	text		29	Protocol Milestone • "INFORMED CONSENT OBTAINED" = "Informed Consent"	Assigned (Source: Sponsor) Annotated CRF [5]

VLM for Multiple Codelists/Use Cases (Continued)

Multiple Use Cases – Single Domain

- RS for Disease Response and Clinical Classifications (RSCAT, RSTESTCD, RSTEST, RSSTRESC all have multiple codelists)

Conformance/Validation

Conformance/Validation

For SDTMIG v3.3:

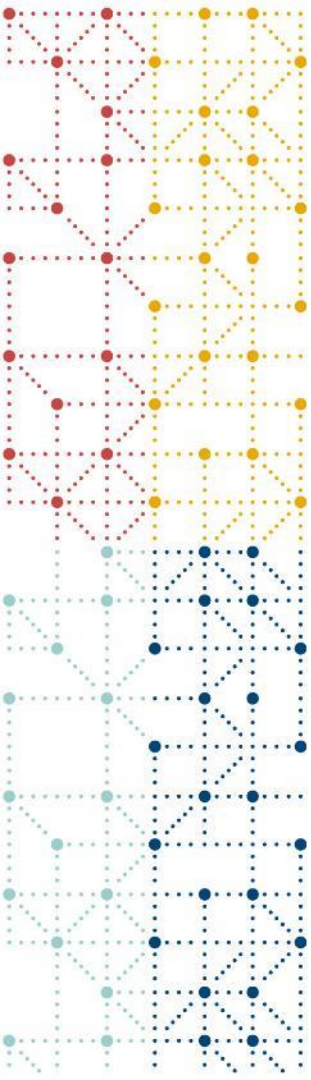
- SDTM and SDTMIG Conformance Rules v2.0

For Define-XML v2.1:

- Conformance Rules for Define-XML v2.1

Rules Engine/Business Rules

- As applicable per Regulatory Agency



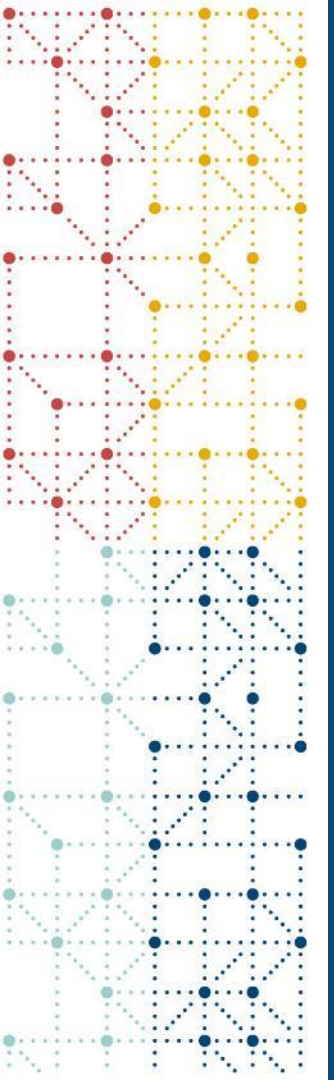
Conclusion

Conclusion

- Practical experiences and insights with SDTMIG v3.3 and Define-XML 2.1
- Best practices and resources for other successful upversioning
- Many of the larger and more subtle changes but not all
- Use the references and guidances
- Contact authors with any related questions

References

SDTMIG v3.3
SDTM v1.7
SDTMIG for Medical Devices v1.1
SDTMIG-AP v1.0
SDTM Metadata Submission Guidelines v2.0
Conformance Rules v1.1 for SDTMIG v3.2 and v3.3
SDTM and SDTMIG Conformance Rules v2.0
Knowledge Base Article - Subject Visits and COVID-19
Guidance for Ongoing Studies Disrupted by COVID-19
Knowledge Base Article - How Should I Represent Whether Physical Exam Was Performed In SDTM
Define-XML v2.1
Conformance Rules for Define-XML v2.1
CDISC Controlled Terminology
CDISC Library



Questions?

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Thank You!