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2023 KOREA INTERCHANGE

SEOUL | 11-14 DECEMBER

Strategizing Successful Implementation of SDTM and ADaM

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Meet the Speakers

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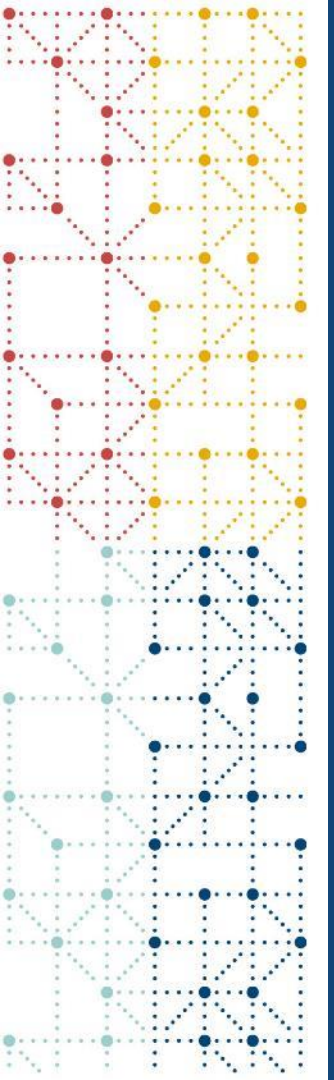
Agenda

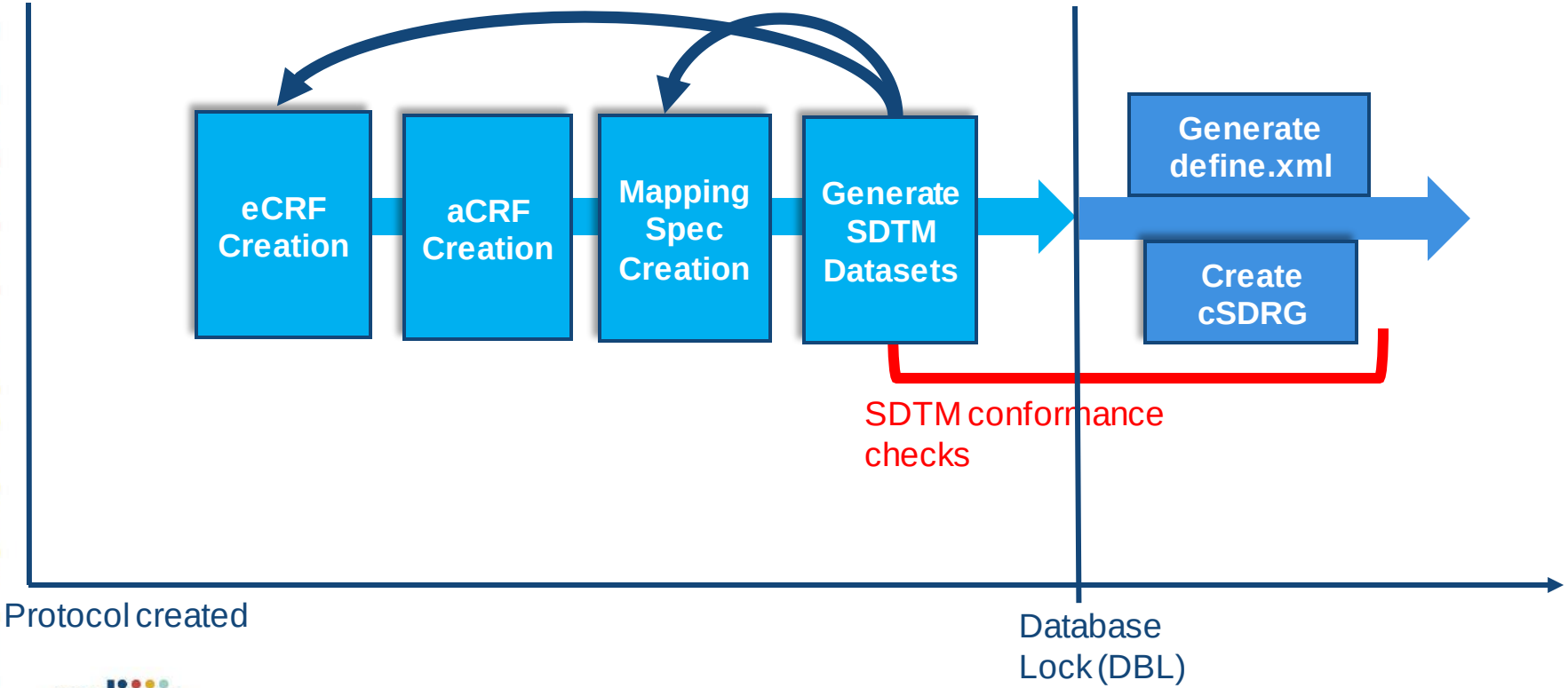
1. SDTM creation
   - Raw to SDTM (Process flow)
   - Resources for aCRF/Mapping Specifications
   - SDTM Conformance Checks
   - Manual Check Examples
2. ADaM creation
   - SDTM to ADaM (Process flow)
   - ADaM Conformance Checks
   - Manual Check Examples



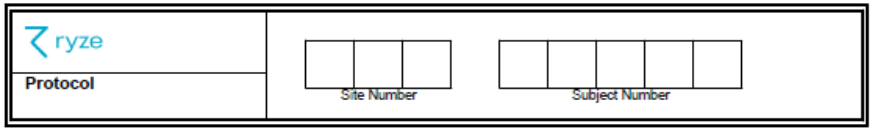
SDTM Creation

From Raw to Standardized

General Process Flow



eCRF Creation



Form RP - Reproductive System Findings

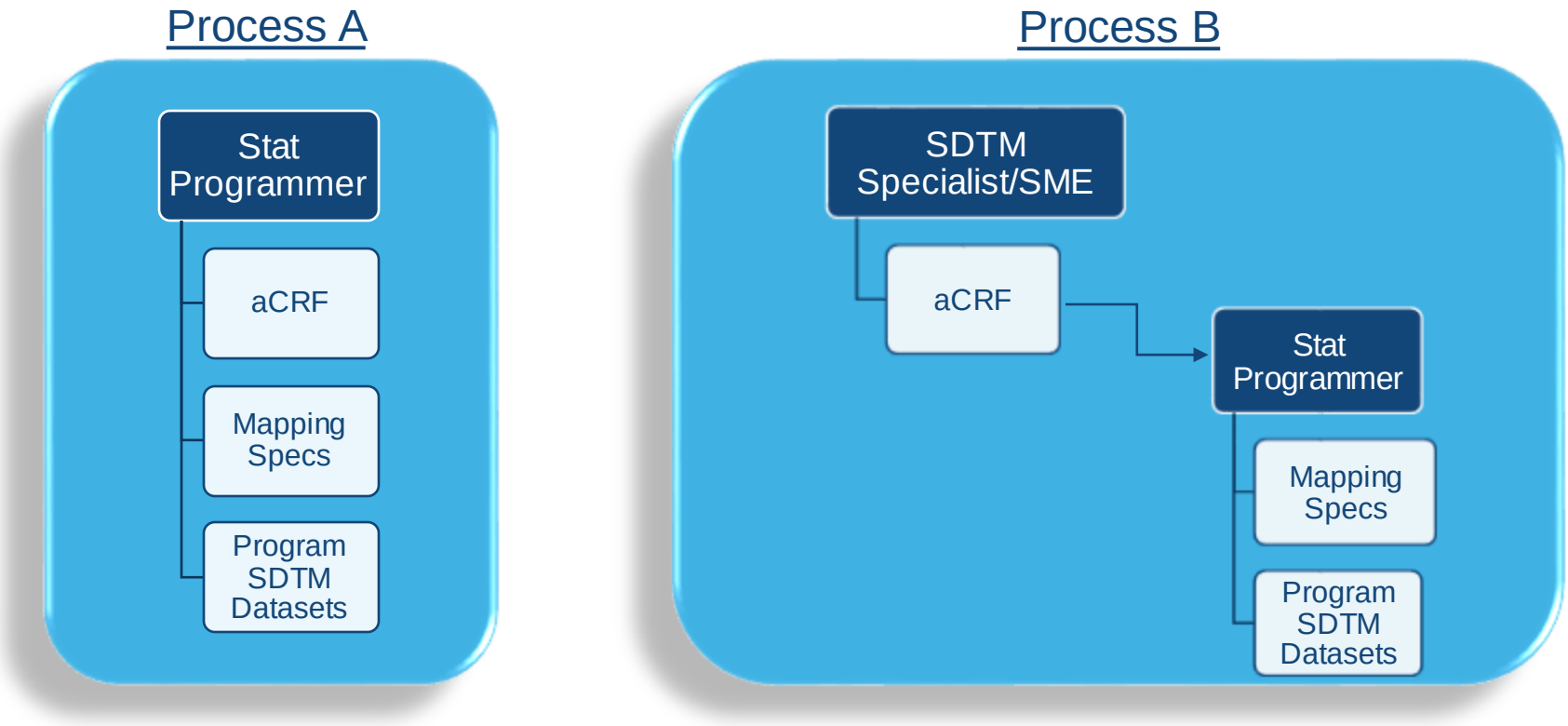
1 RP - Reproductive System Findings

1.1	Was a reproductive system evaluation performed?	[N] No [Y] Yes	RPPERF
1.2	Reason Not Done		RPREASND
1.3	Was the subject of child bearing potential?	[N] No [Y] Yes	CHILDPOT_RPORRES
1.4	Menopause Status	[PRE] Premenopausal [POST] Postmenopausal	MENOSTAT_RPORRES

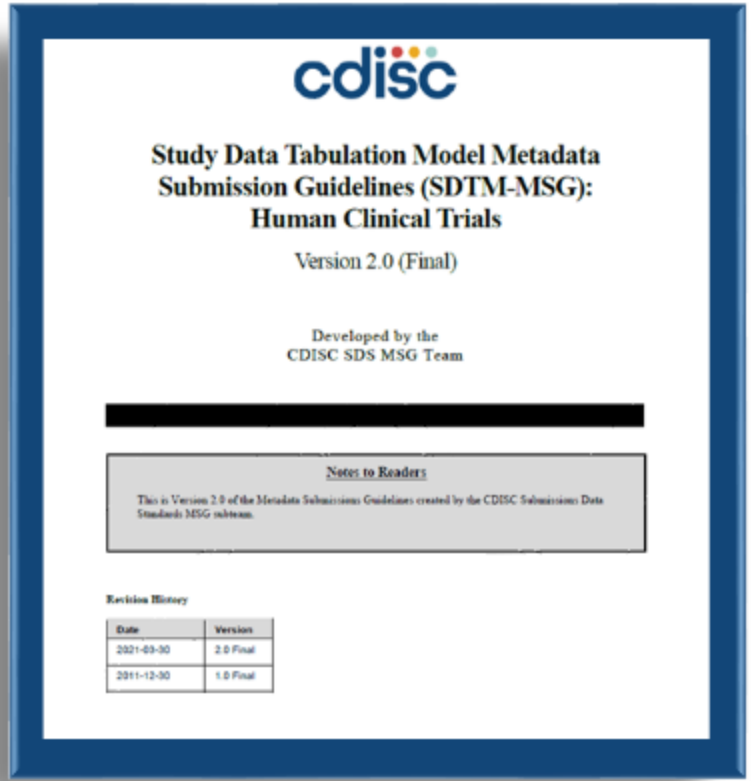
Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format[1]	Role	CDISC Notes	Core
					in numeric format in RPSTRESN. For example, if various tests have results "NONE", "NEG", and "NEGATIVE" in RPORRES, and these results effectively have the same meaning, they could be represented in standard format in RPSTRESC as "NEGATIVE".	
RPSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from RPSTRESC. RPSTRESN should store all numeric test results or findings.	Perm
RPSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized units used for RPSTRESC and RPSTRESN. Example: "mol/L".	Perm
RPSTAT	Completion Status	Char	(ND)	Record Qualifier	Used to indicate that a question was not asked or a test was not done, or a test was attempted but did not generate a result. Should be null or have a value of "NOT DONE".	Perm
RPREASND	Reason Not Done	Char		Record Qualifier	Reason not done. Used in conjunction with RPSTAT when value is "NOT DONE".	Perm
RPLOBXFL	Last Observation Before Exposure Flag	Char	(NY)	Record Qualifier	Operationally-derived indicator used to identify the last non-missing value prior to RFXSTDTC. The value should be "Y" or null.	Perm
RPBLFL	Baseline Flag	Char	(NY)	Record Qualifier	Indicator used to identify a baseline value. Should be "Y" or null. Note that RPBLFL is retained for backward compatibility. The authoritative baseline for statistical analysis is in an ADaM dataset.	Perm
RPDRVFL	Derived Flag	Char	(NY)	Record Qualifier	Used to indicate a derived record. The value should be "Y" or null. Records which represent the average of other records or which do not come from the CRF are examples of records that would be derived for the submission datasets. If RPDRVFL = "Y", then RPORRES may be null, with RPSTRESC and (if numeric) RPSTRESN having the derived value.	Perm
VISITNUM	Visit Number	Num		Timing	Clinical encounter number. Numeric version of VISIT, used for sorting.	Exp
VISIT	Visit Name	Char		Timing	Protocol-defined description of a clinical encounter.	Perm
VISITDY	Planned Study Day of Visit	Num		Timing	Planned study day of VISIT. Should be an integer.	Perm
TAETORD	Planned Order of Element within Arm	Num		Timing	Number that gives the planned order of the Element within the Arm for the Element in which the assessment was made.	Perm
EPOCH	Epoch	Char	(EPOCH)	Timing	Epoch associated with the date/time at which	Perm
RPDTC	Date/Time of Collection	Char	ISO 8601	Timing	Collection date and time of an observation.	Exp
	Visit/Collection/Exam				expressed in integer days relative to the sponsor-defined RFSTDTC in Demographics.	
RPDUR	Duration	Char	ISO 8601	Timing	Collected duration of an event, intervention, or finding represented in ISO 8601 character format. Used only if collected on the CRF and not derived.	Perm
RPTPT	Planned Time Point Name	Char		Timing	Text description of time when a measurement or observation should be taken as defined in the protocol. This may be represented as an	Perm

STUDYID	DOMAIN	USUBJID	RPSEQ	RPTESTCD	RPTEST	RPORRES	RPSTRESC	VSITNUM	RPDTC
CDISC01	RP	CDISC01-01-01	1	CHILDPOT	Childbearing Potential	Y	Y	1	
CDISC01	RP	CDISC01-01-01	1	MENOSTAT	Menopause Status	PREMENOPAUSAL	PREMENOPAUSAL	1	

aCRF/Mapping Specifications Creation



aCRF Creation



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Study Data Tabulation Model Metadata Submission Guidelines (SDTM-MSG): Human Clinical Trials

Version 2.0 (Final)

Developed by the
CDISC SDS MSG Team

[redacted]

Notes to Readers

This is Version 2.0 of the Metadata Submissions Guidelines created by the CDISC Submissions Data Standards MSG subteam.

Revision History

Date	Version
2021-03-30	2.0 Final
2011-12-30	1.0 Final

https://www.cdisc.org/standards/foundational/sdtm/sdtm-metadata-submission-guidelines-v2-0

PORTABLE DOCUMENT FORMAT (PDF) SPECIFICATIONS

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s).

Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

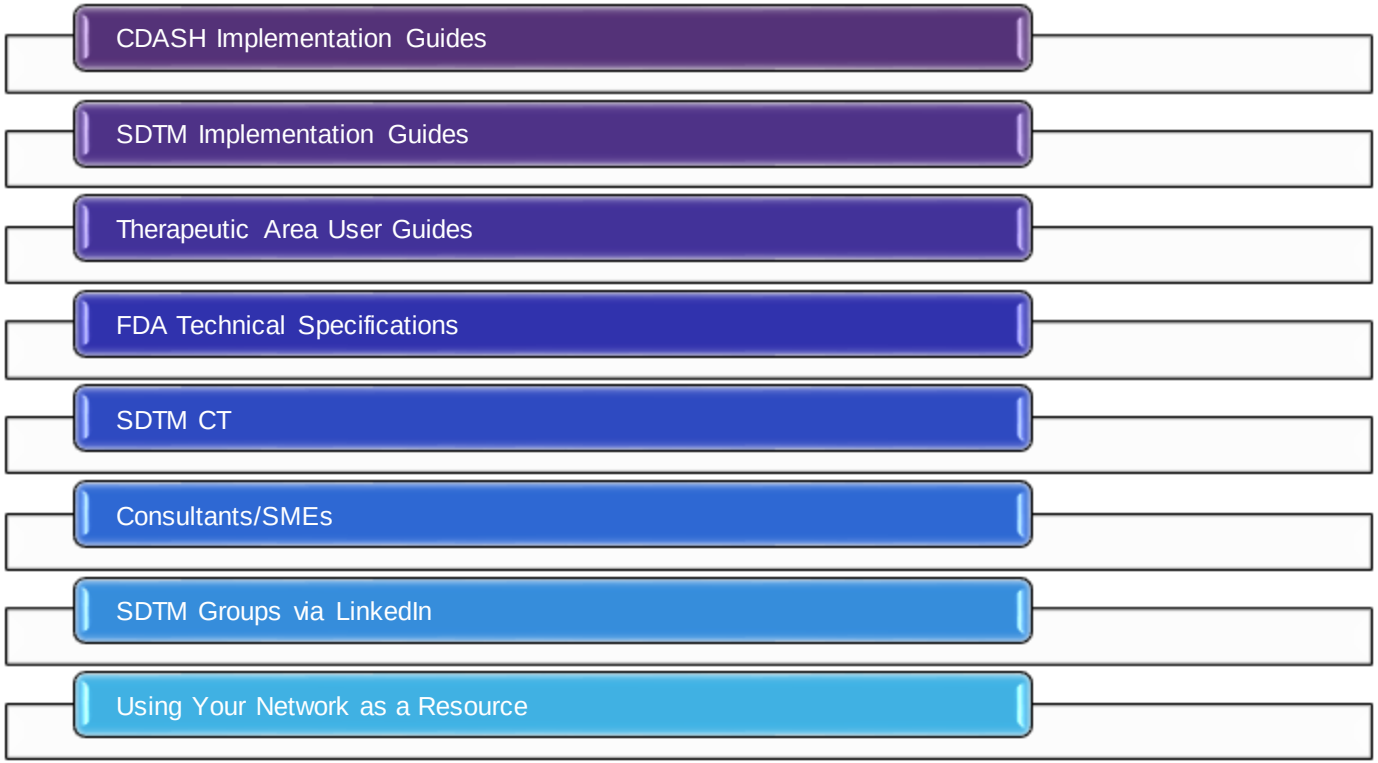
For questions regarding this technical specifications document, contact CDER at esub@fda.hhs.gov or CBER at esubprep@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2016
v4.1

https://www.fda.gov/media/76797/download

aCRF Creation



aCRF Creation - CDASH

Example 1: Meal Log

This is an example CRF used in a study where the contents of the meals were standardized in the protocol.

Title: Meal Log

	Meal Category MLCAT *Hidden/pre-populated*	**Sponsor-Defined**
	Meal Subcategory MLSCAT *Hidden/pre-populated*	**Sponsor-Defined**
Indicate if the subject consumed any meals today. If Yes, include the appropriate details where indicated on the CRF.	Were any meals consumed today? MLYN Not Submitted	○ Yes ○ No *<NY codelist>*
Indicate the type of meal.	What was the type of meal? MLTRT	○ BREAKFAST ○ LUNCH ○ DINNER ○ SNACK
Record the amount of the meal consumed.	What was the amount of the meal consumed? MLDSTXT MLDOSTXT	○ 0 ○ >0 to <25% ○ =>25% to <50% ○ =>50% to <75% ○ =>75% - <100% ○ 100%
	Unit MLDOSU *Hidden/pre-populated*	*%<UNIT codelist>*
Record the date the meal was consumed using this format (DD-MON-YYYY).	What was the date the meal was consumed? MLSTDAT MLSTDTC	
Record the time (as complete as possible) that the meal was started.	What was the meal start time? MLSTTIM MLSTDTC	
Record the date the meal ended using this format (DD-MON-YYYY).	What was the meal end date? MLENDAT MLENDTC	
Record the time (as complete as possible) that the [meal/product] was ended.	What was the meal end time? MLENTIM MLENDTC	

CRF Metadata

Order	CDASH Variable	Question Text	Prompt	CRF Completion Instructions	Type	SDTMIG Target	DTMIG arget lapping	Controlled Terminology Code List Name	Permissible Values	Pre-Populated Value	Query Display	List Style	Hidden
1	MLCAT		Meal Category		Text	MLCAT		N/A		Sponsor-Defined			Y
2	MLSCAT		Meal Subcategory		Text	MLSCAT		N/A		Sponsor-Defined			Y
3	MLYN	Were any meals consumed today?	Any Meals	Indicate if the subject consumed any meals today. If Yes, include the appropriate details where indicated on the CRF.	Text			(NY)	Yes;No;				
4	MLTRT	What was the type of meal?	[Meal]	Indicate the type of meal.	Text	MLTRT		N/A	BREAKFAST;LUNCH;DINNER;SNACK;				
5	MLDSTXT	What was the amount of the meal consumed?	Amount Consumed	Record the amount of the meal consumed.	Text	MLDOSTXT		N/A	0; >0 to <25%; =>25% to <50%; =>50% to <75%; =>75% - <100%; 100%				
6	MLDOSU	What was the unit?	Unit		Text	MLDOSU		(UNIT)		%			Y
7	MLSTDAT	What was the date the meal was consumed?	Start Date	Record the date the meal was consumed using this format (DD-MON-YYYY).	Text	MLSTDTC		N/A					
8	MLSTTIM	What was the meal start time?	Start Time	Record the time (as complete as possible) that the meal was started.	Text	MLSTDTC		N/A					
9	MLENDAT	What was the meal end date?	End Date	Record the date the meal ended using this format (DD-MON-YYYY).	Text	MLENDTC		N/A					
10	MLENTIM	What was the meal end time?	End Time	Record the time (as complete as possible) that the [meal/product] was ended.	Text	MLENDTC		N/A					

CDASHIG v2.3

aCRF Creation - SDTMIG

CE – Examples

Example 1

In this example, data were collected about prespecified events that, in the context of this study, were not reportable as AEs. The data were collected in a log independent of visits, rather than in visit-based CRF modules, so visit and date of collection (CEDTC) data were not collected.

CRF

Record start dates of any of the following signs that occurred during the study.

Clinical Sign	Did it occur?	Start Date of First Episode
Rash	No Yes	
Wheezing	No Yes	
Edema	No Yes	
Conjunctivitis	No Yes	

Rows 1-3: Show 3 symptoms which occurred and their start dates.

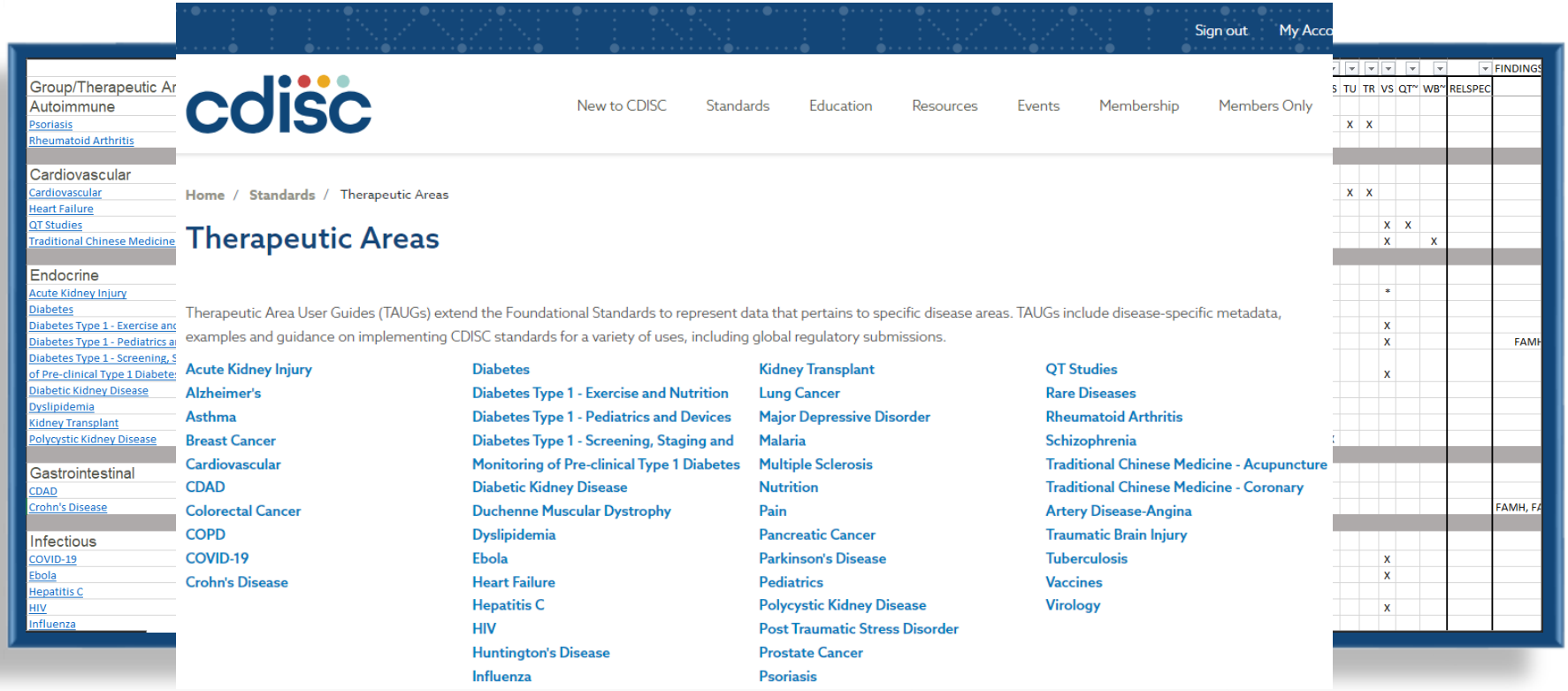
Row 4: Shows that conjunctivitis did not occur. Because there was no event, there is no start date.

ce.xpt

Row	STUDYID	DOMAIN	USUBJID	CESEQ	CETERM	CEPRESP	CEOCCUR	CESTDTC
1	ABC123	CE	123	1	Rash	Y	Y	2006-05-03
2	ABC123	CE	123	2	Wheezing	Y	Y	2006-05-03
3	ABC123	CE	123	3	Edema	Y	Y	2006-05-03
4	ABC123	CE	123	4	Conjunctivitis	Y	N	

SDTMIG v3.4

aCRF Creation – Therapeutic Area User Guides (TAUGs)



aCRF Creation – FDA Technical Specification Documents

Study Data Standards Resources
Tech Spec - HIV
Tech Spec - QT Studies
Tech Spec - Next Gen Sequencing
Tech Spec - Vaccines
Tech Spec - Noncirrhotic Nonalcoholic Steatohepatitits (NASH)

https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources

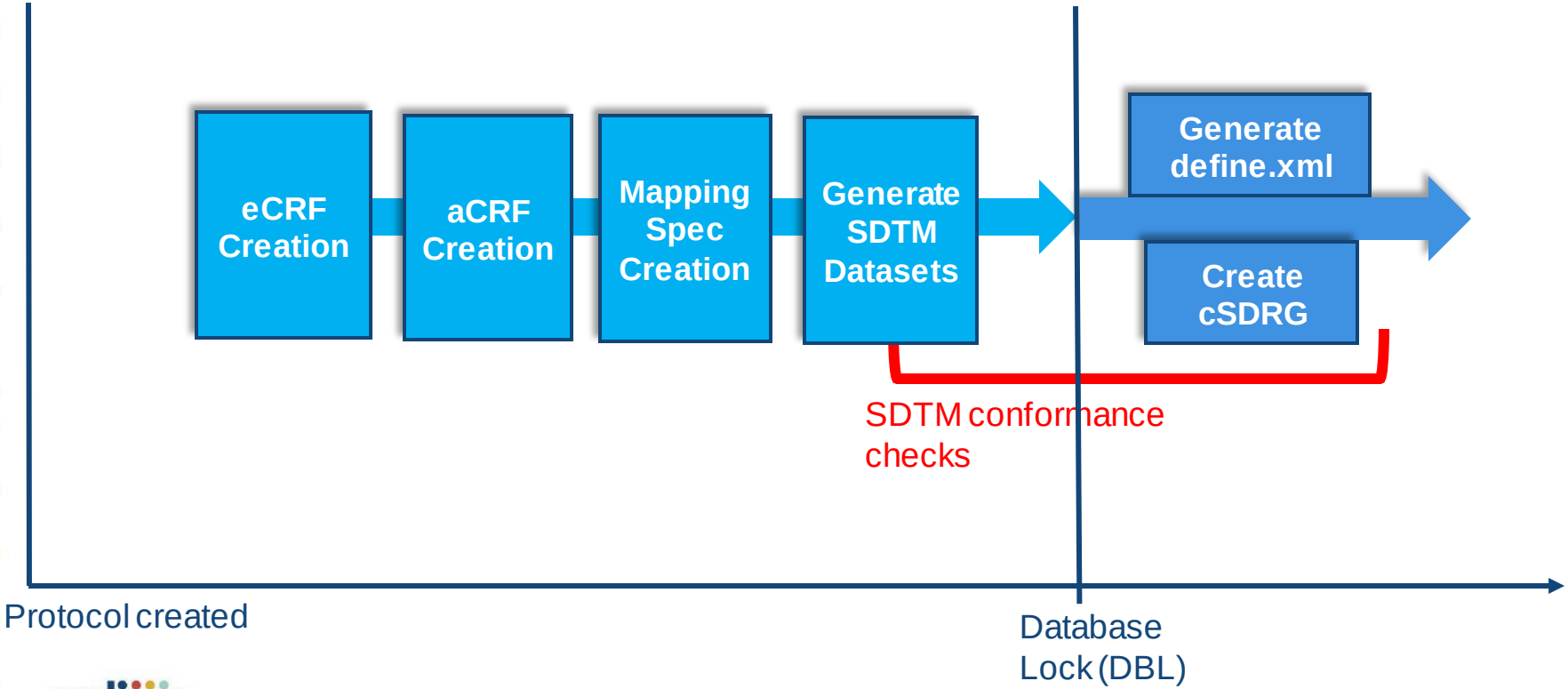
aCRF Creation – SDTM CT

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition	NCI Preferred Term
C141657		No	10-Meter Walk/Run Functional Test Test Code	TENMW1TC	10-Meter Walk/Run Functional Test Test Code	10-Meter Walk/Run test code.	CDISC Functional Test 10-Meter Walk/Run Test Code Terminology
C174106	C141657		10-Meter Walk/Run Functional Test Test Code	TENMW101	TENMW1-Was Walk/Run Performed	10-Meter Walk/Run - Was the 10-meter walk/run performed?	10-Meter Walk/Run - Was Walk/Run Performed
C141700	C141657		10-Meter Walk/Run Functional Test Test Code	TENMW102	TENMW1-Time to Walk/Run 10 Meters	10-Meter Walk/Run - If yes, time to walk or run 10 meters.	10-Meter Walk/Run - Time to Walk/Run 10 Meters
C147592	C141657		10-Meter Walk/Run Functional Test Test Code	TENMW103	TENMW1-Wear Orthoses	10-Meter Walk/Run - If yes, did subject wear orthoses?	10-Meter Walk/Run - Wear Orthoses
C141701	C141657		10-Meter Walk/Run Functional Test Test Code	TENMW104	TENMW1-Test Grade	10-Meter Walk/Run - Test grade.	10-Meter Walk/Run - Test Grade
C141656		No	10-Meter Walk/Run Functional Test Test Name	TENMW1TN	10-Meter Walk/Run Functional Test Test Name	10-Meter Walk/Run test name.	CDISC Functional Test 10-Meter Walk/Run Test Name Terminology
C141701	C141656		10-Meter Walk/Run Functional Test Test Name	TENMW1-Test Grade	TENMW1-Test Grade	10-Meter Walk/Run - Test grade.	10-Meter Walk/Run - Test Grade
C141700	C141656		10-Meter Walk/Run Functional Test Test Name	TENMW1-Time to Walk/Run 10 Meters	TENMW1-Time to Walk/Run 10 Meters	10-Meter Walk/Run - If yes, time to walk or run 10 meters.	10-Meter Walk/Run - Time to Walk/Run 10 Meters
C174106	C141656		10-Meter Walk/Run Functional Test Test Name	TENMW1-Was Walk/Run Performed	TENMW1-Was Walk/Run Performed	10-Meter Walk/Run - Was the 10-meter walk/run performed?	10-Meter Walk/Run - Was Walk/Run Performed
C147592	C141656		10-Meter Walk/Run Functional Test Test Name	TENMW1-Wear Orthoses	TENMW1-Wear Orthoses	10-Meter Walk/Run - If yes, did subject wear orthoses?	10-Meter Walk/Run - Wear Orthoses
C141663		No	4-Stair Ascend Functional Test Test Code	A4STR1TC	4-Stair Ascend Functional Test Test Code	4-Stair Ascend test code.	CDISC Functional Test 4-Stair Ascend Test Code Terminology
C174103	C141663		4-Stair Ascend Functional Test Test Code	A4STR101	A4STR1-Was 4-Stair Ascend Performed	4-Stair Ascend - Was the 4-stair ascend performed?	4-Stair Ascend - Was 4-Stair Ascend Performed
C141706	C141663		4-Stair Ascend Functional Test Test Code	A4STR102	A4STR1-Time to Do 4-Stair Ascend	4-Stair Ascend - If yes, time taken to do 4-stair ascend.	4-Stair Ascend - Time to Do 4-Stair Ascend
C147590	C141663		4-Stair Ascend Functional Test Test Code	A4STR103	A4STR1-Wear Orthoses	4-Stair Ascend - If yes, did subject wear orthoses?	4-Stair Ascend - Wear Orthoses
C141707	C141663		4-Stair Ascend Functional Test Test Code	A4STR104	A4STR1-Test Grade	4-Stair Ascend - Test grade.	4-Stair Ascend - Test Grade
C141662		No	4-Stair Ascend Functional Test Test Name	A4STR1TN	4-Stair Ascend Functional Test Test Name	4-Stair Ascend test name.	CDISC Functional Test 4-Stair Ascend Test Name Terminology
C141707	C141662		4-Stair Ascend Functional Test Test Name	A4STR1-Test Grade	A4STR1-Test Grade	4-Stair Ascend - Test grade.	4-Stair Ascend - Test Grade
C141706	C141662		4-Stair Ascend Functional Test Test Name	A4STR1-Time to Do 4-Stair Ascend	A4STR1-Time to Do 4-Stair Ascend	4-Stair Ascend - If yes, time taken to do 4-stair ascend.	4-Stair Ascend - Time to Do 4-Stair Ascend

SDTM CT 2023-09-29

aCRF Creation – Consultants/SMEs, and more…

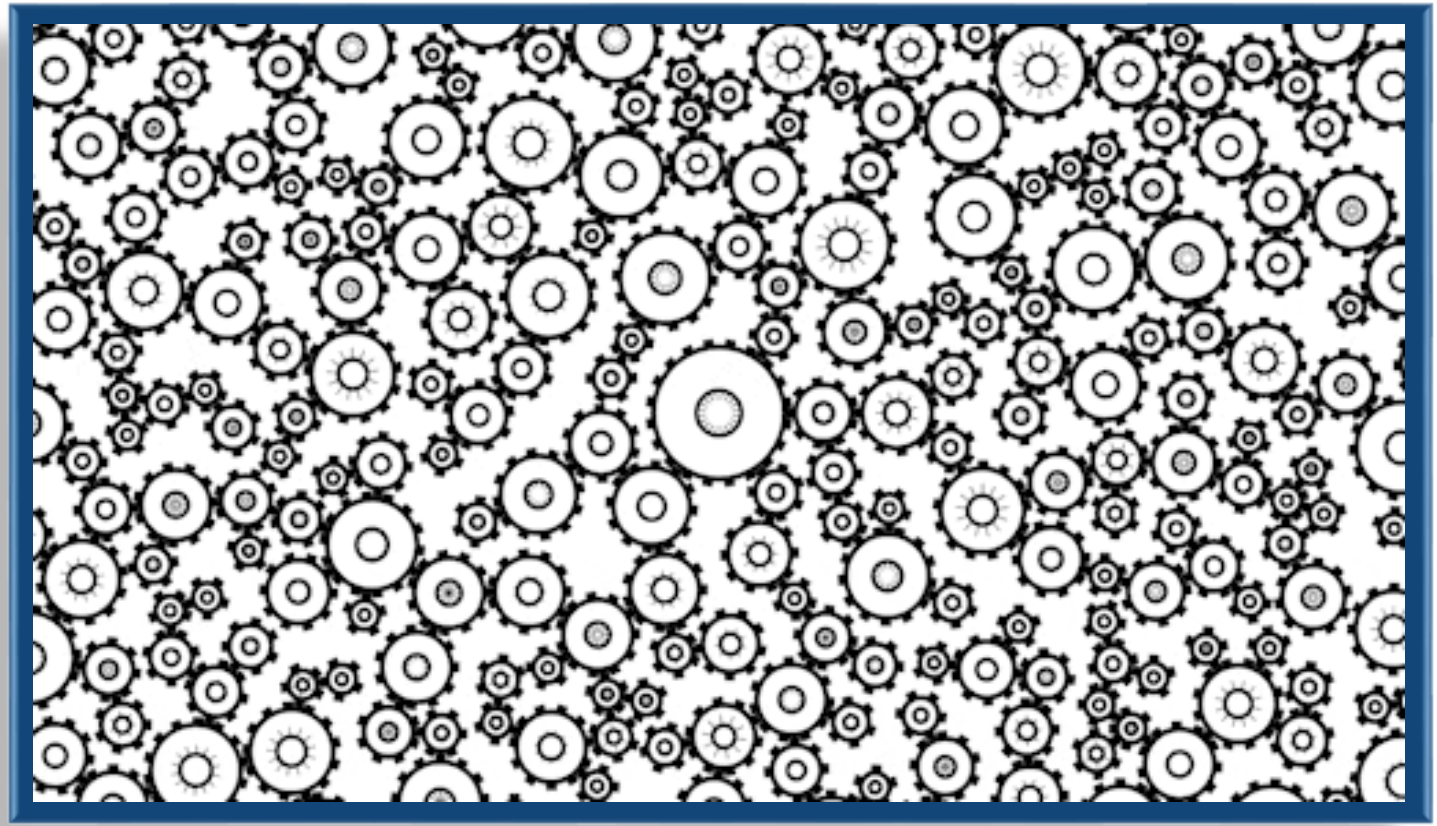
General Process Flow



Conformance Rules

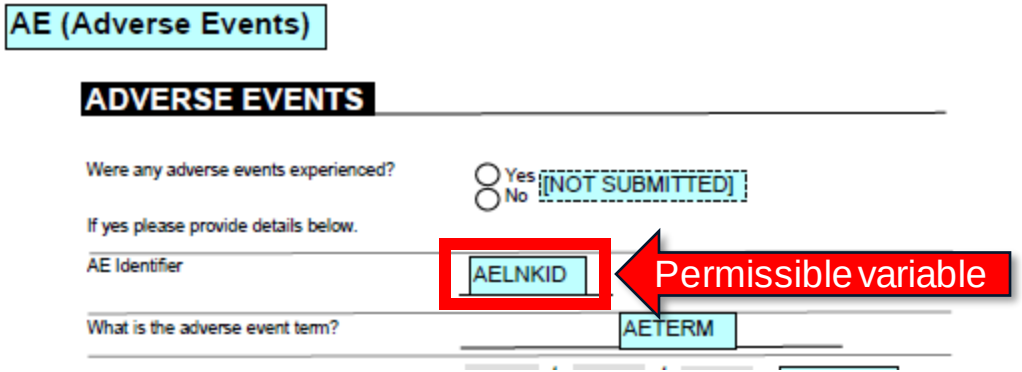
CDISC	FDA	PMDA
• SDTMIG v3.2 • SDTMIG v3.3 • SDTMIG v3.4	• SDTMIG v3.1.2 • SDTMIG v3.1.3 • SDTMIG v3.2 • SDTIMG v3.3	• SDTMIG v3.1.2 • SDTMIG v3.1.3 • SDTMIG v3.2 • SDTIMG v3.3

Validation – Tools



Validation – Explain Issue

aCRF



Validation Report Issue

Dataset	Rule ID	Message
AE	SD1076	Model permissible variable added into standard domain

cSDRG

Check ID	Diagnostic Message	Dataset	Count (Issue Rate)	Explanation
SD1076	Model permissible variable added into standard domain	AE	1 (3.13%)	AELNKID was added to link records in AE causing death with their associated Primary Cause of Death records in DD.

Validation – Fix Issue

Validation Report Issue

Dataset	Rule ID	Message
AE	SD0008C	Value for AEDECOD is in incorrect case

AE Dataset

STUDYID	DOMAIN	USUBJID	AESEQ	AELNKID	AETERM	AELLT	AELLTCD	AEDECOD
CDISC01	AE	CDISC01-01-01	1		FEVER	FEVER	10037660	PYREXIA

Version 1.5 finalized June 2019

FDA Business Rule ID	FDA Business Rule
FDAB017	Controlled terms should use the exact term (case, spelling, and punctuation) used by the terminology maintenance organizations (e.g., MedDRA, CDISC controlled terminology).

Validation – define.xml

Methods

Method	Type	Description
Algorithm to derive AEENTPT	Computation	If AEENRTPT is populated, AEENTPT is DM.RFPENDTC for the subject.
Algorithm to derive CMENTPT	Computation	If CMENRTPT is populated, CMENTPT is DM.RFPENDTC for the subject.
Algorithm to derive DAYCALC	Computation	Study day relative to RFSTDTC. Date - RFSTDTC + 1 if on or after RFSTDTC. Date - RFSTDTC if date precedes RFSTDTC.
Algorithm to derive DISEQ	Computation	Starts at "1" for first device identifier and increments by one for each DIPARM
Algorithm to derive DTHFL	Computation	If DTHDTC is populated then DTHFL='Y'
Algorithm to derive EPOCH	Computation	EPOCH from SE where date >= SESTDTC and date < SEENDTC
Algorithm to derive EXDOSE	Computation	EXDOSE = ECDOSE * ECPSTRG expressed in mg.
Algorithm to derive FTSTRESN	Computation	If FTSTRESC is numeric then FTSTRESN=FTSTRESC in numeric format, else null.
Algorithm to derive IEORRES	Computation	If IECAT=INCLUSION then IEORRES=N, else if IECAT=EXCLUSION then IEORRES=Y
Algorithm to derive LBSTRESC	Computation	LBSTRESC is equal to LBORRES or the value in standard units if a conversion is necessary.
Algorithm to derive LOBXFL	Computation	Set to "Y" for last record with non-null original result on or before the first dose date (RFXSTDTC). Null otherwise.
Algorithm to derive QSSTRESC_PH	Computation	If QSORRES="Not at all" then 0 If QSORRES="Several days" then 1 If QSORRES="More than half the days" then 2 If QSORRES="Nearly every day" then 3
Algorithm to derive QSSTRESC_PH_10_11	Computation	QSSTRESC=QSORRES
Algorithm to derive QSSTRESC_SL	Computation	If QSORRES="Strongly disagree" then 1 If QSORRES="Disagree" then 2 If QSORRES="Slightly disagree" then 3 If QSORRES="Neither agree nor disagree" then 4 If QSORRES="Slightly agree" then 5 If QSORRES="Agree" then 6 If QSORRES="Strongly agree" then 7
Algorithm to derive QSSTRESN	Computation	If QSSTRESC is numeric then QSSTRESN=QSSTRESC in numeric format, else null.

Validation – define.xml & aCRF

SC (Subject Characteristics) - FINDINGS

Location: sc.xpt

Variable	Label / Description	Type	Role	Length or Display Format	Controlled Terms or ISO Format	Origin / Source / Method / Comment
STUDYID	Study Identifier	text	Identifier	12		Protocol
DOMAIN	Domain Abbreviation	text	Identifier	2		Assigned
USUBJID	Unique Subject Identifier	text	Identifier	11		Derived
SCSEQ	Sequence Number	integer	Identifier	1		Derived
SCTESTCD	Subject Characteristic Short Name	text	Topic	8	Subject Characteristic Test Code • "EDULEVEL" = "Level of Education Attained"	Assigned
SCTEST	Subject Characteristic	text	Synonym Qualifier	27	Subject Characteristics Test Name • "Level of Education Attained"	Assigned
SCCAT	Category for Subject Characteristic	text	Grouping Qualifier	9	Category for Subject Characteristic • "EDUCATION"	Assigned
SCORRES	Result or Finding in Original Units	text	Result Qualifier	2		
SCORRESU	Original Units	text	Variable Qualifier	5	Original Units for SC • "YEARS"	CRF Annotated Case Report Form [3]
SCSTRESC	Character Result/Finding in Std Format	text	Result Qualifier	2		
SCSTRESN	Numeric Result/Finding in Standard Units	integer	Result Qualifier	2		Derived
SCSTRESU	Standard Units	text	Variable Qualifier	5	Standard Units for SC • "YEARS"	
SCDTC	Date/Time of Collection	date	Timing		ISO 8601	CRF Annotated Case Report Form [6]
SCDY	Study Day of Examination	integer	Timing	3		Derived

Go to the top of the Define-XML document

Validation – define.xml, cSDRG & SDTM Datasets

define.xml

External Dictionaries

Reference Name	External Dictionary	Dictionary Version
LOINC dict	LOINC	2.74
Medical Dictionary for Regulatory Activities	MedDRA	25.1
Medication Reference Terminology	MED-RT	2023-04-06
Systematized Nomenclature of Medicine	SNOMED	2023-03-01
Unique Ingredient Identifier		
Medications Dictionary		

Go to the top of the Define-XML document

cSDRG

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	•SDTM v1.7 •SDTMIG v3.3
Controlled Terminology	CDISC SDTM Controlled Terminology, 2023-06-30
Data Definitions	Define-XML v2.0
Medications Dictionary	WHODD GLOBALB3Sep22
Medical Events Dictionary	MedDRA v25.1
Other standards (optional)	LOINC 2.74, SNOMED 2023-03-01, UNII 2023-04-13, MED-RT 2023-07-03

SUPPAE

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG	QEVAL
CDISC01	AE	CDISC01-01-01	AESEQ	1	AEVERS	Version of MedDRA	26.1	ASSIGNED	

TS

STUDYID	DOMAIN	TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL	TSVALNF	TSVALCD	TSVCDREF	TSVCDVER
CDISC01	TS	1	1	DOSU	Dose Units	mg		C28253	CDISC	2023-06-30

Validation – define.xml & cSDRG & aCRF

Suppqual Character Values

Search

Dataset	Variable Name (QNAM)	Variable Label (QLABEL)
SUPPAE	AETRTEM	TREATMENT EMERGENT FLAG
SUPPDM	COMPLT16	
SUPPDM	COMPLT24	
SUPPDM	COMPLT8	
SUPPDM	EFFICACY	
SUPPDM	ITT	
SUPPDM	SAFETY	
SUPPLB	ENDPOINT	

SUPPQUAL from Dataset

SUPPQUAL from define.xml

SUPPAE (Supplemental Qualifiers, Adverse Events) - RELATIONSHIP

Location: suppae.xpt

Related Parent Dataset: AE (Adverse Events)

Variable	Label / Description	Type	Role	Length or Display Format	Controlled Terms or ISO Format	Origin / Source / Method / Comment
STUDYID	Study Identifier	text	Identifier	12		Protocol
RDOMAIN	Related Domain Abbreviation	text	Identifier	2		Assigned
USUBJID	Unique Subject Identifier	text	Identifier	11		Derived
IDVAR	Identifying Variable	text	Identifier	5	Identifying Variable in SUPPAE • "AESEQ"	Assigned
IDVARVAL	Identifying Variable Value	text	Identifier	2		Assigned
QNAM	Qualifier Variable Name	text	Topic	7	Qualifier Variable Name for SUPPAE • "AETRTEM" = "TREATMENT EMERGENT FLAG"	Assigned
QLABEL	Qualifier Variable Label	text	Synonym Qualifier	23	Qualifier Variable Label for SUPPAE • "TREATMENT EMERGENT FLAG"	Assigned
QVAL VLM	Data Value	text	Result Qualifier	1		
➤ QNAM = "AETRTEM"	TREATMENT EMERGENT FLAG	text		1	No Yes Response • "N" • "Y"	DERIVED
QORIG	Origin	text	Record Qualifier			
QEVAL	Evaluator	text	Record Qualifier			

SUPPQUAL from cSDRG

3.4.1 AE - Adverse Events

QNAM	Description
AETRTEM	TREATMENT EMERGENT FLAG

Validation – Tips

Keep notes for each issue regarding root cause and resolution

- Helpful when working with sponsor standards
- Enable you to remember and triage rules faster

Create explanations prior to submission

- Avoids having to create explanations from scratch
- Helps to ensure all relevant details are included for clarity

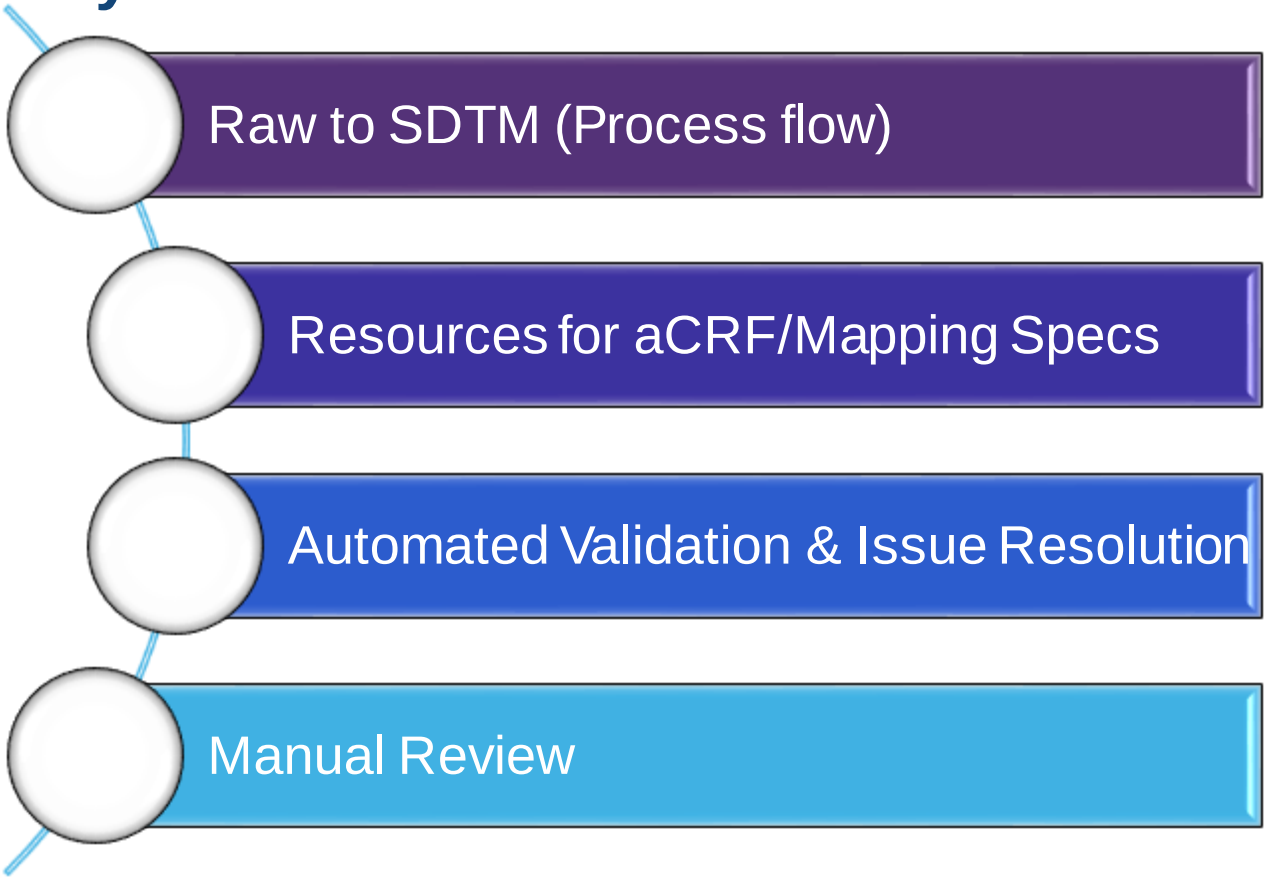
Practice prioritizing issues to fix

- Any issues regarding rejection criteria for an agency must be fixed prior to submission

Manual validation of aCRF, define.xml, and cSDRG is necessary as well as cross-checks between files and datasets

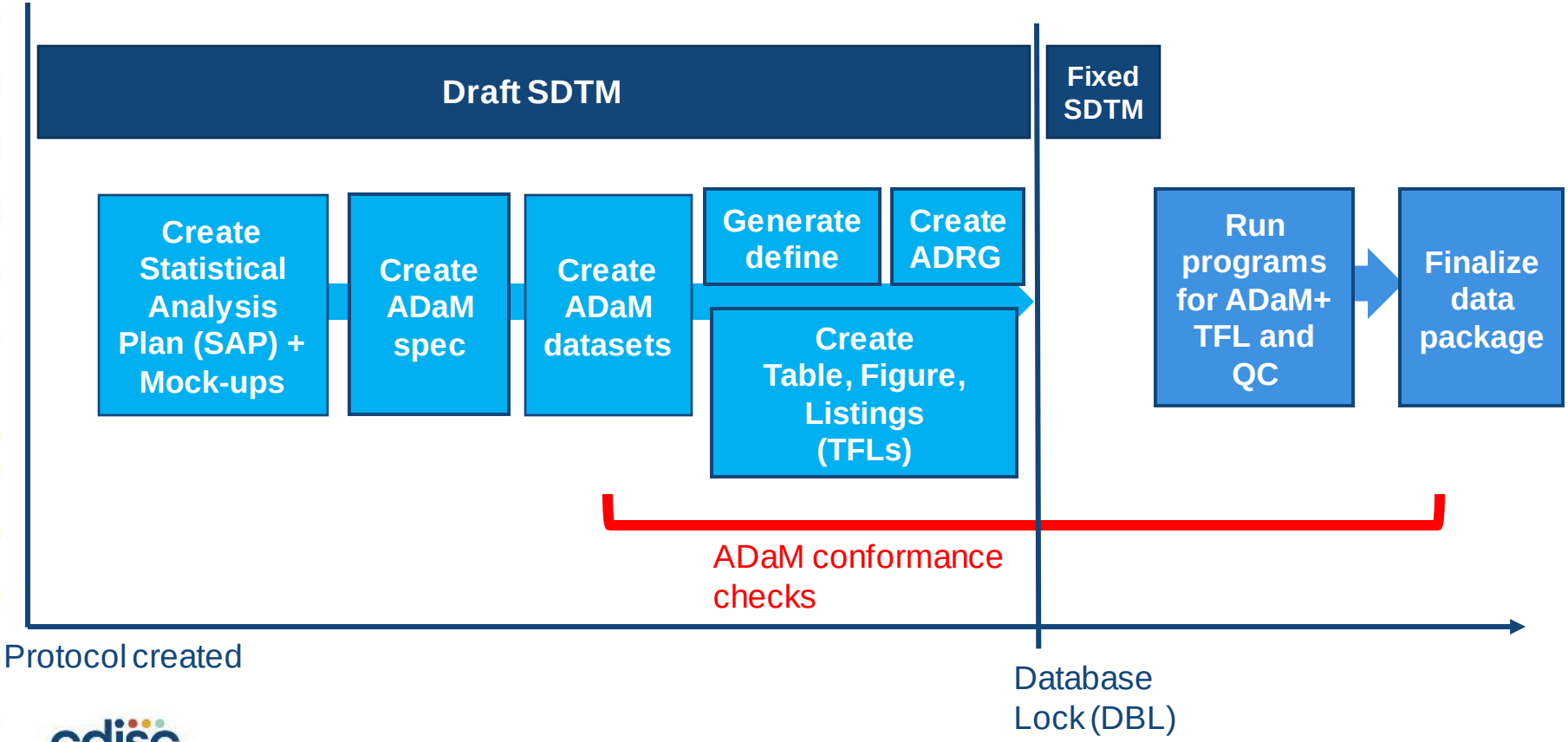
- Keep a checklist of items to check for each document

Summary


Raw to SDTM (Process flow)
Resources for aCRF/Mapping Specs
Automated Validation & Issue Resolution
Manual Review

ADaM Creation

General Stat Process Flow



Cross-check Between Mock-up and SDTM

Mock-up example

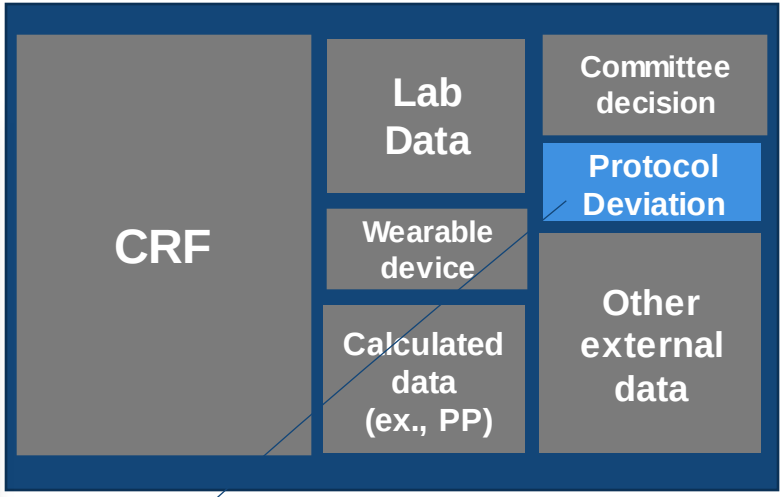
How values of treatment variables stored in SDTM?

Table x Protocol Deviation

	Active (N=x)	Placebo (N=x)	Total (N=x)
ITT Population	xx	xx	xx
Major protocol deviation	xx(xxx.x)	xx(xxx.x)	xx(xxx.x)
<DVTERM>	xx(xxx.x)	xx(xxx.x)	xx(xxx.x)
<DVTERM>	xx(xxx.x)	xx(xxx.x)	xx(xxx.x)
<DVTERM>	xx(xxx.x)	xx(xxx.x)	xx(xxx.x)
<DVTERM>	xx(xxx.x)	xx(xxx.x)	xx(xxx.x)
<DVTERM>	xx(xxx.x)	xx(xxx.x)	xx(xxx.x)

Major/minor category in the data?

SDTM



When are data going to be stored in SDTM?

Check units in SDTM

LB domain

LBTEST	LBORRES	LBORRESU	LBSTRESN	LBSTRESU	LBNAM
Calcium	4.688	mEq/L	2.3441	mmol/L	Hospital **A**
Calcium	4.986	mEq/L	2.4938	mmol/L	Hospital **A**
Calcium	9.695	mg/dL	2.4189	mmol/L	Hospital **B**
Calcium	9.595	mg/dL	2.394	mmol/L	Hospital **B**

Mock-up

Table x Summary of Laboratory Data

Calcium (mg/dL)

	Active	Placebo
Baseline		
N	x	x
Mean (SD)	x.xx (x.xxx)	x.x (x.xxx)
Median	x.xx	x.xx
Min, Max	x.xx, x.xx	x.xx, x.xx
<Visit>		
N	x	x
Mean (SD)	x.xx (x.xxx)	x.x (x.xxx)
Median	x.xx	x.xx
Min, Max	x.xx, x.xx	x.xx, x.xx

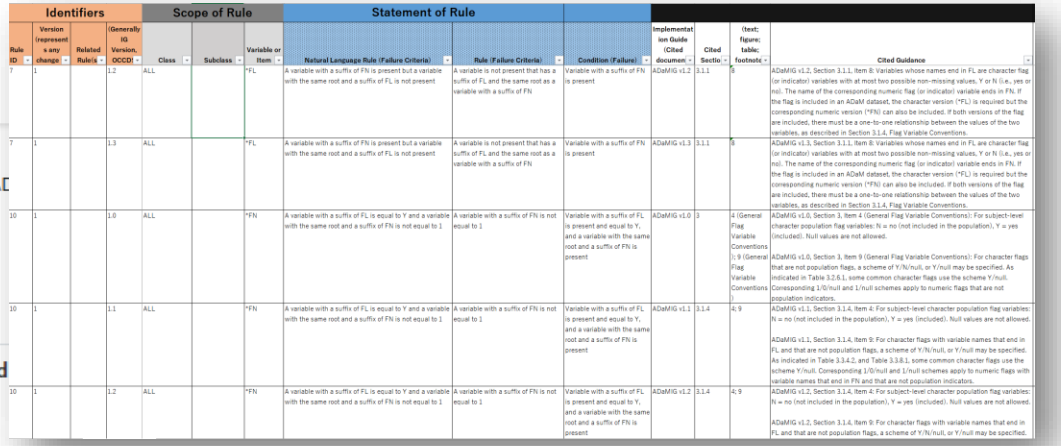
Example questions for creating ADaM for planned analyses

- Can you just keep SDTM variables and observations in ADaM?
- Do you need to derive variables and observations in ADaM?
- In what units, are data stored in SDTM? Are they matching with units to be displayed in the analysis results?
- Check SDTM Treatment variables, study periods, visits
- If some data are not ready at this moment, do you need to prepare dummy data for preparing for programs?

Refer to “SDTM Basics for ADaM Dataset Creation”
https://www.cdisc.org/sites/default/files/2022-06/Session4Seiko%20Yamazaki%26Chikaaki%20Nakao.pdf

ADaM Conformance checks

Conformance check



Identifiers				Scope of Rule			Statement of Rule						
Rule ID	Version (represents any change)	Related Rule's	(Generally IG Version, CCCD)	Class	Subclass	Variable or Item	Natural Language Rule (Failure Criteria)	Rule (Failure Criteria)	Condition (Failure)	Implementation Guide (Cited document)	Cited Section	(text; figure; table; footnote)	Cited Guidance
7	1		1.2	ALL		*FL	A variable with a suffix of FN is present but a variable with the same root and a suffix of FL is not present	A variable is not present that has a suffix of FL and the same root as a variable with a suffix of FN	Variable with a suffix of FN is present	ADaMIG v1.2	3.1.1	6	ADaMIG v1.2, Section 3.1.1, Item 8: Variables whose names end in FL are character flag (or indicator) variables with at most two possible non-missing values. Y or N (i.e., yes or no). The name of the corresponding numeric flag (or indicator) variable ends in FN. If the flag is included in an ADaM dataset, the character version (*FL) is required but the corresponding numeric version (*FN) can also be included. If both versions of the flag are included, there must be a one-to-one relationship between the values of the two variables, as described in Section 3.1.4, Flag Variable Conventions.
7	1		1.3	ALL		*FL	A variable with a suffix of FN is present but a variable with the same root and a suffix of FL is not present	A variable is not present that has a suffix of FL and the same root as a variable with a suffix of FN	Variable with a suffix of FN is present	ADaMIG v1.3	3.1.1	6	ADaMIG v1.3, Section 3.1.1, Item 8: Variables whose names end in FL are character flag (or indicator) variables with at most two possible non-missing values. Y or N (i.e., yes or no). The name of the corresponding numeric flag (or indicator) variable ends in FN. If the flag is included in an ADaM dataset, the character version (*FL) is required but the corresponding numeric version (*FN) can also be included. If both versions of the flag are included, there must be a one-to-one relationship between the values of the two variables, as described in Section 3.1.4, Flag Variable Conventions.
10	1		1.0	ALL		*FN	A variable with a suffix of FL is equal to Y and a variable with the same root and a suffix of FN is not equal to 1	A variable with a suffix of FN is not equal to 1	Variable with a suffix of FL is present and equal to Y, and a variable with the same root and a suffix of FN is present	ADaMIG v1.0	3	4 (General Flag Variable Conventions)	ADaMIG v1.0, Section 3, Item 4 (General Flag Variable Conventions): For subject-level character population flag variables: N = no (not included in the population), Y = yes (included). Null values are not allowed.) 9 (General Flag Variable Conventions	ADaMIG v1.0, Section 3, Item 9 (General Flag Variable Conventions): For character flags that are not population flags, a scheme of Y/N/null, or Y/null may be specified. As indicated in Table 3.2.6.1, some common character flags use the scheme Y/null. Corresponding 1/0/null and 1/null schemes apply to numeric flags that are not population indicators.
10	1		1.1	ALL		*FN	A variable with a suffix of FL is equal to Y and a variable with the same root and a suffix of FN is not equal to 1	A variable with a suffix of FN is not equal to 1	Variable with a suffix of FL is present and equal to Y, and a variable with the same root and a suffix of FN is present	ADaMIG v1.1	3.1.4	4; 9	ADaMIG v1.1, Section 3.1.4, Item 4: For subject-level character population flag variables: N = no (not included in the population), Y = yes (included). Null values are not allowed. ADaMIG v1.1, Section 3.1.4, Item 9: For character flags with variable names that end in FL and that are not population flags, a scheme of Y/N/null, or Y/null may be specified. As indicated in Table 3.3.4.2, and Table 3.3.8.1, some common character flags use the scheme Y/null. Corresponding 1/0/null and 1/null schemes apply to numeric flags with variable names that end in FN and that are not population indicators.
10	1		1.2	ALL		*FN	A variable with a suffix of FL is equal to Y and a variable with the same root and a suffix of FN is not equal to 1	A variable with a suffix of FN is not equal to 1	Variable with a suffix of FL is present and equal to Y, and a variable with the same root and a suffix of FN is present	ADaMIG v1.2	3.1.4	4; 9	ADaMIG v1.2, Section 3.1.4, Item 4: For subject-level character population flag variables: N = no (not included in the population), Y = yes (included). Null values are not allowed. ADaMIG v1.2, Section 3.1.4, Item 9: For character flags with variable names that end in FL and that are not population flags, a scheme of Y/N/null, or Y/null may be specified.

cdisc

Home / Standards / Foundational / ADaM / AD

ADaMIG v1.3

Release Information | Files & Links | Related

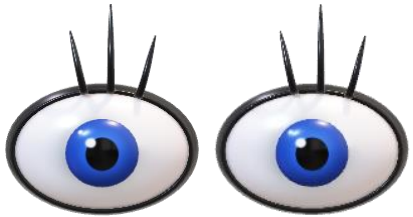
- ADaM v2.1
- ADaM Conformance Rules v5.0
- ADaMIG for Medical Devices v1.0
- ADaMIG for Non-compartmental Analysis Input Data v1.0
- ADaM Structure for Occurrence Data Implementation Guide v1.1
- ADaM Metadata Submission Guidelines v1.0
- ADaM Examples of Traceability v1.0
- ADaM Basic Data Structure (BDS) for Time-to-Event (TTE) Analyses v1.0
- ADaM Examples in Commonly Used Statistical Analysis Methods
- Analysis Results Metadata (ARM) v1.0 for Define-XML v2.0
- ADaM Structure for Occurrence Data (OCCDS) v1.0
- Basic Data Structure for ADaM popPK Implementation Guide v1.0

Refer to **Data Standard Catalog** for supported data standards:

FDA: https://www.fda.gov/media/160564/download

PMDA: https://www.pmda.go.jp/files/000250752.zip

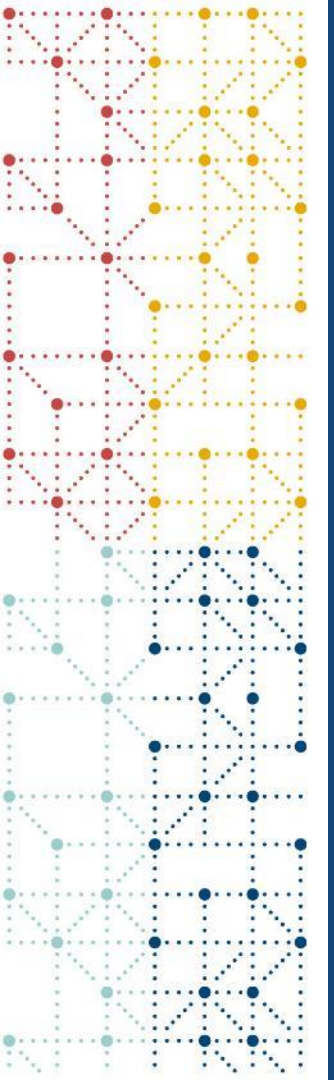
Manual checks are necessary



Automated checks can't check everything for you

Manual checks suggestions:

- Variables needed for analyses are created
- Conditionally required variables are created
- Custom variables are following ADaM rules
- Keep consistency in submission documents



Manual check examples

1. Variables needed for analyses are created

Population Flags in SAP vs ADaM+Define

SAP

4. Analysis Sets

4.1 Full Analysis set

Full analysis set is defined as all subjects who received at least one dose of Drug X……

4.2 Safety Analysis set

Safety analysis set is defined as ……

ADSL

??

USUBJID	FASFL	SAFFL	XYZFL
01-01-0000	Y	Y	Y
01-01-0001	Y	Y	Y
01-01-0002	Y	Y	Y
01-01-0003	Y	N	Y
01-01-0004	N	N	Y

FASFL	Full Analysis Set Population Flag	text	1	No Yes Response • "N" = "No" • "Y" = "Yes"	Derived Set to"Y" if subject received at least one dose of Drug X; else set to "N".
SAFFL	Safety Population Flag	text	1	No Yes Response • "N" = "No" • "Y" = "Yes"	Derived Y if ITTFL='Y' and TRTSDT ne missing. N otherwise

Manual check examples

2. Conditionally required variables

When date/time imputations are done

x.1 Missing Data Handling
In general, missing data will not be imputed except missing/partial missing event adverse event (AE) start date

ADAE

USUBJID	AESEQ	AEDECOD	AESTDTC	ASTDT	TRTSDT	TRTEMFL
01-01-0000	1	Eye Swelling	2020-02	2020-02-01	2020-03-01	
01-01-0000	2	Nausea	2020-03-04	2020-03-04	2020-03-01	Y
01-01-0000	3	Cough	2020	2020-01-01	2020-03-01	

When date/time imputations are done

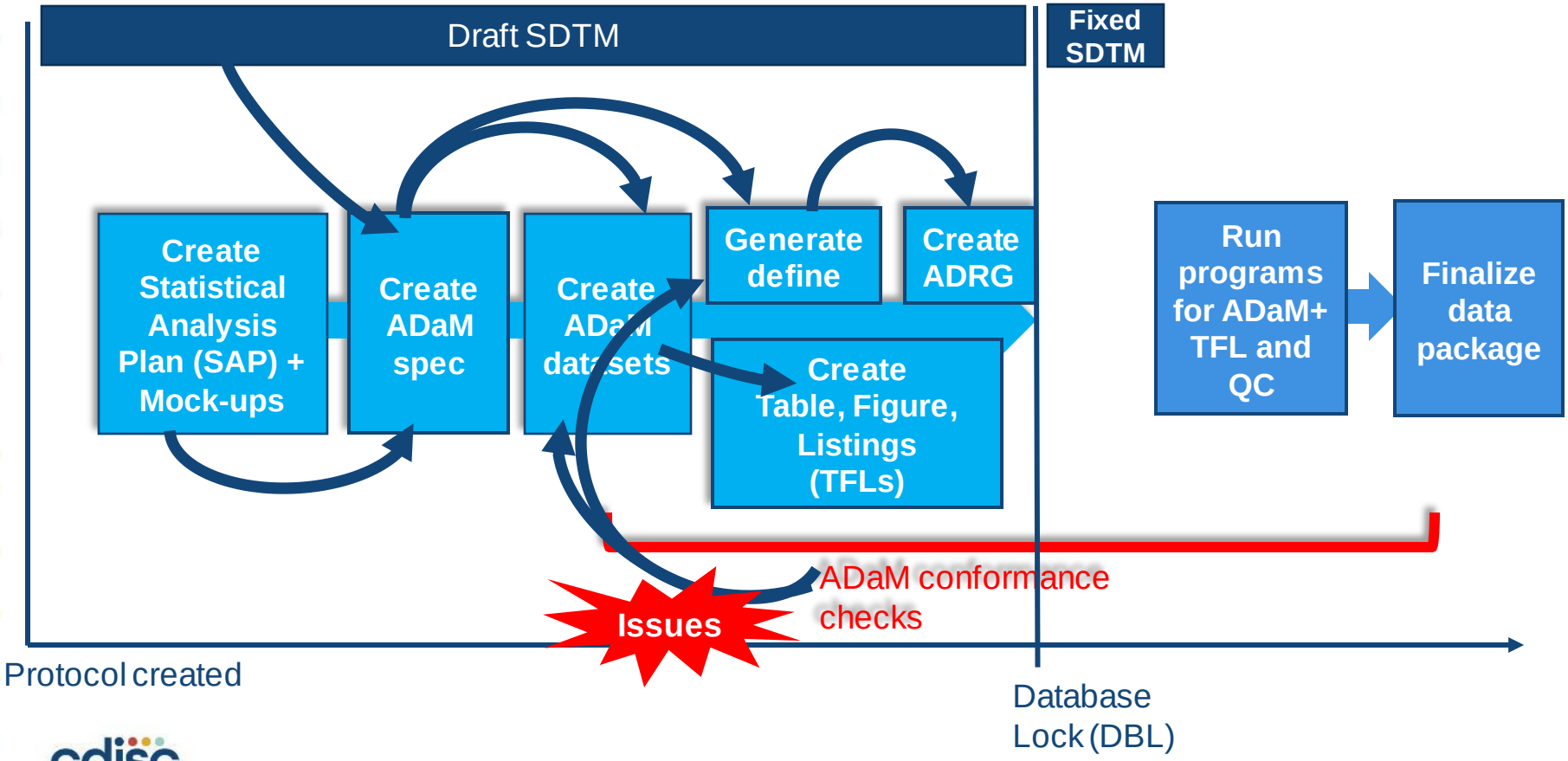
USUBJID	AESEQ	AEDECOD	AESTDTC	ASTDT	ASTDTF	TRTSDT	TRTEMFL
01-01-0000	1	Eye Swelling	2020-02	2020-02-01	D	2020-03-01	
01-01-0000	2	Nausea	2020-03-04	2020-03-04		2020-03-01	Y
01-01-0000	3	Cough	2020	2020-01-01	M	2020-03-01	

- Don't forget to add imputation flags
- Automated checks can check the values of imputation flags (Y/M/D) or (H/T/S) but not if you create imputation flags based on SAP!

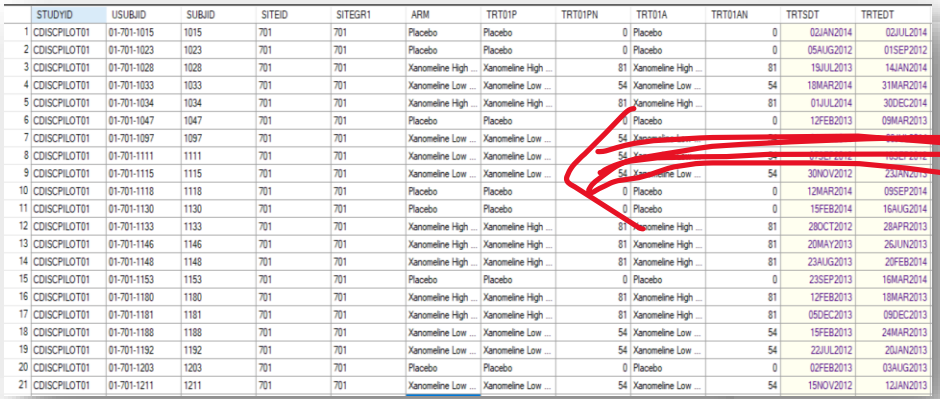
Manual check examples

3. Consistency in submission documents

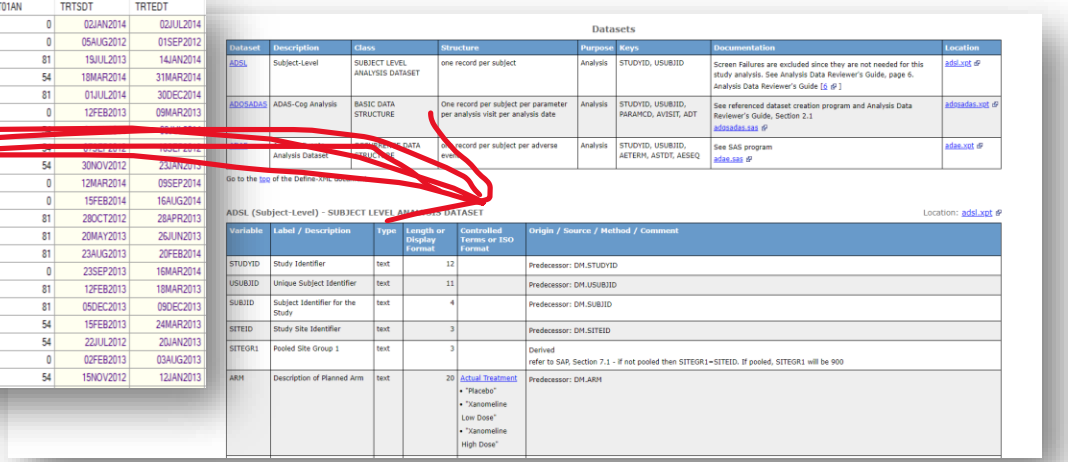
Updates need to be reflected until deliverables are fixed



Keep consistency between datasets and define



	STUDYID	USUBJID	SUBJID	SITEID	SITEGR1	ARM	TRT01P	TRT01PN	TRT01A	TRT01AN	TRTSDT	TRTEDT
1	CDISCPILOT01	01-701-1015	1015	701	701	Placebo	Placebo	0	Placebo	0	02JAN2014	02JUL2014
2	CDISCPILOT01	01-701-1023	1023	701	701	Placebo	Placebo	0	Placebo	0	05AUG2012	01SEP2012
3	CDISCPILOT01	01-701-1028	1028	701	701	Xanomeline High ...	Xanomeline High ...	81	Xanomeline High ...	81	15JUL2013	14JAN2014
4	CDISCPILOT01	01-701-1033	1033	701	701	Xanomeline Low ...	Xanomeline Low ...	54	Xanomeline Low ...	54	18MAR2014	31MAR2014
5	CDISCPILOT01	01-701-1034	1034	701	701	Xanomeline High ...	Xanomeline High ...	81	Xanomeline High ...	81	01JUL2014	30DEC2014
6	CDISCPILOT01	01-701-1047	1047	701	701	Placebo	Placebo	0	Placebo	0	12FEB2013	09MAR2013
7	CDISCPILOT01	01-701-1097	1097	701	701	Xanomeline Low ...	Xanomeline Low ...	54	Xanomeline Low ...	54	30NOV2012	23JAN2013
8	CDISCPILOT01	01-701-1111	1111	701	701	Xanomeline Low ...	Xanomeline Low ...	54	Xanomeline Low ...	54	30NOV2012	23JAN2013
9	CDISCPILOT01	01-701-1115	1115	701	701	Xanomeline Low ...	Xanomeline Low ...	54	Xanomeline Low ...	54	30NOV2012	23JAN2013
10	CDISCPILOT01	01-701-1118	1118	701	701	Placebo	Placebo	0	Placebo	0	12MAR2014	09SEP2014
11	CDISCPILOT01	01-701-1130	1130	701	701	Placebo	Placebo	0	Placebo	0	15FEB2014	16AUG2014
12	CDISCPILOT01	01-701-1133	1133	701	701	Xanomeline High ...	Xanomeline High ...	81	Xanomeline High ...	81	28OCT2012	28APR2013
13	CDISCPILOT01	01-701-1146	1146	701	701	Xanomeline High ...	Xanomeline High ...	81	Xanomeline High ...	81	20MAY2013	26JUN2013
14	CDISCPILOT01	01-701-1148	1148	701	701	Xanomeline High ...	Xanomeline High ...	81	Xanomeline High ...	81	23AUG2013	20FEB2014
15	CDISCPILOT01	01-701-1153	1153	701	701	Placebo	Placebo	0	Placebo	0	23SEP2013	16MAR2014
16	CDISCPILOT01	01-701-1180	1180	701	701	Xanomeline High ...	Xanomeline High ...	81	Xanomeline High ...	81	12FEB2013	18MAR2013
17	CDISCPILOT01	01-701-1181	1181	701	701	Xanomeline High ...	Xanomeline High ...	81	Xanomeline High ...	81	05DEC2013	09DEC2013
18	CDISCPILOT01	01-701-1188	1188	701	701	Xanomeline Low ...	Xanomeline Low ...	54	Xanomeline Low ...	54	15FEB2013	24MAR2013
19	CDISCPILOT01	01-701-1192	1192	701	701	Xanomeline Low ...	Xanomeline Low ...	54	Xanomeline Low ...	54	22JUL2012	20JAN2013
20	CDISCPILOT01	01-701-1203	1203	701	701	Placebo	Placebo	0	Placebo	0	02FEB2013	03AUG2013
21	CDISCPILOT01	01-701-1211	1211	701	701	Xanomeline Low ...	Xanomeline Low ...	54	Xanomeline Low ...	54	15NOV2012	12JAN2013



Datasets

Dataset	Description	Class	Structure	Purpose	Keys	Documentation	Location
ADSL	Subject-Level	SUBJECT LEVEL ANALYSIS DATASET	one record per subject	Analysis	STUDYID, USUBJID	Screen Failures are excluded since they are not needed for this study analysis. See Analysis Data Reviewer's Guide, page 6. Analysis Data Reviewer's Guide [6]	adsl.xpt
ADOSADAS	ADAS-Cog Analysis	BASIC DATA STRUCTURE	One record per subject per parameter per analysis visit per analysis date	Analysis	STUDYID, USUBJID, PARAMCD, AVISIT, ADT	See referenced dataset creation program and Analysis Data Reviewer's Guide, Section 2.1 adosadas.sas	adosadas.xpt
[illegible]	Analysis Dataset	[illegible]	one record per subject per adverse event	Analysis	STUDYID, USUBJID, AETERM, ASTDT, AESEQ	See SAS program adae.sas	adae.xpt

Go to the top of the Define-XML doc

ADSL (Subject-Level) - SUBJECT LEVEL ANALYSIS DATASET

Location: adsl.xpt

Variable	Label / Description	Type	Length or Display Format	Controlled Terms or ISO Format	Origin / Source / Method / Comment
STUDYID	Study Identifier	text	12		Predecessor: DM.STUDYID
USUBJID	Unique Subject Identifier	text	11		Predecessor: DM.USUBJID
SUBJID	Subject Identifier for the Study	text	4		Predecessor: DM.SUBJID
SITEID	Study Site Identifier	text	3		Predecessor: DM.SITEID
SITEGR1	Pooled Site Group 1	text	3		Derived refer to SAP, Section 7.1 - If not pooled then SITEGR1=SITEID. If pooled, SITEGR1 will be 900
ARM	Description of Planned Arm	text	20	Actual Treatment • "Placebo" • "Xanomeline Low Dose" • "Xanomeline High Dose"	Predecessor: DM.ARM

Check any discrepancy

- Datasets metadata matching with ADaM dataset content info?
- Variable metadata matching with ADaM dataset content info?
- Variable attribute info accurate?
- Variable derivation accurate?
- VLM where clause accurate?
- Core variables accurate?
- Codelist added? C code added?
- If ARM is created, selection criteria is accurate?

Cross-check ADRG and define

Contents

1.1 Purpose
1.2 Acronyms
1.3 Study Data Standards and Dictionary Inventory
1.4 Source Data Used for Analysis Dataset Creation
2.1 Protocol Number and Title
2.2 Protocol Design in Relation to ADaM Concepts
3.1 Core Variables
3.2 Treatment Variables
3.3 Subject Issues that Require Special
3.4 Use of Visit Windowing, Unschedul
3.5 Imputation/Derivation Methods
4.1 Split Datasets
4.2 Data Dependencies
4.3 Intermediate Datasets
5.1 Overview
5.2 Analysis Datasets
6.1 Conformance Inputs
6.2 Issues Summary
7.1 ADaM Programs
7.2 Analysis Output Programs
7.3 Macro Programs
3.1 Issues Encountered and Resolved

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	•SDTM v1.7 •SDTMIG v3.3
SDTM Controlled Terminology	CDISC SDTM Controlled Terminology, 2023-03-31
ADaM	•ADaM v2.1 •ADaMIG v1.1
ADaM Controlled Terminology	CDISC ADaM Controlled Terminology, 2022-06-24
Data Definitions	Define-XML v2.1
TAUG (if applicable)	
Medical Events Dictionary	MedDRA 24.1
Other standards (optional)	

Define

Study Name

Study Descript...

Protocol Name CDISC-Sample

Metadata Name Study CDISC-Sample Data Definitions

Standards for Study CDISC-S

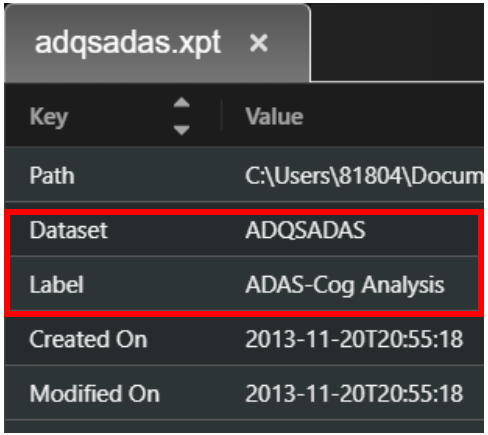
Standard	Type
ADaMIG 1.1	IG
CDISC/NCI ADaM 2020-11-06	CT
CDISC/NCI SDTM 2023-03-31	CT

Cross-check ADRG, define, and xpt

ADRG

5.2 Analysis Datasets

Dataset - Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
ADSL - Subject Level Analysis	SUBJECT LEVEL ANALYSIS DATASET			X			one record per subject
ADAE - Adverse Events Analysis	OCCURRENCE DATA STRUCTURE		X				one record per subject per adverse event
ADQSADAS - ADAS-Cog Analysis	BASIC DATA STRUCTURE	X					One record per subject per parameter per analysis visit per analysis date



XPT Dataset contents

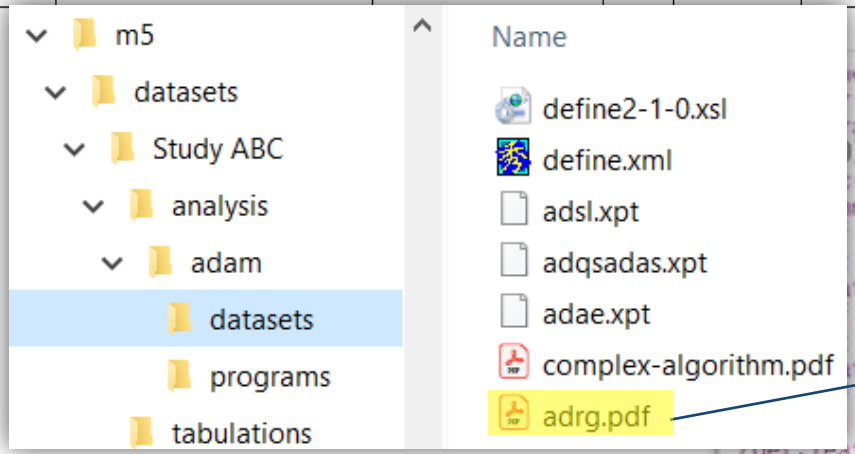
Define

Datasets

Dataset	Description	Class - SubClass	Structure	Purpose	Keys
ADSL [ADaMIG 1.1]	Subject-Level Analysis	SUBJECT LEVEL ANALYSIS DATASET	one record per subject	Analysis	STUDYID, USUBJID
ADQSADAS [ADaMIG 1.1]	ADAS-Cog Analysis	BASIC DATA STRUCTURE	One record per subject per parameter per analysis visit per analysis date	Analysis	STUDYID, USUBJID, PARAMCD, AVISIT, ADT

Can you open documents after placing data packages into a specific file directory structure?

AVAL VLM		Analysis Value	float	3		Derivations are described per parameter in the parameter value level metadata
	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)	Analysis Value	float			Derived (Source: Sponsor) Sum of ADAS scores for items 1, 2, 4, 5, 6, 7, 8, 11, 12, 13, and 14, see Complex algorithm (Page 1) for details on adjusting for missing values. Complex Algorithm




```
iption>↓
anslatedText>Get denominators for percentages from ADSL and counts
) keeping only records in ADAE for the numerator.</TranslatedText>
ription>↓
mentDef>↓
  ID="LF.ADQSADAS.PGM" xlink:href="../programs/adqsadas-sas.txt">↓
itle>adqsadas.sas</def:title>↓
f>↓
  ID="LF.ADRG" xlink:href="analysis-data-reviewers-guide.pdf">↓
itle>Analysis Data Reviewer's Guide</def:title>↓
f>↓
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/def:leaf>↓
def:leaf ID="LF.COMP" xlink:href="complex-algorithm.pdf">↓
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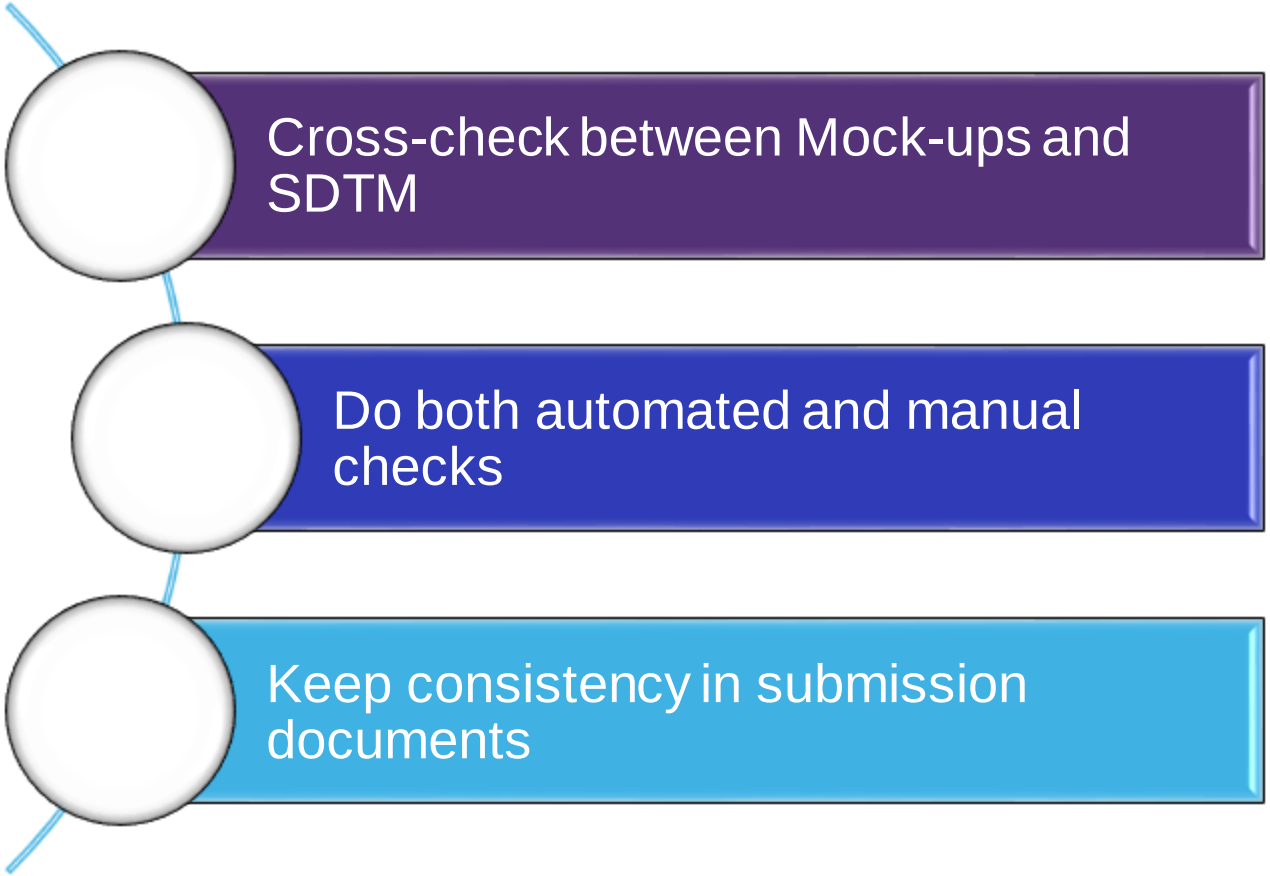
Conclusion- ADaM



References:

- FDA Study Data Standards Resources: https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources
- PMDA Notification: https://www.pmda.go.jp/english/review-services/reviews/0002.html
- CDISC: SDTM document: https://www.cdisc.org/standards/foundational/sdtm
- CDISC: ADaM document: https://www.cdisc.org/standards/foundational/adam
- SDTM Basics for ADaM Dataset Creation: https://www.cdisc.org/sites/default/files/2022-06/Session4Seiko%20Yamazaki%26Chikaaki%20Nakao.pdf

Thank You!