Implementing CDISC standards in an organization that doesn’t require CDISC

Presentation by DAAN VAN NIEUWENHUIJZEN AND MARION KASPERS at the PHUSE SDE Utrecht, September 2023

AGENDA

- Background
- SDTM Implementation at DNR
- Collaboration DNR – OCS Life Sciences
- ADaM Implementation at DNR
- Next Steps

BACKGROUND

Danone is a global nutrition company

- Essential dairy and plant-based product
- Waters
- Specialized nutrition (early life nutrition and medical nutrition)

Danone's mission "BRINGING HEALTH THROUGH FOOD TO AS MANY PEOPLE AS POSSIBLE"

Research for Health				
Nutrition for Life	Epilepsy	Physical Frailty	Gut Health	Muscle
Allergy	Growth & Metabolism	Stroke & Dysphagia	Human Milk Research	Neuroscience
Alzheimer's Disease	Oncology	Critical Care	Immunology	

Source https://www.danoneresearch.com/

STANDARDIZATION

Benefits of using a data standard

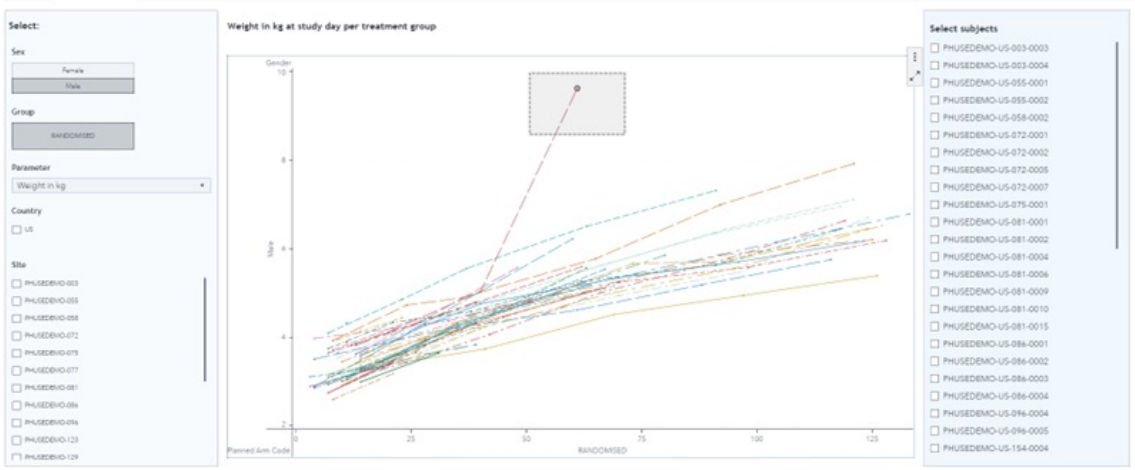
- Allows data integration
- Improves clarity
- Enables re-use of programs
- Simplifies data sharing

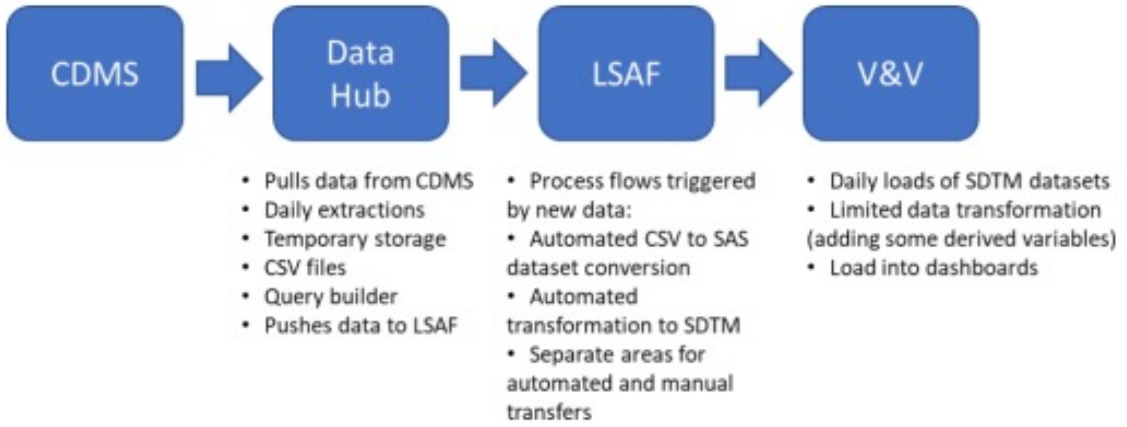
Why then SDTM

- Existing standard, developed and maintained by CDISC
- Simplifies data monitoring and review
- Be prepared for data submissions to regulators like FDA (CDISC not currently required)

DATA USED FOR iCDM

iCDM Interactive Central Data Monitoring - a range of dashboards using SDTM data that allow for near real-time data monitoring during the study conduct.
Example: Anthropometrics - finding outliers for weight (kg)



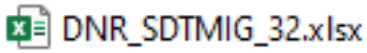


PHUSE EU Connect 2022 Belfast Presented by Paul Vervuren (Danone Nutricia Research) and Dennis Menkveld (P&W consulting)
https://phuse.s3.eu-central-1.amazonaws.com/Archive/2022/Connect/EU/Belfast/PAP_AR05.pdf
https://phuse.s3.eu-central-1.amazonaws.com/Archive/2022/Connect/EU/Belfast/PRE_AR05.pdf

SDTM CREATION PROCESS AT DANONE NUTRICIA RESEARCH (DNR)

Building on the experiences gained in creating the data warehouse for infant nutrition (see presentation by Paul Vervuren at PHUSE EU connect 2016 in Barcelona https://phuse.s3.eu-central-1.amazonaws.com/Archive/2016/Connect/EU/Barcelona/PRE_CD09.pdf), nowadays most clinical studies are converted into SDTM standards to be used for the study reporting.

Metadata



- Based on the CDSIC SDTM IG 3.2
- Added domains from SDTM IG 3.3 (ML, FT, MK) and SDTM IG 3.4 (BE) and XS (custom for SAE)
- Additional columns to describe the implementation of SDTM at DNR
- Added supplemental qualifiers to domains (instead of SUPP dataset)

Controlled Terminology

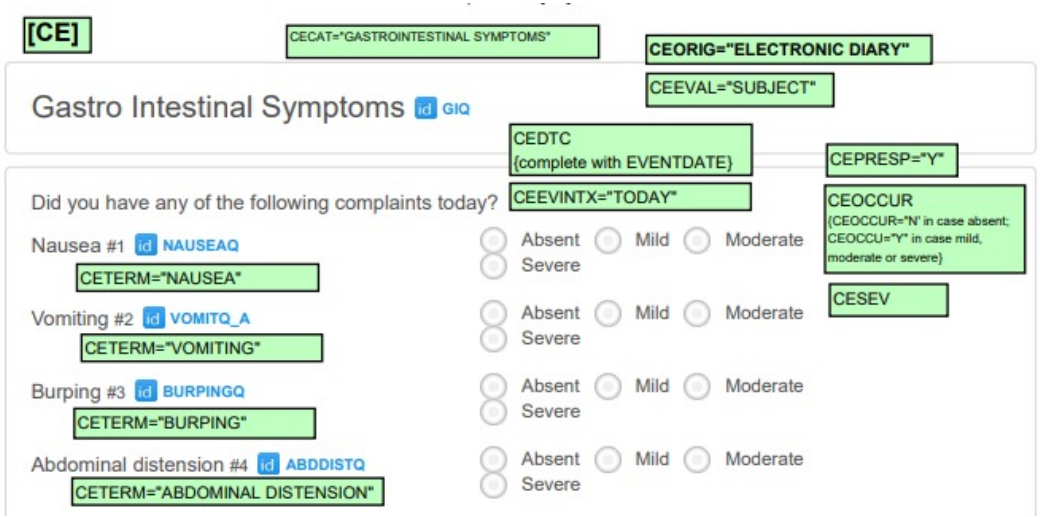
- SDTM controlled terminology (provided by CDSIC)
- Developing additional DNR controlled Terminology

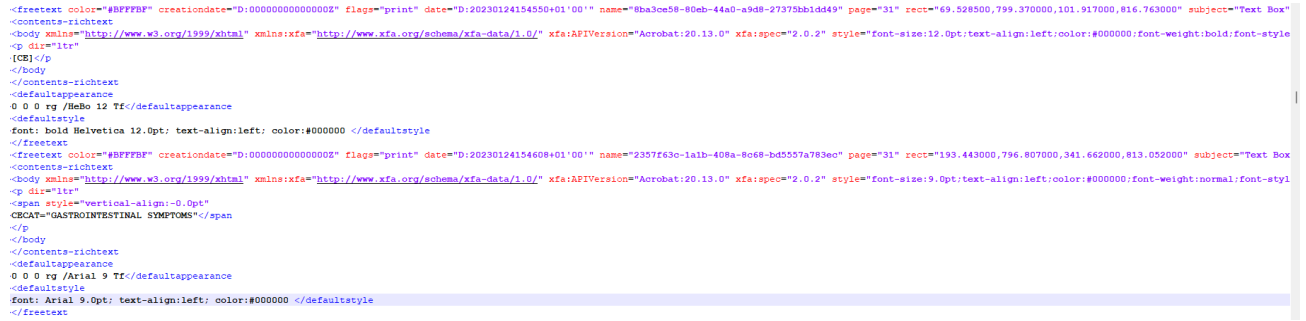
CDISC members can download CDISC metadata from the CDISC library

SDTM CREATION PROCESS AT DNR – ANNOTATION OF THE CRF

Annotation of CRF

- Add domains and domain variables as comments to the annotated CRF (PDF) from the EDC (Viedoc)
- Export the comments to Forms Data Format file on XML basis (XFDF)
- Use the Annotations in creating the define.xml (origin page number in the CRF, value level metadata)





SDTM CREATION PROCESS AT DNR – CREATING THE DOMAINS

Creating the domain datasets (OCS Life Sciences)

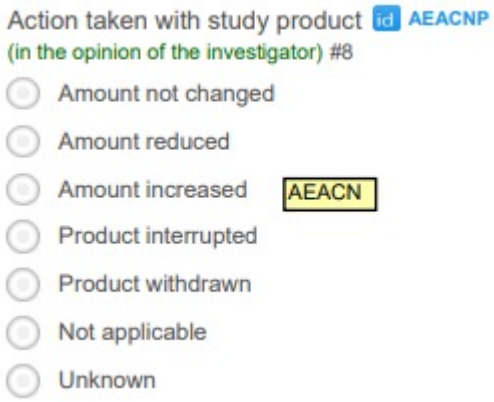
```
array vars (9) ABDPAINQ ABDDISTQ BURPINGQ PASSWQ_A REGURGQ_A NAUSEAQ VOMITQ_A DIARRHQ CONSTIPQ;
array vals (9) $200 ("ABDOMINAL PAIN", "ABDOMINAL DISTENSION", "BURPING", "FLATULENCE", "REGURGITATION", "NAUSEA", "VOMITING", "DIARRHOEA", "CONSTIPATION");

do i = 1 to dim(vars);
  /* For each subject, a record with CETERM is created */
  ceterm = substr(vals(i),1,1)||lowcase(substr(vals(i),2));

  /* Derive CESTAT and temporary variable _CESEV for later CESEV derivation*/
  if ^missing(vars(i)) then do;
    _cesev  = vars(i);
    call missing(cestat);
    output;
  end;
  else if missing(vars(i)) then do;
    call missing(_cesev);
    cestat  = "NOT DONE";
    output;
  end;
end;
```

```
/* Design is applied and checks are made. */
%sdtm_create_domain ( domain     = &sdtm_domain
                    , inset      = &sdtm_domain
                    , keys       = studyid usubjid ceterm cedtc visitnum
                    , deldupkeys = N);
```

PINNACLE21

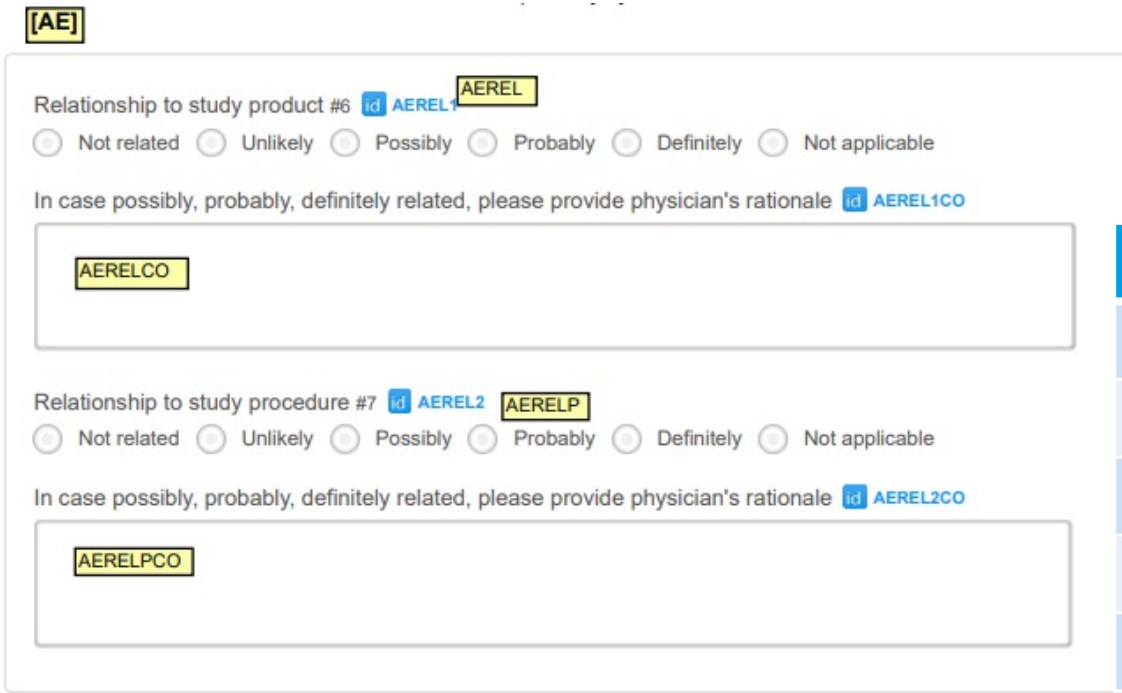
DNR IMPLEMENTATION OF SDTM - CONTROLLED TERMINOLOGY

Nutritional studies typically specify the amount of study product administered (often in a single bolus)



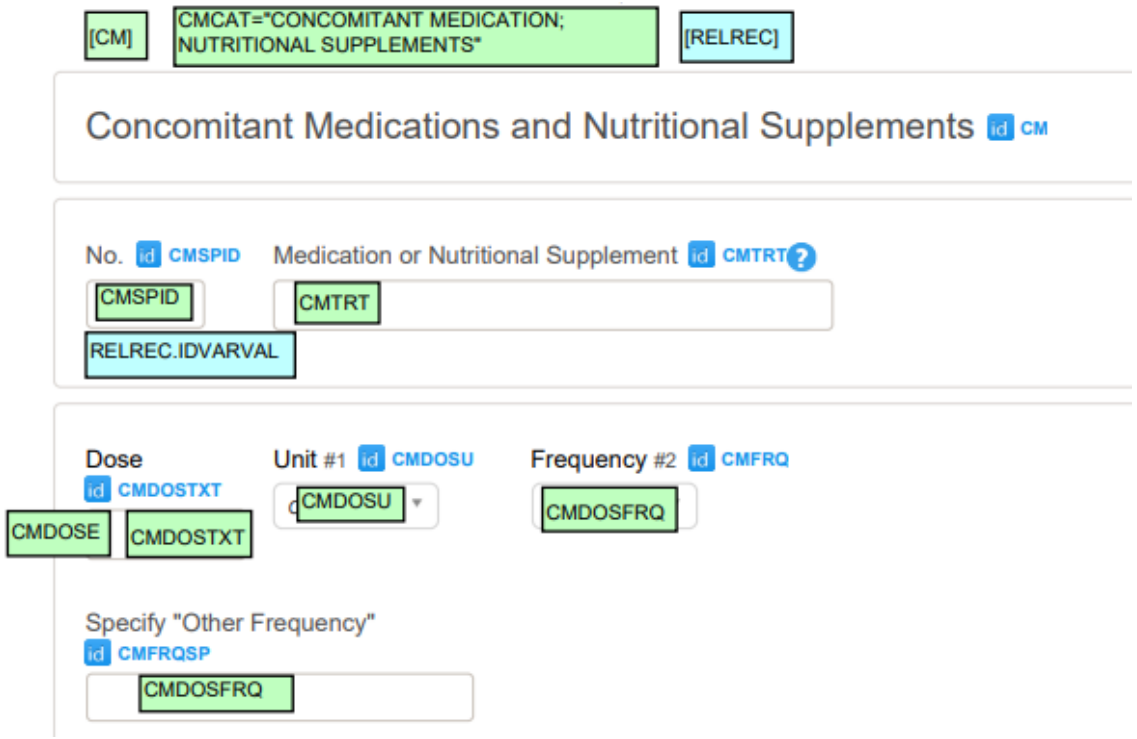
ACN (Codelist NOT Extensible)	DNR_ACN
DOSE INCREASED	AMOUNT INCREASED
DOSE NOT CHANGED	AMOUNT NOT CHANGED
DOSE RATE REDUCED	
DOSE REDUCED	AMOUNT REDUCED
DRUG INTERRUPTED	PRODUCT INTERRUPTED
DRUG WITHDRAWN	PRODUCT WITHDRAWN
NOT APPLICABLE	NOT APPLICABLE
UNKNOWN	UNKNOWN

DNR IMPLEMENTATION OF SDTM – SUPPLEMENTAL QUALIFIERS



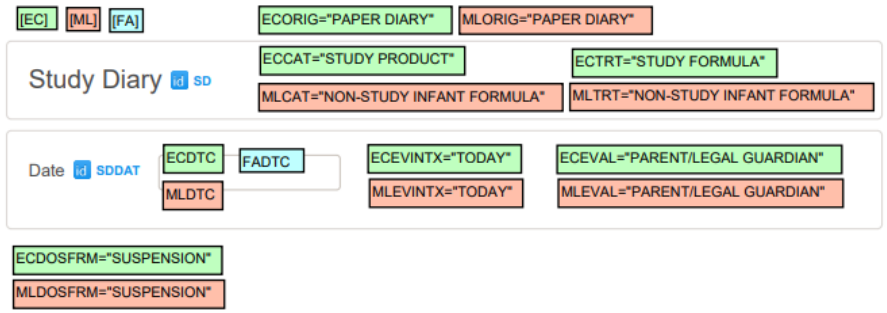
Variable Name	Variable Label
AERELCO	Physician's rationale for relationship to study product
AERELP	Causality to Study Procedure
AERELPCO	Physician's rationale for relationship to study procedure
AEDICT	Dictionary and Version
AESOCLST	Primary and Secondary SOC Abbreviations
CodedOnDate	Coded on date (UTC)
InitiatedDate	Initiated date (UTC)
LastEditedDate	Last edited date (UTC)
SUBJID	Subject Identifier for the Study

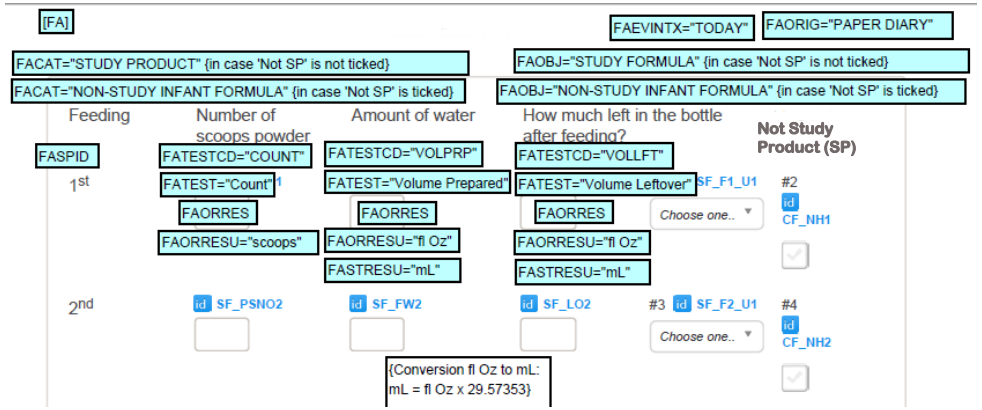
DNR IMPLEMENTATION OF SDTM – SUPPLEMENTAL QUALIFIERS

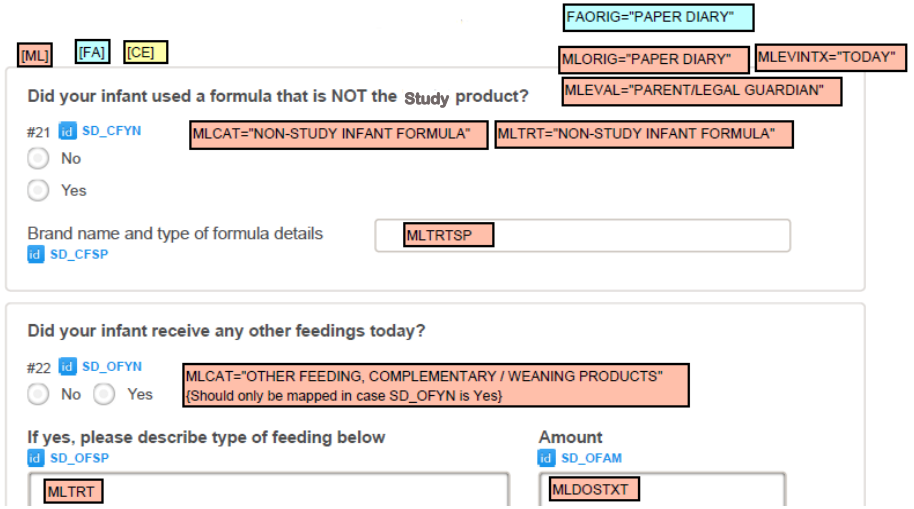


Variable Name	Variable Label
CMATC1	ATC level 1
CMATC2	ATC level 2
CMATC3	ATC level 3
CMATC4	ATC level 4
CMDICT	Dictionary and Version
CodedOnDate	Coded on date (UTC)
InitiatedDate	Initiated date (UTC)
LastEditedDate	Last edited date (UTC)
SUBJID	Subject Identifier for the Study

DNR IMPLEMENTATION OF SDTM – INFANT FORMULA







DNR IMPLEMENTATION OF SDTM – PROCEDURES (PR)

[PR] [CM] [FA]

Anti-cancer treatment id CANCTREAT
PRCAT="ANTI-CANCER TREATMENT DETAILS"
CMCAT="ANTI-CANCER TREATMENT DETAILS"

Treatment Cycle id TRTSEQ
PRSPID where PRMOOD="PLANNED", "PERFORMED"

Type of cancer #1 id SUBJSP1
- CRC
- NSCLC

CMINDC
PRINDC

Type of treatment #2 id TREATSP2
- Chemotherapy
- Concurrent chemoradiotherapy
- Immunotherapy
- Targeted therapy
- Combination of chemotherapy and immunotherapy

{Not mapped}
{For visibility purposes only}

#3 id TRTNS
Treatment cycle not started
PRCYCND where PRMOOD="PERFORMED" {NOT DONE if ticked}

id TREATDELYN
Was the start of the treatment cycle delayed? #4
- Yes
- No

PRMOOD = "PLANNED", "PERFORMED"
{Not mapped}
{Leading question for visibility purposes only}

Actual Start Date of this cycle id ACTCYCLSTDAT
PRSTDTC where PRMOOD="PERFORMED"

Planned Start Date of this cycle id PLCYCLSTDAT
PRSTDTC where PRMOOD="PLANNED"

Number of days delayed id DELDAYS
PRDDEL where PRMOOD="PERFORMED"

Reason for delay #5 id TREATDELREAS
PRREAS where PRMOOD="PERFORMED"

Other please specify id DELOTHREAS
PRREASSP where PRMOOD="PERFORMED"

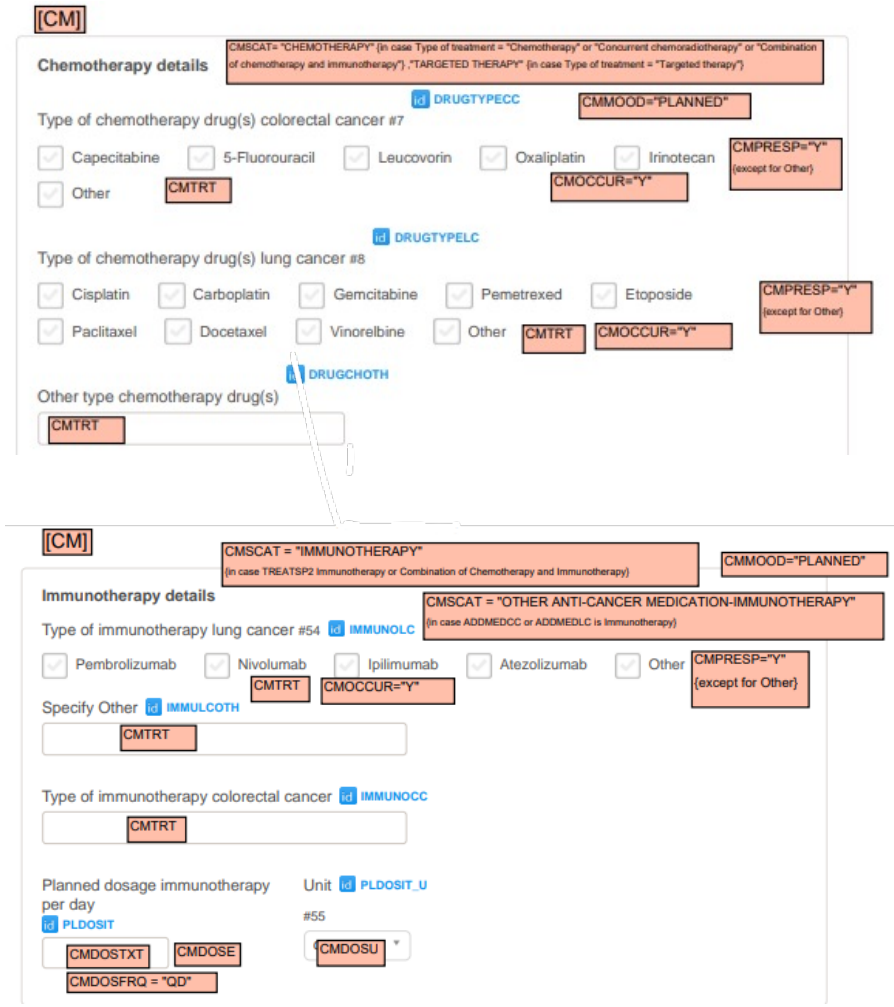
TRTSEQ	SUBJSP1	TREATSP2	ACTCYCLSTDAT	PLCYCLSTDAT	DELDAYS	SAMETREAT
1	CRC	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	2022-01-23	2022-01-16	7	
2	CRC	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	2022-02-20	2022-02-06	14	N
3	CRC	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	2022-03-07			Y

DRUGTYPECCOT	DRUGCHOTH	IMMUNOCC
OTHER	Lonsurf	Bevacizumab
		Bevacizumab

DOSRDOC1	DOSRDIMM	TRTSTPROC1	TRTSTPRIMM	TRTINTOC1	TRTINTIMM
N	N	N	N	N	N
	N		N		N

PRSPID	PRLNKID	PRTRT	PRINDC	PRSTDTC	PRMOOD	PRDDEL
1		COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-01-23	PERFORMED	7
1	CMPR3	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-01-16	PLANNED	
2		COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-02-20	PERFORMED	14
2	CMPR4	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-02-06	PLANNED	
3		COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-03-07	PERFORMED	
3	CMPR5	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-03-07	PLANNED	

DNR IMPLEMENTATION OF SDTM – CONCOMITANT MEDICATION (CM)



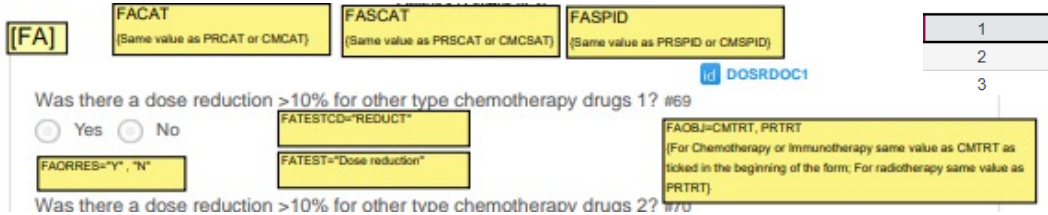
TRTSEQ	SUBJSP1	TREATSP2	ACTCYCLSTDAT	PLCYCLSTDAT	DELDAYS	SAMETREAT
1	CRC	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	2022-01-23	2022-01-16	7	
2	CRC	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	2022-02-20	2022-02-06	14	N
3	CRC	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	2022-03-07			Y

DRUGTYPECCOT	DRUGCHOTH	IMMUNOCC
OTHER	Lonsurf	Bevacizumab
		Bevacizumab

DOSRDOC1	DOSRDIMM	TRTSTPROC1	TRTSTPRIMM	TRTINTOC1	TRTINTIMM
N	N	N	N	N	N
	N		N		N

CMSPID	CMTRT	CMSCAT	CMSTDTC	CMMOOD	CMLNKID	CMLNKGRP
	Bevacizumab	IMMUNOTHERAPY	2022-01-16	PLANNED	CMFA4	CMPR3
	Lonsurf	CHEMOTHERAPY	2022-01-16	PLANNED	CMFA5	CMPR3
	Bevacizumab	IMMUNOTHERAPY	2022-02-06	PLANNED	CMFA6	CMPR4
	Bevacizumab	IMMUNOTHERAPY	2022-03-07	PLANNED	CMFA7	CMPR5

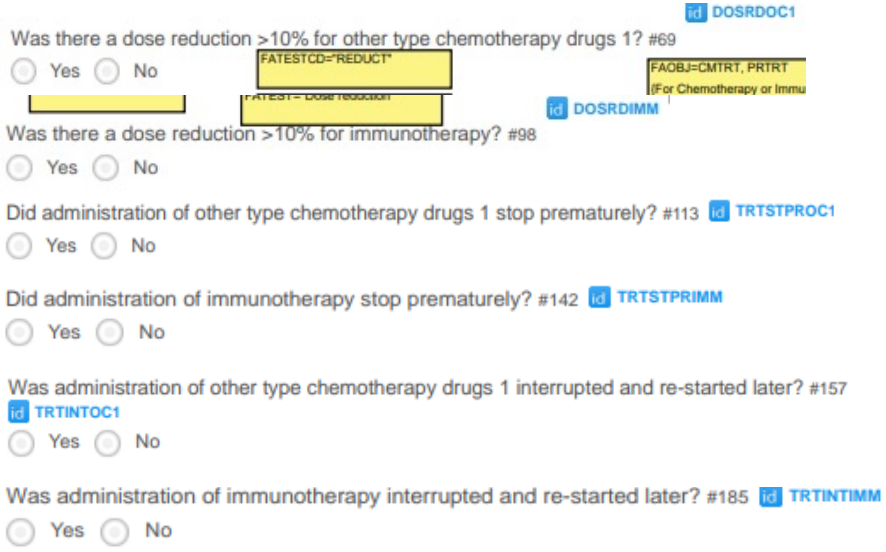
DNR IMPLEMENTATION OF SDTM – FINDINGS ABOUT (FA)



TRTSEQ	SUBJSP1	TREATSP2	ACTCYCLSTDAT	PLCYCLSTDAT	DELDAYS	SAMETREAT
1	CRC	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	2022-01-23	2022-01-16	7	
2	CRC	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	2022-02-20	2022-02-06	14	N
3	CRC	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	2022-03-07			Y

DRUGTYPECCOT	DRUGCHOTH	IMMUNOCC
OTHER	Lonsurf	Bevacizumab
		Bevacizumab

DOSRDOC1	DOSRDIMM	TRTSTPROC1	TRTSTPRIMM	TRTINTOC1	TRTINTIMM
N	N	N	N	N	N
	N		N		N



FASPID	FATESTCD	FATEST	FAOBJ	FASCAT	FAORRES	FASTRESC	FALNKGRP	SAMETRT
1	INTERRUP	Interruptions and re-starts	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA4	
1	REDUCT	Dose reduction	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA4	
1	STOPPED	Prematurely stopped	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA4	
1	INTERRUP	Interruptions and re-starts	Lonsurf ...	CHEMOTHERAPY ...	N	N	CMFA5	
1	REDUCT	Dose reduction	Lonsurf ...	CHEMOTHERAPY ...	N	N	CMFA5	
1	STOPPED	Prematurely stopped	Lonsurf ...	CHEMOTHERAPY ...	N	N	CMFA5	
2	INTERRUP	Interruptions and re-starts	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA6	N
2	REDUCT	Dose reduction	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA6	N
2	STOPPED	Prematurely stopped	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA6	N
3	INTERRUP	Interruptions and re-starts	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA7	Y
3	REDUCT	Dose reduction	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA7	Y
3	STOPPED	Prematurely stopped	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA7	Y

DNR IMPLEMENTATION OF SDTM – RELATIONS (RELREC)

RDOMAIN	IDVAR	IDVARVAL	RELTYPE	RELID
CM	CMLNKID		ONE	CMFA
FA	FALNKGRP		MANY	CMFA
PR	PRLNKID		ONE	CMPR
CM	CMLNKGRP		MANY	CMPR

CMSPID	CMTRT	CMSCAT	CMSTDTC	CMMOOD	CMLNKID	CMLNKGRP
1	Bevacizumab ...	IMMUNOTHERAPY	2022-01-16	PLANNED	CMFA4	CMPR3
1	Lonsurf	CHEMOTHERAPY	2022-01-16	PLANNED	CMFA5	CMPR3
2	Bevacizumab ...	IMMUNOTHERAPY	2022-02-06	PLANNED	CMFA6	CMPR4
3	Bevacizumab ...	IMMUNOTHERAPY	2022-03-07	PLANNED	CMFA7	CMPR5

PRSPID	PRLNKID	PRTRT	PRINDC	PRSTDTC	PRMOOD	PRDDEL
1		COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-01-23	PERFORMED	7
1	CMPR3	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-01-16	PLANNED	
2		COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-02-20	PERFORMED	14
2	CMPR4	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-02-06	PLANNED	
3		COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-03-07	PERFORMED	
3	CMPR5	COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY	CRC	2022-03-07	PLANNED	

FASPID	FATESTCD	FATEST	FAOBJ	FASCAT	FAORRES	FASTRESC	FALNKGRP	SAMETRT
1	INTERRUP	Interruptions and re-starts	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA4	
1	REDUCT	Dose reduction	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA4	
1	STOPPED	Prematurely stopped	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA4	
1	INTERRUP	Interruptions and re-starts	Lonsurf ...	CHEMOTHERAPY ...	N	N	CMFA5	
1	REDUCT	Dose reduction	Lonsurf ...	CHEMOTHERAPY ...	N	N	CMFA5	
1	STOPPED	Prematurely stopped	Lonsurf ...	CHEMOTHERAPY ...	N	N	CMFA5	
2	INTERRUP	Interruptions and re-starts	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA6	N
2	REDUCT	Dose reduction	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA6	N
2	STOPPED	Prematurely stopped	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA6	N
3	INTERRUP	Interruptions and re-starts	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA7	Y
3	REDUCT	Dose reduction	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA7	Y
3	STOPPED	Prematurely stopped	Bevacizumab ...	IMMUNOTHERAPY ...	N	N	CMFA7	Y

COLLABORATION DNR AND OCS

>10 years – data management, SAS programming, statistics

Data warehouse for infant nutrition studies
- Completed studies added to data warehouse
- OCS and DNR providing SDTM knowledge and experience
- OCS developing tooling (mapping, programs, macros)

Delivery-and-collaboration model – OCS is part of SDTM team
- More SDTM domains for legacy studies
- Apply SDTM on ongoing studies
- Apply SDTM on new studies:
  - More pressure on timelines
  - Kick off meeting to explain CRF
  - SDTM annotated CRF → used for define.xml
  - Regular meetings to discuss implementation issues
  - Good quality test data

COLLABORATION DNR – OCS

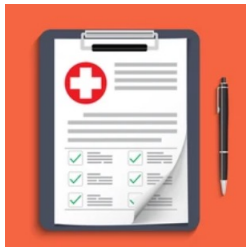
Transfer metadata, test/study data, SDTM annotations and tools to create SDTM domains

Development SDTM domain programs (SAS Server on Windows)

Delivery of SDTM domain programs

Upload SDTM domain programs (LSAF on Linux)
Create jobs and run programs
Compare results to OCS

STANDARDIZATION PROCESS



SDTM

ADaM

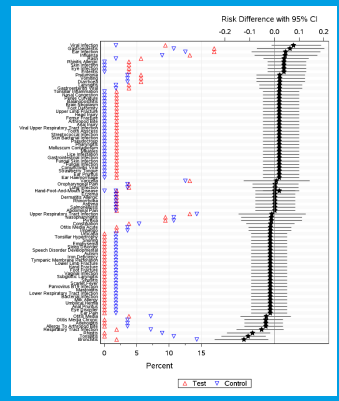
Table 02.1: Medical history, number of medical history events and number and percentage of subjects with at least one medical history event, by System Organ Class, Preferred Term and study group – *Population*

Preferred term (*MedDRA xx.x*)	<group 1> N=xx			<group 2> N=xx			<etc.> N=xx		
	k	n	%	k	n	%	k	n	%
Any System organ class									
Any Event		xx	x.x%		xx	x.x%		xx	x.x%
SOC1									
Any Event		xx	x.x%		xx	x.x%		xx	x.x%
PT1	xx	xx	x.x%	xx	xx	x.x%	xx	xx	x.x%
PT2									
SOC2									
Any Event		xx	x.x%		xx	x.x%		xx	x.x%
PT3	xx	xx	x.x%	xx	xx	x.x%	xx	xx	x.x%

N = Number of subjects of the analysis population; k = number of medical history events; n = number of subjects with one or mo medical history event; % relates n to N

Listing 03.3: Comparison of Concomitant medication (CM) and Adverse Event (AE) information, sorted by Subject ID, , and AE number

Subject ID	Study group	AE #	Verbatim	Action taken	AE start date	Medication, verbatim	CM start date	Old/ new/amended
xxx-xx-xxx	<group 1>/<group 2>/<etc.>			Medication				



Standardized case report forms

Standardized reports

IMPLEMENTATION OF ADAM - PREPARATIONS

ADaM training provided by OCS

- Introduction to ADaM
- Overview of variables
  - ADSL
  - Basic Data Structure (BDS)
  - Occurrence Dataset (OCCDS)
- DNR specific part

ADaM implementation workgroup

- Templates for ADaM datasets for safety (AE, MH, CM)
- Working towards standardized reports
- By-weekly meetings
- Stand-by for questions

IMPLEMENTATION OF ADAM - DOCUMENTATION

Milestones: Safety Review, Data Review Meeting, Interim Analysis, Key Results, Study Report, Post-hoc Analysis,…

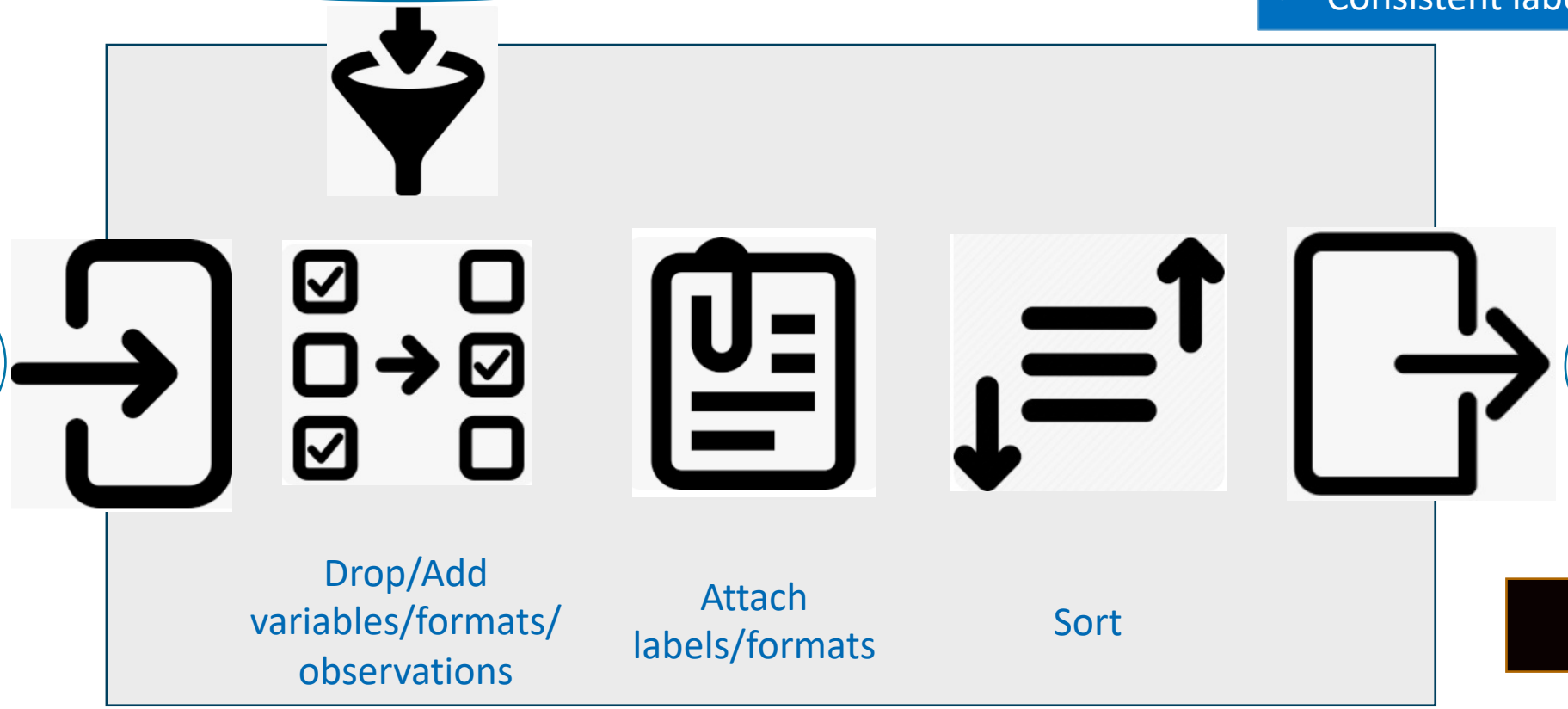
OLD WAY	NEW WAY
Analysis Conventions Document Advantages: - One document Disadvantages: - A lot of work - Specified topics, but no template	define-xml Analysis Data Reviewer's Guide (ADRG) Advantages: - Macro to create define-xml - Template for standard variables Disadvantages: - Two documents - ADRG complex

Document in between Analysis Conventions Document and ADRG

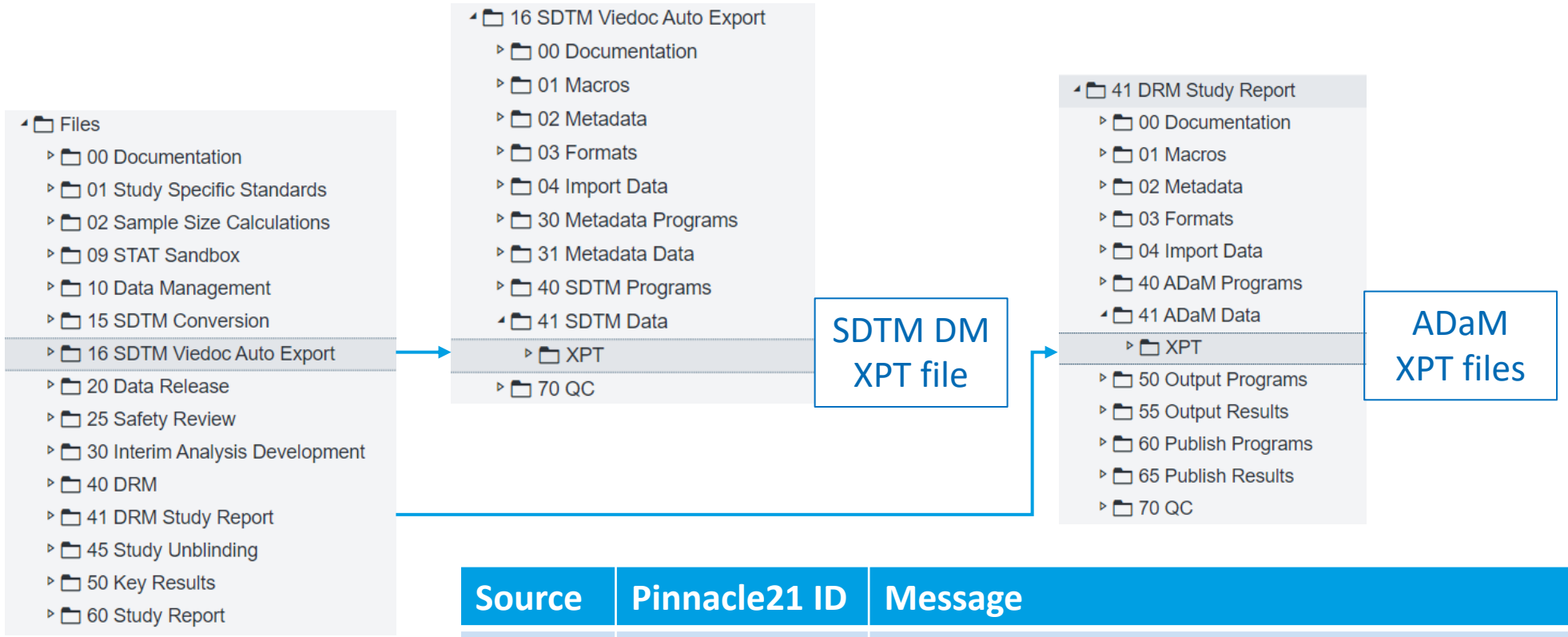
SAS MACROS %SDTM_CREATE_DOMAIN AND %ADAM_CREATE_AD

Metadata: DNR-IG
ADaM-IG for ADSL and BDS, OCCDS
Controlled Terminology

Benefits:
- Order of variables
- Sorting order
- Consistent labels and formats



IMPLEMENTATION OF ADAM - PINNACLE21 VALIDATOR ISSUES



Source	Pinnacle21 ID	Message
GLOBAL	DD0101	Missing define.xml file
GLOBAL	AD0126	Traceability rules not executed due to missing EX dataset
ADSL	CT2002	RACE value not found in 'Race' extensible codelist
ADxx	AD0034	xxxFL value is not Y or null

NEXT STEPS

SDTM:

- Training of data managers outside SDTM implementation workgroup
- define.xml

ADaM:

- ADaM-IG for DNR
- Standardization of reports other than safety (growth, gastro-intestinal symptoms)
- Template for documentation
- define.xml

QUESTIONS?