Preparing an e-submission ready ISS – lost in the jungle?

Presented by Stefanie Sturm,
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Meet the Speaker

Stefanie Sturm

Title: Principal Statistical Programmer

Organization: mainanalytics GmbH

Stefanie is a principal statistical programmer at the CRO mainanalytics GmbH in Germany and has 30 years of experience in the pharmaceutical industry. Her focus is on the implementation of CDISC standards like SDTM, ADaM and Define-XML and the preparation of e-submission ready data packages.

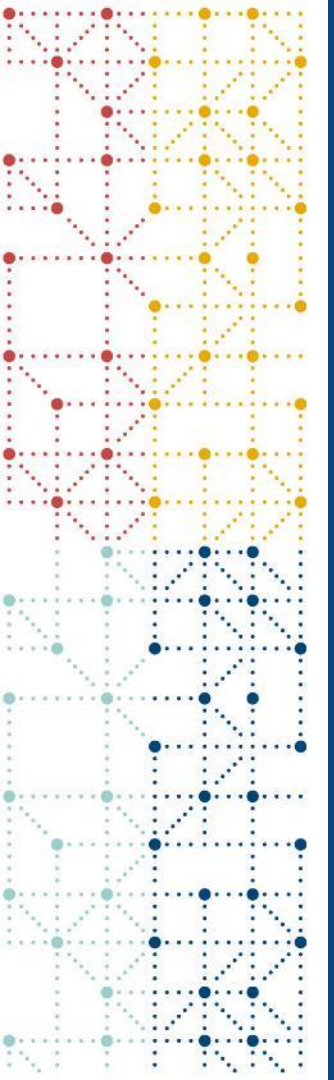
In addition, she is member of the steering committee of the CDISC German User Network.

Disclaimer and Disclosures

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

Agenda

1. Introduction
2. Plan Your Journey
3. A Travel Report
4. Arrival



Introduction

Welcome to the Jungle

Preparing an e-submission ready Integrated Summary of Safety (ISS)

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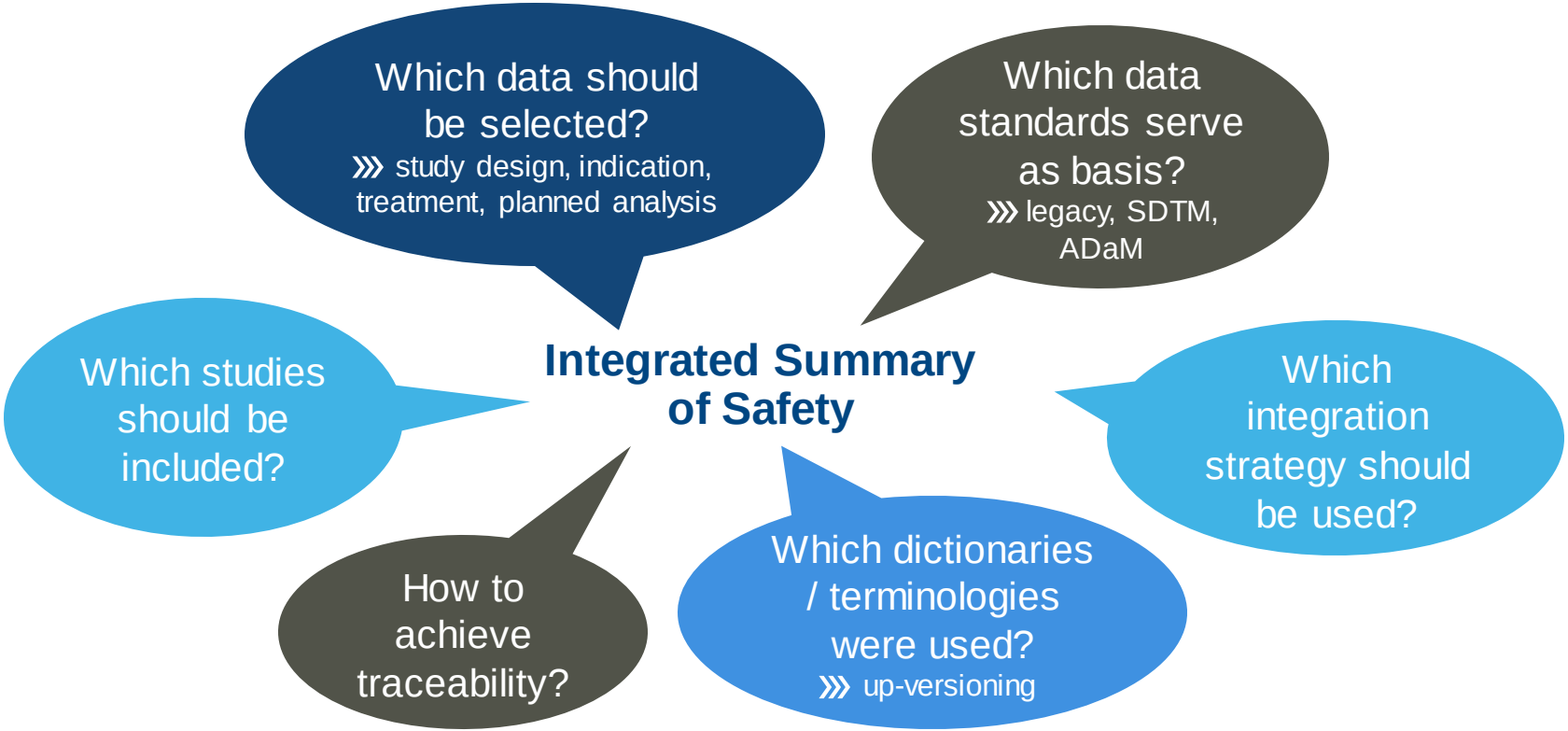
Like a journey through the jungle?

General Considerations

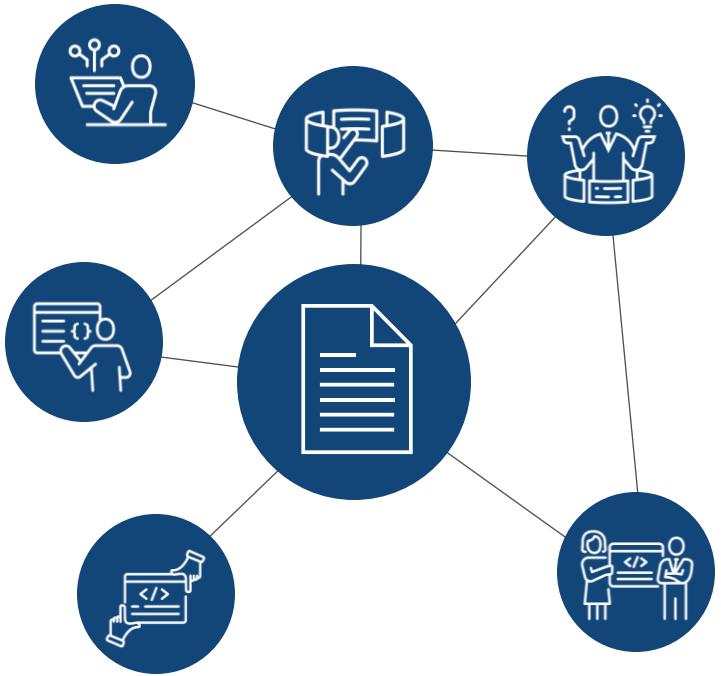


Plan Your Journey

Where to find information

Important Travel Information

- Integration Strategies in Support of ISS/ISE Submissions
  Version 1.0 (PHUSE, Oct 2020)
- Study Data Standardization Plan (SDSP), Template
  Version 1.0 (PHUSE, Jan 2018), incl. examples and completion guideline
- The Integrated Analysis Data Reviewer's Guide (iADRG), Template
  Version 1.0 (PHUSE, Sep 2023), incl. examples and completion guideline
- Standard Safety Tables and Figures: Integrated Guide
  (FDA, Aug 2022)



Integration Strategies in Support of ISS/ISE Submissions (PHUSE)

Keynotes

- Variety of scenarios how to prepare integrated databases
- Recommendation to prepare SDSP for documentation of integration strategy
- ISS Statistical Analysis Plan (SAP) is a prerequisite
- Only subset of studies and data may be required for ISS/ISE analyses
- Determine the need for up-versioning of used dictionaries and terminologies

Study Data Standardization Plan

Plan for describing the data standardization approach for clinical and nonclinical studies within a development program of a compound

- A template is provided by PHUSE
- List of data standards, dictionaries / terminologies used
  - per single study (nonclinical, clinical)
  - for data pools
- CBER appendix to provide additional information on
  - SDTM / ADaM datasets per study
  - pooled ADaM datasets for ISS / ISE

➡ SDSP completion guideline with detailed descriptions and examples

Study Data Standardization Plan (Example)

List of Studies and Standards

(Excerpt from SDSP Example (Oncology), PHUSE)

4. List of Studies and Standards

4.1 Nonclinical

4.2 Clinical

Study Identifier	Brief Title	Study Design	Study Status	Study Start Date	Exchange Standards	Terminology Standards
Phase 1 Interventional Studies - Advanced Solid Tumors						
ABC-AST-001	Maximum Tolerated Dose of MyNewDrug Administered Intr with Tur	Nonrandomized, Control None, Single Group Assignment,	COMPLETED	2008-03-01	TABULATIONS LEGACY	Sponsor Defined Terminology

4.3 Pooled Studies

Data Pool Identifier	Data Pool (List of Studies)	Pool Status	Pool Description	Exchange Standards	Terminology Standards
ISS-RRPTCL	ABC-AM-001 ABC-AM-002 ABC-AML-001 ABC-MM-001 ABC-OVB-001 ABC-TC-001 ABC-TC-002 ABC-TC-003	CURRENT	ISS - Relapsed or Refractory Peripheral T-Cell Lymphoma - Interim Analysis 1	ADaM v2.1 / ADaM IG 1.0 ADaM define.xml 2.0	CDISC SDTM Terminology 2015-06-26 MedDRA (Adverse Events/ Medical History) Initial: 18.1 Final: 18.1 WHO-DD (Medications) 2015-03

Study Data Standardization Plan (Example)

CBER Appendix

(Excerpt from SDSP Example (Vaccine), PHUSE)

5. ISS and ISE

The following table summarizes the Integrated Summary of Safety and Integrated Summary of Efficacy using ADaM (ISS and ISE).

List all ADaM domains that will be used in the submission.

Dataset Label	Efficacy	Safety	Other*	Included Trials	Phase	Contributing Datasets
ADSL (Analysis Dataset – Subject Level)	X	X		ABC-HS-004 ABC-HS-006	2 and 3	DM, DS, SV, EX, DV
ADAE (Adverse Events)		X		ABC-HS-004 ABC-HS-006	2 and 3	AE, FA, DD, VS, MH, HO, LB

The Integrated Analysis Data Reviewer's Guide

- A template is provided by PHUSE
- Analysis Data Reviewer's Guide (ADRG) adapted to the needs of an integrated analysis
- Specific sections to document
  - data standards and dictionaries / terminologies for integrated datasets
  - source data used for integrated analysis dataset creation
  - traceability

➡ iADRG completion guideline with detailed descriptions and examples

The Integrated Analysis Data Reviewer's Guide (Example)

Source Data Used

Description of

- source data standards and
- additional content of interest, e.g., selection of data

1.4 Source Data Used for Integrated Analysis Dataset Creation

(Insert your text here: data sources for each study for data used for pooling.)

Study Identifier (STUDYID)	Protocol Number	Source Data Standard	Cutoff-Date or DBL-Date / Study Status
		SDTM Model/IG <version> Legacy Tabulation Legacy Analysis ADaM Model/IG <version>	01-20-2021/Ongoing

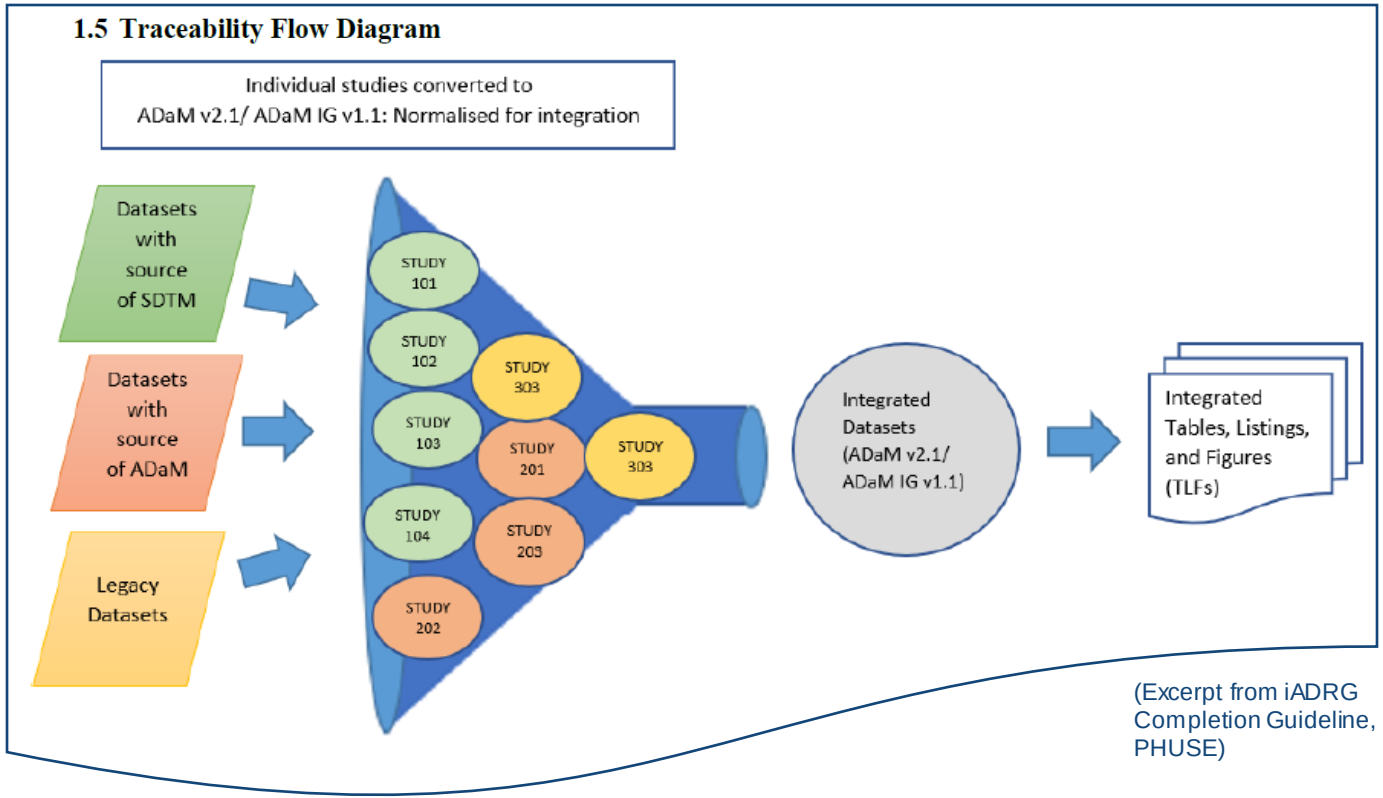
Additional Content of Interest

(See the iADRG Completion Guidelines for additional content of interest.)

(Excerpt from iADRG Template, PHUSE)

The Integrated Analysis Data Reviewer's Guide (Example)

Traceability



(Excerpt from iADRG Completion Guideline, PHUSE)

Standard Safety Tables and Figures: Integrated Guide (FDA)

- Provision of a standard set of safety analytic tables and figures and associated instructions.
- Tables and figures are examples, modifications can be made based on the specific study design.
- Custom and therapeutic area specific analyses maybe required in addition.

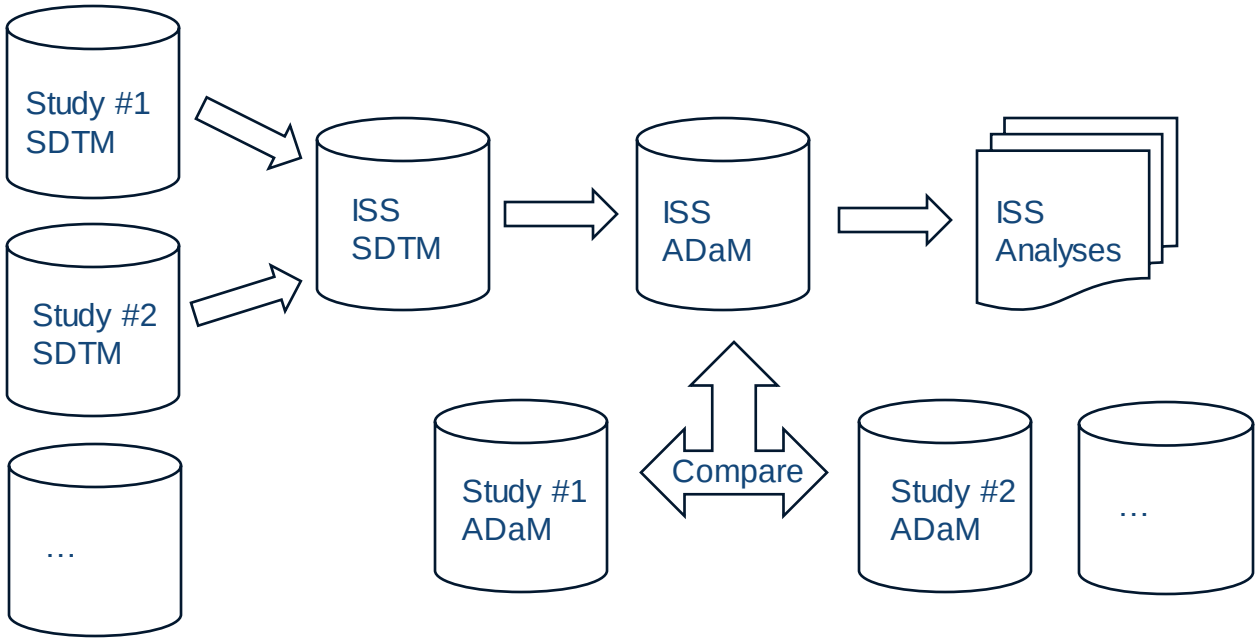
A Travel Report

Preparing an ISS ready for submission to the FDA

OUR EXPERIENCE

CRO PERSPECTIVE

General Strategy



Before Starting Integration

- Check current FDA study data standards catalog for accepted standards for SDTM, ADaM and Define-XML against standards used in the single studies.
- Check versions of dictionaries / terminologies used in the single studies.
- Check availability of ISS SAP and table shells.

Creating ISS SDTM

Integrate only SDTM datasets needed for analysis

Keep only data needed for ISS analysis

- e.g., selection of specific lab parameters or vital signs parameters

Implement unit conversions, if necessary

- e.g., harmonize the results of lab tests or vital signs assessments to a consistent unit for ISS analysis

Perform up-versioning, if necessary

- e.g., up-versioning of MedDRA coding in the integrated AE dataset to most current version, if different have been used in the single study SDTMs

Implement accepted version of SDTM model / IG.
Perform harmonization, if necessary.

Creating ISS SDTM

Start with integrated DM dataset: select subject set needed for ISS analysis.

All other ISS SDTM datasets: merge with integrated DM to get selected subject set.

Creating ISS SDTM

Example: selection of subject set

- When “Standard Safety Tables and Figures: Integrated Guide (FDA)” serves as basis for table shells, not only the safety population have to be selected.

Table 4. Patient Disposition, Pooled Analyses[1,2]

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)
Patients randomized	**n (%)**	**n (%)**
ITT/mITT population[3]	n (%)	n (%)
Safety population	n (%)	n (%)
Per-protocol population	n (%)	n (%)
Discontinued study drug	**n (%)**	**n (%)**
Adverse event	n (%)	n (%)
Lack of efficacy	n (%)	n (%)
Protocol deviation	n (%)	n (%)
Death	n (%)	n (%)
Withdrawal by subject	n (%)	n (%)
Other	n (%)	n (%)
Discontinued study	**n (%)**	**n (%)**
Death	n (%)	n (%)
Lost to follow-up	n (%)	n (%)
Withdrawal by subject	n (%)	n (%)
Physician decision	n (%)	n (%)
Protocol deviation	n (%)	n (%)
Other	n (%)	n (%)

Table 3. Patient Screening and Enrollment, Trials A and B

Disposition		
Patients screened	XX	XX
Screening failures	XXX (XX.X%)	XXX (XX.X%)
Inclusion/exclusion criteria not met	XXX (XX.X%)	XXX (XX.X%)
Patient noncompliance	XXX (XX.X%)	XXX (XX.X%)
Consent withdrawn	XXX (XX.X%)	XXX (XX.X%)
Other	XXX (XX.X%)	XXX (XX.X%)
Patients enrolled	XXX (XX.X%)	XXX (XX.X%)
Patients randomized	XXX (XX.X%)	XXX (XX.X%)

Documentation for ISS SDTM

Reviewer's guide

- Create a clinical study data reviewer's guide for the integrated SDTM.
- Describe the integration strategy:
  - selection of datasets and data from single study SDTMs
  - unit conversions
  - up-versioning and harmonization activities.

define.xml

- Implement an accepted version of the Define-XML standard.
- Follow predecessor concept for variables kept from single study SDTMs.

Documentation for ISS SDTM

Example define.xml

DM (Demographics) - SPECIAL PURPOSE

Variable	Label / Description	Type	Role	Length or Display Format	Controlled Terms or ISO Format	Origin / Source / Method / Comment
STUDYID	Study Identifier	text	Identifier	11	Study Identifier • [redacted] • [redacted]	Protocol
DOMAIN	Domain Abbreviation	text	Identifier	2	SDTM Domain Abbreviation (Subset DM) • "DM" = "Demographics"	Assigned Set to 'DM'
USUBJID	Unique Subject Identifier	text	Identifier	20		Predecessor: DM.USUBJID
SUBJID	Subject Identifier for the Study	text	Topic	8		Predecessor: DM.SUBJID
RFSTDTC	Subject Reference Start Date/Time	datetime	Record Qualifier		ISO 8601	Predecessor: DM.RFSTDTC

Creating ISS ADaM

Create analysis datasets for ISS as needed.

Source: integrated SDTM

Implement accepted version of ADaM model / IG.

Provide traceabilty from integrated SDTM to integrated ADaM.

Creating ISS ADaM

Example: Adverse Event Analysis Dataset (ADAE)

- When “Standard Safety Tables and Figures: Integrated Guide (FDA)” serves as basis for table shells, FDA Medical Queries (FMQs) have to be analyzed.

> The FMQs are standardized groupings of related Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs), categorized as either narrow or broad, that have been developed by FDA reviewers to facilitate safety signal detection in the premarket safety database. Narrow terms indicate a high degree of certainty that the FMQ concept occurred, while broad terms should be considered more exploratory or hypothesis generating. Preferred terms can appear within more than one FMQ. For instance, the PT Cerebral Hemorrhage occurs in the narrow category for both the FMQs Hemorrhage and Stroke-TIA. Therefore, to avoid double counting of adverse events, the results of different FMQs should not be added together. For tables that include FMQs, all FMQs should be run. In general, PTs are ordered by decreasing risk difference (RD). In displays of FMQ data, tables are arranged by SOC; if there are multiple FMQs within the SOC, FMQs are ordered by decreasing RD. For further analyses, including analyses by PT, refer to the Standard Expanded Safety Tables and Figures.

➡ Currently 104 FMQs (broad / narrow) are specified.

Creating ISS ADaM

Example: Adverse Event Analysis Dataset (ADAE)

- Specification for FMQs (excerpt):

DATAS	ORDER	NAME	LABEL	TYPE	LENGTH	CTREF	ORIGIN	COMMENT
ADAE	93	FMQ001NM	FDA Medical Query 001 Name	text	50		Derived	FMQ001NM='Abdominal Pain' if the AEDECOD is included in this FMQ. Identify by merging respective preferred terms from FMQ list to AE dataset.
ADAE	94	FMQ001CS	FDA Medical Query 001 Class	text	6	FMQCLAS	Derived	Identify by merging respective preferred terms from FMQ list to AE dataset. Select only preferred terms with final classification = 'Narrow'.
ADAE	95	FMQ002NM	FDA Medical Query 002 Name	text	50		Derived	FMQ002NM='Abnormal Uterine Bleeding' if the AEDECOD is included in this FMQ. Identify by merging respective preferred terms from FMQ list to AE dataset.
ADAE	96	FMQ002CS	FDA Medical Query 002 Class	text	6			Identify by merging respective preferred terms

	CTREF	CTNAME	TYPE	ORDER	CODE
8	FMQCLAS	Classification of FMQ	text	1	Broad
9	FMQCLAS	Classification of FMQ	text	2	Narrow

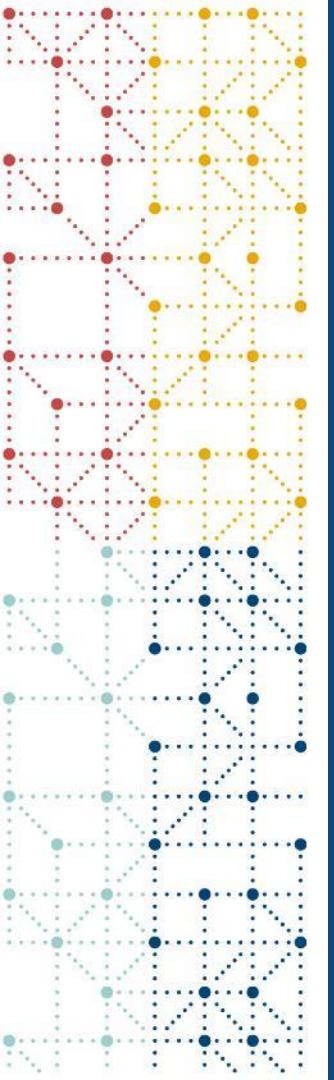
Documentation for ISS ADaM

Reviewer's guide

- Create an integrated analysis data reviewer's guide to provide information about
  - included studies
  - standards used in the integration
  - source data used to create ISS ADaM
  - analysis considerations

define.xml

- Implement an accepted version of the Define-XML standard.



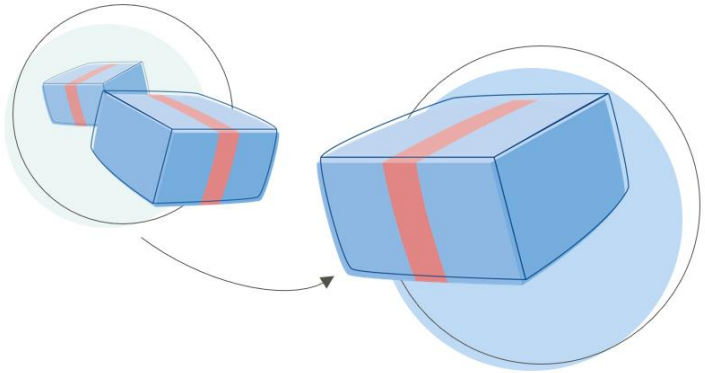
Arrival

Ready for Submission

Content of the ISS Submission Package

Organized in subfolders as needed for e-submission

- adam
  - datasets
    - ✓ define.xml + stylesheet (+ define.pdf*)
    - ✓ iadrg.pdf
    - ✓ ADaM datasets (*.xpt)
  - programs
    - ✓ (SDTM creation programs*)
    - ✓ ADaM creation programs
    - ✓ Table/Listing/Figure generation programs
    - ✓ macro/tool programs
- sdtm
  - ✓ pooled SDTM datasets (*.xpt)
  - ✓ define.xml + stylesheet (+ define.pdf*)
  - ✓ csdrg.pdf



* not required

Thank You!