OCS LIFE SCIENCES
A DIVISION OF OCS CONSULTING

CDISC-Compliant ISS Submission: A Use Case

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Disclaimer

All the information presented here is based on a specific use case and may not necessarily align with the requirements of regulatory authorities in a different submission.

Agenda

- Introduction
- ISS Strategy
- ISS Deliverables
- Key Messages

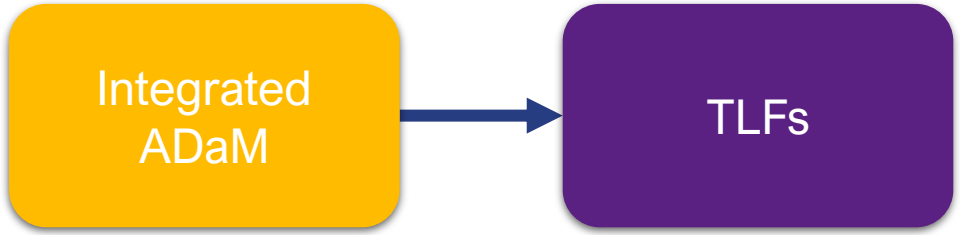
Introduction

- **Legacy study conversion**
  - Phase I trials converted to SDTM
  - Phase II trials converted to SDTM and ADaM, and reproduction of main endpoints

- **Support ISS preparation**

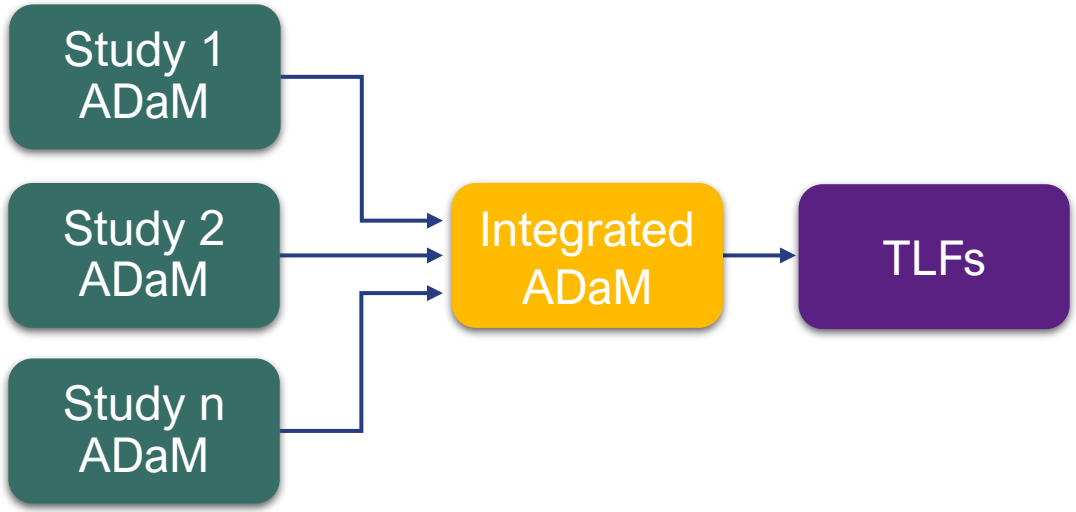
ISS Introduction

- **Integrated Summary of Safety (ISS)**
  - Required regulatory submission document
  - Safety analyses based on pool of clinical trials
  - Different integration strategies

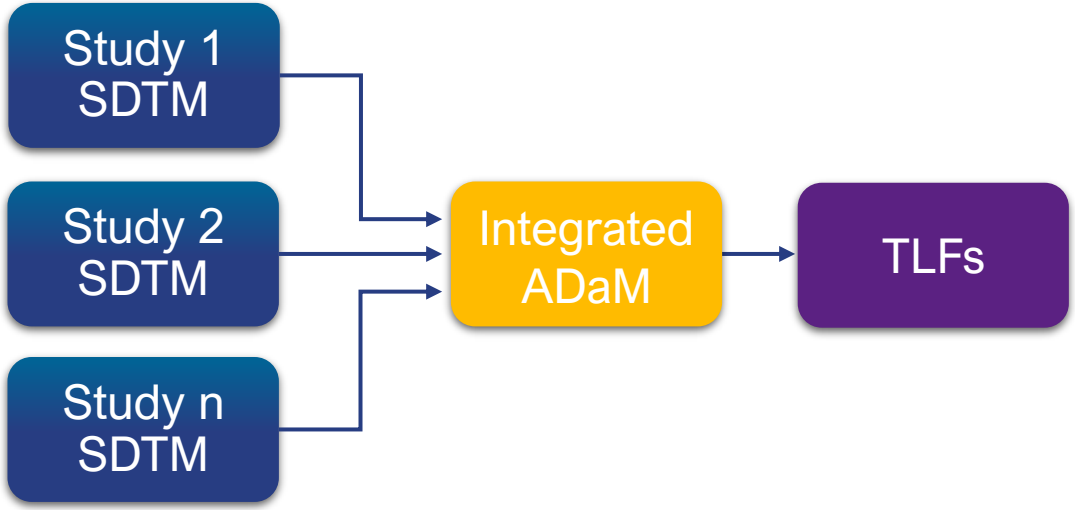


Most Common Integration Strategies

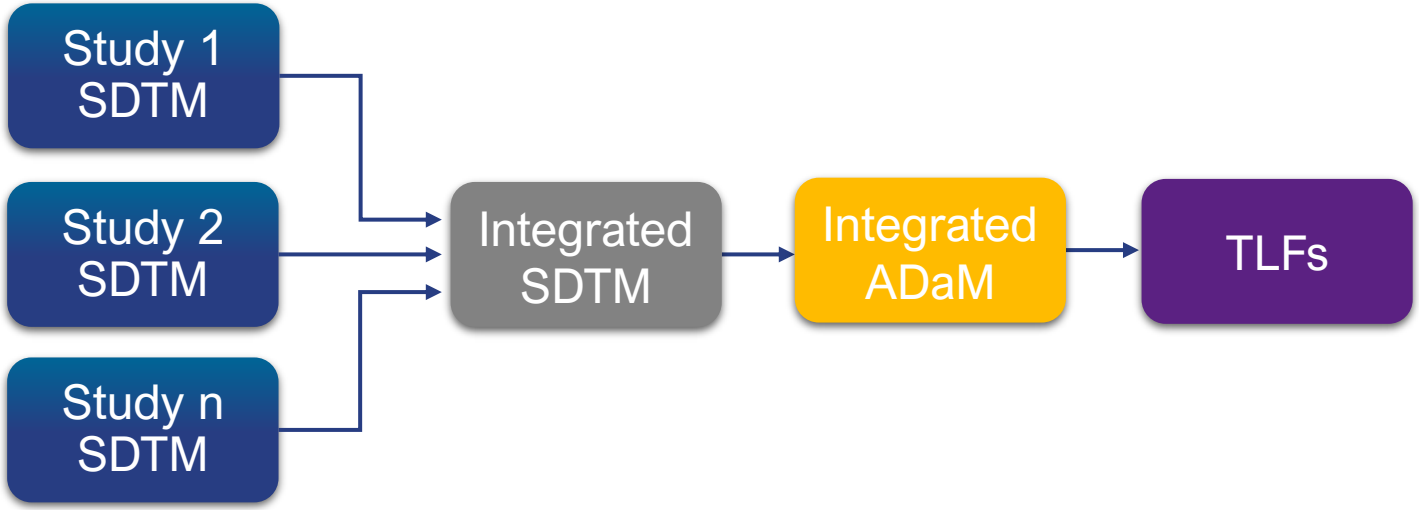
Option 1



Option 2

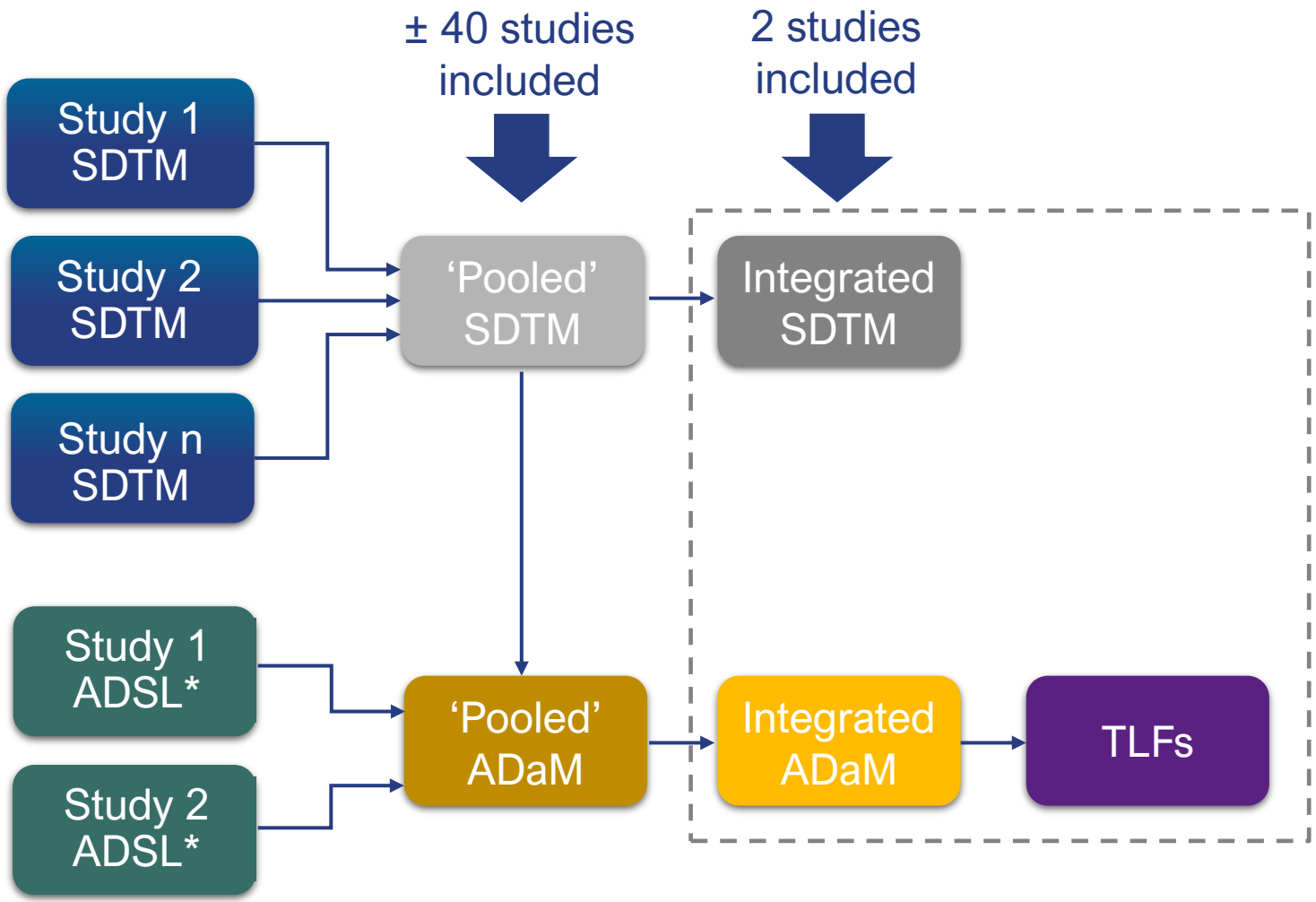


Option 3



Our Integration Strategy

Approach according to Submission Data Management Plan / Study Data Standardization Plan



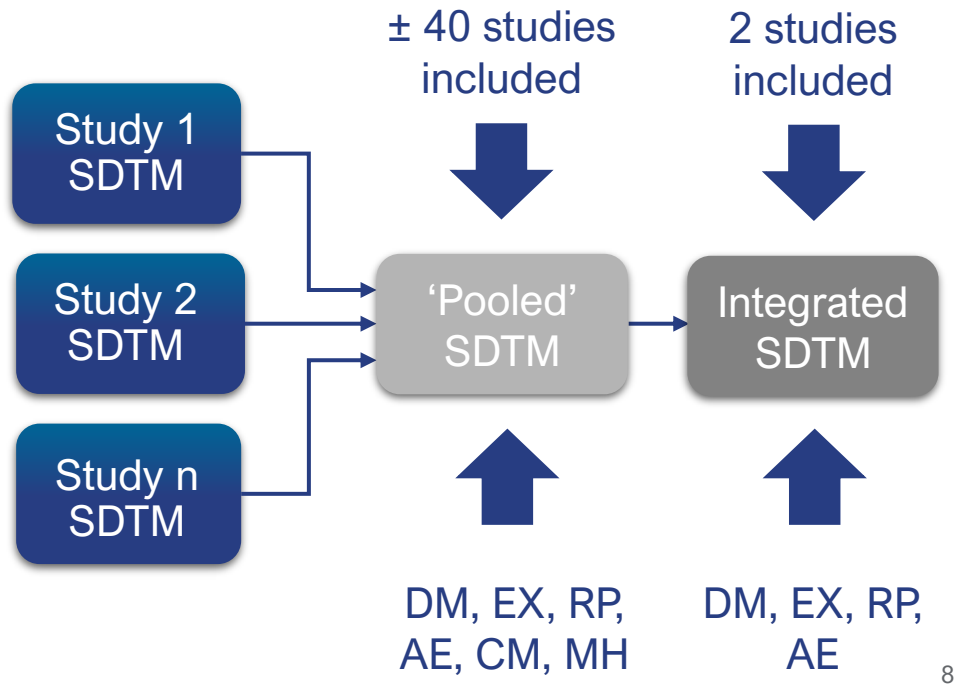
*Only for selected parameters

Harmonisation in ‘Pooled’ SDTM according to versions used in pivotal trial

- SDTM IG: version 3.2 and 3.3 → 3.2
- SDTM controlled terminology, e.g. ETHNIC, RPTESTCD
- Sponsor-defined terminology, e.g. ARM(CD), EXTRT, AEREL, QNAM
- MedDRA recoding: AE and MH
- WHODrug recoding: CM

Adherence to FDA Study Data Technical Conformance Guide

- ‘Screen Failure’, ‘Not Assigned’, and ‘Not Treated’ not specified as treatment arm



ADaM

No SAP

ADSL

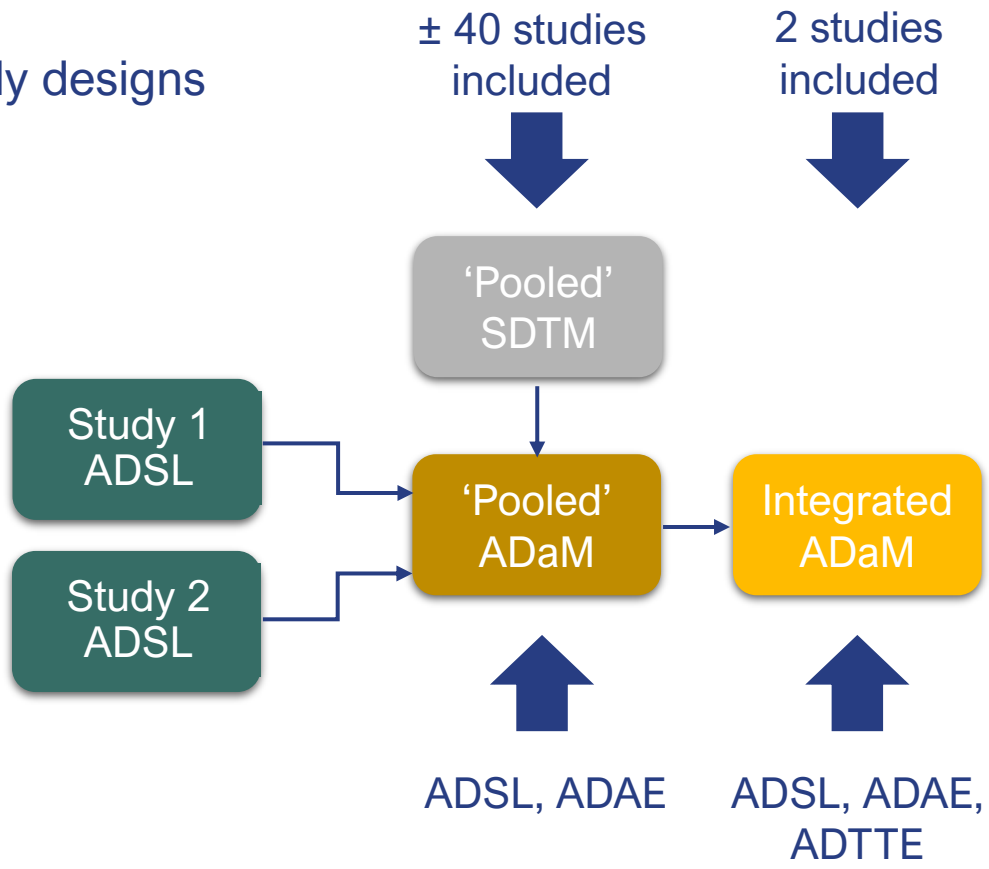
- Treatment variables
  - Challenging / time-consuming because of different study designs
- Subgroup variables

ADAE

- Treatment emergent derivation
- Flagging of Adverse Events of Special Interest (AESIs)
- First occurrence flags

ADTTE

- Exposure years

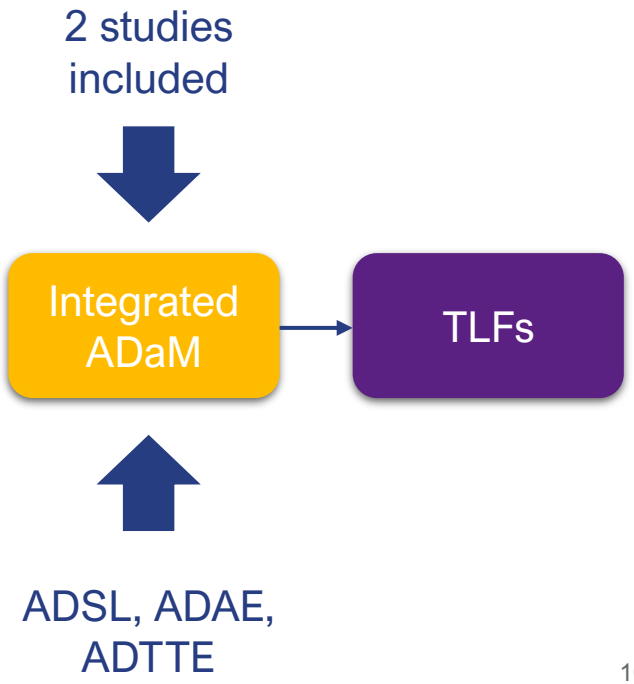


Tables and Listings

Table 1: Treatment-emergent adverse events (TEAEs) by system organ class and preferred term

	Study 1					Study 2				
	Active dose 1 (N=XXX)		Placebo (N=XXX)		EAIR diff. est.	Active dose (N=XXX)		Placebo (N=XXX)		EAIR diff. est.
System Organ Class Preferred Term	n (%) [m]	EAIR	n (%) [m]	EAIR	EAIR diff. (95% CI)	n (%) [m]	EAIR	n (%) [m]	EAIR	EAIR diff. (95% CI)
TEAEs	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)
System Organ Class 1	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)
Preferred Term 1	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)
Preferred Term 2	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)
System Organ Class 2	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)
Preferred Term 1	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)
Preferred Term 2	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)	xx (xx.x) [xx]	xx.x	xx (xx.x) [xx]	xx.x	x.xx (x.xx;x.xx)

EAIR = Exposure-adjusted incidence rate.



SDTM and ADaM Define.XML

- No literature, specifications, examples
- General Define-XML v2.0 specifications used

- Main differences:
  - General study information

  - SDTM Define-XML:
    - No aCRF
    - “Predecessor” origin

  - ADaM Define-XML
    - No differences

Standard	SDTM-IG 3.2
Study Name	<study 1> and <study 2>
Study Description	Integrated Summary of Safety for <drug> in <indication>
Protocol Name	ISS <indication>
Metadata Name	Study <study 1> and <study 2> Data Definitions

Pinnacle 21 Validator Report

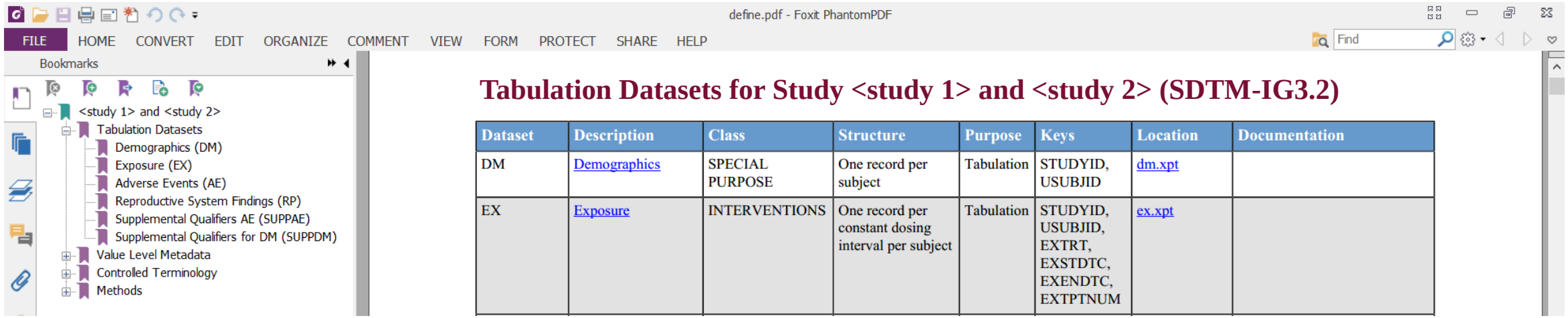
Issue Summary

Source	Pinnacle 21 ID	Message	Severity	Found
DM				
	SD1349	Inconsistent STUDYID		244
DEFINE				
	DD0102	Invalid Annotated CRF document name		1
	DD0105	Origin for Study Day variable 'AEENDY' is not set to Derived		1
	DD0105	Origin for Study Day variable 'AESTDY' is not set to Derived		1
	DD0105	Origin for Study Day variable 'DMDY' is not set to Derived		1
	DD0105	Origin for Study Day variable 'EXENDY' is not set to Derived		1
	DD0105	Origin for Study Day variable 'EXSTDY' is not set to Derived		1
	DD0105	Origin for Study Day variable 'RPDY' is not set to Derived		1
	DD0106	Origin for DOMAIN variable is not set to Assigned		4
	DD0107	Origin for RDOMAIN variable is not set to Assigned		2
	DD0108	Origin for STUDYID variable is not set to Protocol		6

Define.PDF

- FDA request

- Java application “Apache Formatting Objects Processor” (FOP)[1] in combination with define XSL stylesheet
  - Converts XML to PDF
  - Working bookmarks and hyperlinks



Tabulation Datasets for Study <study 1> and <study 2> (SDTM-IG3.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	
EX	Exposure	INTERVENTIONS	One record per constant dosing interval per subject	Tabulation	STUDYID, USUBJID, EXTRT, EXSTDTC, EXENDTC, EXTPTNUM	ex.xpt	

[1]Brian Mabe, Define.XML to Define.PDF, Just F.O.P It, PHUSE US Connect 2018

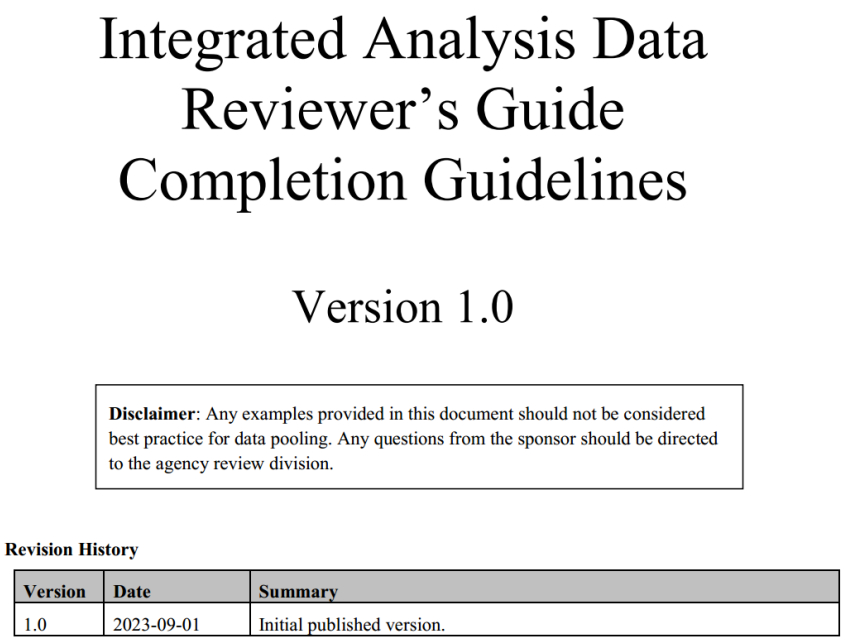
icSDRG and iADRG

- Purpose:
  - Provide reviewers with additional context

- For integrated SDTM: Integrated Clinical Study Data Reviewer's Guide (icSDRG)
  - Proprietary version
    - Study data standards and dictionary versions
    - Description of integrated studies
    - Integration strategy with traceability flow diagram
    - Overview of integrated datasets and any special considerations (e.g. recoding)
    - Data conformance issues summary

icSDRG and iADRG

- For integrated ADaM: Integrated Analyis Data Reviewer's Guide (iADRG)
  - Preliminary PHUSE template for iADRG
  - In addition to icSDRG:
    - Analysis considerations, e.g. core variables, treatment variables, imputations, AESI flagging
    - Integrated analysis output programs



Integrated Analysis Data
Reviewer's Guide
Completion Guidelines

Version 1.0

Disclaimer: Any examples provided in this document should not be considered best practice for data pooling. Any questions from the sponsor should be directed to the agency review division.

Revision History

Version	Date	Summary
1.0	2023-09-01	Initial published version.

M5 Folder Structure for ISS

- Per FDA Study Data Technical Conformance Guide

Folder	Files to be included
iss	N/A
analysis	N/A
adam	N/A
datasets	ISS ADaM datasets, as well as associated Define-XML/Define.PDF and iADRG
split	N/A
programs	Programs for ISS ADaM datasets and TFLs
misc	AESI file
tabulations	N/A
sdtm	N/A
datasets	ISS SDTM datasets, as well as associated Define-XML/Define.PDF and icSDRG

Key Messages

- Carefully consider different integration strategies
- ISS SAP
- Communication is the key
- ISS Define.XML/Define.PDF and icSDRG/iADRG rather straightforward

Thank you! Any questions?

- **Further reading:**

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