ISS/ISE and CDISC

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Agenda

- Introduction to ISS/ISE Requirements
- Data Integration
- Key Learnings from Cytel Use Cases
- Conclusions

Introduction to ISS/ISE Requirements

- Purpose of the ISS/ISE
- Planning the ISS/ISE

Purpose of ISS/ISE

Integrated Summary of Safety (ISS) is required by the US FDA

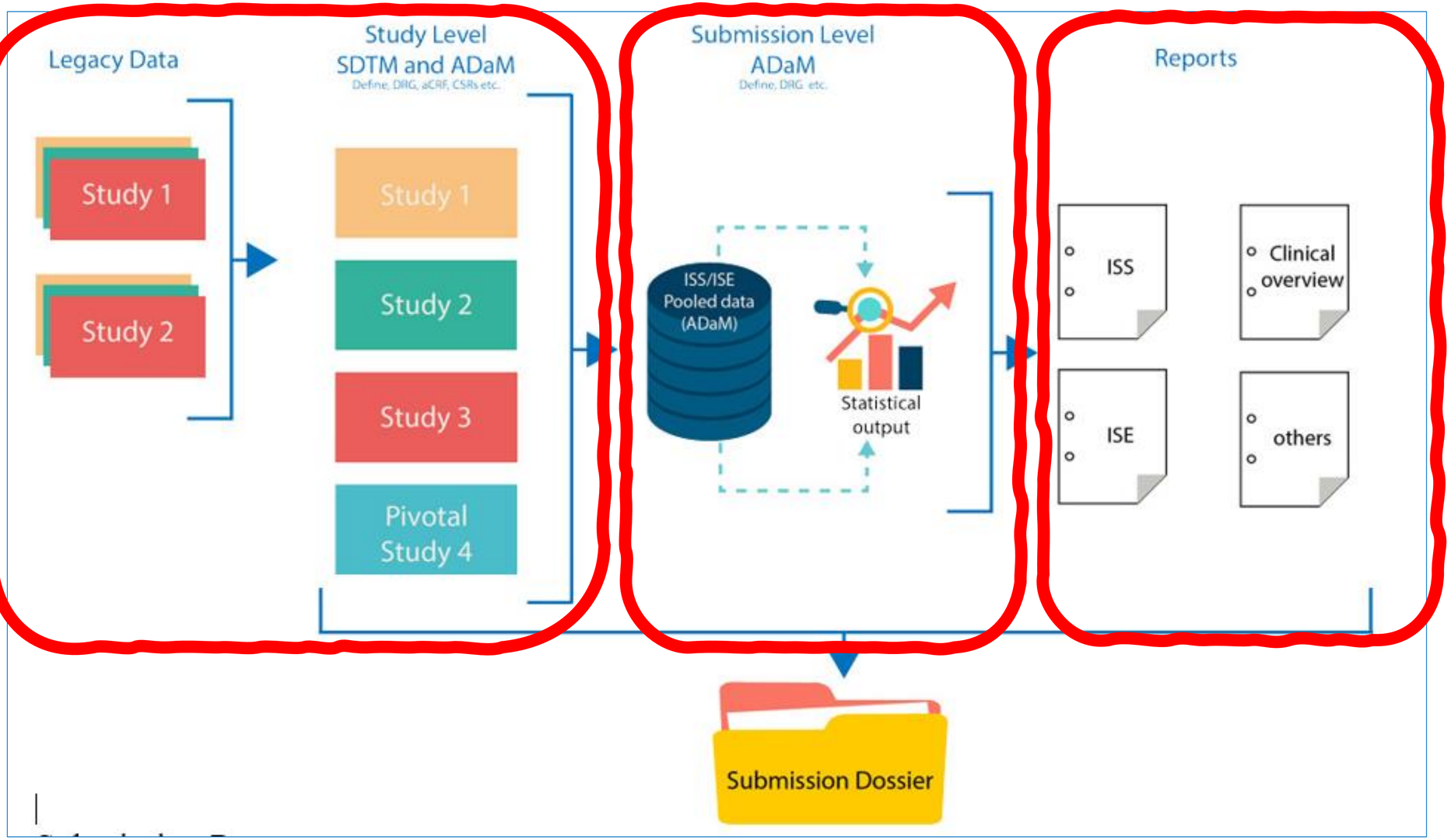
This is a **detailed integrated analysis** of all relevant data **from individual studies**

The aim is to provide a **more robust safety profile** across different populations

Integrated Summary of Efficacy (ISE) might be also needed

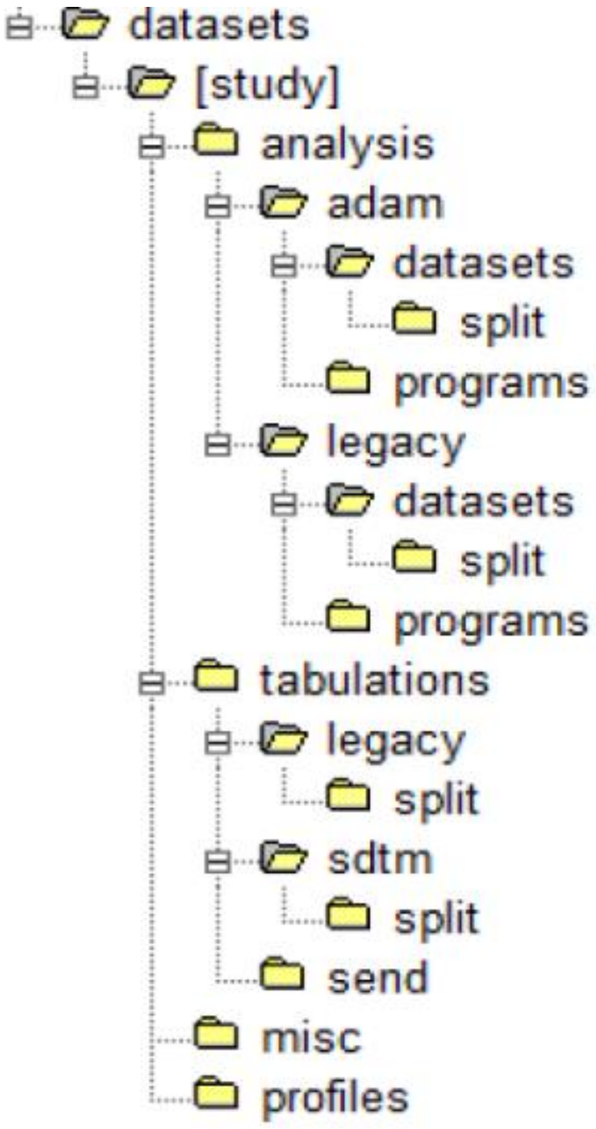
With ISS, and ISE, **a single database is formed by pooling** the results of all concerned studies

Purpose of ISS/ISE



Planning the ISS/ISE

This is also where supporting SDTM and ADaM datasets are placed if submitted



Planning the ISS/ISE

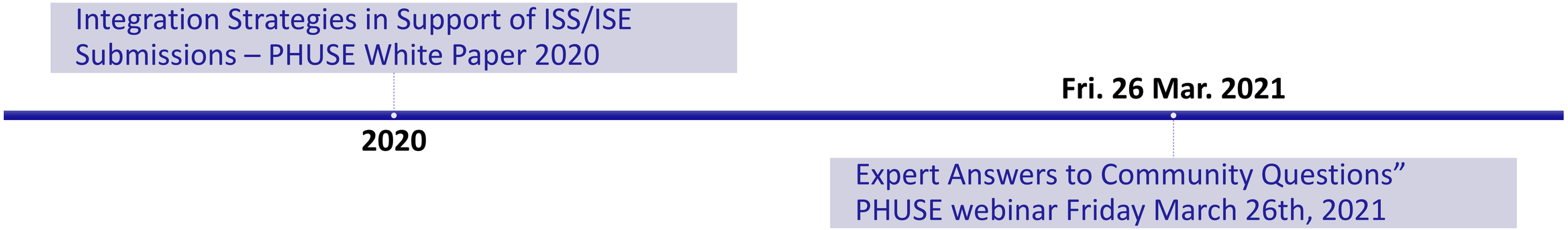
Data Integration

Data Integration Options

- **Things to take care with Data Integration**
- **SDTM(s) → iADaM**
- **ADaM(s) → iADaM**
- **SDTM(s) → iSDTM → iADaM**

Planning the Data Integration

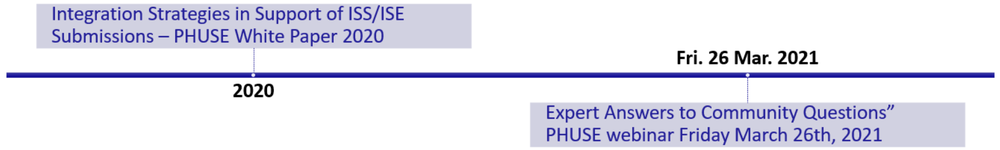
Data Integration - **Things to take care with Data Integration**



- Subjects participating to **more than one study**
- **Medical dictionaries up-versioning** e.g., MedDRA
- **Terminology alignment** used by different studies for major items and when applicable and possible e.g., CDISC-CT, Visit Naming Conventions
- **Standard Unit Conversion** e.g., labs
- **Data Filtering** e.g., not all laboratory parameters need to be integrated
- **CDISC Conformance**

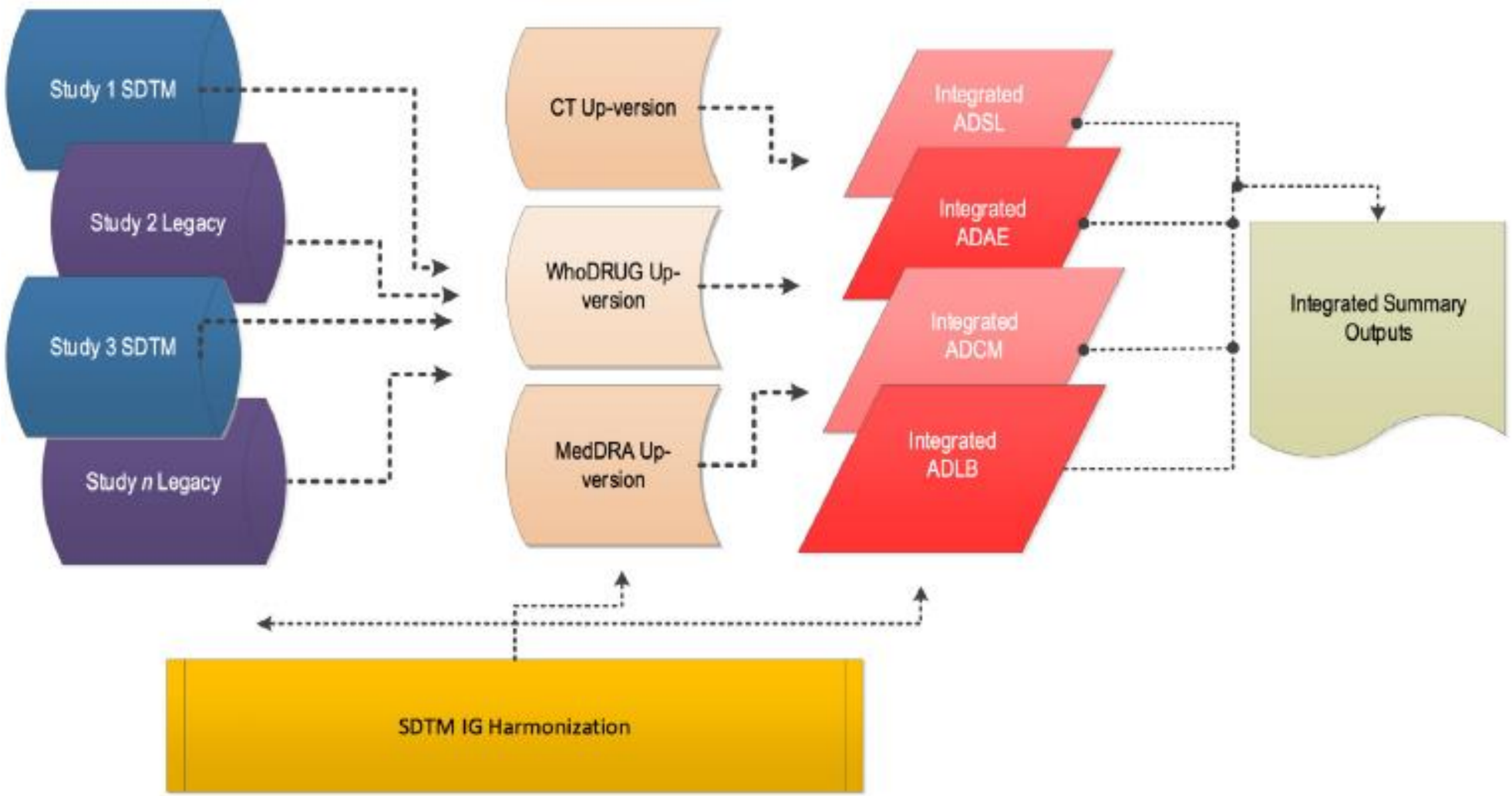
Data Integration - **Things to take care with Data Integration**

- **ADaM Integration (iADaM)** is required to support all ISS (and ISE) analysis
- The question: **what should be the source of iADaM**?
- 3 options are provided in the PHUSE White Paper
  - **Integrate from SDTM(s)**
  - **Integrate from ADaM(s)**
  - **Create an intermediate iSDTM from which iADaM is derived**
- In all three scenario, integration from **both legacy, either raw data or analysis datasets, and CDISC datasets**, is allowed



Data Integration Options: **SDTM(s) → iADaM**

Pooling in ADaM from Individual Study SDTM datasets



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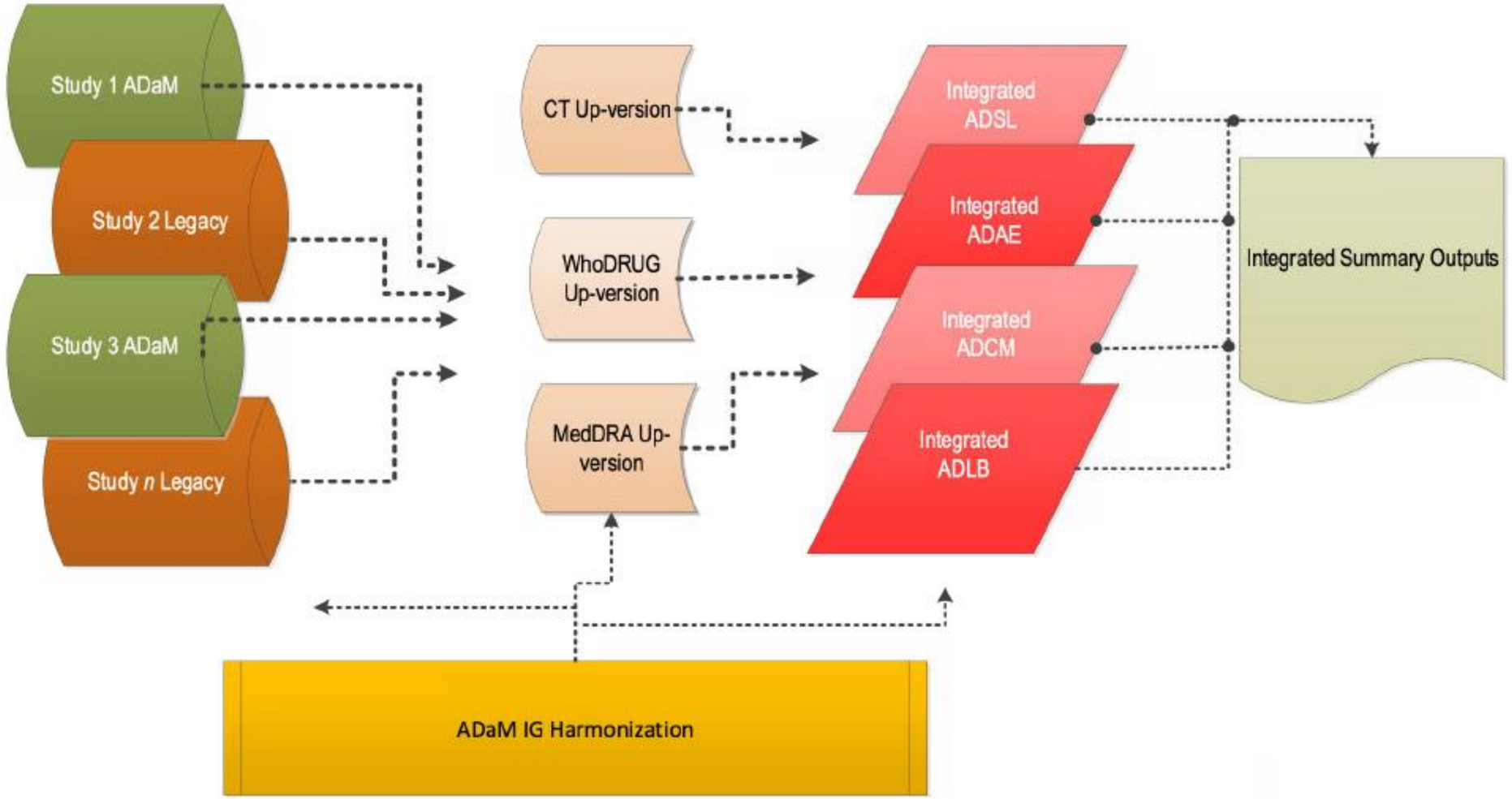
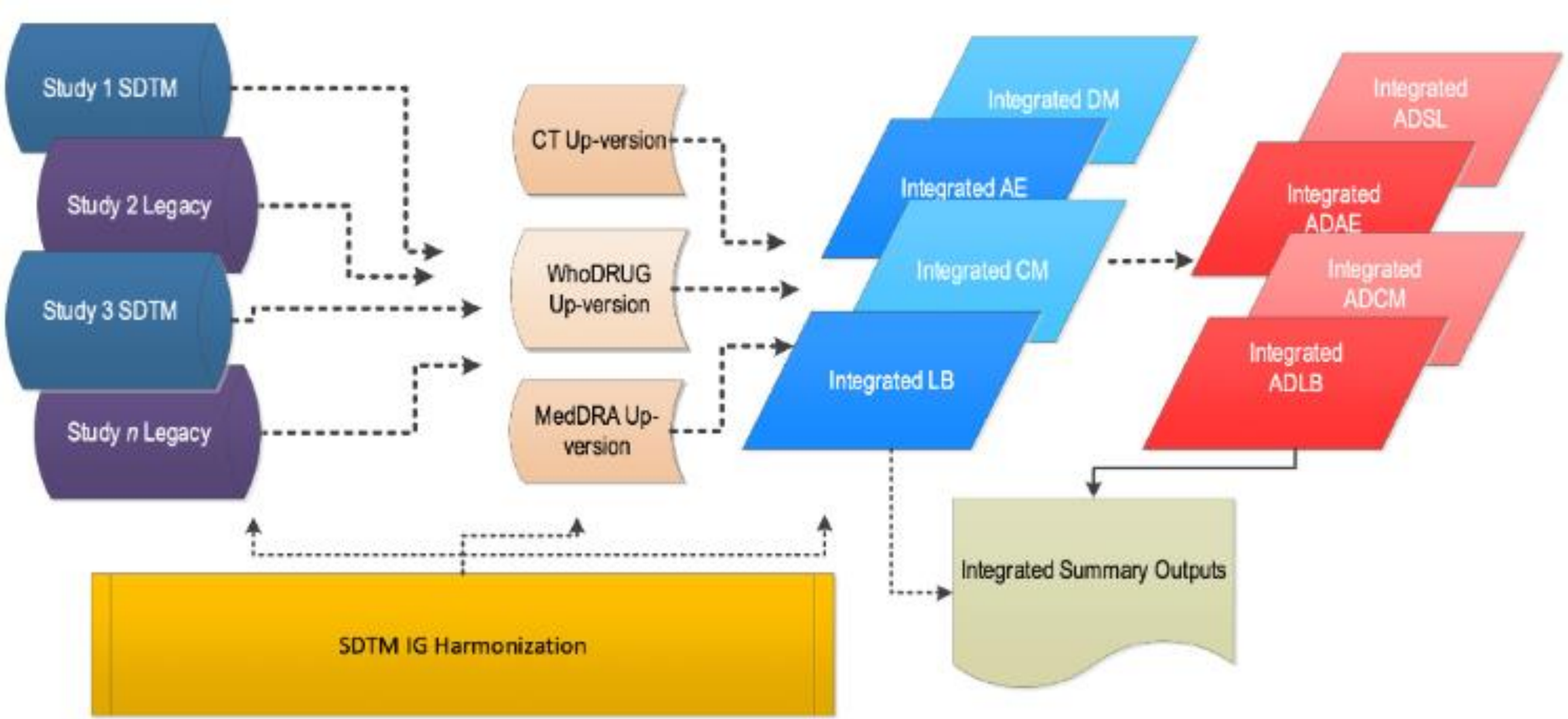
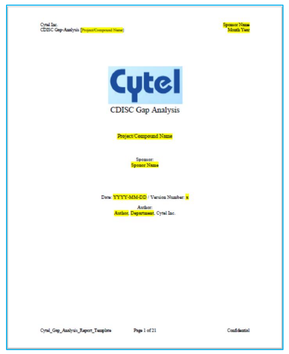


Data Integration Options: **SDTM(s) → iSDTM → iADaM**

Pooling in iSDTM, then iADaM



Planning the Data Integration


Cytel Inc.
CDISC Gap Analysis [Project/Compound Name]
Sponsor Name
Schedule Name

Cytel

CDISC Gap Analysis

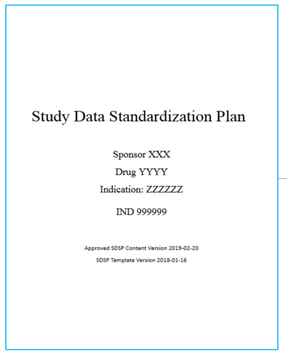
[Project/Compound Name]

Sponsor:
Sponsor Name

Date: YYYY-MM-DD - Version Number: x

Author:
Author, Department, Cytel Inc.

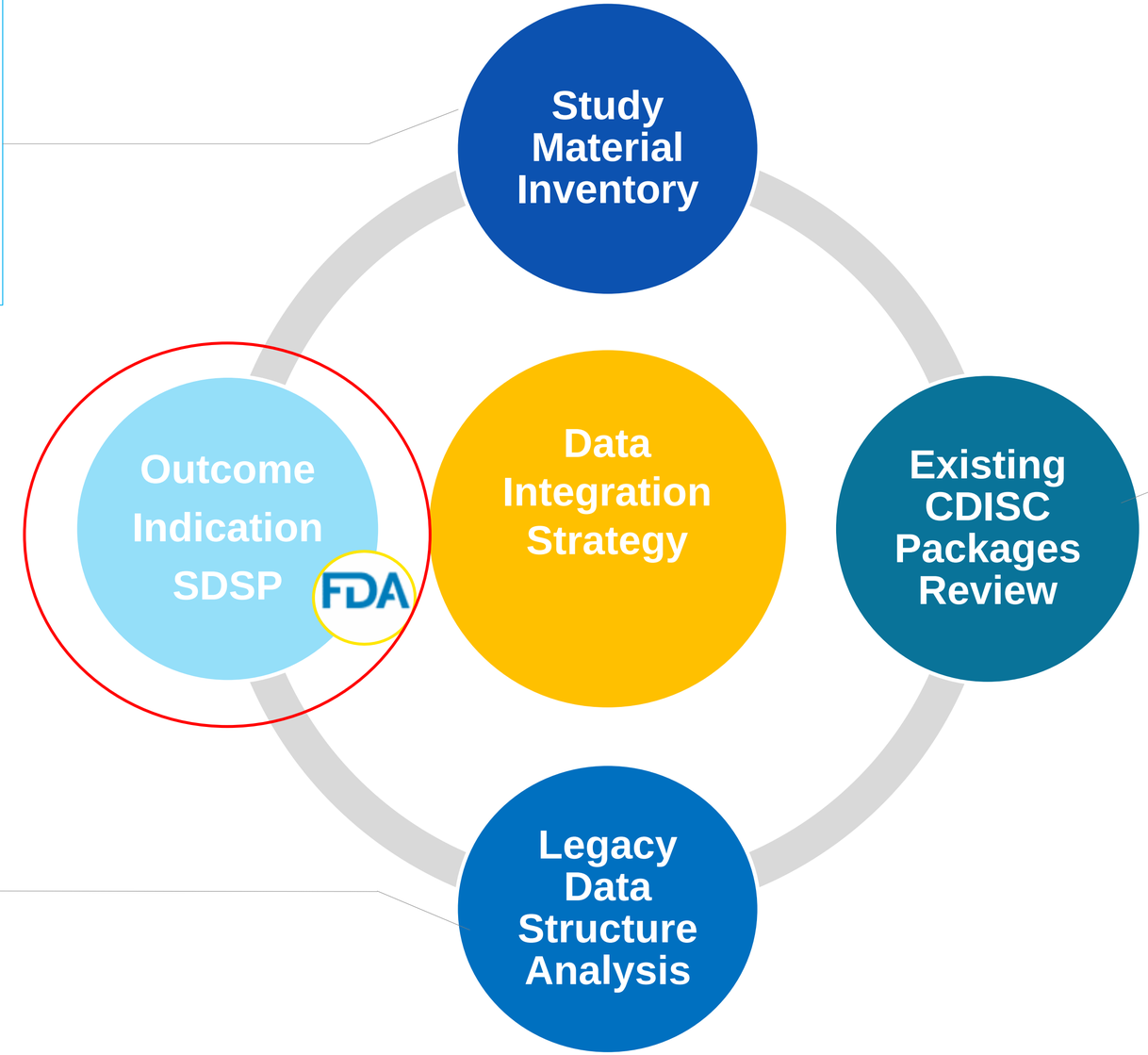
Cytel_Gap_Analysis_Report_Template Page 1 of 21 Confidential


Study Data Standardization Plan

Sponsor XXX
Drug YYYY
Indication: ZZZZZZ

IND 999999

Approved SDSP Content Version 2019-02-20
SDSP Template Version 2018-01-16



Item	Study 1	Study 2
Datasets		
Data Available?	YES	YES
Source Data (SDTM/Legacy)	SDTM	SDTM
(Comments)		
Analysis Datasets (ADAM/Legacy)	ADAM	ADAM
(Comments)		
Supporting Legacy Datasets Documentation (if applicable)		
SDTM Package		
SDTM Package (N=Only Datasets but no xpt, define, sdrg, etc.)	YES	YES
SDTM Ig	3.2	3.1.3
SDTM CT	2017-03-31	2017-03-31
SDTM define.xml	2.0	2.0
SDTM csdrg	YES	YES
SDTM acrf	YES	YES
ADaM Package		
ADaM Package (N=Only Datasets but no xpt, define, sdrg, etc.)	YES	YES
ADaM Ig	1.0	1.0

DOM	QNAM	QLABEL	QORIG	Study 1	Study 2	.....
AE	ACN1	Action Taken With Trt 1	CRF	X	X	
AE	ACN2	Action Taken With Trt 2	CRF	X	X	
AE	ACNCONM	Other Action, Concomitant Medication	CRF	X	X	X
AE	ACNCONP	Other Action, Concomitant Procedure	CRF	X	X	X
AE	AEACNOR	Orig. Action Taken with Study Trt	CRF			
AE	AEACNOR	Orig. Action Taken with Study Trt	eDT	X	X	X
AE	AEACNREG	Action Taken With Trt: Regimen Modified	CRF	X	X	X
AE	AECHANGE	Change in Toxicity Grade	CRF	X	X	X
AE	AEOUTOR	Orig. Outcome	CRF			
AE	AEOUTOR	Orig. Outcome	eDT	X	X	X
AE	AERELNS1	Relationship to Non-study TRT 1	CRF			

DOMAIN	TESTCD	TEST	STRESU	Study 1	Study 2	.....
LB	AMYLASE	Amylase	U/L		X	
LB	AST	Aspartate Aminotransferase	U/L	X	X	X
LB	BANDS	Bands	10^9/L			
LB	BASO	Basophils	10^9/L	X	X	X
LB	BASOLE	Basophils/Leukocytes	%	X	X	X
LB	BBRAB	Borrelia burgdorferi Antibody	LIV			
LB	BILI	Bilirubin	umol/L	X	X	X
LB	BUN	Blood Urea Nitrogen	mmol/L	X	X	X

Key Learnings from Cytel Use Cases

- Data Integration Options Applied at Cytel and Main Challenges
- Some Hints

Data Integration Options Applied at Cytel

Last 10 major FDA submissions we did at Cytel in the last three years

Data Integration Option	N
Option Individual Study SDTMs to iADAM	4
Option 2 Individual Study ADaMs to iADAM	2
Option 3 Individual Study Datasets to iSDTM to iADaM	4

Main Challenges

- **Timeline-alignment** when two different vendors are appointed for pivotal study and ISS/ISE
- **Sponsor(s)**
- **Unavoidable Conformance Issues**
- **Inconsistent ADaM(s)** when choosing option 2

Some Hints

Share your Strategy with the Agency - SDSP

4.3 Pooled Studies

In addition to study data packages for XXXX Phase II/III studies (see section 4.1), <Sponsor> will create pooled Integrated SDTM (iSDTM) datasets for the domains that will be used for the ISS; the iSDTM will be used to create the Integrated ADaM (iADaM), from which ISS summaries will be created e.g., tables. Both iSDTM and iADaM datasets will be submitted together with define-xml and cSDRG and ADRG respectively for iSDTM and iADaM.

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- Based on the current versions of the ISS SAP, at least the SDTM domains listed in the following table will be integrated from all studies contributing to the ISS

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No iSDTM Trial Design Datasets will be provided as well as special purpose domain SV (Subject Visits) and SE (Subject Elements). "Visit Windowing" will be applied in iADaM wherever applicable and needed the ISS planned analysis.

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002	001-001-001	001-015	WHITE	1975-01-01	46	2021-01-01

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001	001-001-001	001-001	ANEMIA	2020-01-12	2020-01-13
002	001-001-001	001-015	NAUSEA	2021-01-04	2021-01-07

More details about standards <Sponsor> intends to use i.e., SDTM Ig, Controlled Terminology and MedDRA versions, are detailed in the table on the next page.
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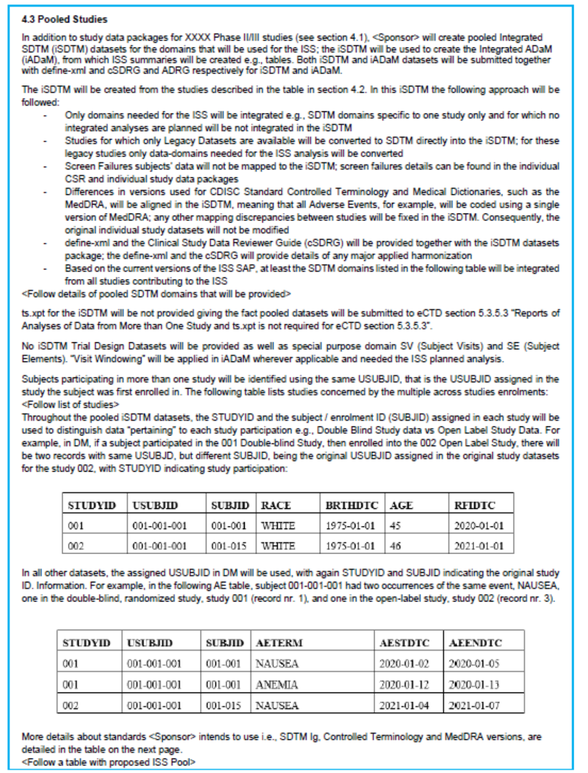

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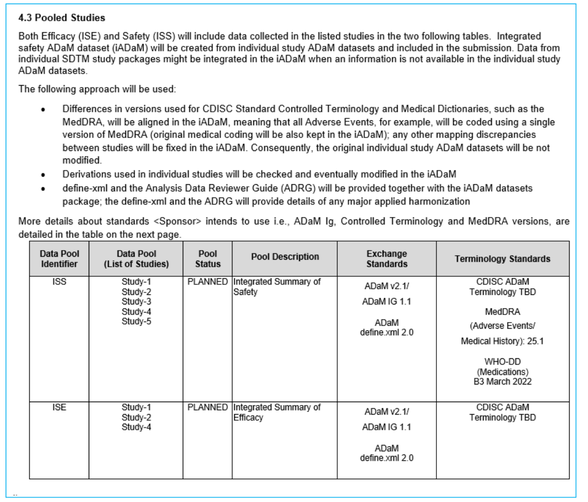

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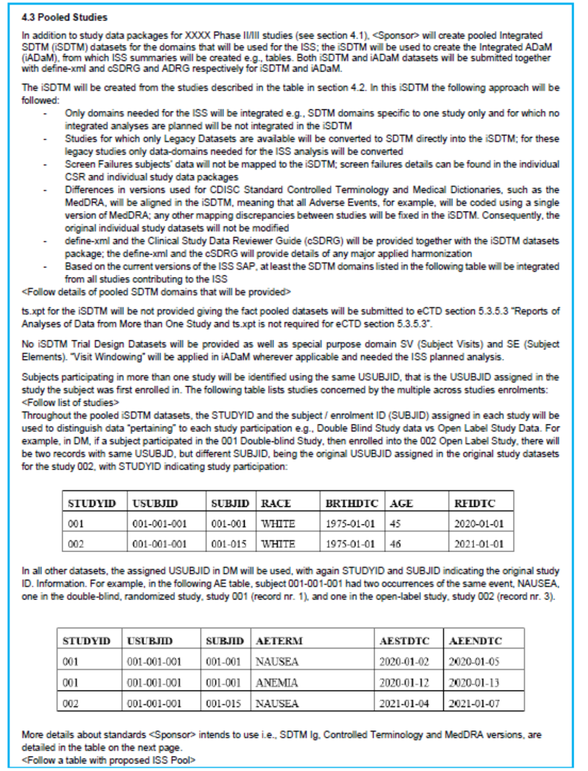

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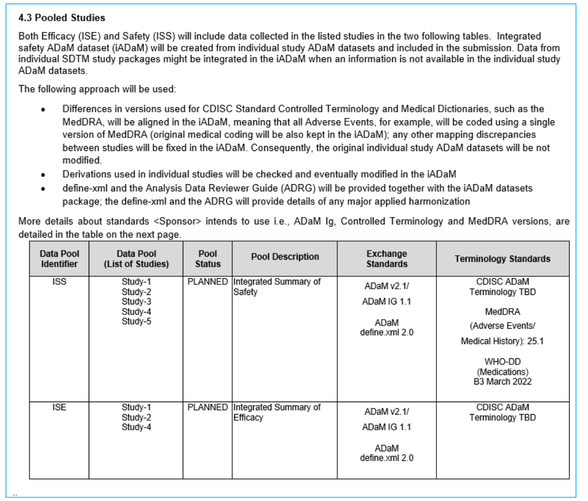
<Follow a table with proposed ISS Pool>



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- Differences in versions used for CDISC Standard Controlled Terminology and Medical Dictionaries, such as the MedDRA, will be aligned in the iADaM, meaning that all Adverse Events, for example, will be coded using a single version of MedDRA (original medical coding will be also kept in the iADaM); any other mapping discrepancies between studies will be fixed in the iADaM. Consequently, the original individual study ADaM datasets will be not modified.
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Some Hints

Share your Strategy with the Agency - SDSP

With Option 2 ADaM(s) → iADaM

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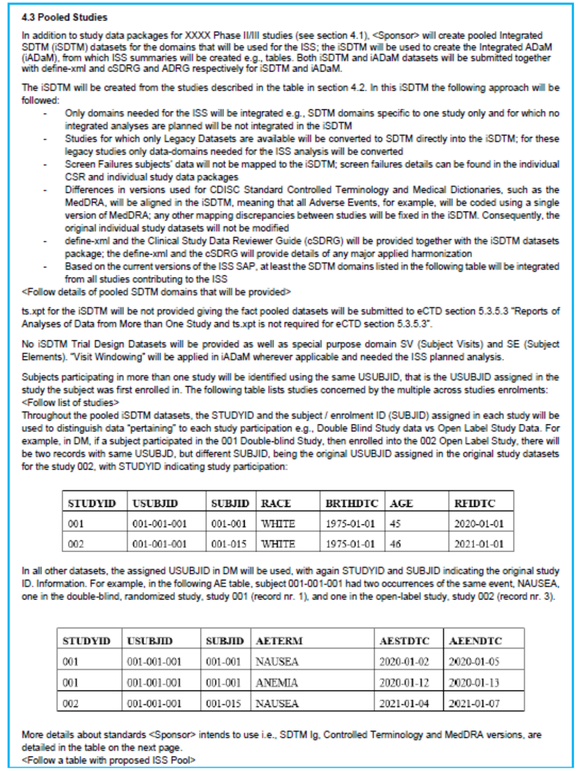

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In addition to study data packages for XXXX Phase II/III studies (see section 4.1), <Sponsor> will create pooled Integrated SDTM (iSDTM) datasets for the domains that will be used for the ISS; the iSDTM will be used to create the Integrated ADaM (iADaM), from which ISS summaries will be created e.g., tables. Both iSDTM and iADaM datasets will be submitted together with define-xml and cSDRG and ADRG respectively for iSDTM and iADaM.

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No iSDTM Trial Design Datasets will be provided as well as special purpose domain SV (Subject Visits) and SE (Subject Elements). "Visit Windowing" will be applied in iADaM wherever applicable and needed the ISS planned analysis.

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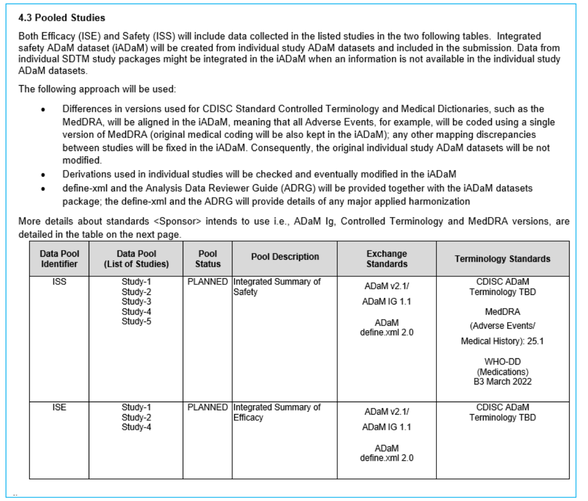

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Some Hints

No need to provide TS if iSDTM is provided (or any other TDMs), If you are worried about rejection criteria

The pooled datasets should be submitted to eCTD section 5.3.5.3 Reports of Analyses of Data from More than One Study. ***Ts.xpt is not required for eCTD section 5.3.5.3***

edata@fda.hhs.gov

Some Hints

Medical Coding Up-versioning – Numbers from one of our ISS

Item	N
Number of AE terms to up-version	22129
Number of different MedDRA versions applied in individual studies	11
Number of AEs previously not coded	25
Wrong casing in original coding	13
Number of coding changes caused by the up versioning (any)	4676
Number of coding changes caused by the up versioning (SOC)	195
Number of coding changes caused by the up versioning (Preferred term)	1179

Store original coding in the datasets

and / or

Document changes in the cSDRG or ADRG

Some Hints

Handling “Unavoidable” conformance issues

- CDISC Conformance Rules are not built to handle data integration
- It is expected to have conformance issues when iSDTM or iADaM are validated
- Provide Clear Rationale in either the cSDRG or ADRG

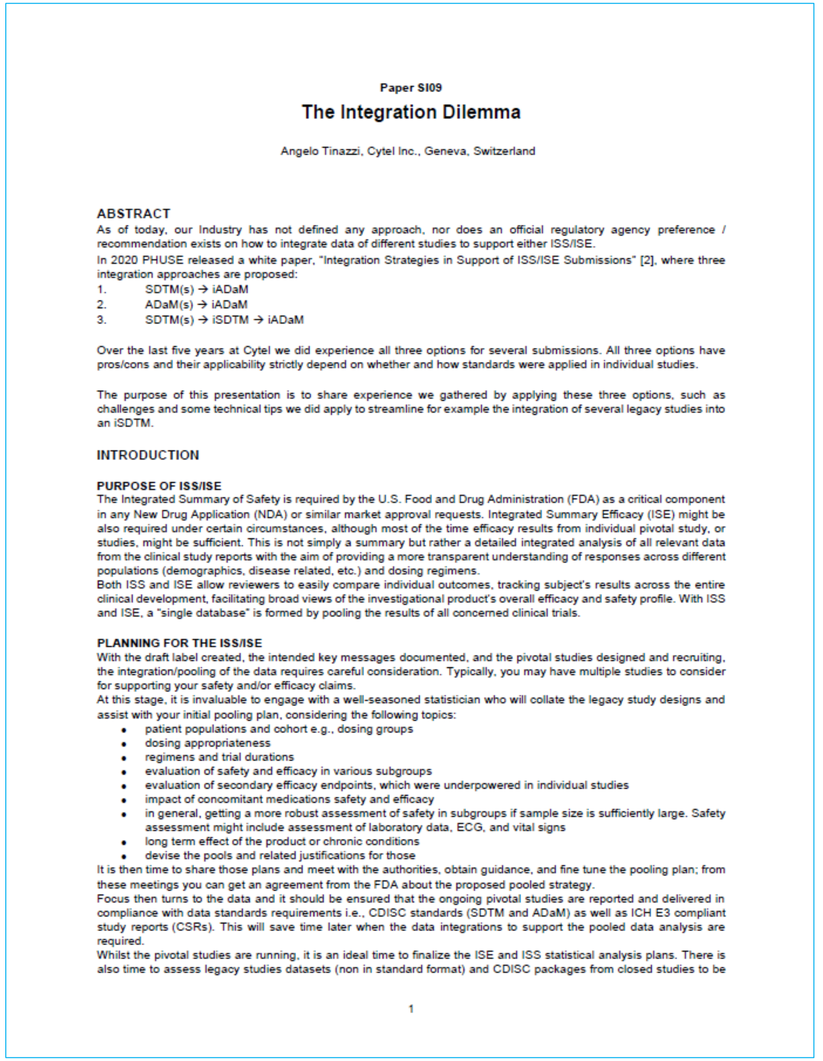
Missing TS dataset (SD1115)
As per communication with the FDA eData team, TS is not applicable for eCTD section “5.3.5.3”.

Incorrect value for AESTDY variable (SD1090)
This occurs when subjects participated in more than one study. The Pinnacle check doesn’t take into consideration the STUDYID in getting the reference start date from DM.

Inconsistent STUDYID (SD1349)
This is because we have pooled subjects from different studies, so STUDYID contains the original Study id.

Some Hints
More in the PHUSE paper

- Aligning CDISC Terminology Harmonization through code generated from specs
- Reviewing previous classification e.g., reason for end of study
- Handling multiple baseline in iADaM when subjects did attend >1 study
- Other ADaM considerations
- Reproducibility of selected CSR results from the iADaM
- Data Gap-Analysis Examples
- …..More



Paper SI09

The Integration Dilemma

Angelo Tinazzi, Cytel Inc., Geneva, Switzerland

ABSTRACT

As of today, our Industry has not defined any approach, nor does an official regulatory agency preference / recommendation exists on how to integrate data of different studies to support either ISS/ISE.

In 2020 PHUSE released a white paper, "Integration Strategies in Support of ISS/ISE Submissions" [2], where three integration approaches are proposed:

1. SDTM(s) → iADaM
2. ADaM(s) → iADaM
3. SDTM(s) → iSDTM → iADaM

Over the last five years at Cytel we did experience all three options for several submissions. All three options have pros/cons and their applicability strictly depend on whether and how standards were applied in individual studies.

The purpose of this presentation is to share experience we gathered by applying these three options, such as challenges and some technical tips we did apply to streamline for example the integration of several legacy studies into an iSDTM.

INTRODUCTION

PURPOSE OF ISS/ISE

The Integrated Summary of Safety is required by the U.S. Food and Drug Administration (FDA) as a critical component in any New Drug Application (NDA) or similar market approval requests. Integrated Summary Efficacy (ISE) might be also required under certain circumstances, although most of the time efficacy results from individual pivotal study, or studies, might be sufficient. This is not simply a summary but rather a detailed integrated analysis of all relevant data from the clinical study reports with the aim of providing a more transparent understanding of responses across different populations (demographics, disease related, etc.) and dosing regimens.

Both ISS and ISE allow reviewers to easily compare individual outcomes, tracking subject's results across the entire clinical development, facilitating broad views of the investigational product's overall efficacy and safety profile. With ISS and ISE, a "single database" is formed by pooling the results of all concerned clinical trials.

PLANNING FOR THE ISS/ISE

With the draft label created, the intended key messages documented, and the pivotal studies designed and recruiting, the integration/pooling of the data requires careful consideration. Typically, you may have multiple studies to consider for supporting your safety and/or efficacy claims.

At this stage, it is invaluable to engage with a well-seasoned statistician who will collate the legacy study designs and assist with your initial pooling plan, considering the following topics:

- patient populations and cohort e.g., dosing groups
- dosing appropriateness
- regimens and trial durations
- evaluation of safety and efficacy in various subgroups
- evaluation of secondary efficacy endpoints, which were underpowered in individual studies
- impact of concomitant medications safety and efficacy
- in general, getting a more robust assessment of safety in subgroups if sample size is sufficiently large. Safety assessment might include assessment of laboratory data, ECG, and vital signs
- long term effect of the product or chronic conditions
- devise the pools and related justifications for those

It is then time to share those plans and meet with the authorities, obtain guidance, and fine tune the pooling plan; from these meetings you can get an agreement from the FDA about the proposed pooled strategy.

Focus then turns to the data and it should be ensured that the ongoing pivotal studies are reported and delivered in compliance with data standards requirements i.e., CDISC standards (SDTM and ADaM) as well as ICH E3 compliant study reports (CSRs). This will save time later when the data integrations to support the pooled data analysis are required.

Whilst the pivotal studies are running, it is an ideal time to finalize the ISE and ISS statistical analysis plans. There is also time to assess legacy studies datasets (non in standard format) and CDISC packages from closed studies to be

1

Conclusions

Conclusions

Regardless of which option you adopt for your next ISS/ISE, **traceability and proper documentation** are crucial

The data integration option to adopt **depends on the status and conformance**, and **variability** of **individual study datasets** and in some cases on sponsor preference

Document, document and document …..

Need for an Industry Standard

ADaM Data Structures for Integration Document → Status?

PhUSE Integrated Reviewer Guide for ADaM (iADRG) → Under Finalization

More……

References

- “Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document”, FDA Guidance for the Industry
- “Integration Strategies in Support of ISS/ISE Submissions” – PHUSE White Paper 2020, https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/Integration+Strategies+in+Support+of+ISS+ISE+Submissions.pdf
- “ADaM Structures for Integration: A Preview”, W. Zhong, K. Minkalis and D. Bauer, PharmaSUG 2018
- “ADaMIG v1.2 & ADaM Integration”, CDISC Webinar, 2019, https://www.cdisc.org/events/webinar/adamig-v1-2-adam-integration
- “Expert Answers to Community Questions” PHUSE webinar Friday March 26th, 2021 https://event.on24.com/eventRegistration/EventLobbyServlet?target=reg20.jsp&referrer=&eventid=3023348&sessionid=1&key=15BC66BD7480E5D87BBC2202C798E76C&regTag=&V2=false&sourcepage=register
- “Study Data Standardization Plan” https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/SDSP.zip
- “The PHUSE Recommendations for Pooled Submissions with WHODrug B3 Format Data White Paper”, https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/Recommendations+for+Pooled+Submissions+with+WHODrug+B3+Format+Data.pdf

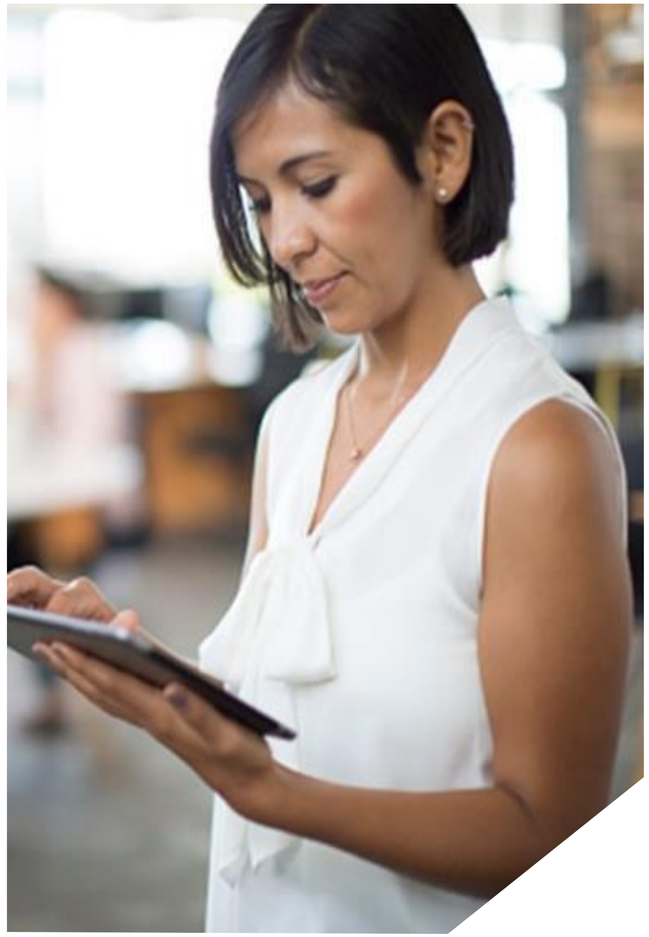
Recommended Readings - 1

Background

- “Navigating FDA requirement: ISS/ISE build strategies”, PhUSE-EU Connect, 2019
- “Processes and Techniques for creating Integrated Summary of Safety (ISS)”, G. Jangid and J. Marrer, PhUSE-US Connect 2021

SDTM and ADaM

- “Challenges involved with using legacy clinical trials study data during integration”, A. Opasanya and A. Bonwick, PhUSE-EU 2019
- “Simplifying the Integration Riddle”, A. Sri Krishna Mani, PhUSE-EU Connect, 2019



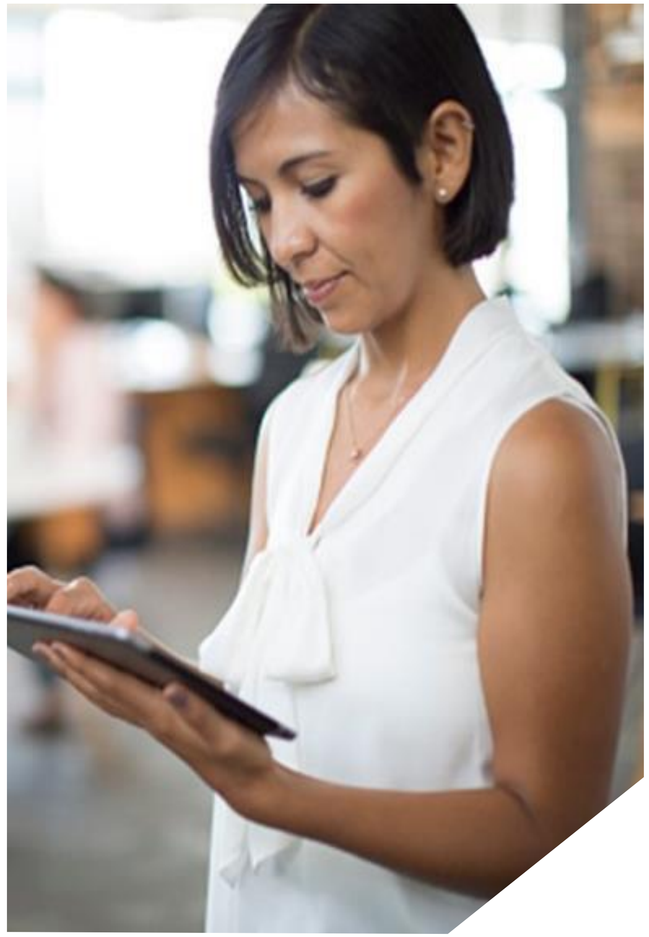
Recommended Readings - 2

ADaM

- “Integrated ADSL”, Nate Freimark and T. Clinch, PhUSE 2012

- “Choosing the right path to follow when integrating ADaM”, PhUSE-EU Connect, 2019
- “Best Practices for ISS/ISE Dataset Development”, B. Donthi, PharmaSUG 2019

- “Integrated Summary of Safety and Efficacy Production Strategies”, N. Agnihotri and S. Pradham, PhUSE-EU Connect, 2021



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Subscribe to Cytel Blog to receive update on my **Good Data Submission Doctor** Blog Series
https://www.cytel.com/blog/topic/cdisc

Thank you.

Cytel

Backup Slides

Purpose of ISS/ISE

- Patient populations and **cohort** e.g., dosing groups
- **Dosing appropriateness**
- Regimens and trial durations
- Evaluation of **safety** and **efficacy** in **various subgroups**
- Evaluation of **secondary efficacy endpoints**, which were underpowered in individual studies
- Impact of **concomitant medications** on safety and efficacy
- In general, getting a **more robust assessment of safety in subgroups** if sample size is sufficiently large. Safety assessment might include assessment of laboratory data, ECG, and vital signs
- **Long term effect** of the product or chronic conditions
- Devise the pools and related justifications for those

Which Option to Choose

Pros / Cons	Option 1 SDTM(s) →iADaM	Option 2 ADaM(s) →iADaM	Option 3 SDTM(s)→iSDTM→ iADAM
Alignment of algorithms, controlled terminology, and data domain			
Sole source for the iADaM			
Sole source data for the reviewer			
Cost: additional datasets, define-xml and cSDRG for iSDTM			
Full Traceability to Individual study CSRs/ADaMs			
Requires consistent analysis approach and terminology			
Can keep original dictionary versions	Standard variables in OCCDS	Standard variables in OCCDS	In SUPP datasets (?)

Some Hints

Share your Strategy with the Agency - SDSP

Subjects participating to more than one study

Subjects participating in more than one study will be identified using the same USUBJID, that is the USUBJID assigned in the study the subject was first enrolled in. The following table lists studies concerned by the multiple across studies enrolments:
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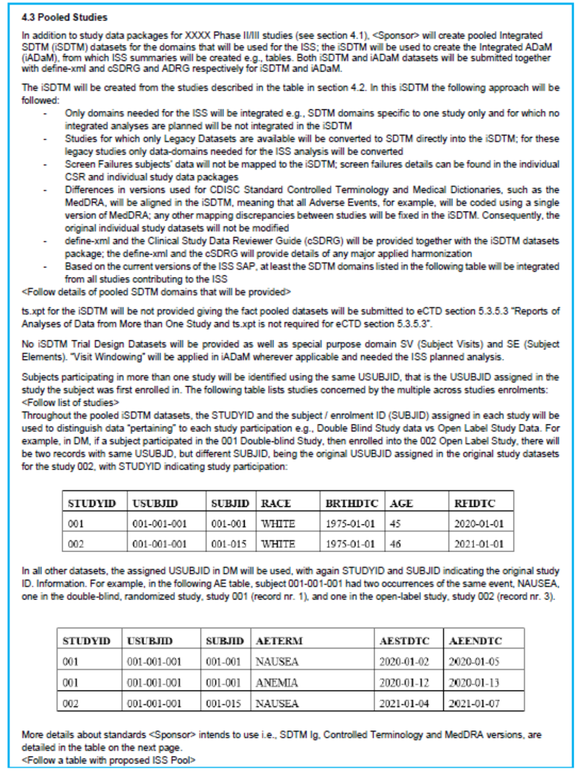

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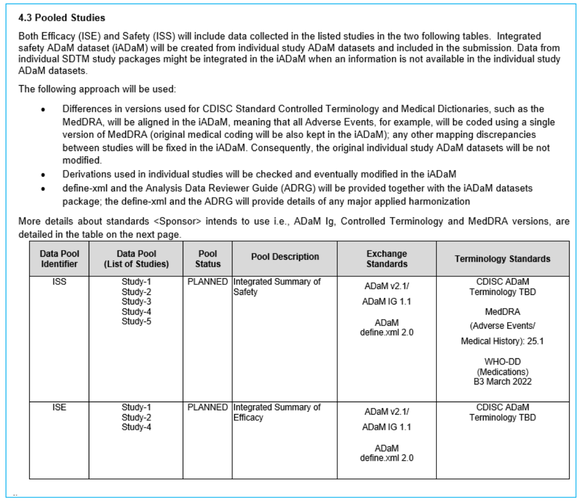

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More details about standards <Sponsor> intends to use i.e., ADaM Ig, Controlled Terminology and MedDRA versions, are detailed in the table on the next page.

Data Pool Identifier	Data Pool (List of Studies)	Pool Status	Pool Description	Exchange Standards	Terminology Standards
ISS	Study-1 Study-2 Study-3 Study-4 Study-5	PLANNED	Integrated Summary of Safety	ADaM v2.1/ ADaM IG 1.1 ADaM define.xml 2.0	CDISC ADaM Terminology TBD MedDRA (Adverse Events/ Medical History): 25.1 WHO-DD (Medications) B3 March 2022
ISE	Study-1 Study-2 Study-4	PLANNED	Integrated Summary of Efficacy	ADaM v2.1/ ADaM IG 1.1 ADaM define.xml 2.0	CDISC ADaM Terminology TBD