



13-16 November
ICC Belfast

EU 2022

The Clinical Data
Science Conference

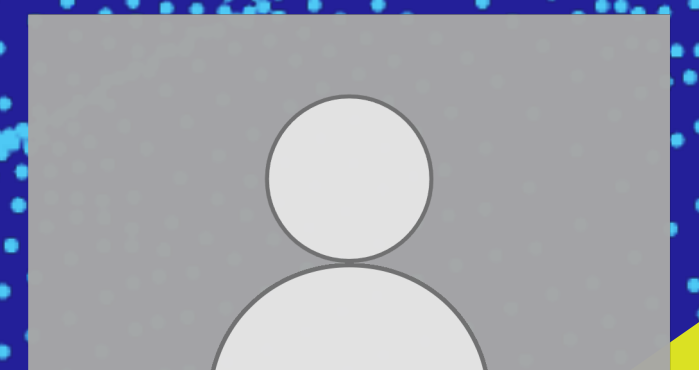
The Integration Dilemma

Angelo Tinazzi, Cytel Inc.

PHUSE EU Connect 2022

13^h -16th November 2022

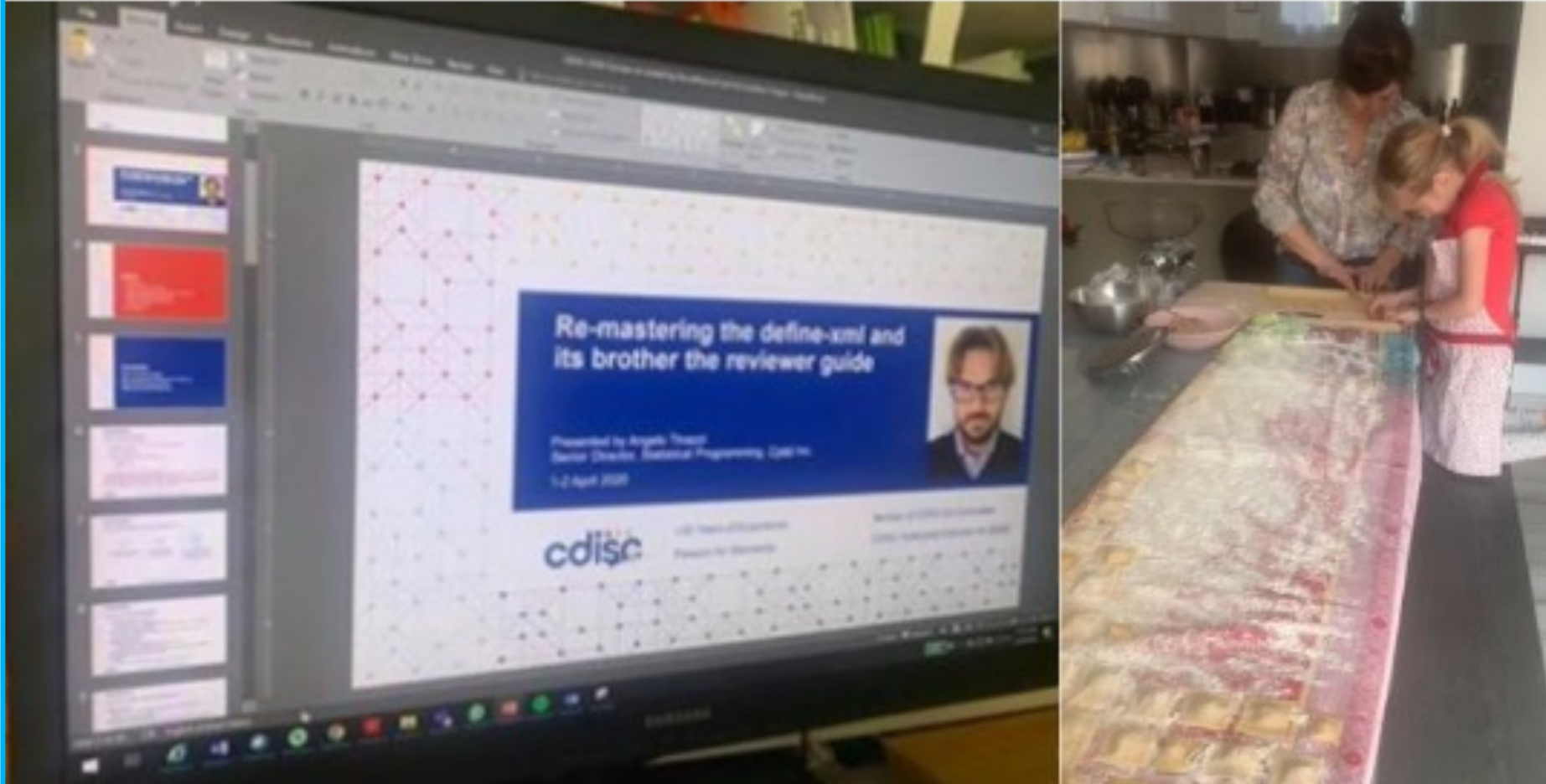
Paper SI09 – Standards Implementation (SI)



No more Virtual Conferences

Angelo Tinazzi • Tu
Programming, Data and Standards, Standards, Standards,
2 anni •

The virus has locked down our societies, but life goes on and while I'm getting prepared for my speech for the **#CDISC** EU Interchange virtual conference next Wednesday, my girls are taking care of our Sunday (Italian) lunch with meat Ravioli. Registrations to the CDISC event, and not to the lunch, will remain open until Tuesday night. **#cytel**



64 13 commenti • 2 diffusioni post

Consiglia Commenta Diffondi il post Invia

4.796 impressioni Vedi statistiche

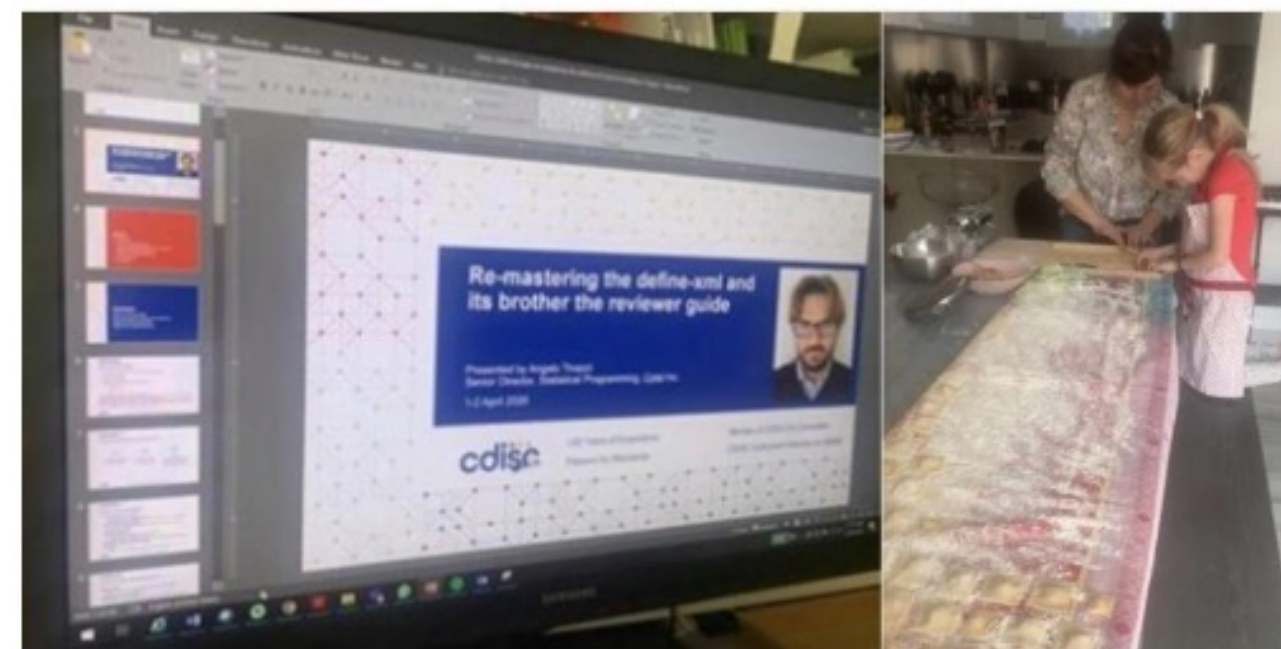
Angelo Tinazzi • Tu
Programming, Data and Standards, Standards, Standards,
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More than 3k of visualizations, about 60 like, the most successful post I have ever had, the Ravioli and Girls power. Anyhow for those that liked my post for professional reasons, my speech will be today at 13.20 CET **#cdisc #cytel**

Angelo Tinazzi
Senior Director, Standards, Systems, CDISC Consulting, Statistical Programming at Cytel Inc
2 giorni •

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Vedi traduzione



56 8 commenti • 3'055 visualizzazioni

Consiglia Commenta Condividi

3'055 visualizzazioni del tuo post

- **4796+3055** Views
- **64+56** Likes
- **2** re-post
- **13+8** Comments

Jozef Aerts • 1°
2 anni •
Passionate about standards in clinical research and healthcare, and thei...

Can I get both ravioli and the presentation? The latter will presumably still need to wait a few days ...

Anthony Chow • 1°
2 anni •
#加油 #FuelUp Career geek specializes in data standards, data modelin...

Recipe in the slide deck, please?

Consiglia 1 | Rispondi 1 risposta

Angelo Tinazzi Autore
2 anni •
Programming, Data and Standards, Standards, Standards,
I need to convince my wife :-)) I found so far a good one but just for the filling <https://www.foodandwine.com/recipes/meat-ravioli>

Consiglia | Rispondi

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



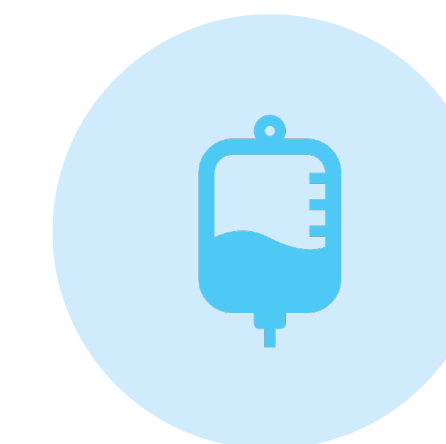
Integrated Summary of Safety (ISS) is required by the US FDA



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

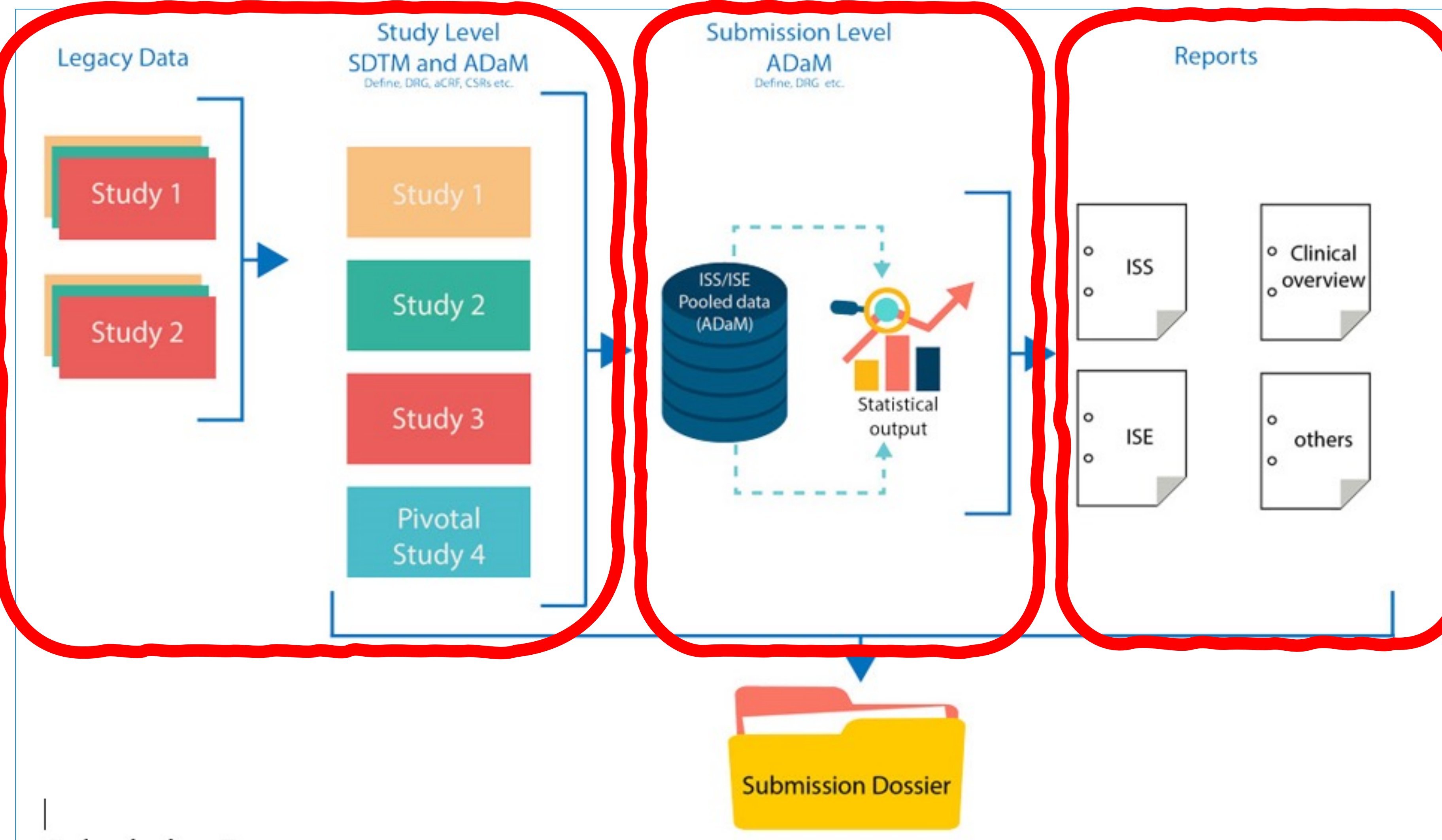


Integrated Summary of Efficacy (ISE) might be also needed

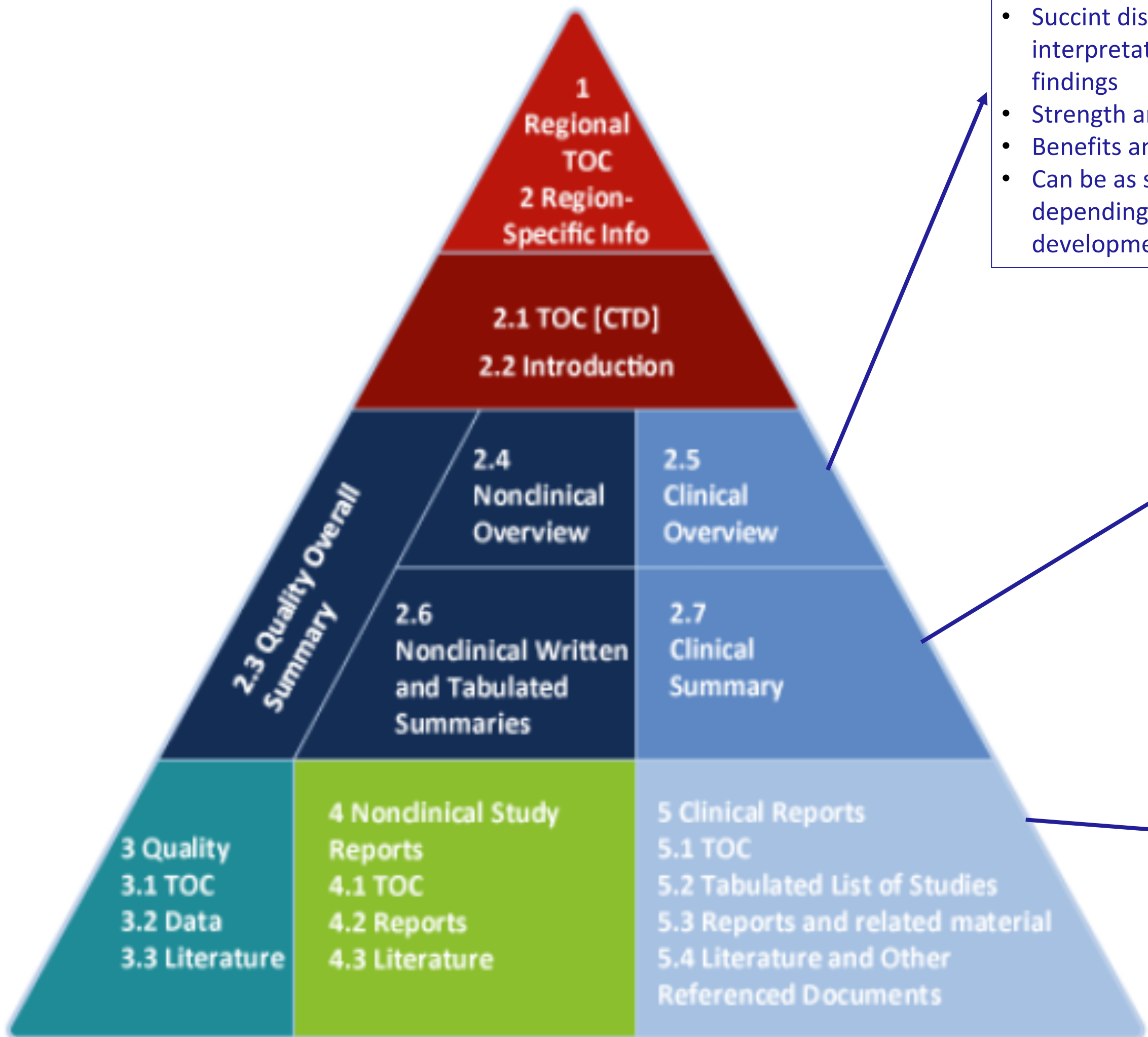


With ISS, and ISE, a **single database is formed by pooling** the results of all concerned studies

Purpose of ISS/ISE



Planning the ISS/ISE



2.5 - Clinical Overview

- Critical summary of clinical data
- Succinct discussion and interpretation of clinical findings
- Strength and limitations
- Benefits and Risks of new drug
- Can be as small as 30 pages depending on size of drug development

2.7.2 - Summary of Clinical Pharmacology Studies

2.7.3 - Summary of Clinical Efficacy

2.7.4 - Summary of Clinical Safety

- Detailed factual summary of all the clinical information in the CTD (from individual reports or pooled/integrated analyses)
- Factual rather than interpretation/discussion (covered in CO)

5.3.5 Reports of Efficacy and Safety Studies

- 5.3.5.1 Study reports of controlled clinical studies pertinent to the indication
- 5.3.5.2 Study reports of uncontrolled clinical studies
- 5.3.5.3 Reports of Analyses for more than one Study

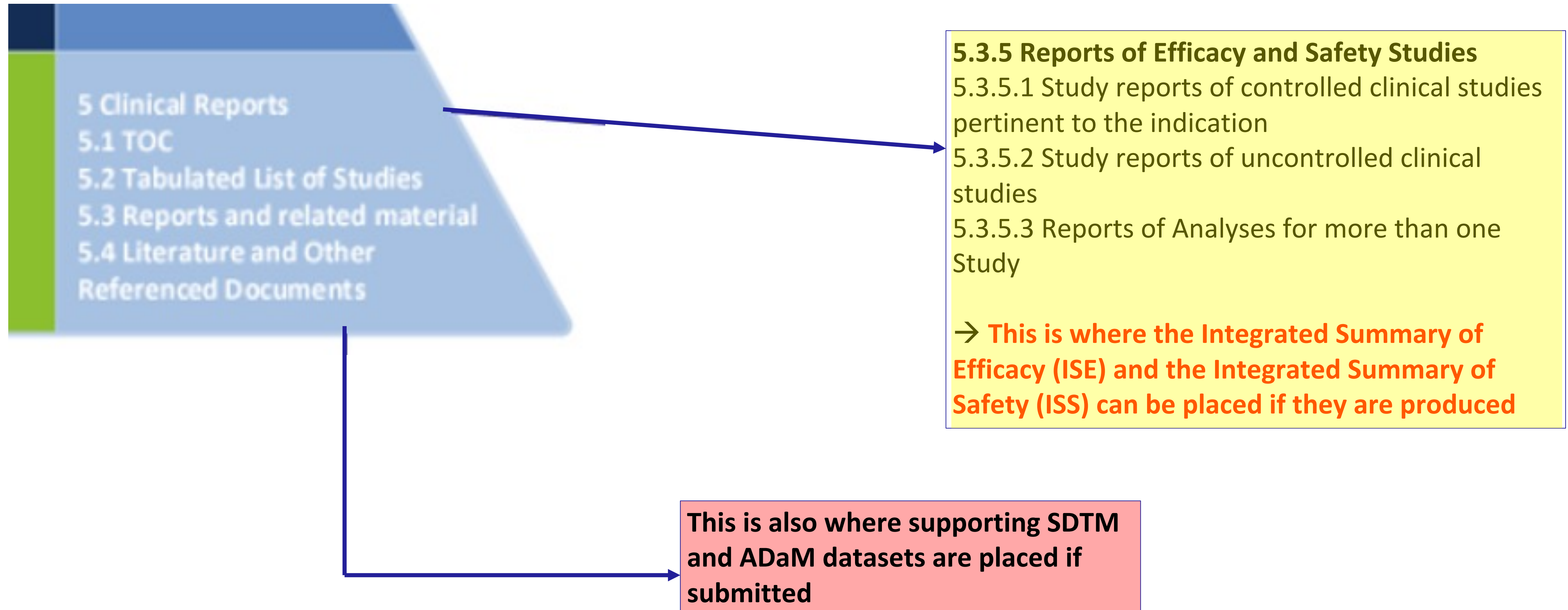
→ **This is where the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) can be placed if they are produced**

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

- CTD format is defined in ICH M4 guidance (full TOC + guidance)
- More details as you go down the triangle

Planning the ISS/ISE

- CTD format is defined in ICH M4 guidance (full TOC + guidance)
- More details as you go down the triangle



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

Integration Strategies in Support of ISS/ISE
Submissions – PHUSE White Paper 2020

Fri. 26 Mar. 2021

2020

Expert Answers to Community Questions”
PHUSE webinar Friday March 26th, 2021

- 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**

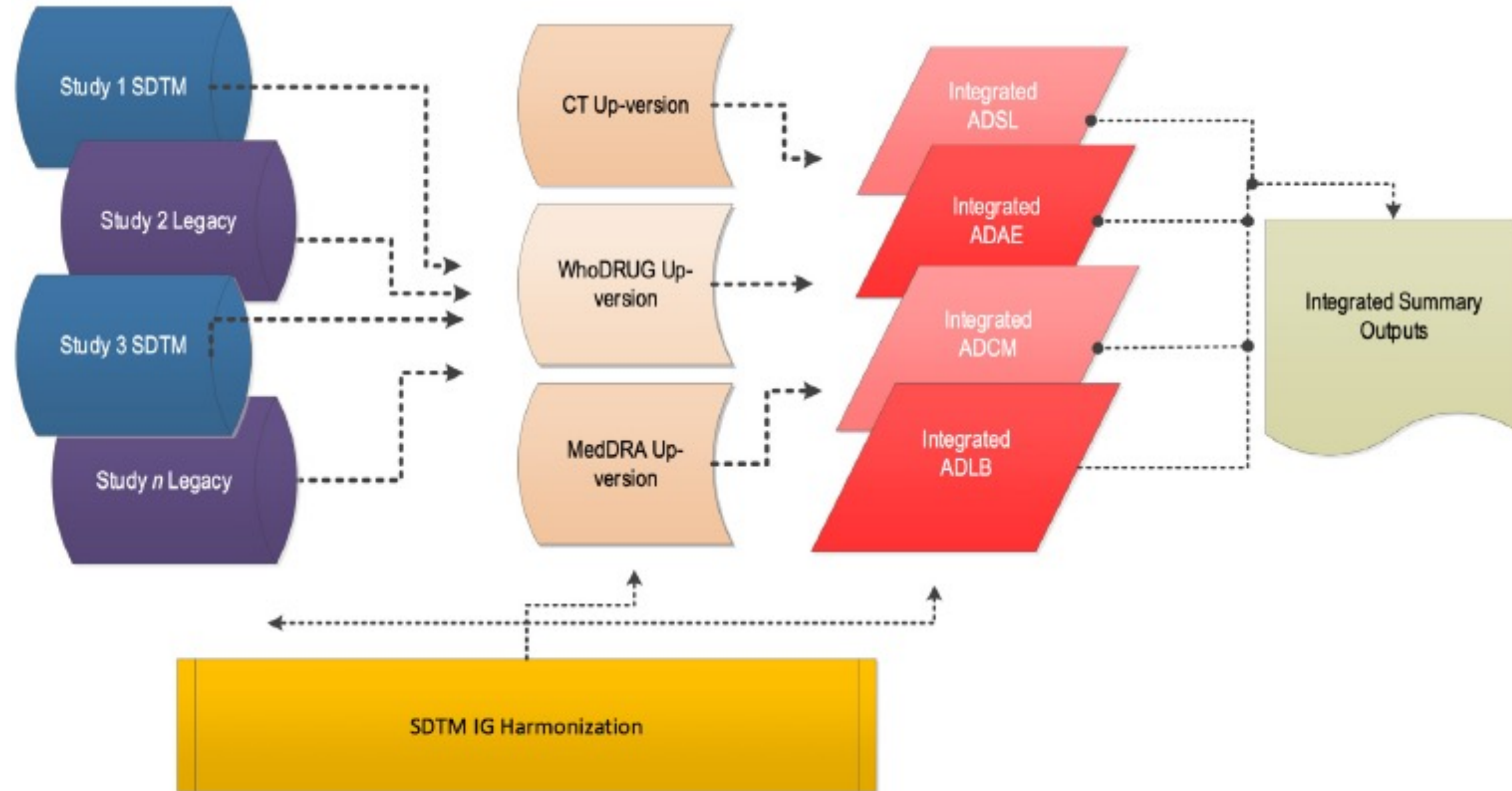
Data Integration - Things to take care with Data Integration

- **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



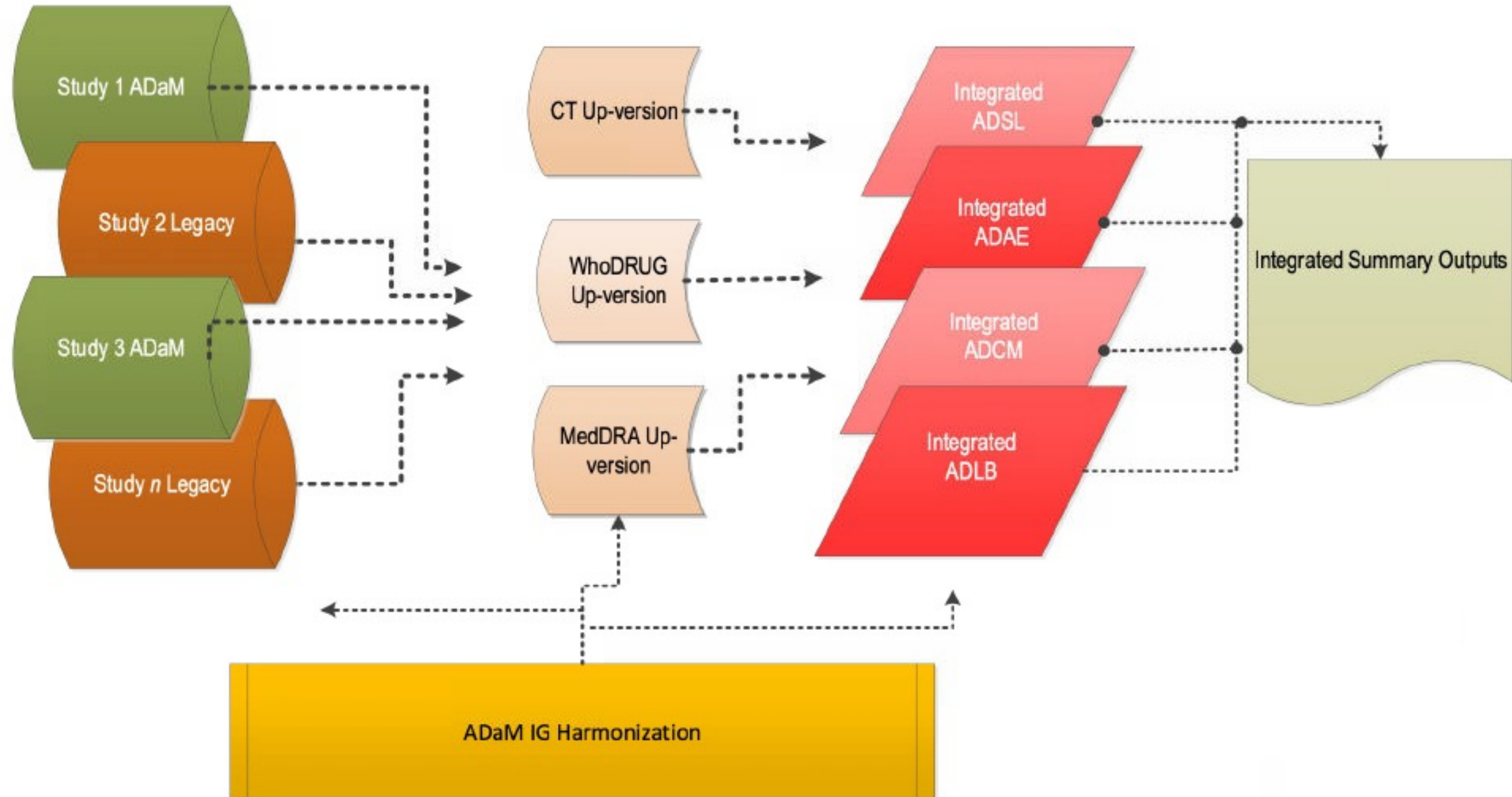
Data Integration Options: SDTM(s) → iADaM

Pooling in ADaM from Individual Study SDTM datasets



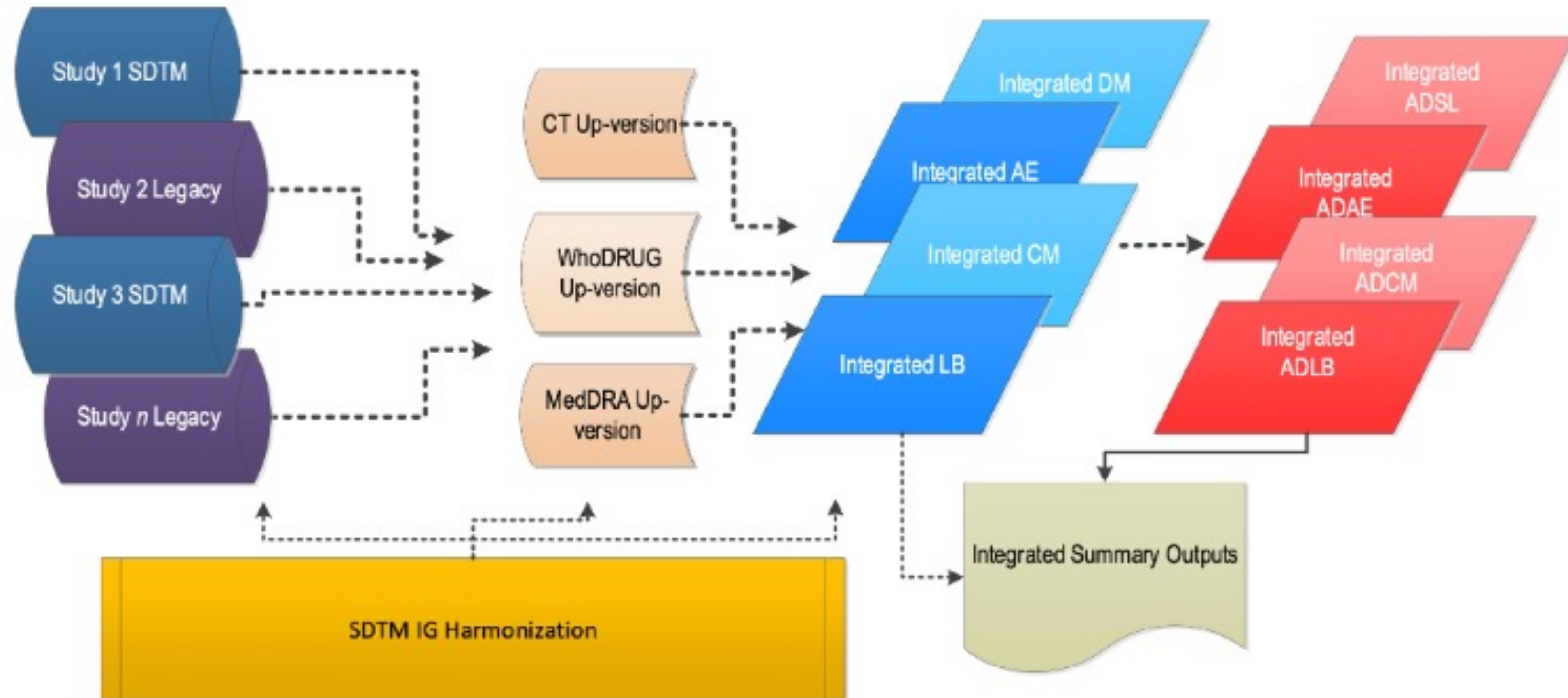
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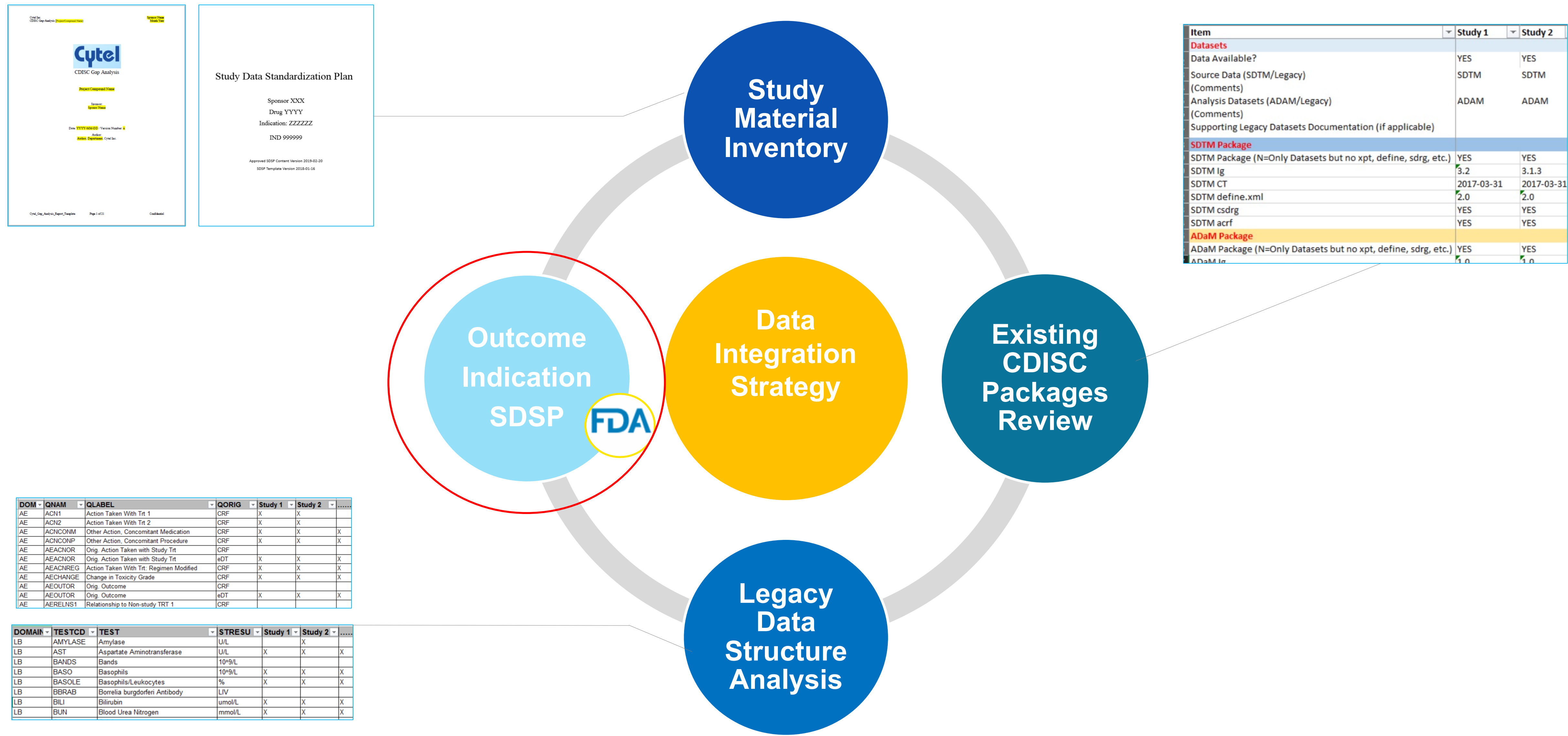


Data Integration Options: SDTM(s) → iSDTM → iADaM

Pooling in iSDTM, then iADaM



Planning the Data Integration



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 1 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.

The iSDTM will be created from the studies described in the table in section 4.2. In this iSDTM the following approach will be followed:

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001	001-001-001	001-001	WHITE	1975-01-01	45	2020-01-01
002	001-001-001	001-015	WHITE	1975-01-01	46	2021-01-01

In all other datasets, the assigned USUBJID in DM will be used, with again STUDYID and SUBJID indicating the original study ID. Information. For example, in the following AE table, subject 001-001-001 had two occurrences of the same event, NAUSEA, one in the double-blind, randomized study, study 001 (record nr. 1), and one in the open-label study, study 002 (record nr. 3).

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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

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Some Hints

Share your Strategy with the Agency - SDSF

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Cytel

The Integration Dilemma, A. Tinazzi, PHUSE EU Connect 2022

Key Learnings from Cytel Use Cases

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Some Hints

Share your Strategy with the Agency - SDSP

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Some Hints

Share your Strategy with the Agency - SDS

With Option 2 ADaM(s) → iADaM

Both Efficacy (ISE) and Safety (ISS) will include data collected in the listed studies in the two following tables. **Integrated safety ADaM dataset (iADaM) will be created from individual study ADaM datasets** and included in the submission. Data from individual SDTM study packages might be integrated in the iADaM when an information is not available in the individual study ADaM datasets.

4.3 Pooled Studies

In addition to study data packages for XXXX Phase I/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.

The iSDTM will be created from the studies described in the table in section 4.2. In this iSDTM the following approach will be followed:

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<Follow details of pooled SDTM domains that will be provided>

ts.xpt for the iSDTM will be not provided giving the fact pooled datasets will be submitted to eCTD section 5.3.5.3 "Reports of Analyses of Data from More than One Study and ts.xpt is not required for eCTD section 5.3.5.3".

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.

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

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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.

<Follow a table with proposed ISS Pool>

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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

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 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 S109

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

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®Tag=&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>

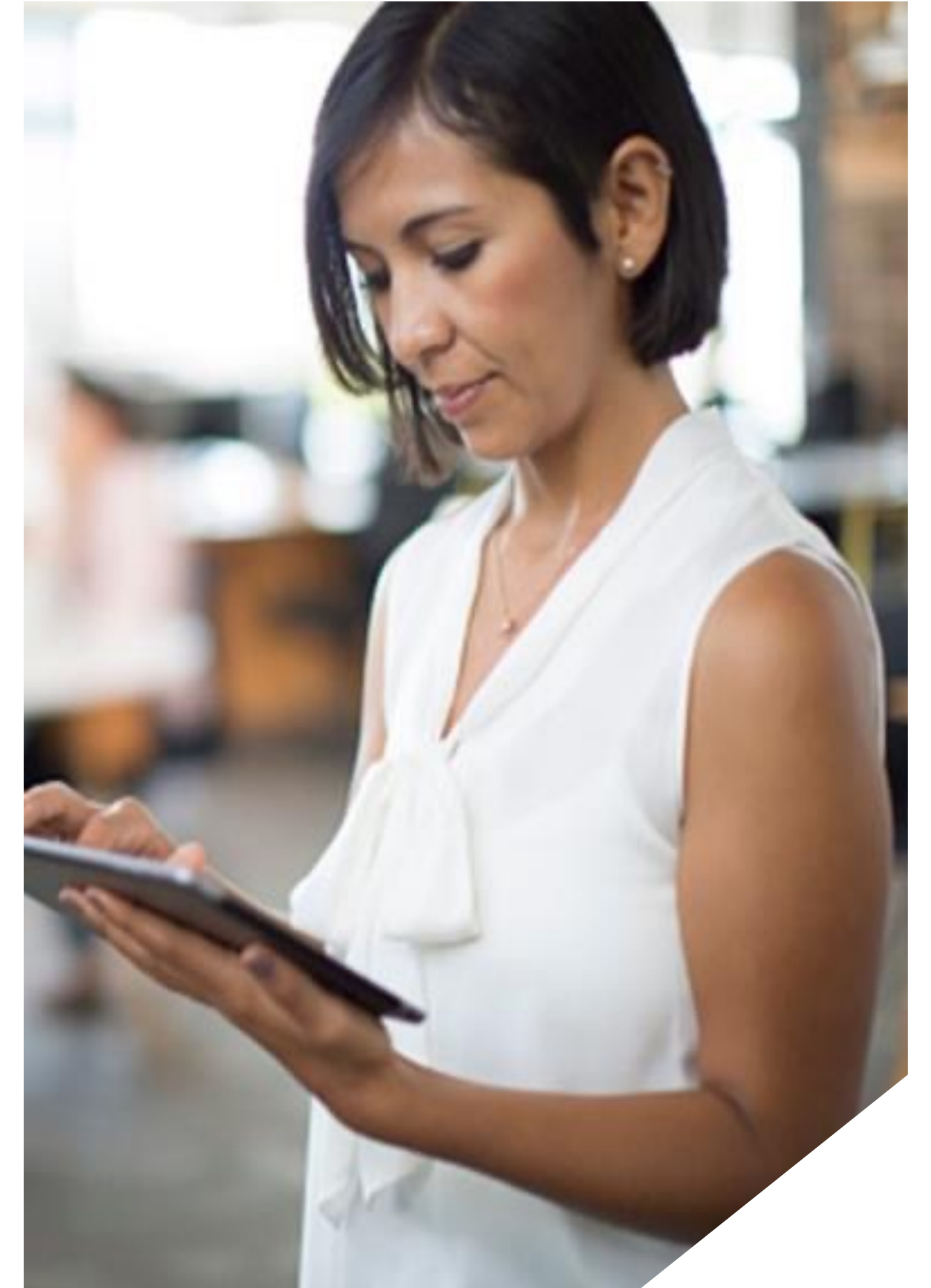
Recommended Readings - 1

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

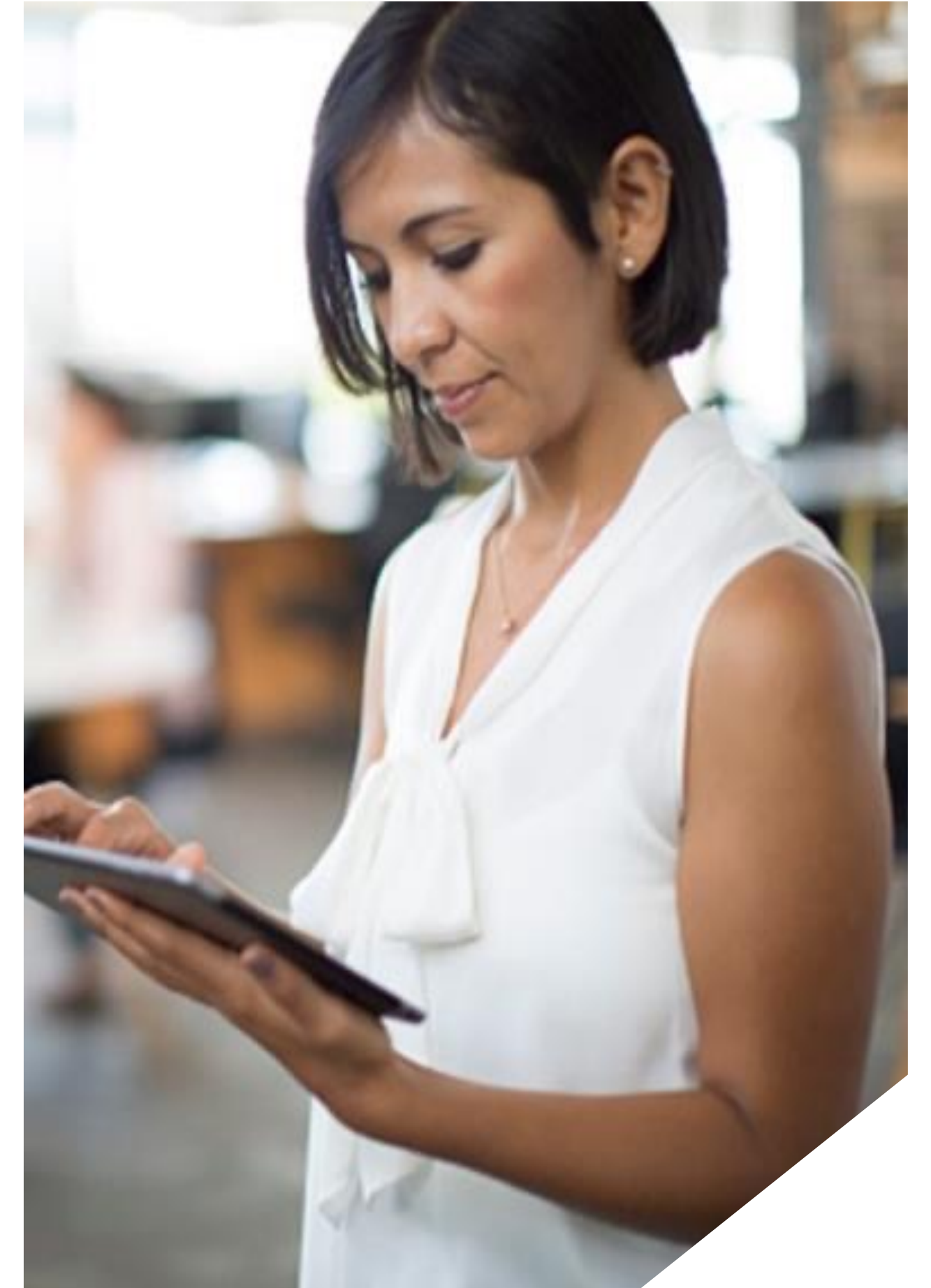
- “Challenges involved with using legacy clinical trials study data during integration”, A. Opasanya and A. Bonwick, PhUSE-EU 2019
- “Simplifying the Integration Riddle”, A. Sri Krishna Mani, PhUSE-EU Connect, 2019



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



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.

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Thank you.

Angelo Tinazzi, Senior Director
Cytel Inc.

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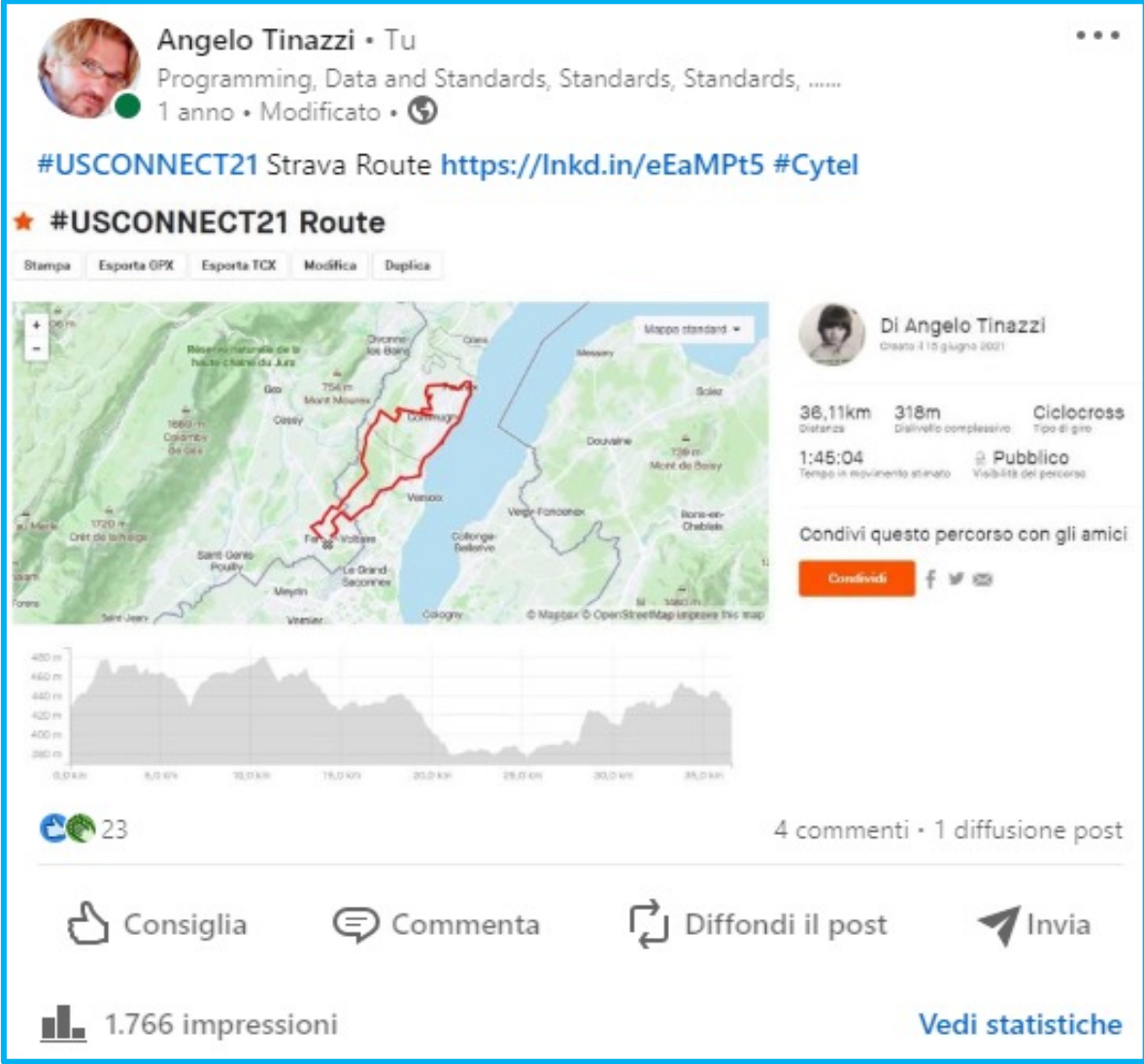
PHUSE-EU 2020



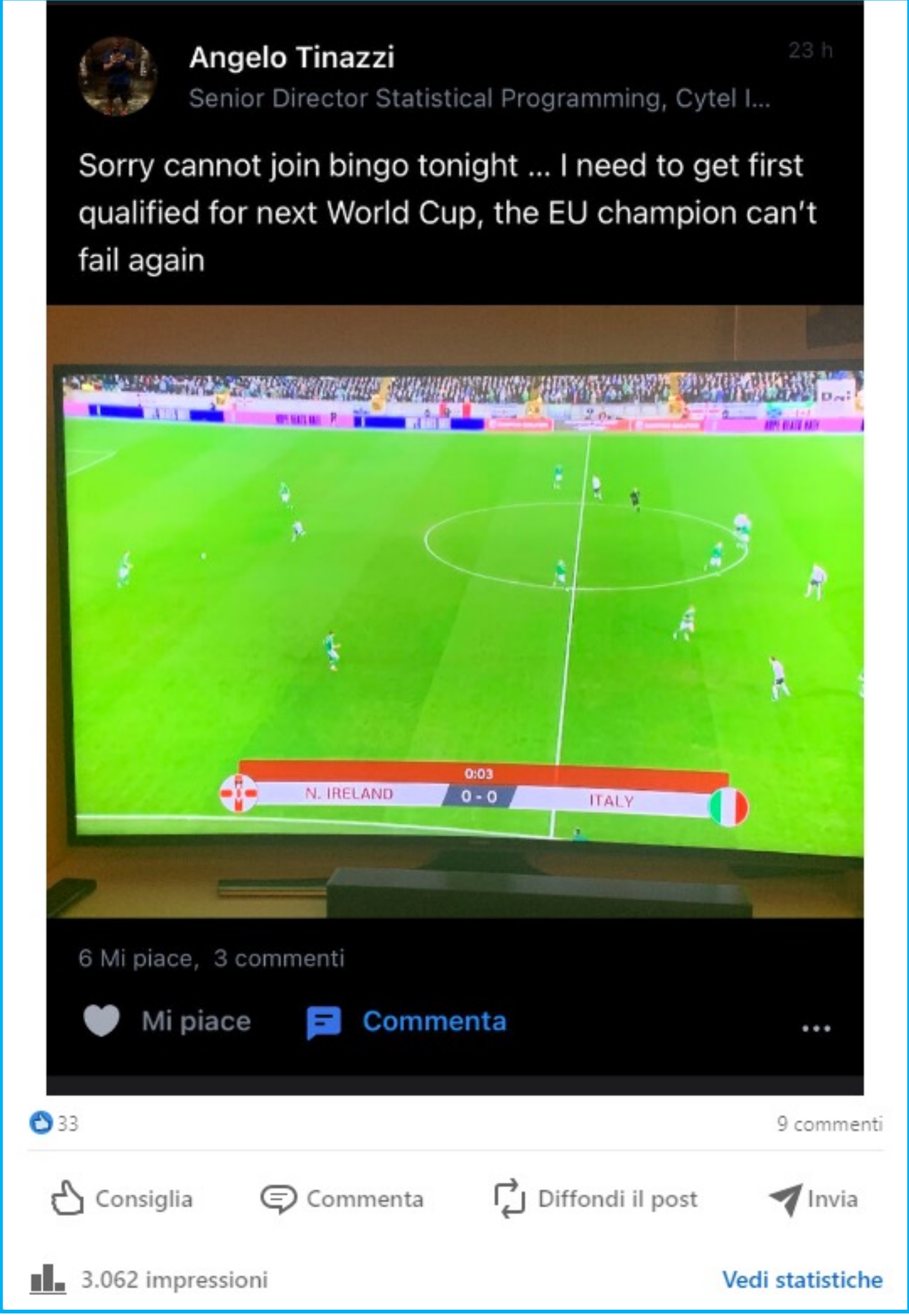
PHUSE-EU 2020



PHUSE-US 2021



PHUSE-EU 2021



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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The Integration Dilemma, A. Tinazzi, PHUSE EU Connect 2022

Data Integration

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