

Processes and Techniques for creating Integrated Summary of Safety (ISS)

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Purpose/Scope

- Explain ways to address the unique challenges for Integrated Summary of Safety (ISS) packages for a compound with multiple trials having ongoing submissions
 - Example: Oncology Medication being submitted for multiple tumor types/indications
- Suggest processes and techniques to efficiently build and maintain a reusable library of reference safety datasets (safety stack) that reflect the compounds safety profile
- Discuss methods to harmonize datasets to support Integrated analysis with multiple data sources to ensures
 - Harmonized variable attributes across multiple trials
 - Compliance of integrated ADaM datasets
 - Alignment with pivotal trial Clinical Study Report
 - Common dictionaries

Topics

- Reference Safety Dataset Library Overview
- High level process for Reference Safety Dataset (RSD) library creation and maintenance
- Reference Safety Dataset Library Uses
- Analysis Populations
- Best Practices for ISS datasets
- Reference Safety Dataset Library Templates and Standards
- Integrated analysis standards and templates
- Programming Important points and checks
- MedDRA leveling and dictionary conversion
- Unique challenges and solutions
- QC of outputs
- Conclusion

Reference Safety Dataset (RSD) Library high level development and maintenance

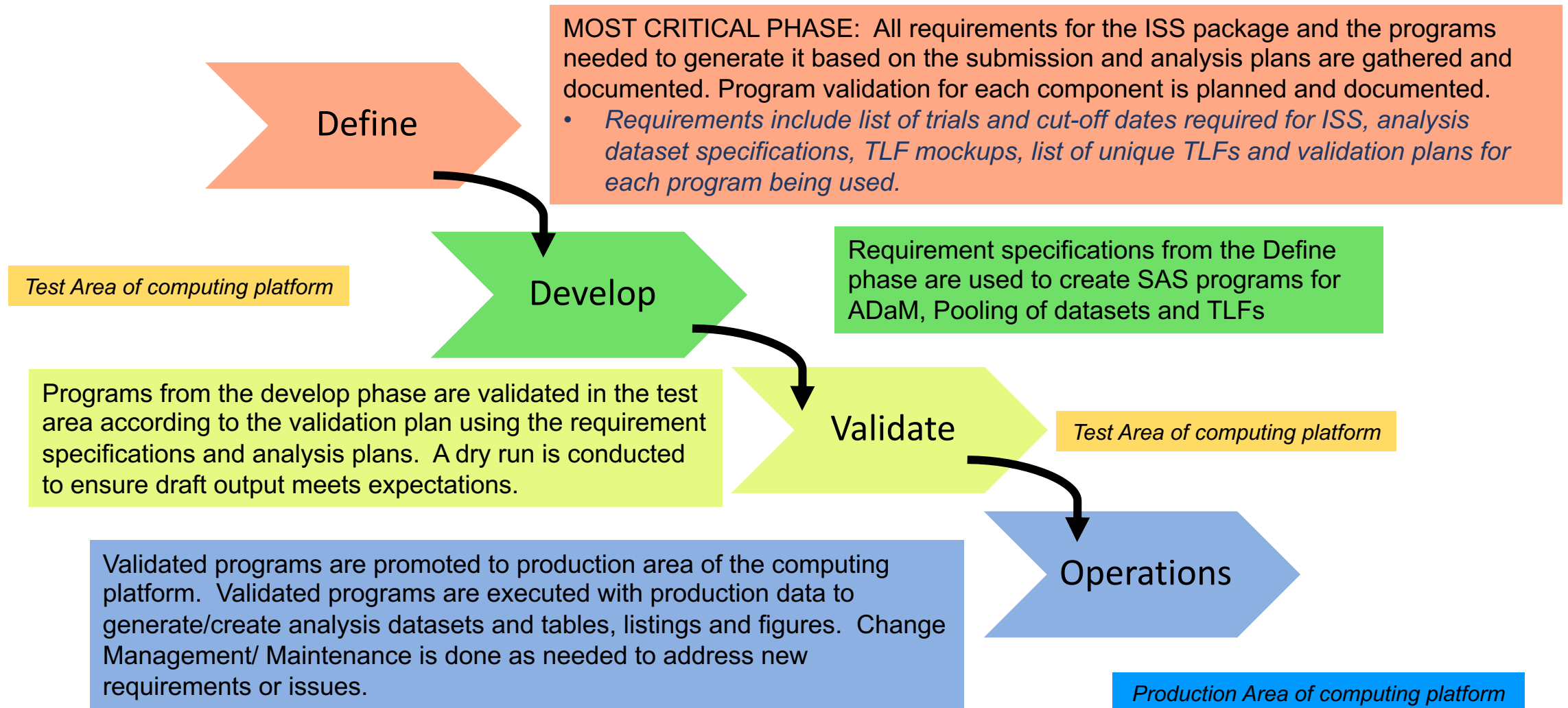
Library of Submission-Ready ADaM datasets supporting the safety profile of a compound

- RSD population defined by Regulatory based on submission and approval status of each clinical trial
- Submission-ready ADaM datasets for each individual trial created and validated by a central ISS team as per programming SOP
 - *For efficiency and consistency, begin work with the CSR analysis datasets*
- RSD datasets stored in a central area in sub-folders by MedDRA version
- RSD datasets are re-usable across each individual submission

RSD Library is updated as needed to support:

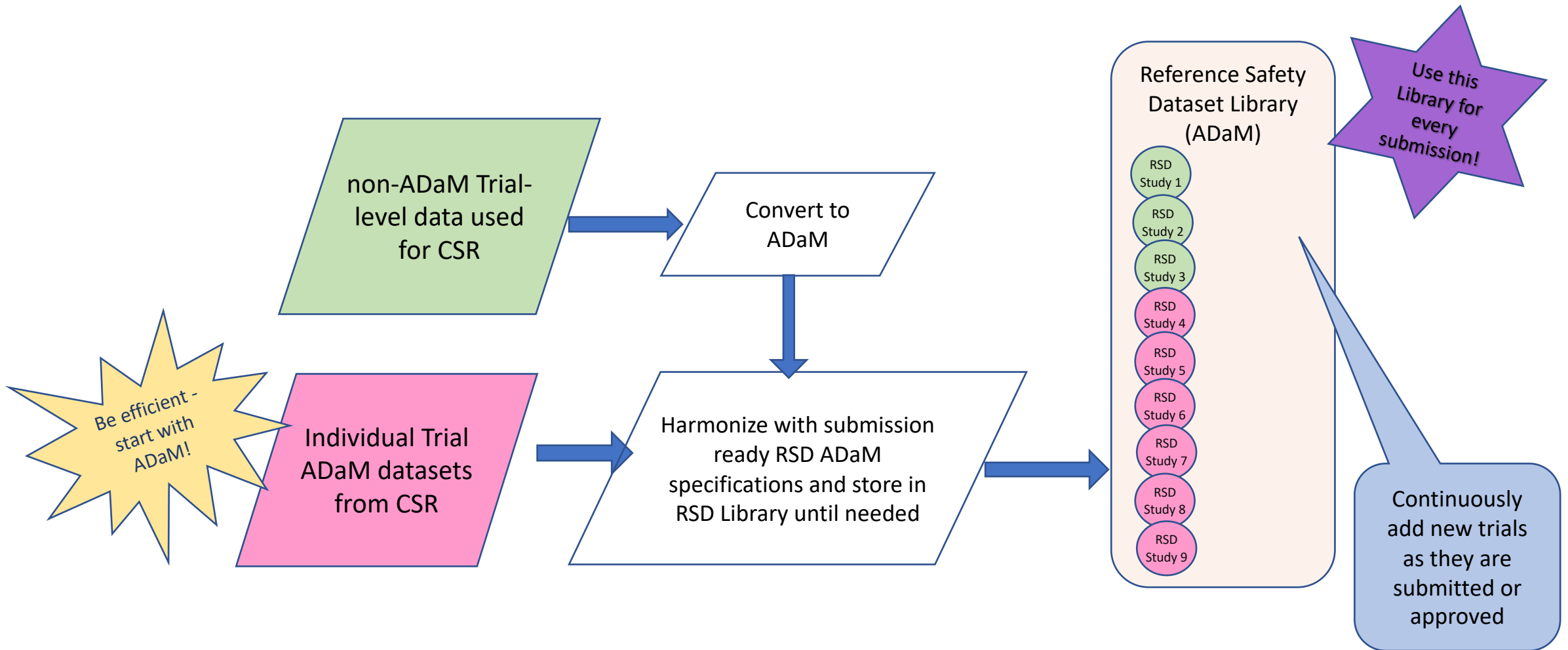
- Additional trials identified for inclusion in RSD library
- ADaM standard updates
- New dictionary versions

System Development Life Cycle (SDLC): Supports compliance of ISS programs



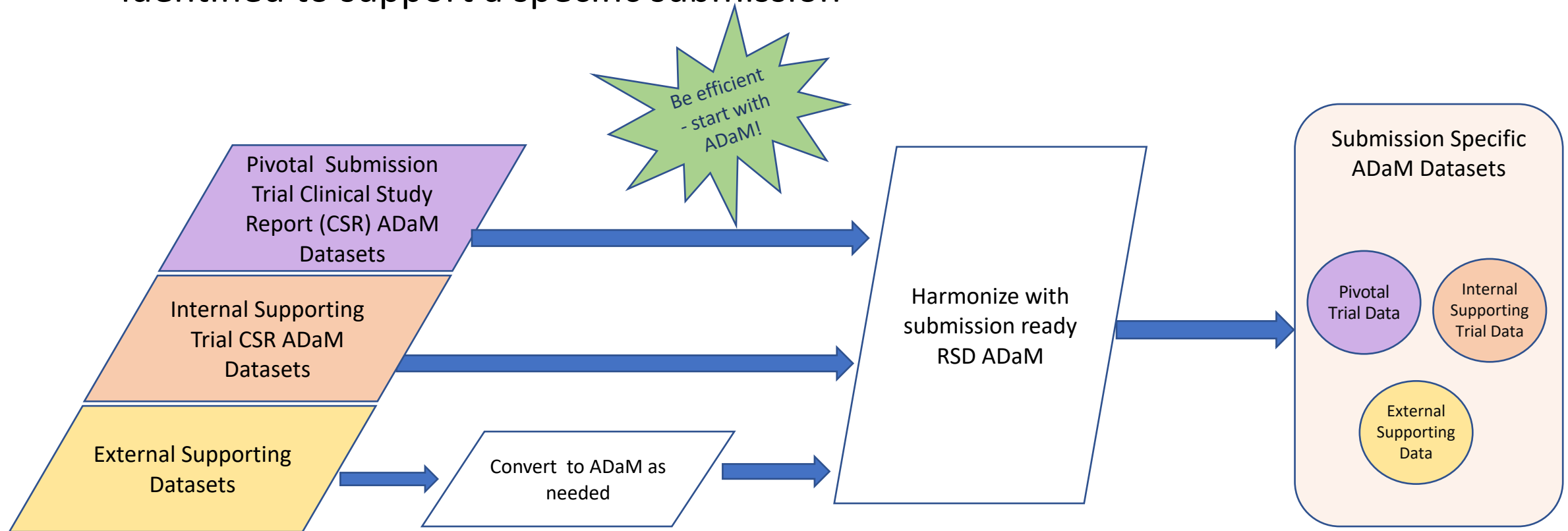
Process: Step 1: Create the RSD Library

Create a library of submission-ready ADaM datasets containing all trials identified in the compound's reference safety data (RSD) population



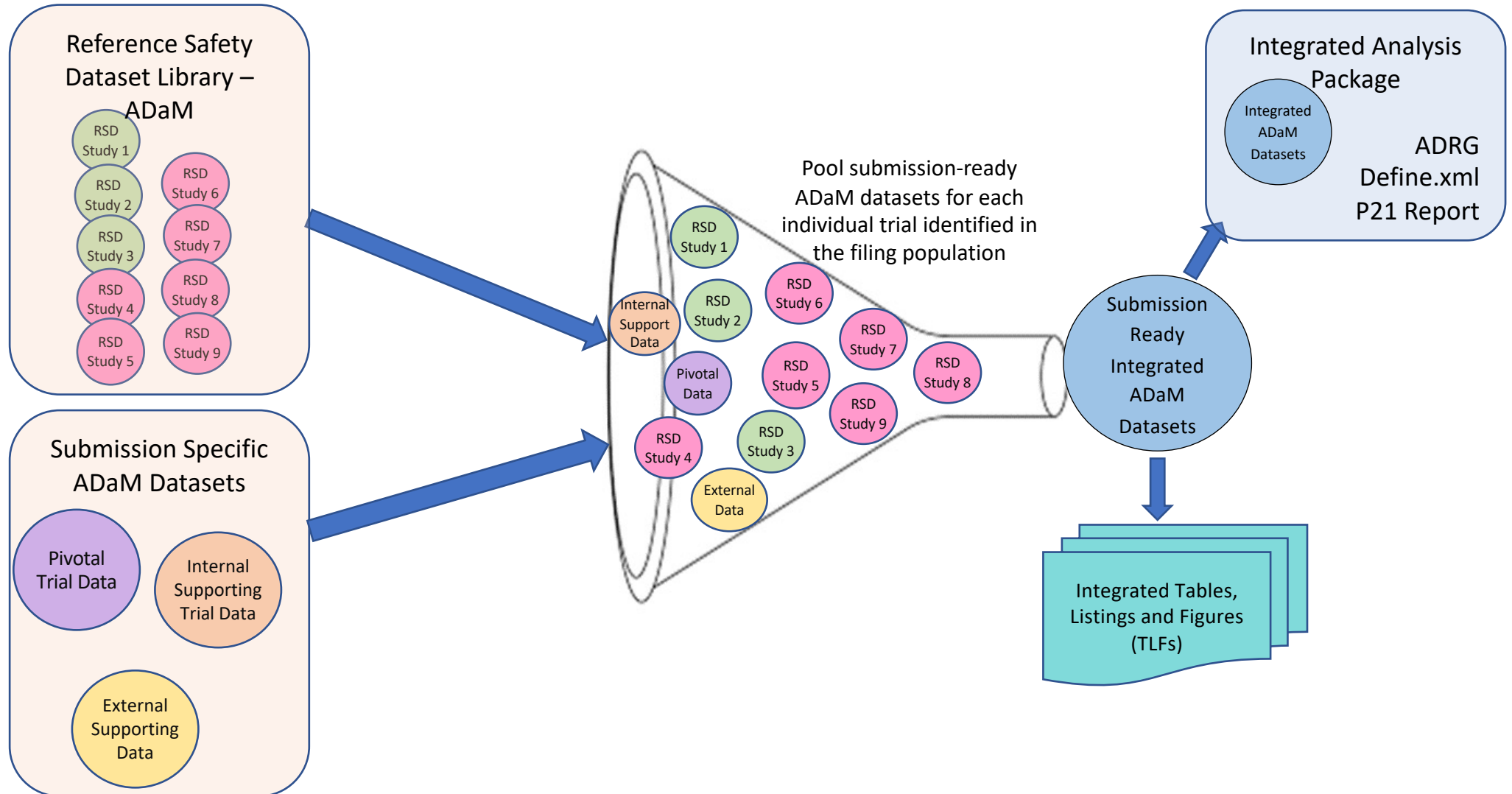
Process: Step 2: Prepare Submission specific datasets

Create and harmonize submission-ready ADaM datasets for additional trials identified to support a specific submission



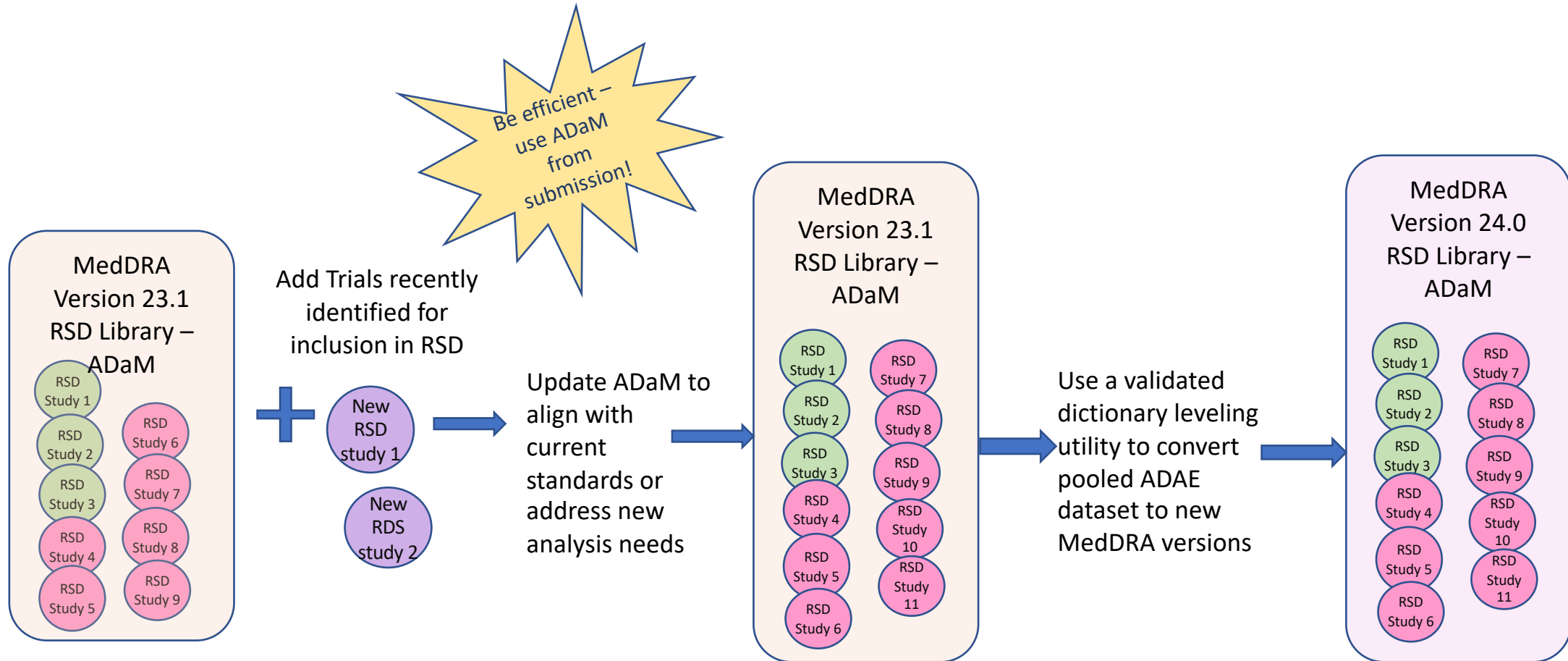
Process: Step 3: Create a submission ISS dataset

Pool submission specific ADaM datasets with Reference Safety Datasets



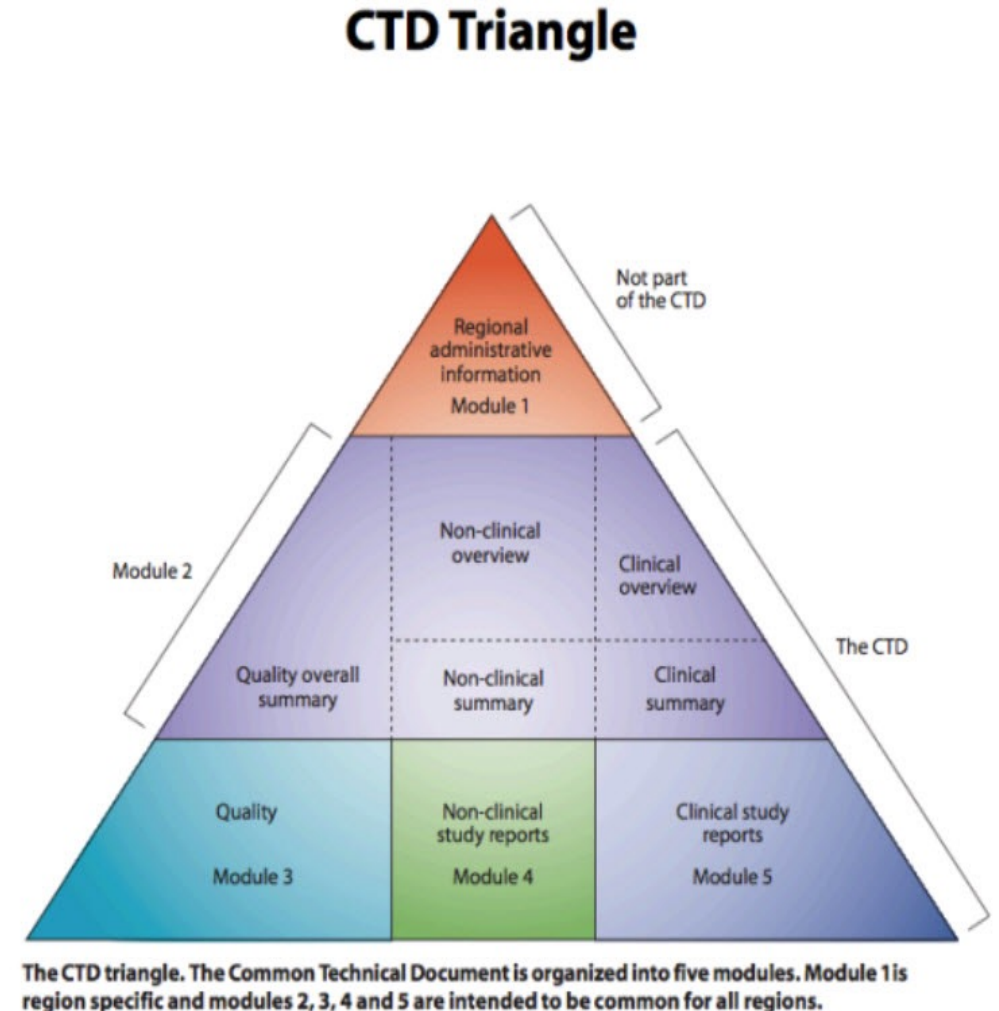
Process: Step 4: Update and Maintain the RSD library

Update as needed to align with current safety population and standards



Reference Safety Dataset Library Uses

- eCTD Modules 1 and 5:
 - 5.3.5: Reports of analyses of data from more than one study (ISS)
 - 1.16: Risk Management Plans
 - 1.14: Labelling and Investigational Brochure
 - 1.13.15 Development safety update report (DSUR)
- Aggregate Safety Assessment
- Agency Requests



Integrated Analysis Populations

- Specifications must clearly define all trials and cut-off dates to include in each population
 - ❖ *For trials supporting multiple indications or tumor types, indication specific cohorts and cut-off dates must also be defined*
- RSD library should contain all trials needed to support unique submission populations
 - Startup program allows users to select sub-set of trials identified for each unique population
- Packages/Populations may include
 - Indication Populations – Pivotal Trial PLUS supporting trials in the same indication
 - US Reference Safety Population – Trials/cohorts submitted in US with defined cut-off dates
 - EU Reference Safety Population – trials/cohorts for all EU indications approved at the time of the respective submission with defined cut-off dates (continually add new trials)
 - Cumulative Running Safety Populations – trials submitted to major agencies within 6 weeks of submission PLUS trials related to the submission indication with defined cut-off dates (varies per submission)

Best Practices for ISS datasets

- Key data points impacting the primary and secondary objectives of overall trials must be harmonized
 - Align ISS analysis with pivotal trial CSR analysis
 - Always indicate trial cut off dates in requirements and make sure to use in analysis
 - Follow company SOPs for development and validation of all programs used
 - Follow Technical Conformance Guidance
 - Use current versions of ADaM for both standard datasets and Implementation Guidelines
 - Use standard dictionaries including MedDRA and WHO Drug
 - Use common versions of MedDRA across all trials in Integrated population
 - Mixed versions of MedDRA in Integrated Trials is not permitted
- ❖ *Note: Permissible to submit in mixed WHO DD versions*
- Use standards and templates to support the efficient, high quality and consistent RSD components

Reference Safety Dataset Library Templates and Standards

- Specification and Planning Templates
 - ADaM Dataset Specifications
 - TLF Mockup
 - TLF tracker
 - Validation Tracker
- Standard re-usable validated Programs/Macros/Utilities to:
 - Harmonize ADaM datasets
 - Pool ADaM datasets
 - Generate Integrated TLFs: when possible, use departmental standards – avoid ISS specific versions
 - Convert/level dictionaries
 - Check counts and ensure data is harmonized
- eSubmission Analysis package
 - ADRG
 - Define



Programming: Important points and checks when harmonizing

- Harmonize variable attributes: making sure variables with same name across individual trials have the same attributes
- Check on variable types, length, formats, labels etc. should be performed
- Ensure consistent programming logic is used across trials
- Check consistency of categorical variables, perform PROC FREQ procedure when combining data in integrating datasets
- Make sure all CODE and DECODE variables to ensure they maintain a one-to-one mapping
- Create additional variables to handle such situation or to filter any records of interest
- Watch for any special handling that might be needed for variables in some trials
- Use a table look-up approach to maintain consistencies across all pooled ADaM datasets

ISS MedDRA leveling Additional Points

- Upon Completion of leveling, apply updated flags for adverse event terms of interest using flag assignments aligned with new MedDRA version
- Conduct QC to Compare the old adae dataset with the new adae dataset
 - Compare all encoded terms for values before and after
 - Ensure no blanks for previously encoded terms
 - Check that new terms match and make sense (i.e., no garbled preferred terms)
 - Make sure no records were added or removed

adae	AEBODSYS
adae	AEDECOD
adae	AEHLGT
adae	AEHLT
adae	AELLT

- Store updated datasets in centralized location in folder for new MedDRA version
 - ❖ *Save data in old MedDRA versions for traceability and support future requests*

Converting to Standard dictionaries

- Addressing company specific dictionary when standard dictionary is required
 - For example: Legacy trials using company specific drug dictionary and not WHO Drug Dictionary (WHO-DD)
- Datasets from Legacy trials in RSD need to be converted to WHO-DD prior to pooling with newer trials in WHO DD to ensure compliance with regulatory agencies
- High Level Process to convert to WHO DD
 1. Create mappings for each unique term in RSD library ADCM datasets to WHO-DD terms/variables
 - Limit terms to those used for integrated safety analysis (i.e. concomitant meds of interest)
 2. Use mapping to programmatically convert the existing ADCM RSD from legacy dictionary to WHO-DD
 - Give output dataset unique name to not confuse with ADCM
 - Limit new dataset to contain only terms of interest
- *Repeat regularly as additional legacy trials with new unique terms of interest are added to RSD*

Unique challenges and solutions

Challenge: Harmonizing data across many trials over a long period of time uses extensive programming resources

Solution:

- Create a re-usable library of ADaM datasets to avoid re-work for each submission
- Use standard ADaM specs and programs
- Pre-process data to allow use of standard TLF programs

Challenge: Lab data from different local and central laboratories can bring significant challenges to standardizing the lab parameter

Solution:

- Create table look-up to align Lab test and testcd
- Carefully review derivations and harmonize critical variables such as mcirt1, mcrit2, Analysis flag etc. across different trials

Unique challenges and solutions (cont)

Challenge: The process requires extensive documentation to explain the data transformation and standardization to prevent any confusion during review and inspection

Solution

- Create template tools to track programming, validation, outputs.
- Create ADRG and define templates

Challenge: Difficult to review multiple TLFs for consistency and quality when each is a unique output file

Solution:

- Combine all TLF pages into one single RTF for STAT review

Challenge: Truncation can occur in variable values when stacking up ADaM data with variables of different lengths can occur

Solution:

- Find maximum real values for all variables; set length for each variable and then stack up all the datasets

QC of Outputs : Consistency of summary tables

Ensure counts in summary tables match historic analysis:

- ISS summaries match old trials in previous ISS packages
 - ✓ If a trial appears in a historic ISS with the same date cut off, all numbers in summaries should match
- Ensure that ISS summaries match CSRs for pivotal and supportive trials
 - ✓ For pivotal trial, the number in the ISS summary should match the number in the CSR summary
- **Logic:** Calculate AE summary broken by trial/cohort
 - AE Summary
 - AE Summary for terms of special interest
 - AE Summary by baseline characteristics
 - AE Summary by Demographic information (Age, Sex, Region, etc.)

QC of outputs: Consistency of data

Check for consistency between current ISS and previous ISS

- Print the important tabs in Excel spreadsheet and check
 - ✓ Data Cut Off against data pooling plan, Alert trial team if any findings
 - ✓ Numbers against previous ISS/CSR
 - ✓ Number of subjects per trial
 - ✓ Number of AE/SAE/DEATH/AEOSI, etc.
 - ✓ Number of AE by Demo category
 - ✓ Consistency check between US and EU table sets
- ❖ *Use a macro to compare table counts*
- Randomly check 5 -10 files
 - ✓ Only Reference Database Column will have change, nothing else (assume we will make Errata correction in US database)

QC of outputs: Terminology

Ensure there are no surprise sin Controlled Terms for each trial

- Logic: Scan all related variables and list all the distinct values in the pooled dataset
 - ✓ AGEU
 - ✓ SEX
 - ✓ RACE
 - ✓ REGINE
 - ✓ etc.,
- Programmer needs to handle the unexpected cases accordingly to avoid mistake in summary table
 - ✓ Upper case/lower cases
 - ✓ Leading space
 - ✓ Missing values

Conclusion

- ❑ There are unique challenges to conducting integrated analysis for a compound with multiple submissions occurring over a span of multiple years
- ❑ Establishing a library of reference safety datasets will ensure a consistent ability to efficiently create high-quality integrated analysis which accurately reflects the safety profile of the compound
- ❑ Defined packages of deliverables and following established processes and techniques will increase efficiency, quality and consistency
- ❑ Templates and standardized tools and macros/programs are essential for harmonizing data across studies and leveling/converting dictionaries
- ❑ The use of standard macros and utility tools to conduct consistency checks and compare counts will save significant time and improve quality

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What questions do you have?

