ISS and ISE Dataset Preparation Best Practices: A PhUSE Whitepaper

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Introduction

It is a constant struggle for sponsors to establish an integration strategy for standard (CDISC compliant) and non-standard data at SDTM and/or ADaM level, as no specific strategy or requirements exist within the industry and from regulatory agencies. The industry continues to face challenges and hurdles with pooling, leveling, traceability and compliance checks.

While there are a variety of scenarios that will arise during the preparation of the integrated databases in support of the Integrated Summary of Safety (ISS) and the Integrated Summary of Efficacy (ISE), this white paper is created by PhUSE SDTM and ADaM Implementation FAQ team to address frequently asked questions on guidance on how to prepare ISS/ISE, with the focus to be on two most common scenarios; note that any scenario used will require upfront discussions with the FDA and PMDA:

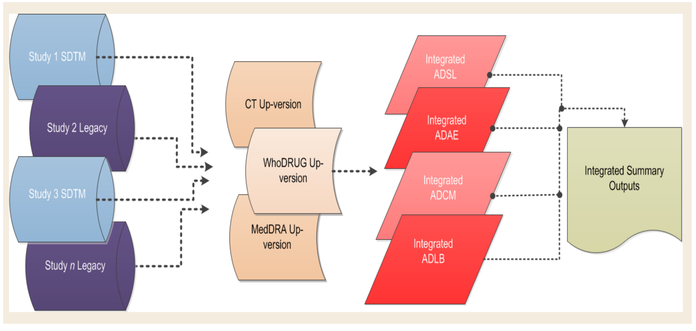
- ADaM-only Integration
- SDTM and ADaM Integration

Scenario 1: ADaM-only Integration

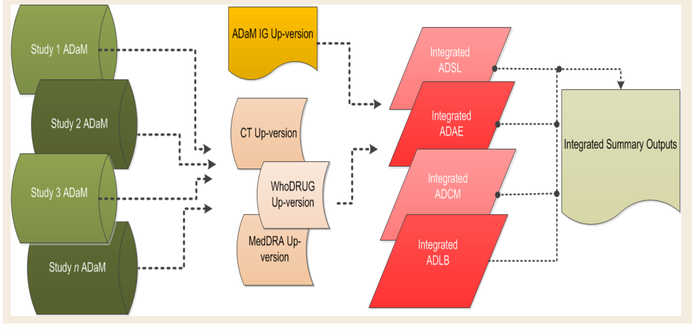
ADaM-only integration strategy may be more suitable when:

- ✓ The majority or all of the ISS and ISE analyses and resulting tables, figures and listings (TFLs) can be generated using the ADaM datasets
- ✓ The ADaM datasets robust and complete enough to be used to conduct all the analyses required by the ISS and ISE
- ✓ A very small number of the studies selected to be included in the integration analysis are not CDISC complaint with SDTM standards
- ✓ There are little to no new derivation needed in the ISS and ISE analyses
- ✓ There is minimal dictionary or controlled terminology up-versioning required
- ✓ There was sufficient pre-planning for integration included in the ADaM datasets
- ✓ Not all data that is required for the ISS and ISE analyses is included in the study ADaM datasets and it is necessary to obtain it from the study SDTM datasets
- ✓ Study analysis datasets are not CDISC compliant

Study SDTM and/or Legacy Data → Integrated ADaM



Study ADaM → Integrated ADaM

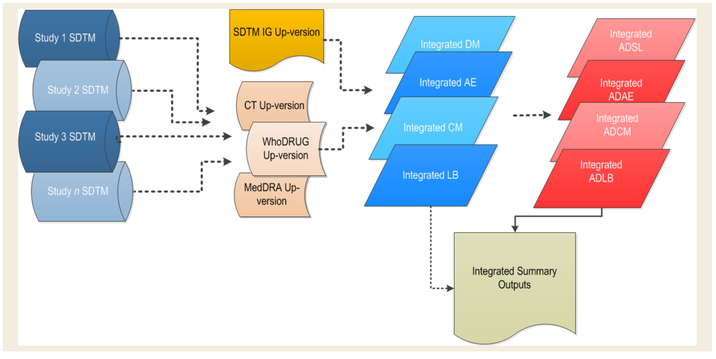


Scenario 2: SDTM + ADaM Integration

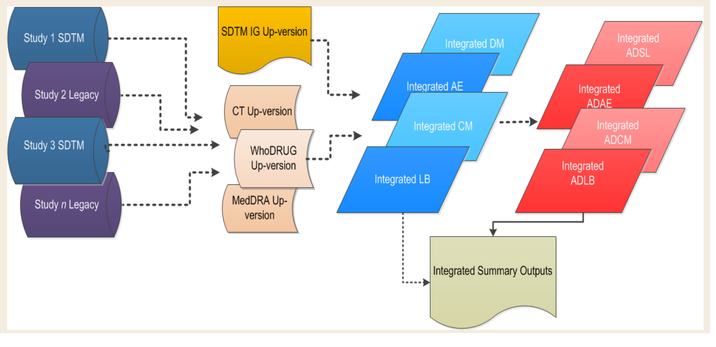
Sponsor may choose to integrate both the SDTM and the ADaM databases when:

- ✓ The majority of the studies to be included in the integration have CDISC-compliant SDTM and ADaM databases in place
- ✓ There is a large mixture of studies with standard and non-standard study data to be included in the integrated analyses
- ✓ There are too many different standards versions , controlled terminology versions, or dictionary versions that need to be harmonized
- ✓ The number of ISS and ISE TFLs that can use SDTM as the data source is significant
- ✓ Not all the data that is required for the ISS and ISE analyses is included in the study ADaM datasets and it is necessary to obtain it from the study SDTM datasets
- ✓ Integration needs extend beyond ISS and ISE analyses and are required for other tasks

Study SDTM → Integrated SDTM → Integrated ADaM



SDTM + Legacy Data → Integrated SDTM → Integrated ADaM [1]



Adherence to Regulatory Agency Guidance

Up-versioning of Controlled Terminology (CT)

- ❖ The FDA TCG[2] specifically discuss the use of standardized and custom controlled terminology
  - ➢ emphasis on using standardized CT at a study-level
  - ➢ avoid the use of study-specific or sponsor-defined CT as much as possible
- ❖ Recommended to harmonize the CT (most current version available at the time) during integration activities.
- ❖ Note: up-versioning of standardized CT is not required within the individual SDTM or ADaM study-level datasets.
- ❖ Examples of CT harmonization to consider at an integration level: PARAM and PARAMCD, TRT01P and TRT01PN, TRT01A and TRT01AN, TRTA and TRTAN, TRTP and TRTPN, AVISIT and AVISITN, VISIT and VISITNUM, APERIOD and APERIODC.

Harmonization of Coding Data

- ❖ FDA and PMDA recommend to utilize MedDRA to code adverse events (AE) and WHODrug Global to code concomitant medications (CM).
- ❖ AEs and CMs should be coded to a single version of the respective dictionaries in the ISS and the most recent versions should be used at the time that the studies are pooled.
- ❖ When harmonizing coding dictionaries like MedDRA and WHODrug, the FDA has strongly recommended to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one dictionary version to another.
- ❖ Refer to PhUSE white paper[3] on CMs across different formats of the WHODrug classification.

Define.xml and DRG Generation

- ❖ The define.xml and DRG will need to be created for the new integrated datasets. For scenario 2, provide these documents for both databases if both are included in the submission.
- ❖ Harmonizing of coding dictionaries: provide a table of converted data from one dictionary version to another[2].

Traceability and Compliance Considerations

- ❖ Scenario 1 may require the generation of intermediary datasets for dictionary, CT, or standards version harmonization
  - ➢ these intermediary datasets will not be submitted to FDA or PMDA
- ❖ Scenario 2 provides a clear, traceable path from study data to integrated ADaM datasets
  - ➢ eliminates the need to generate intermediary datasets
  - ➢ each step of the process (study level data, integrated SDTM data, integrated ADaM data) is submitted to FDA and PMDA
- ❖ Variables – e.g. xxSEQ, ASEQ, SRCVAR, SRCDOM, SRCSEQ -- that are generally used in study level SDTM and ADaM datasets to depict traceability may not be applicable in integrated datasets
  - ➢ Scenario 1: xxSEQ can be used to show traceability to study level data
  - ➢ Scenario 2: xxSEQ will need to be regenerated in the integrate SDTM datasets and will not provide traceability to study level data
- ❖ Recommended to run P21 checks, even though FDA and PMDA validation rules are written for study SDTM data and study ADaM data
  - ➢ Scenario 2 may generate more compliance errors/warnings than Scenario 1, one set for integrated SDTM data and another set for integrated ADaM

Conclusion

The whitepaper is a work in progress and is aimed to be published in Q3 2019. We are always looking for more members! Contact the author to join us.

Acknowledgments

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References

[1] "Study Level Traceability Considerations Best Practices for Non-Linear Data Flow" . Published October 2014. Available at https://www.phuse.eu/documents//working-groups/deliverables/white-paper-study-level-traceability-in-a-non-linear-data-flow-18672.pdf

[2] FDA. "Study Data Technical Conformance Guide" Published March October 2018. Available at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624939.pdf

[3] PhUSE. "White Paper Recommendations for Pooled Submissions with WHODrug B3 Format Data" Published June 2018. Available at https://www.phuse.eu/white-papers

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