

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:

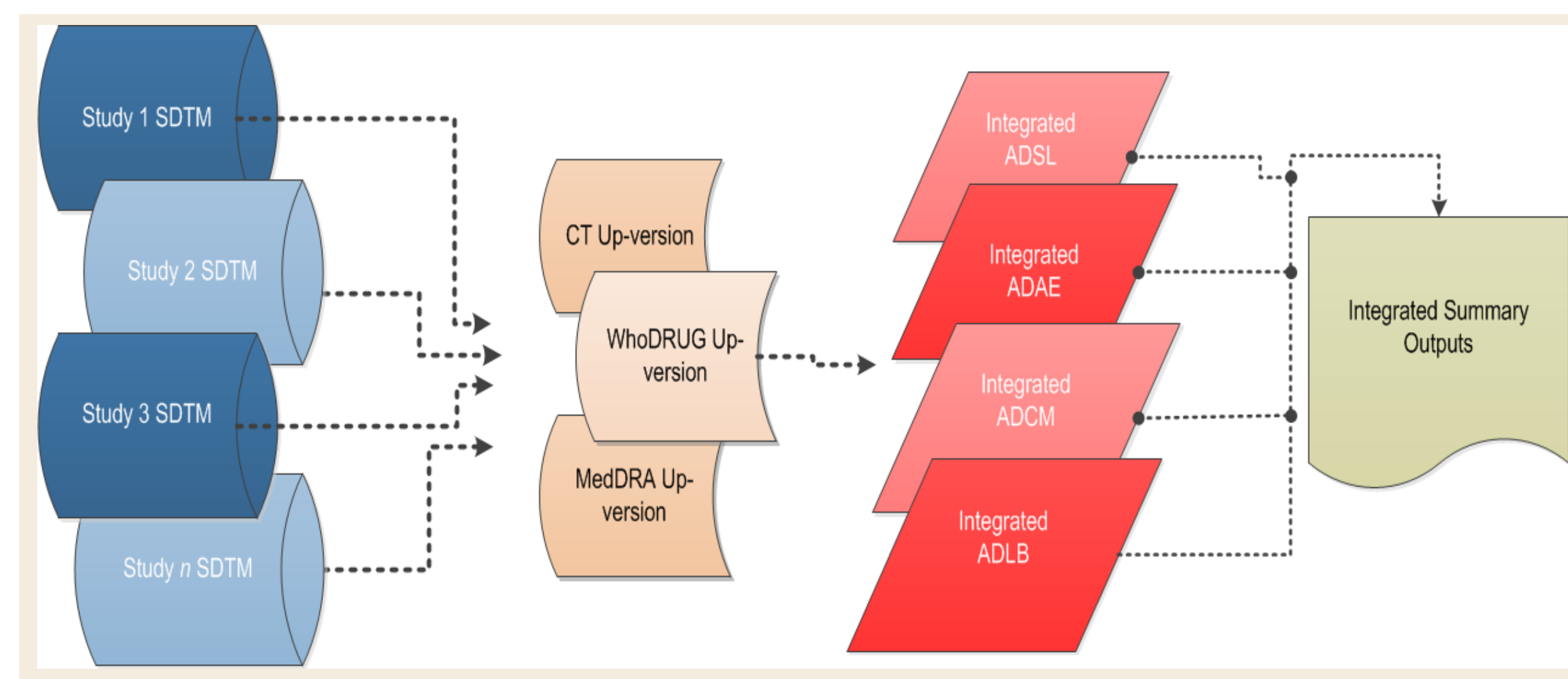
- ◆ ADaM-only Integration
- ◆ SDTM and ADaM Integration

Scenario 1: ADaM-only Integration

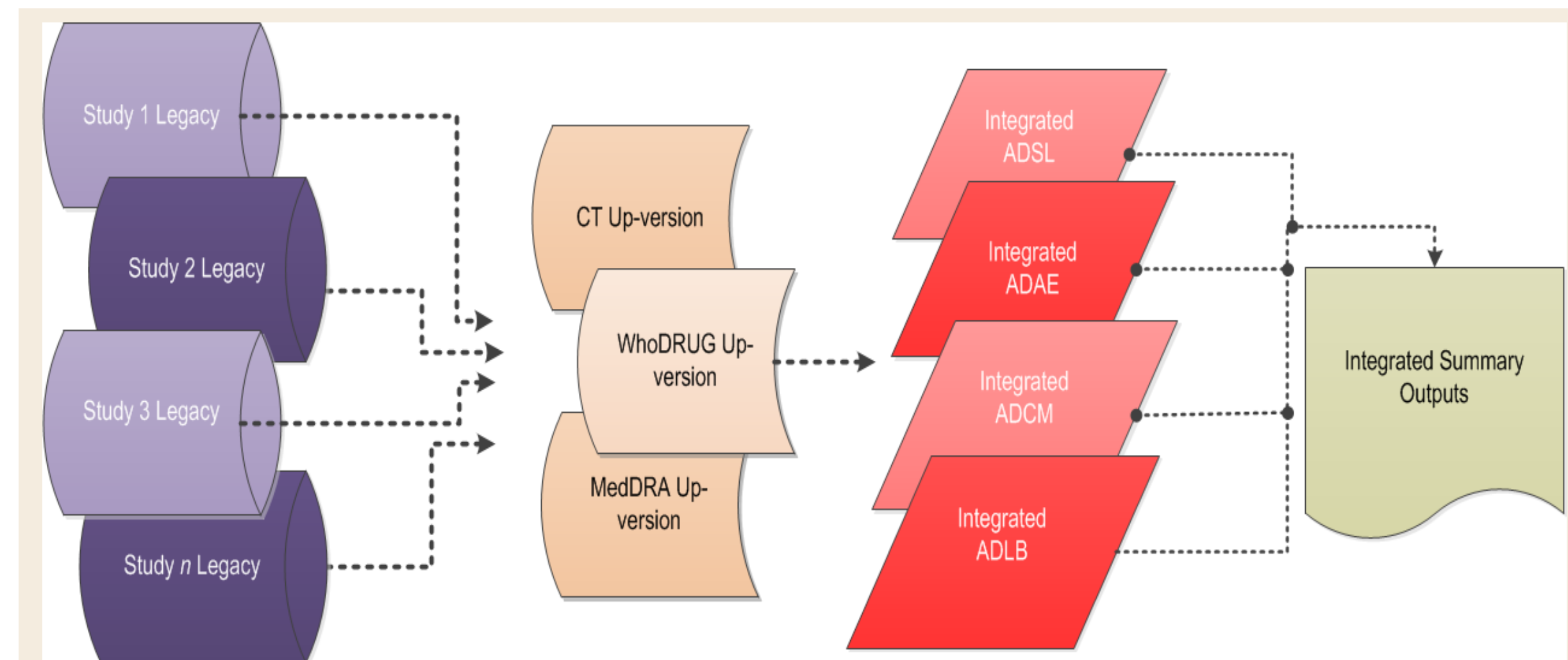
If the answer to the following questions is **YES**, the ADaM-only integration strategy may be more suitable:

- ✓ Will none of the ISS and ISE analyses and resulting tables, figures and listings (TFLs) be generated using SDTM datasets?
- ✓ Are the ADaM datasets robust and complete enough to be used to conduct all the analyses required by the ISS and ISE?
- ✓ Are some of the studies selected to be included in the integration analysis not CDISC compliant with respect to the SDTM data?

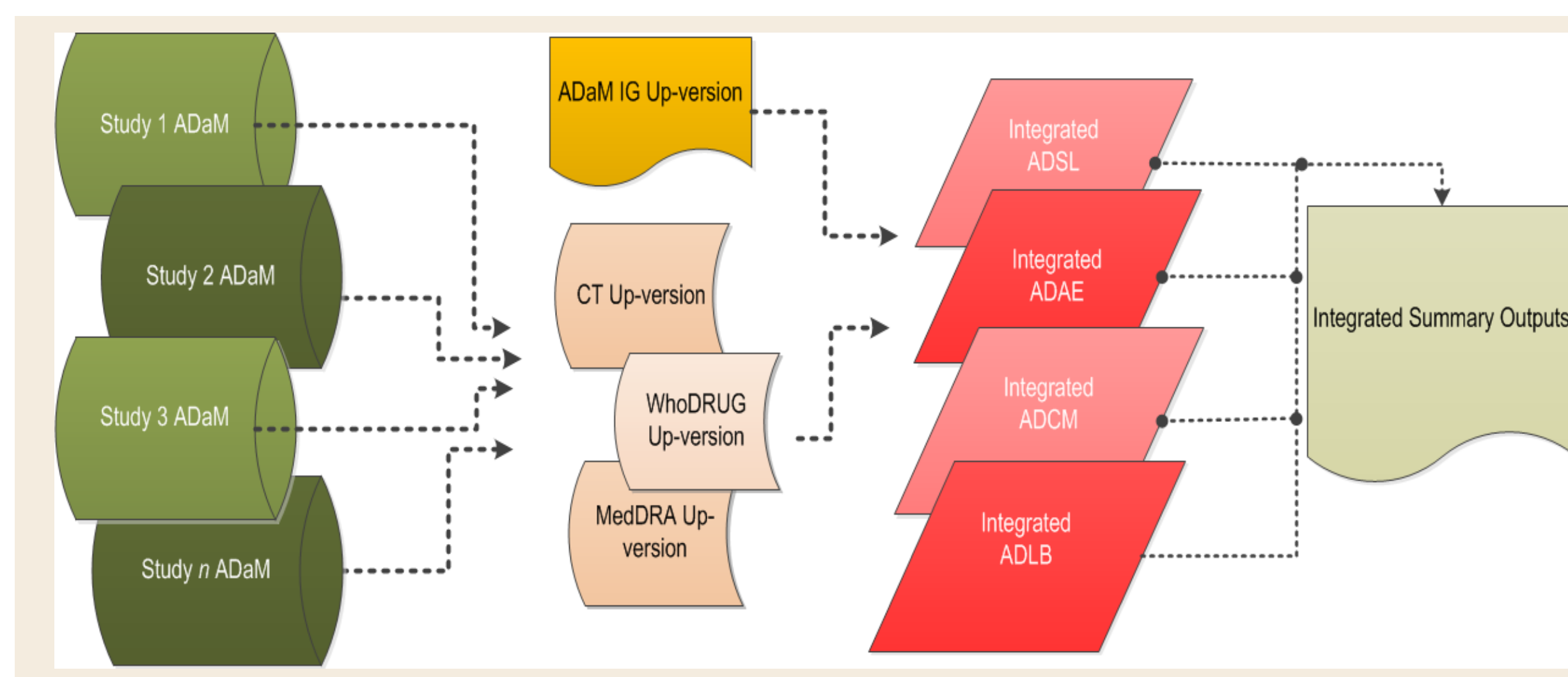
Study SDTM → Integrated ADaM



Non-Standard Legacy Data → Integrated ADaM



Study ADaM → Integrated ADaM

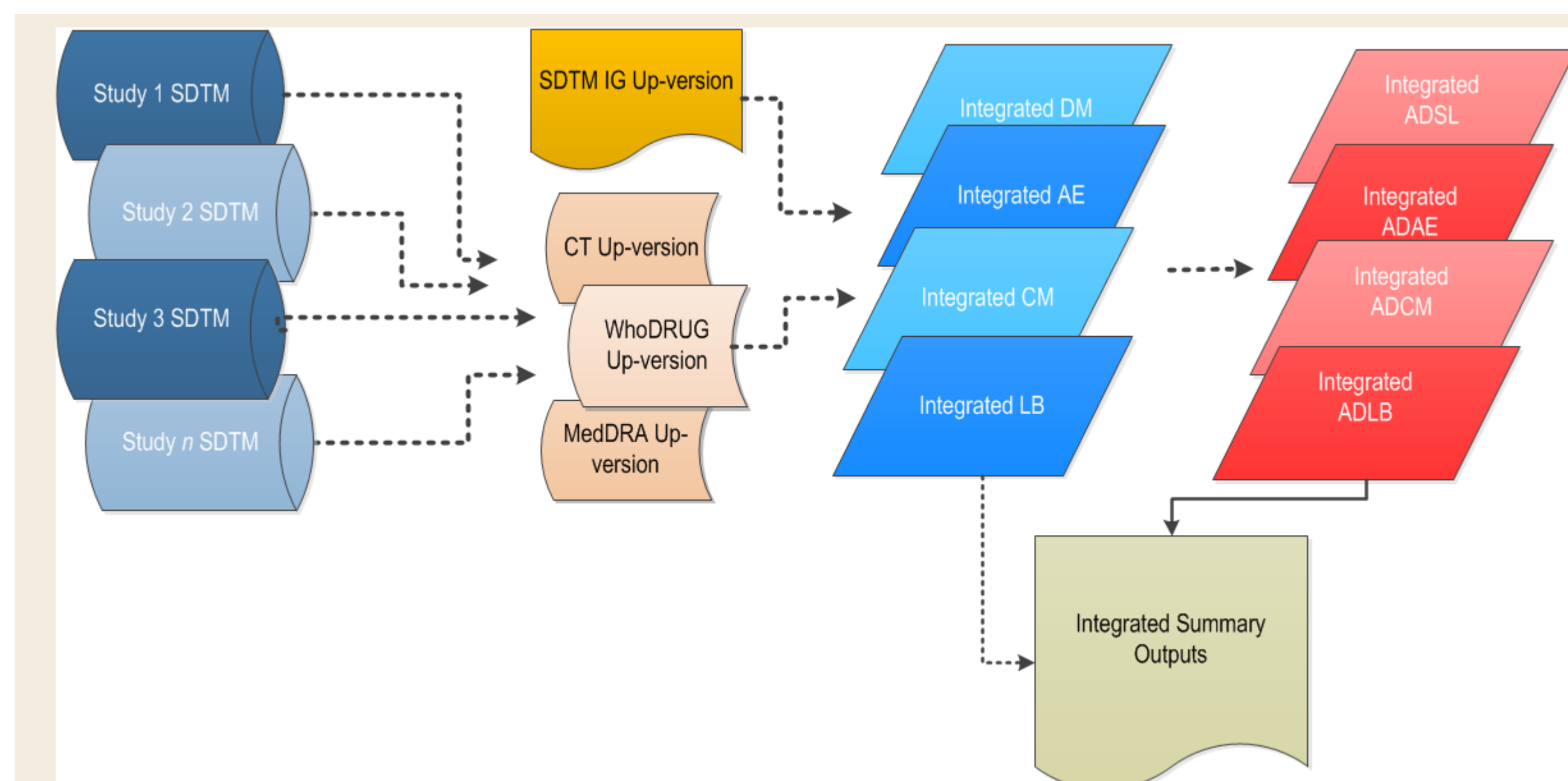


Scenario 2: SDTM + ADaM Integration

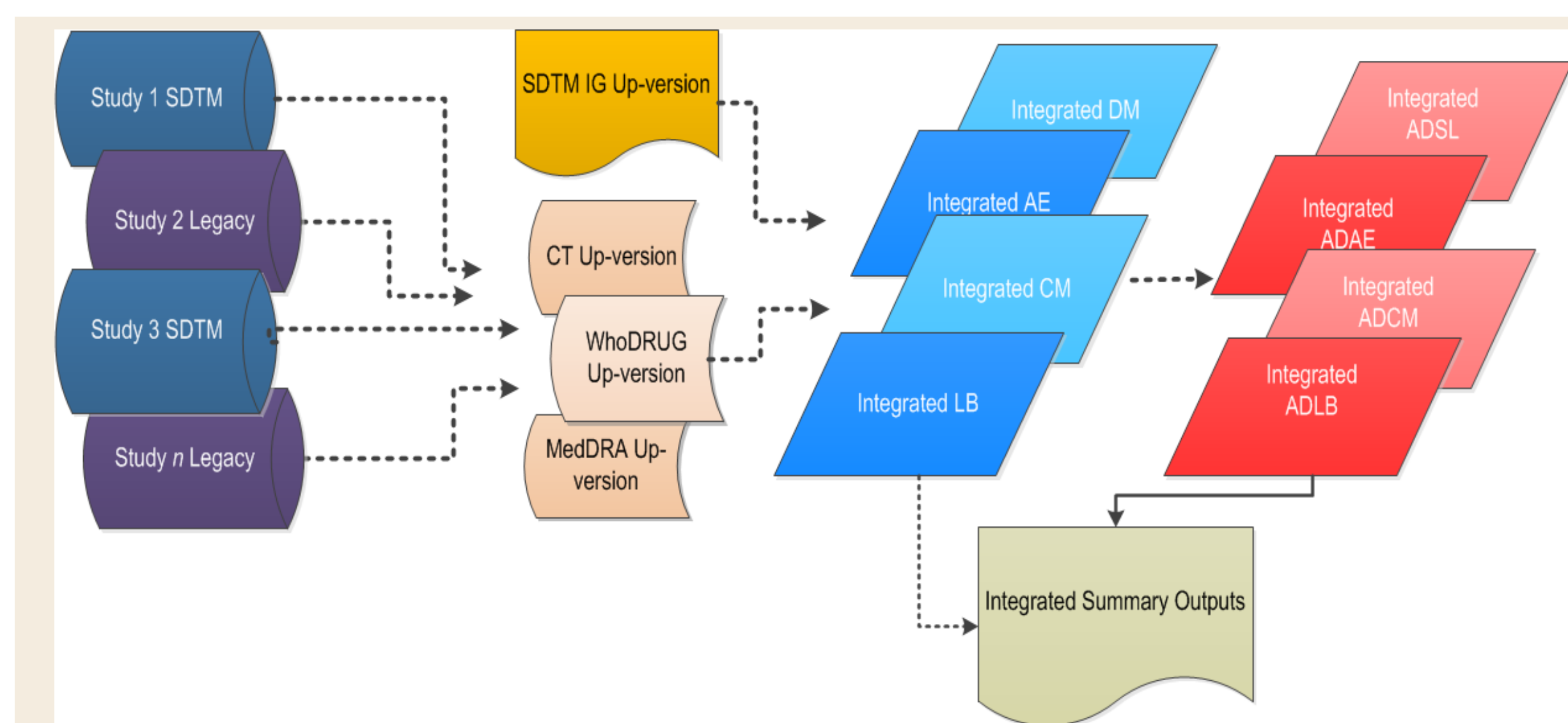
If the answer to the following questions is **YES**, the Sponsor may choose to integrate both the SDTM and the ADaM databases:

- ✓ Do the majority of the studies to be included in the integration have CDISC-compliant SDTM and ADaM databases in place?
- ✓ Is there a mixture of studies with standard and non-standard study data included in the integrated analyses?

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 TCG² 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 study SDTM or ADaM 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

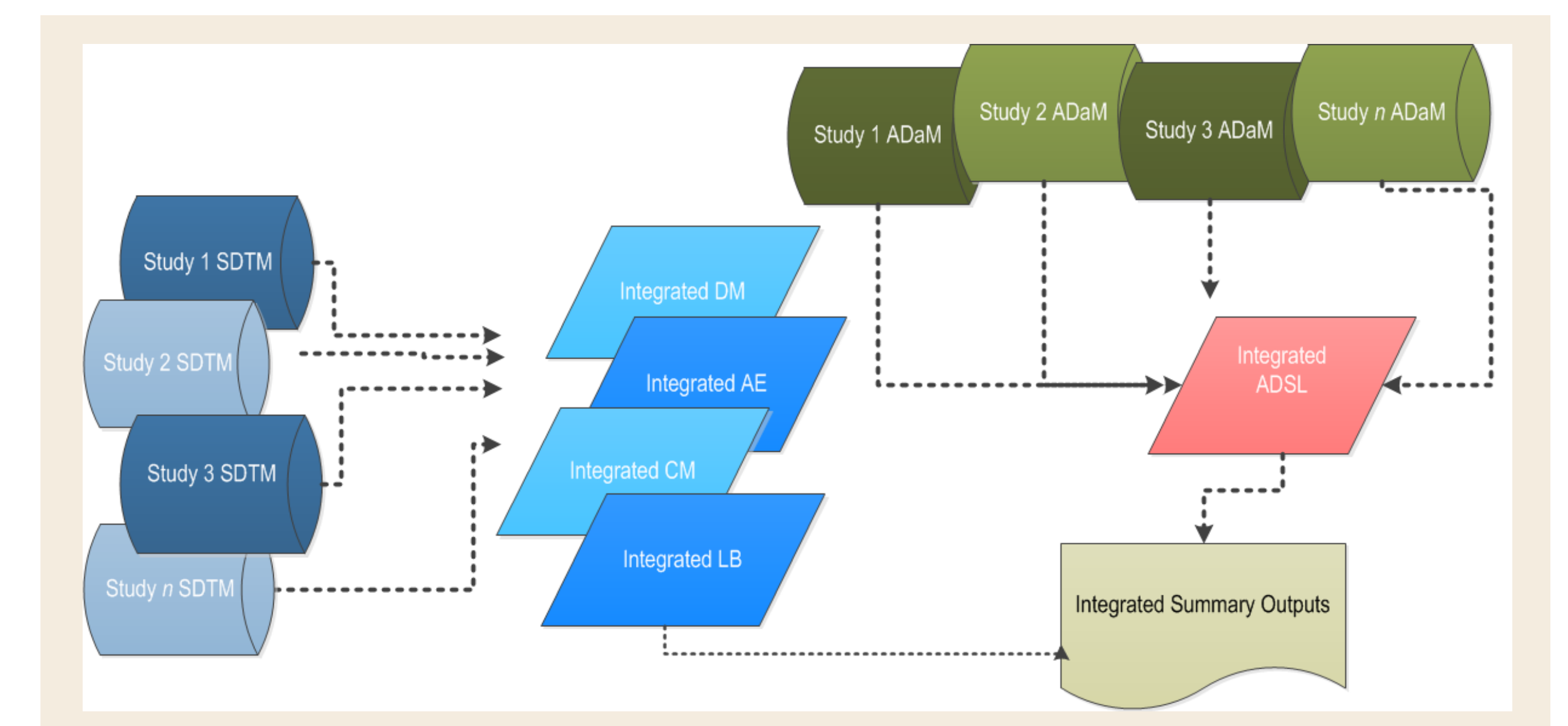
- ❖ FDA recommendation to utilize MedDRA to code adverse events (AE) and WHODrug Global to code concomitant medications (CM).
- ❖ AEs and CMs should be coded to a single version of the respective dictionaries in the ISS and the most recent versions used at the time that the studies are pooled.
- ❖ When 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 paper³ 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 another².

Study SDTM → Integrated SDTM & Study ADaM → Integrated ADaM

Not Recommended: There may be a scenario in which the Sponsor may choose to generate the integrated summary outputs using an integrated the SDTM database and integrated ADSL. This method will cause extensive traceability, verification, and documentation challenges.



Conclusion

The whitepaper is a work in progress and is aimed to be published in Q2 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>