

SA04

Making SDTM/ADaM CRT Packages Submission Ready

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Agenda

- **What are SDTM CRT and ADaM CRT Packages?**
 - SDTM CRT Package
 - ADaM CRT Package
- **Regulatory Requirements**
- **Legacy Conversions**
 - SDTM
 - ADaM
- **Up-Version**
- **Conclusion**
- **Questions**

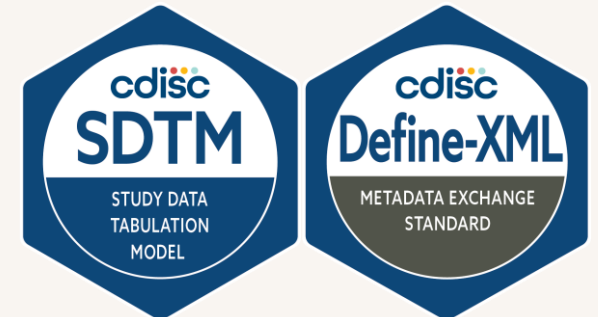


What are SDTM CRT and ADaM CRT Packages?

What are SDTM CRT and ADaM CRT Packages?

SDTM CRT PACKAGE

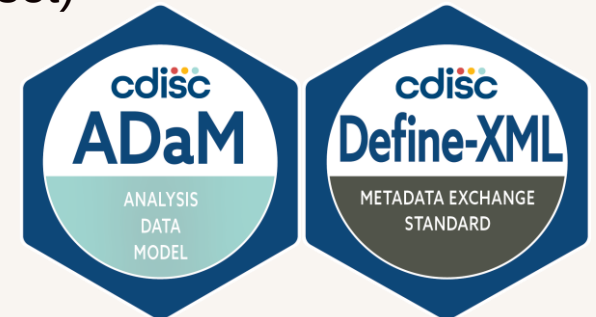
- Study Data Tabulation Model Case Report Tabulation (SDTM CRT)
- Each submitted study should contain an SDTM CRT package, comprising of:
 - annotated CRF (aCRF)
 - SDTM datasets in xpt format
 - define.xml and stylesheets
 - Clinical Study Data Reviewer's Guide (cSDRG)
 - Pinnacle21 reports
- Optional Extras
 - SDTM programs
 - define.pdf



What are SDTM CRT and ADaM CRT Packages?

ADaM CRT PACKAGE

- Analysis Data Model Case Report Tabulation (ADaM CRT)
- Each submitted study should contain an ADaM CRT package, comprising of:
 - ADaM datasets in xpt format
 - define.xml and stylesheets
 - Analysis Data Reviewer's Guide (ADRG)
 - Pinnacle21 reports
 - ADaM programs
 - Other data sources (non-SDTM datasets used as an input to an ADaM dataset)
 - Analysis Results Metadata (ARM), if performed.
- Optional Extras
 - define.pdf





Regulatory Requirements



Regulatory Requirements

- When a study is submitted the data should be presented within a CRT packages.
- SDTM and ADaM datasets should adhere to a supported implementation guide (IG) version.
 - Standards catalogs are available on the regulatory body's websites.
- SDTM and ADaM datasets >5GB in size should be split.
- The define.xml should adhere to a supported define.xml version.
- The CRT packages should be validated using pinnacle21.



Regulatory Requirements

- Data not presented in SDTM or ADaM format, require a legacy conversion to create the CRT packages.
- Data presented in SDTM or ADaM format but not within a supported IG or define.xml version, require:
 - An exemption/waiver form to be submitted and approved.
 - An up-version to the existing CRT package to a supported IG or define.xml version.



Legacy Conversions



Legacy Conversions

SDTM

What is an SDTM legacy conversion?

- 21JUL2004 - SDTM selected as the standard specification for submitting tabulation data for clinical studies
- 05JUL2011 - SDTM selected as the standard specification for submitting tabulation data for non-clinical studies.
- 2016 - SDTM becomes a requirement.
- Legacy data - Data collected on the study from the CRF or external data transfers, not converted into SDTM and used for the analysis on a study.
- Legacy conversion - process of converting the legacy data into SDTM.

Legacy Conversions

SDTM



- Confirm
 - Required studies
 - SDTM IG version
 - Coding dictionary versions
 - Regulatory bodies

Legacy Conversions

SDTM



Legacy conversions require all the source data and some study documentation.

Common issues:

- Study has been archived
- Multiple sponsors involved with the compound
- Programming performed by multiple vendors
- Only paper versions of documents are available

Legacy Conversions

SDTM



Essential Documents:

- CRF
- CSR
- Protocol
- Raw data
- SAP and TFL Shells

Legacy Conversions

SDTM



The critical step of the process.

A thorough review of the source data and study documents should assist with:

- A mapping document that identifies data to be retained or discarded.
- Creation of the SDTM specification and aCRF
- Alignment with sponsor
- Upgrading coding dictionaries
- Aligning with regulatory bodies

Legacy Conversions

SDTM



The legacy conversion is similar to the standard process in the production of SDTM datasets.

- Produce SDTM specification and aCRF
- Program and validate SDTMs
- Produce and validate define.xml
- Produce cSDRG
 - Use the Legacy Data Conversion Plan and Report Appendix.
- Sponsor Review

Legacy Conversions

SDTM



Send the final SDTM CRT packages to the sponsor for submission





Legacy Conversions

ADAM

What is an ADaM legacy conversion?

- 2005 - ADaM datasets introduced
- 2008 - v1.0 ADaM IG released as draft.
- 2009 - v1.0 ADaM IG released as final.
- 2016 - ADaM becomes a requirement.
- Legacy data – Intermediate analysis data used to aid the produce of TFLs.
- Legacy conversion - process of converting the legacy data into ADaM.

Legacy Conversions

ADAM



- Source data should be the SDTM CRT package.
- The SDTM CRT package doesn't need to be final for production to begin.
 - The final ADaM CRT package use the final SDTM CRT package.

Legacy Conversions

ADAM



- Request:
 - Intermediate datasets, if any
 - TFL programs
 - TFL outputs
 - Same documents requested for the SDTM conversion.
- The issues seen with the SDTM legacy conversion, apply to the ADaM legacy conversion.

Legacy Conversions

ADAM



This is the critical step of the process.

A thorough review of the TFL programs, TFL outputs, source data and study documents should assist with:

- Required ADaM datasets
 - Including any a regulatory body would expect
- Creation of the ADaM specification
- Any participant exclusions

Legacy Conversions

ADaM



The legacy conversion should follow the standard process for production of ADaM.

- Produce ADaM specification
- Program and validate ADaM datasets
- Produce and validate define.xml
- Produce ADRG
- Sponsor Review

Legacy Conversions

ADAM



Send the final ADaM CRT packages to the sponsor for submission





Up-Version

Up-Version

INTRODUCTION

- The development of a compound can take many years. Sponsors prefer the latest version of IG and define.xml to be used.
 - Leading to the potential for multiple IG and define.xml versions. This is acceptable provided the regulatory bodies support all versions of IG or define.xml.
- When a new version of IG or define.xml version is rolled out, regulatory bodies will set a date requirement for when the new version begins and a date for when the support and requirement of the previous version will end.
- One problem is that studies on a compound have not gone to plan, with some studies no longer being in a version of IG or define.xml that is accepted. When this occurs an up-version is required.

Up-Version

INTRODUCTION

There are two forms of up-version.

1. SDTM and/or ADaM up-version

- Updating an IG version no longer supported to a version that is supported

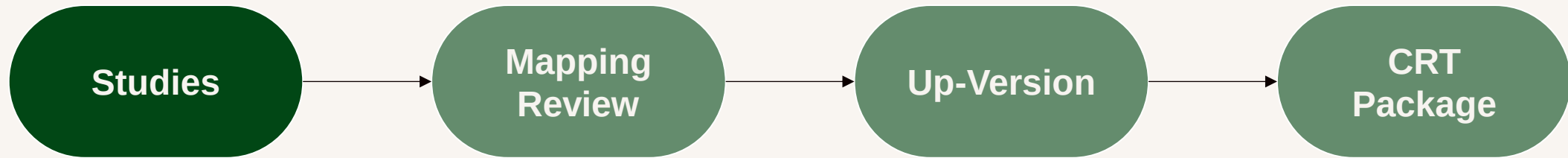
2. Define.xml up-version

- Updating a define.xml version no longer supported to a version that is supported

- In the last 5 years we've seen the FDA end support for SDTM IG versions: 3.1.2, 3.1.2 amendment 1, 3.1.3 and 3.2, ADaM IG version: 1.0, and Define.xml version: 1.0

Up-Version

UP-VERSION OF SDTM/ADAM IG

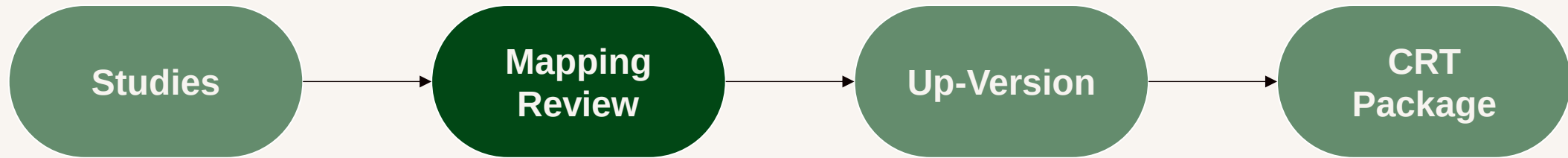


Confirm:

- Required studies
- SDTM and ADaM IG version

Up-Version

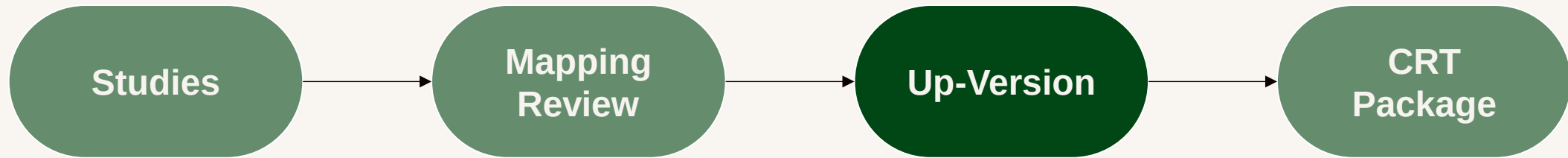
UP-VERSION OF SDTM/ADAM IG



- Assess differences between old and new IG version
- Ensure changes from the up-version do not impact the initial analysis
- Existing documentation needs to be reviewed.
 - An up-version can lead to changes in the aCRF, specifications and reviewer's guides.
 - Standard expectation is a new define.xml will be required.
- When only the SDTMs require an up-version, ensure that the ADaM datasets would not be affected.
 - If ADaM datasets would be affected, check with the sponsor if they want the ADaM datasets updating.

Up-Version

UP-VERSION OF SDTM/ADAM IG



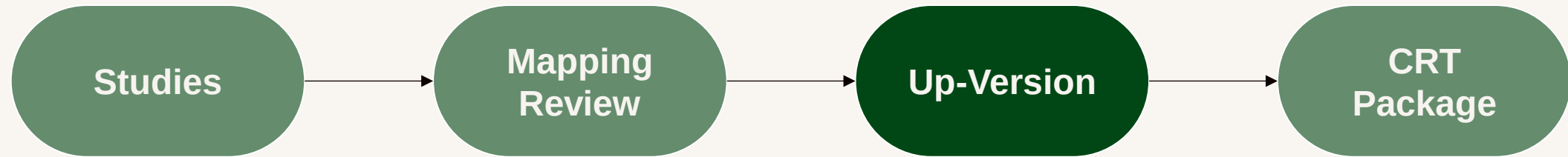
The up-version will lead to updates to the following deliverables:

- aCRF*
- SDTM/ADaM Specification
- SDTM/ADaM datasets
- define.xml
- cSDRG/ADRG

*aCRF doesn't always change depending on what occurred on the study.

Up-Version

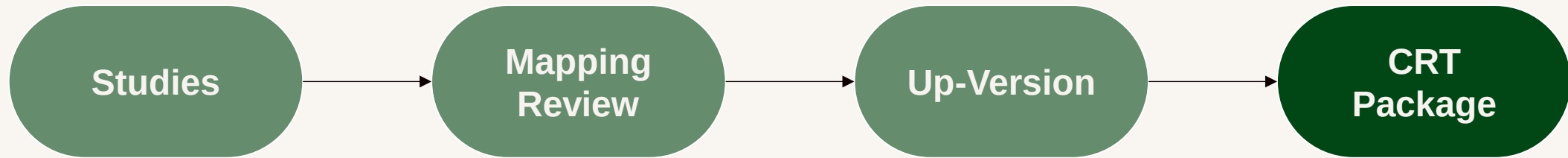
UP-VERSION OF SDTM/ADAM IG



- Validate with pinnacle21
- Pinnacle 21 findings should be discussed in the cSDRG/ADRG.

Up-Version

UP-VERSION OF SDTM/ADAM IG



Send the final CRT packages to the sponsor for submission.



Up-Version

UP-VERSION OF DEFINE.XML



Confirm:

- Required studies
- Define.xml version

Up-Version

UP-VERSION OF DEFINE.XML



- Documents that require an update are:
 - Define.xml
 - Stylesheets
 - Reviewer's guide
- The aCRF, specifications and datasets, should be available.
- The define.xml up-version should use the existing aCRF, specifications and datasets.

Up-Version

UP-VERSION OF DEFINE.XML



Send the final CRT packages to the sponsor for submission.





Conclusion

Conclusion

- SDTM and ADaM CRT submission packages require:
 - Regulatory supported IG and define.xml versions.
 - An accepted exemption/waiver form for versions of IG or define.xml no longer supported.
- Studies with legacy data, require a legacy conversion to create submission ready CRT packages.
- Up-versions are required when an existing CRT package IG/define.xml version is not regulatory supported, and an exemption/waiver has been rejected.

Conclusion

- The mapping review is critical for any legacy conversion or up-version of a CRT package.
- The legacy conversion requires more planning than the up-version, due to the source data being in an array of formats, SAS datasets, excel files, csv files, text files, etc.
- Pinnacle21 validation should be performed.
- Recommended to use the templates for the reviewer's guides from the PHUSE websites.



Questions

