



Ensuring Consistent and Supported Standards Across Data and Metadata in a Large Regulatory Filing is Tricky Business

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Disclaimer:

I am not a Regulatory Professional, I only play one on TV. Although I am often asked about planning data submissions, I am no regulatory expert. This presentation is based solely on my own experience. Data submission decisions are very complicated and require written FDA agreement.

Preparing Clinical Data for a Large Regulatory Filing

OUTLINE

- Set the Stage
- Act I
- Intermission
- Act II
- Curtain Call
- Post Production Meeting

Gap Analysis - What do we got?

- How many studies are pivotal, phase I-III, bridging, QT, included in pooled analysis, or needed for special reports? Reviewers are likely to spend time on the most interesting 5 studies plus the ISE/ISS. These are often considered important studies.
- Do we have all versions of the protocol, ICF, CRF, data specs, imported data files (randomization, pv, pk, lab), analysis programs, TLFs, hard code explanations, study reports, and CSRs?
- What is the status of studies? Can we assess and impact compliance? When did the study start?
- What version of data standards were used and are they supported by FDA: SEND, SDTM, ADaM, CT, MedDRA, WHODD, LOINC, SNOMED, XML?

Set the Stage

Is the Standard Supported?

Check the Data Standards Catalog

SUPPORTED: “For the purposes of this catalog, “supported” means the receiving FDA Center has established processes and technology to support receiving, processing, reviewing, and archiving files in the specified standard.”

DATE SUPPORT ENDS: “Sponsors cannot use the standard or terminology after this date. Generally, a waiver process may be available. Sponsors and applicants should consult with their review division. An empty field in this column means that a support end date has not been established.”

Set the Stage

Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Supported Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends
Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1.1	3.1.1	CDER, CBER	Ongoing	01/28/2015		

As of March 2019 the following will not be supported for NDAs:

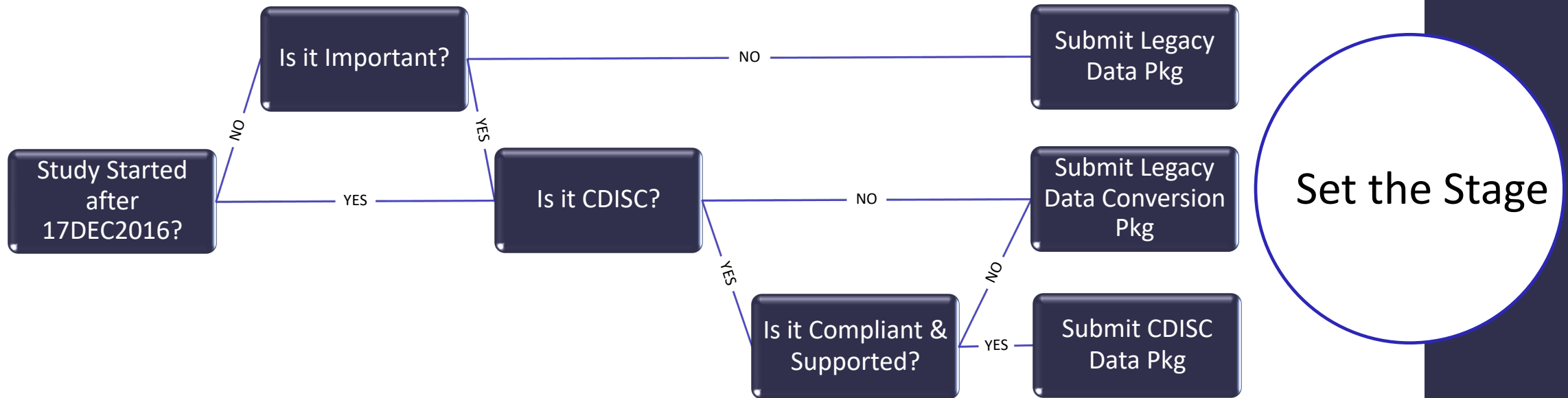
Data Exchange Standard	Exchange Format	Version	Implementation Guide Version	Date Support Ends for NDA
SDTM	XPT	1.1	3.1.1	01/28/2015
SDTM	XPT	1.2	3.1.2	03/15/2019
SDTM	XPT	1.2	Version 3.1.2 Amendment 1	03/15/2019
ADaM	XPT	2.1	1.0	03/15/2019
SEND	XPT	1.2	3.0	03/15/2019
Define	XML	1.0	N/A	03/15/2018

Set the Stage

Terminology Standard	Version(s)	Date Support Ends for NDA	Supported Version
Medical Dictionary for Regulatory Activities (MedDRA)	8 or earlier	03/15/2019	Anything after Version 8 to the Current Version
WHO Drug Dictionary	Not Specified	03/15/2019	Supported standard is WHODrug Global Current Version-B3 Format

What Standards are not Supported?

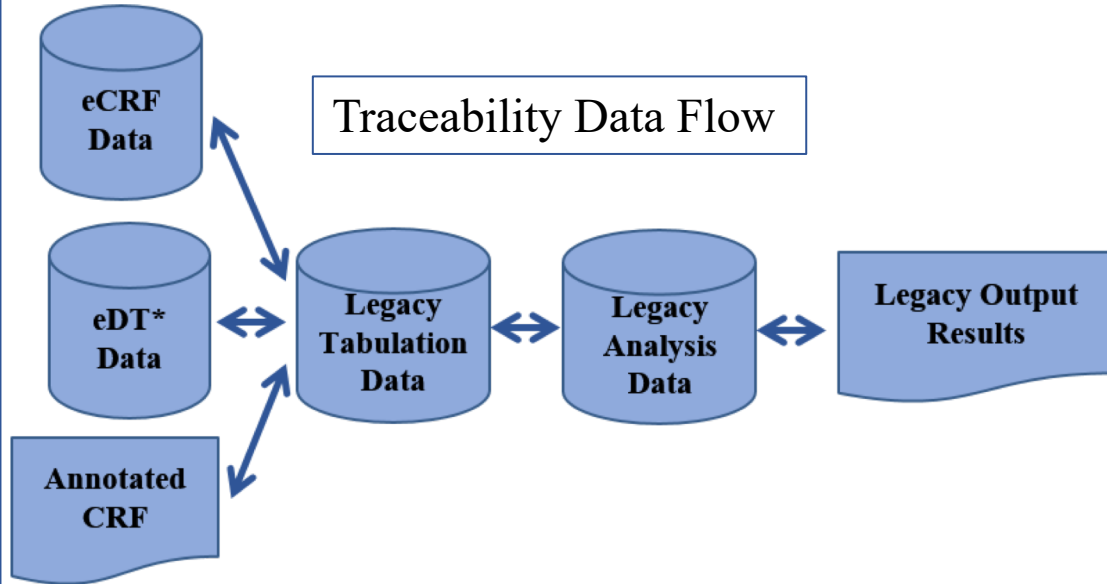
Building a Data Submission Strategy Study by Study – A Simplified Decision Tree



Study Start Date is defined as the informed consent date of the first enrolled subject.

Legacy Data Package

Traceability Data Flow



*eDT = Electronic Data Transfer (e.g. central lab data, ECG vendor data, PK data, etc.)

Folder Structure and Contents

[study]
analysis
 legacy
 datasets
 programs
tabulations
 legacy

analysis-legacy-datasets folder:

1. legacy analysis data
2. define.pdf (or define.xml modified for non-CDISC study)
3. adrg.pdf (modified for non-CDISC study)

analysis-legacy-programs folder:

1. SAS® programs for legacy analysis derivation
2. SAS programs for analysis tables, listings and figures (TLFs)

tabulations-legacy folder:

1. legacy tabulation data
2. define.pdf (or define.xml modified for non-CDISC study)
3. acrf.pdf (annotated for legacy tabulation data)
4. csdrg.pdf (modified for non-CDISC study)

Set the Stage

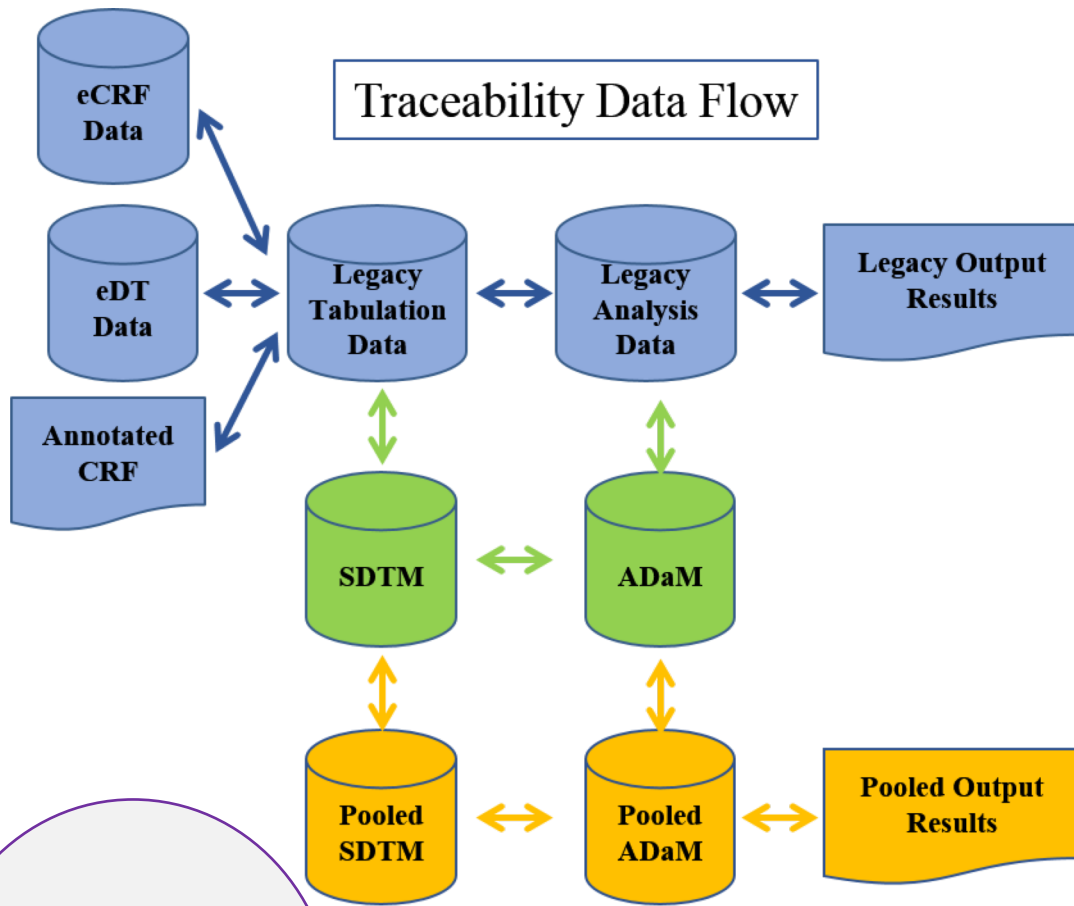
Legacy Data Package

- Only for studies that started before December 17, 2016
- Studies are not particularly important (for example, early ClinPharm studies under another indication)
- Will need to be made into submission ready data*

*Guidance for Industry: Providing Regulatory Submissions in Electronic Format — NDAs (see references) under the section “Item 11: Case Report Tabulations (CRTs).”

Set the Stage

Legacy Data Conversion Package



Set the Stage

Folder Structure and Contents

```
[study]
├── analysis
│   ├── adam
│   │   ├── datasets
│   │   ├── programs
│   │   └── legacy
│   ├── datasets
│   ├── programs
│   └── tabulations
│       ├── sdtm
│       └── legacy
```

analysis-adam-datasets folder:

1. ADaM data
2. define.xml
3. adrg.pdf (with LDCP, if needed)

analysis-adam-programs folder:

1. SAS® programs for ADaM

tabulations-sdtm folder:

1. SDTM and TDM
2. define.xml
3. acrf.pdf (annotated for SDTM data)
4. csdrg.pdf (with LDCP, if needed)

Note: legacy folders are the same as Legacy Data Package

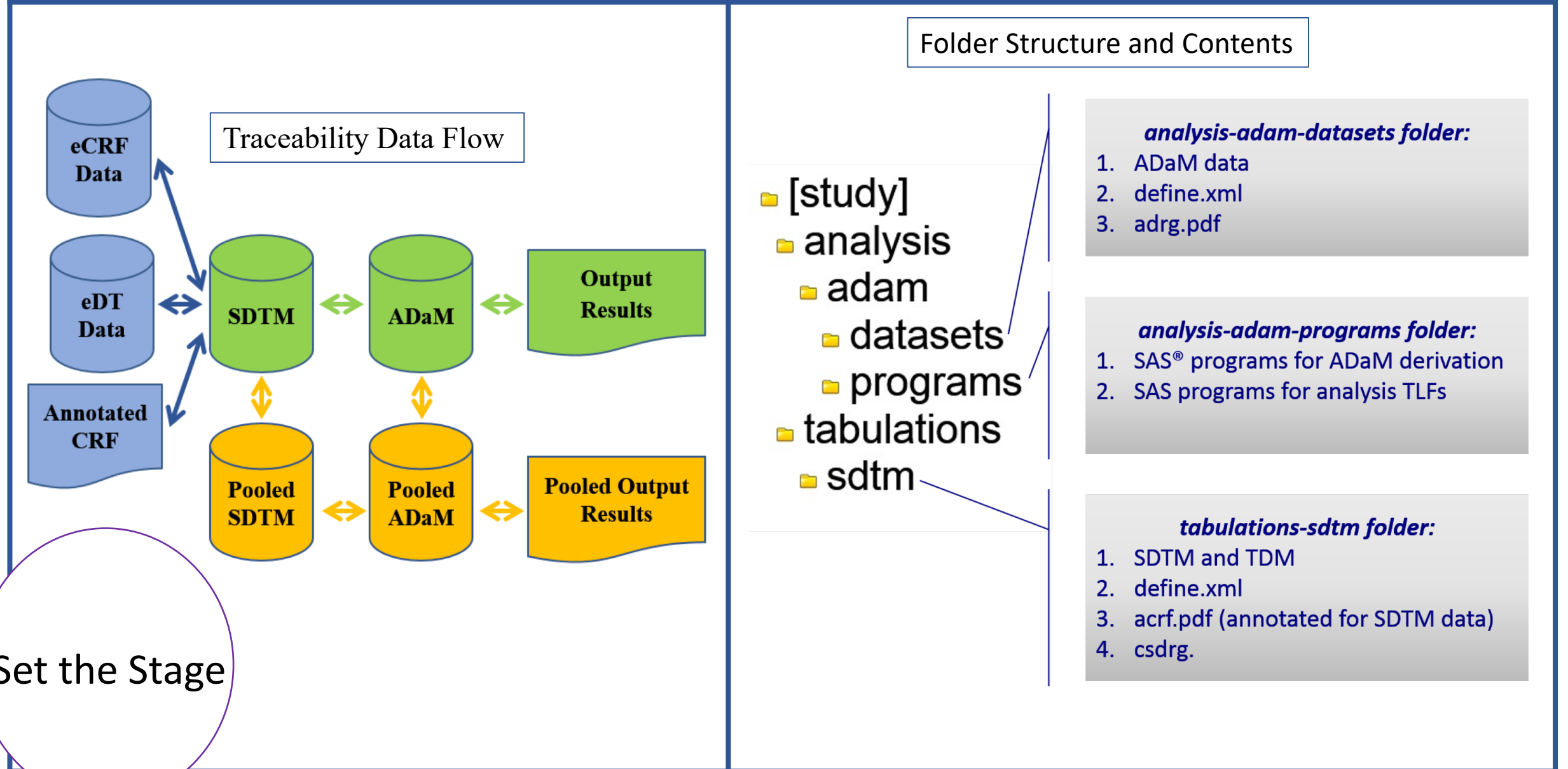
Legacy Data Conversion Package

Why convert to CDISC?

- A sponsor wants to submit electronic data in CDISC format, the study started on or before December 17, 2016, the study is important, the CDISC data may be needed for a pooled analysis or special report, and/or the data used to generate the CSR appendices was not in CDISC format.
- The study started after December 17, 2016, CDISC study standards are required, and the data used to generate the CSR appendices was not in CDISC compliant format. In this case both SDTM and ADaM compliant data are required for submission.
- The FDA may request that data be submitted in CDISC format even if it is not required.

Set the Stage

CDISC Data Package

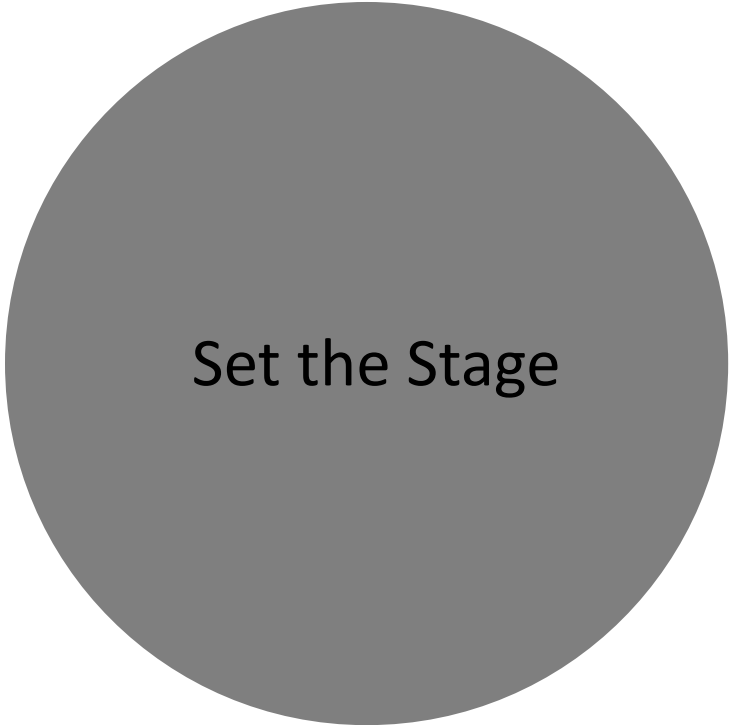


CDISC Data Package

- The CDISC data package is submitted for studies with CSR appendix TLFs generated from ADaM data which were generated from SDTM data.
- If the study started after December 17, 2016, data in CDISC format is required for an NDA submission.
- Study Start Date is defined as the informed consent date of the first enrolled subject.
- CDISC data that was prepared in the past, may not be up to existing standards and could require remediation.

Set the Stage

- Compare your Gap Analysis to your SDSP and update accordingly.
- If you don't have an SDSP, now is the time to make one!
- Try to get stakeholders to consider data pooling as early as possible.
- Sponsor stakeholders review and buy-in to SDSP and overall data strategy.
- The SDSP should be the authoritative document for standards versions.



Set the Stage

Study Data Standardization Plan

Study Identifier	Brief Title	Study Design	Study Status	Study Start Date	Exchange Standards	Terminology Standards
Phase I Interventional Studies - Healthy Subjects						
DRG-102	The Protocol Title in a Brief Way for Study DRG-102	SINGLE DOSE, RANDOMIZED, OPEN LABEL PLACEBO CONTROL, PHARMACOKINETIC, SAFETY, TOLERABILITY	COMPLETED	2014-11-13	ANALYSIS LEGACY define.pdf TABULATIONS LEGACY define.pdf	MedDRA (Adverse Events/ Medical History) 17.0 WHO-DD (Medications) 2013-Q3
Phase I Interventional Studies - Healthy Subjects						
DRG-103	The Protocol Title in a Brief Way for Study DRG-103	SINGLE DOSE, RANDOMIZED, OPEN LABEL, CROSS-OVER, BIOAVAILABILITY, BIOEQUIVALENCE, PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY, TOLERABILITY	COMPLETED	2015-03-14	ADaM v2.1/ ADaM IG 1.0 ADaM define.xml 2.0 SDTM v1.3/ SDTM IG 3.1.3 SDTM define.xml 2.0	CDISC ADAM Terminology 2014-07-22 CDISC SDTM Terminology 2014-06-27 MedDRA (Adverse Events) 17.0 WHO-DD (Medications) 2013-Q3

Legacy Package

CDISC Package

Example SDSP

Study Identifier	Brief Title	Study Design	Study Status	Study Start Date	Exchange Standards	Terminology Standards
Phase I Interventional Studies - Healthy Subjects						
DRG-104	The Protocol Title in a Brief Way for Study DRG-104	MULTIPLE DOSE, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROL, PARALLEL SAFETY, TOLERABILITY	COMPLETED	2017-12-12	ANALYSIS LEGACY define.pdf ADaM v2.1/ ADaM IG 1.1 ADaM define.xml 2.0 TABULATIONS LEGACY define.pdf SDTM v1.4/ SDTM IG 3.2 SDTM define.xml 2.0	CDISC ADAM Terminology 2017-09-29 CDISC SDTM Terminology 2017-09-29 MedDRA (Adverse Events) 20.1 WHO-DD (Medications) 2017-Q1

Legacy Data
Conversion Package

Example SDSP

ACT I

Run the Plan by FDA

- Include SDSP in End of Phase 2 or Pre-NDA briefing documents
- Ask FDA in writing if they agree with the SDSP with the intention of obtaining a formal written response

ACT I

Request FDA Waivers

- Submission Data Exchange Standards (SEND v3.0, SDTM v3.1.2 and earlier, ADaM v1.0, and Define v1.0)
- Submission Terminology Standards (MedDRA v8.0 and earlier, WHODD not Global Current Version-B3 Format)
- See FDA Website “Guidelines for Requesting Waiver to Current Supported Study Data Standard Version” ([hyperlink at the end of presentation](#))

ACT I

Submit Sample Submission to FDA

- See FDA Website “Submit an eCTD or Standardized Data Sample to the FDA” (hyperlink at the end of presentation)
- Request a Sample Application #
- Select a study:
 - Important, but not pivotal
 - CDISC study (SDTM & ADaM)
- Prepare sample submission – SDTM, ADaM, and metadata prepared in the past may require remediation to bring to compliance with new guidance. Run latest version of validator to determine if any issues can be corrected while maintaining data traceability. Update reviewer guides with explanations for issues that cannot be fixed without disrupting traceability.
- Work with regulatory to send sample submission to FDA.

ACT I

Address Sample Submission Findings

- You may not agree with all the findings.
- The Division Reviewer that will review the NDA, will not be the same person who looked at the sample submission and will likely not be aware of the findings.
- Address what findings you can.
- Do not re-submit an updated sample.
Apply resolutions to actual submission.

Create a Submission Readiness Checklist

ACT I

Are data packages compliant and informative?

Are standards consistent across data and metadata (SDSP, ts.xpt, Reviewer Guides, and Defines)?

Check things not covered by validation software!

Is the checklist comprehensive?

Is the data package readable?

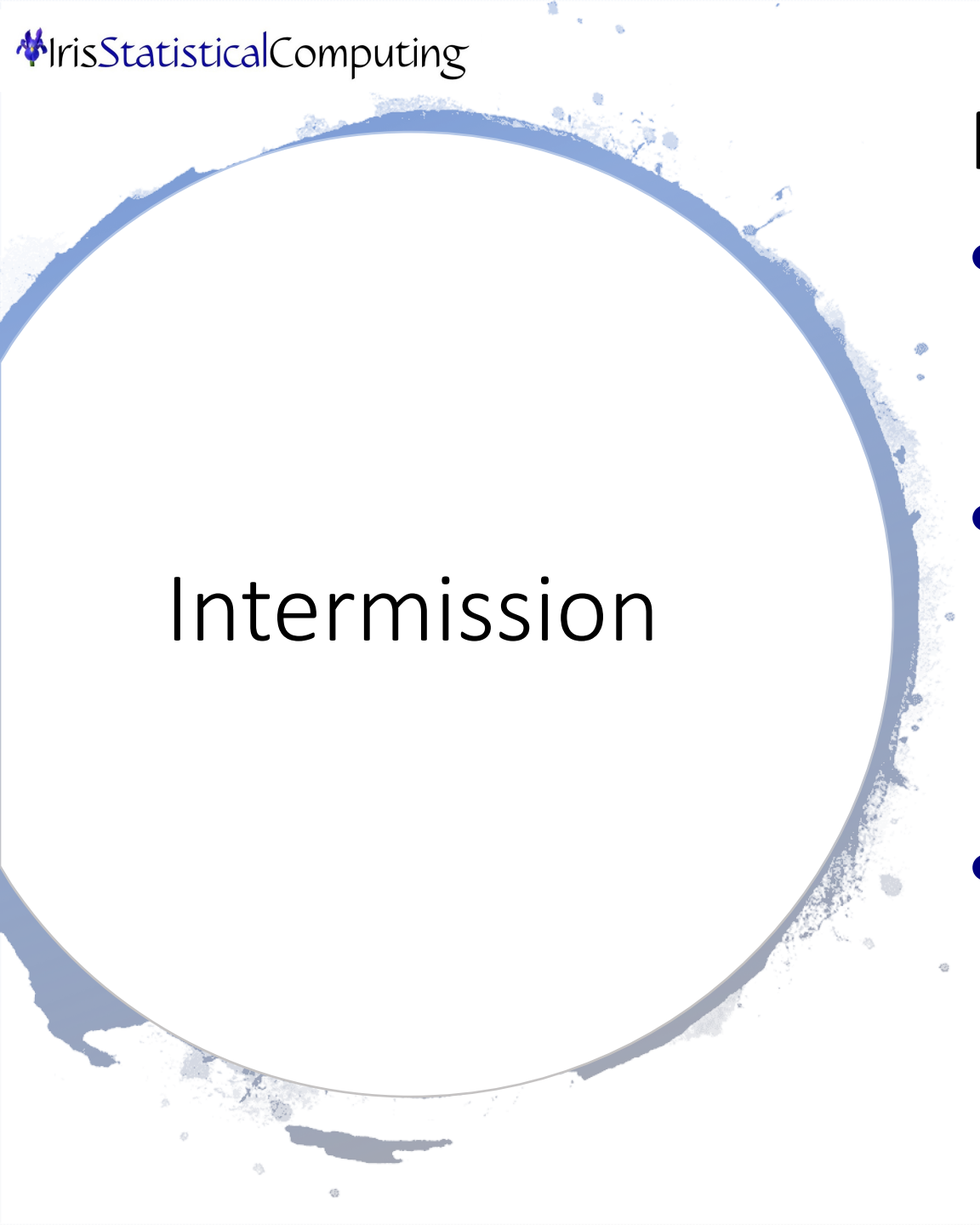
Includes lessons learned from sample submission?

Are my checks backed up by regulatory or sponsor requirements?

Is this checklist up to date?

Does it cover any recent changes to the TCG?

Data Pkg	Types of Checks to Include (example)
ADaM data	- Meets Technical Rejection Criteria (contains an ADSL) - Dataset size (datasets are less than 5 gigabyte or split)
adrg.pdf	- Complete and well written (all sections match the PhUSE template) - Listed standards are consistent with SDSP, cSDRG, data & define files - Legacy Data Conversion Plan & Report Appendix is included as needed
ADaM define.xml	- Meets Technical Rejection Criteria (define.xml is in a supported version) - Parameter Value Level Metadata includes all possible values - Computational algorithms use English language and not SAS lingo
SAS programs for ADaM and analysis TLFs	- Filename meets requirement in TCG - Programs are appropriate, no excessive comments, no heavy macro use - All programs are present
SDTM and TDM Data	- Meets Technical Rejection Criteria (contains ts.xpt) - TDM matches protocol and dm.xpt - ti.xpt has all versions of inclusion/exclusion criteria from the protocol
acrf.pdf	- All fields are fully annotated - All annotated variables are documented in define.xml - Duplicate pages are marked "For annotations see CRF page X"
cSDRG.pdf	- Complete and well written (all sections match the PhUSE template) - Inclusion/Exclusion Appendix includes original and amended criteria - Legacy Data Conversion Plan & Report Appendix is included as needed
SDTM define.xml	- Meets Technical Rejection Criteria (define.xml is in a supported version) - Standards are supported (SDTM version is supported) - Global variables match the study protocol



Intermission

Reassess Strategy

- Based on FDA feedback on Sample Submission and SDSP
- Based on lessons learned from preparing sample submission study
- Double check FDA Guidance for updates (Technical Conformance Guide, Rejection Criteria, and Standards Catalog)

Intermission

Check-in with Study Team

- Are the studies you plan to convert still important?
- Has there been a decision to add any studies to pooled analysis?
- Amend Submission Readiness Checklist based on sample submission and updates to guidance.

ACT II

SDSP

- Update SDSP based on:
 - Changes to strategy
 - FDA feedback on waiver
 - Update section on FDA Data Standards Discussions based on waiver request response and other communications
 - FDA response to briefing document question
- Provide the SDSP to the programmers to ensure that documented standards are implemented.

ACT II

Prepare and Review Deliverables

- Ensure resources are readily available to prepare and evaluate submission deliverables based on checklist and confirming primary endpoints

Populate eCTD

- Have a CDISC Subject Matter Expert work directly with Regulatory Publishing to ensure the files uploaded to software are the correct files prepared for the submission.

Curtain Call

Take a bow because you have just masterminded a Study Data Submission for a filing and that is pretty cool.

Post Production Meeting



But wait! It isn't over yet, next comes...



FDA Information Requests



Ad Hoc Analysis



Approval



THANK YOU!

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REFERENCES

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- CDISC SDS Metadata Team, CDISC, **“Study Data Tabulation Model Metadata Submission Guidelines (SDTM-MSG)”** CDISC website, December 2011. <https://www.cdisc.org/metadata-submission-guideline-%28msg%29-package-preface>