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PRESENTER

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CDER | US FDA

Lina Cong has a medical and computer background with over ten years of experience on study data standards and study data submissions. She also has ten years of experience on clinical trial data analysis and clinical data management within the pharmaceutical industry.

U.S. FOOD & DRUG ADMINISTRATION

Technical Rejection Criteria for Study Data (TRC) and Beyond

PharmaSUG SDE

October 21, 2022

Presenter: Lina Cong

Co-host: Jiang Xu

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Agenda

- Technical Rejection Criteria for Study Data (TRC)
- Tools to Help Industry Pass TRC Validation
- Study Data Validation Overview
- Addressing Common TRC Errors:
  - Error 1734
  - Error 1735
  - Error 1736
- Summary
- Frequently Asked Questions

Technical Rejection Criteria for Study Data (TRC)

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Technical Rejection Criteria for Study Data (TRC) – What's New

- CBER Non-clinical study requirements will start after March 15, 2023
- Rule 1734 will no longer check for study ID matching

- Changes to other study data validations:
  - New Validation Rule 1738 for study ID matching
  - Change of scope for Validation Rule 1737

eCTD Validation Updates

- Study Data Validation Effective Date for CBER Module 4 Sections: 3/16/2023

Error	Severity	Description
1734	High	A dataset named ts.xpt with information on study start date must be present for each study in required sections*
1735	High	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*
1736	High	For SEND data, DM dataset and define.xml must be submitted in Module 4 required sections* For SDTM data, DM dataset and define.xml must be submitted in Module 5 required sections* For ADaM data, ADSL dataset and define.xml must be submitted in Module 5 required sections*

* *Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4*
Module 5 sections: 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

Please review eCTD Validation Specification *all details are not included in this presentation*

eCTD Validation Updates

- Effective date for changes to Rule 1737 and new Rule 1738: 3/16/2023
- Applies to clinical and non-clinical study data submitted to CDER or CBER as part of an NDA, BLA, IND, ANDA, or master file submission

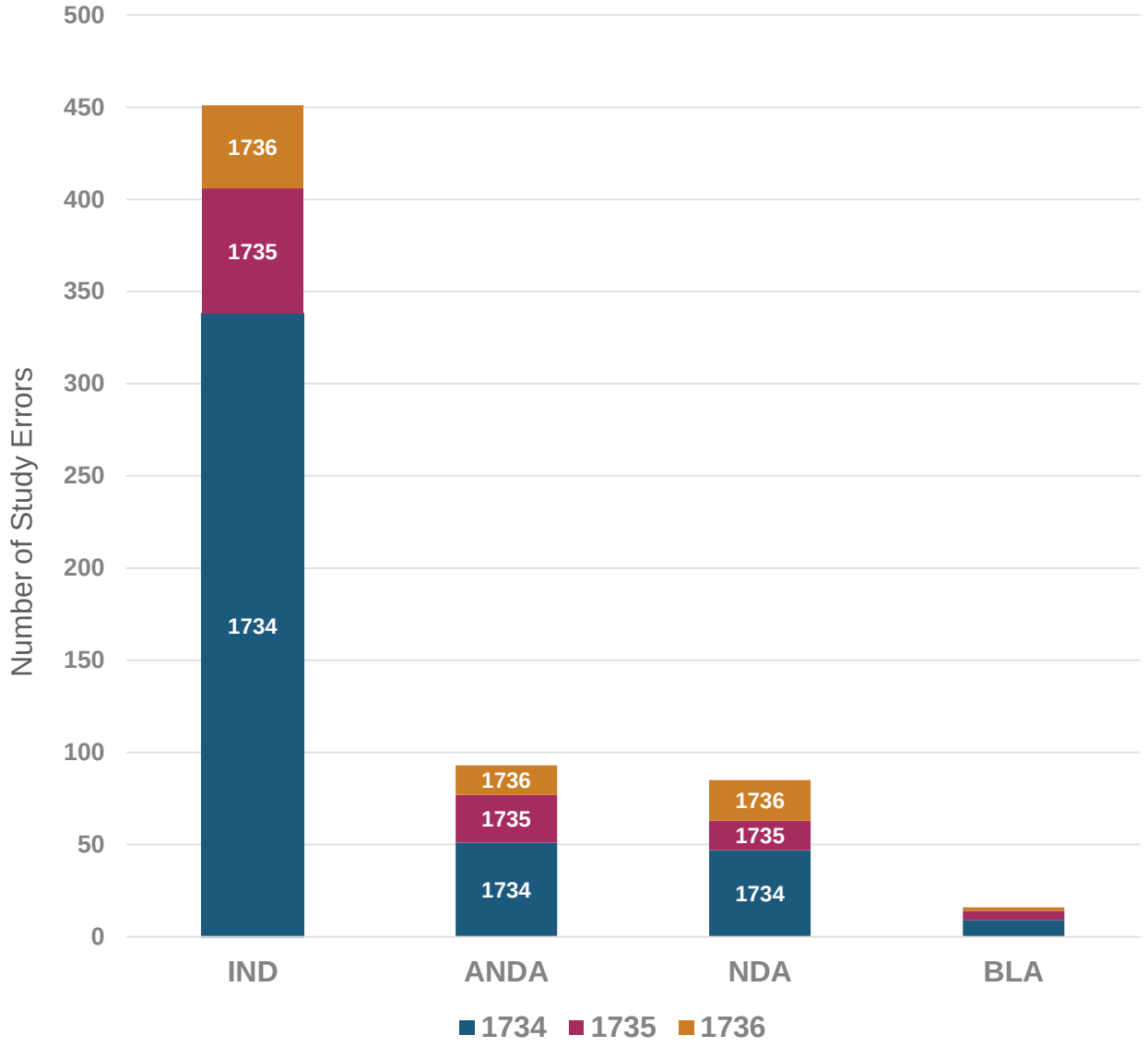
Error	Severity	Description
1737	Medium	For each study referenced by an STF file in Module 4 and Module 5, no more than one dataset of the same file name and leaf title should be submitted using the lifecycle operator 'new'*
1738	Medium	Study ID for STF should match STUDYID listed in the referenced Trial Summary (ts.xpt) file*

* *Applies to all sections except 4.3, 5.2, 5.4, & 5.3.6 Postmarketing reports*

Please review eCTD Validation Specification *all details are not included in this presentation*

Rejected Submissions

- 1734 is the most common error and rejection reason for a missing ts.xpt
- Commercial IND submissions have the highest number of errors and rejections overall



Notes: *Metrics generated from data between September 15, 2021 - September 15, 2022*
CDER began rejecting submissions with TRC errors on September 15, 2021

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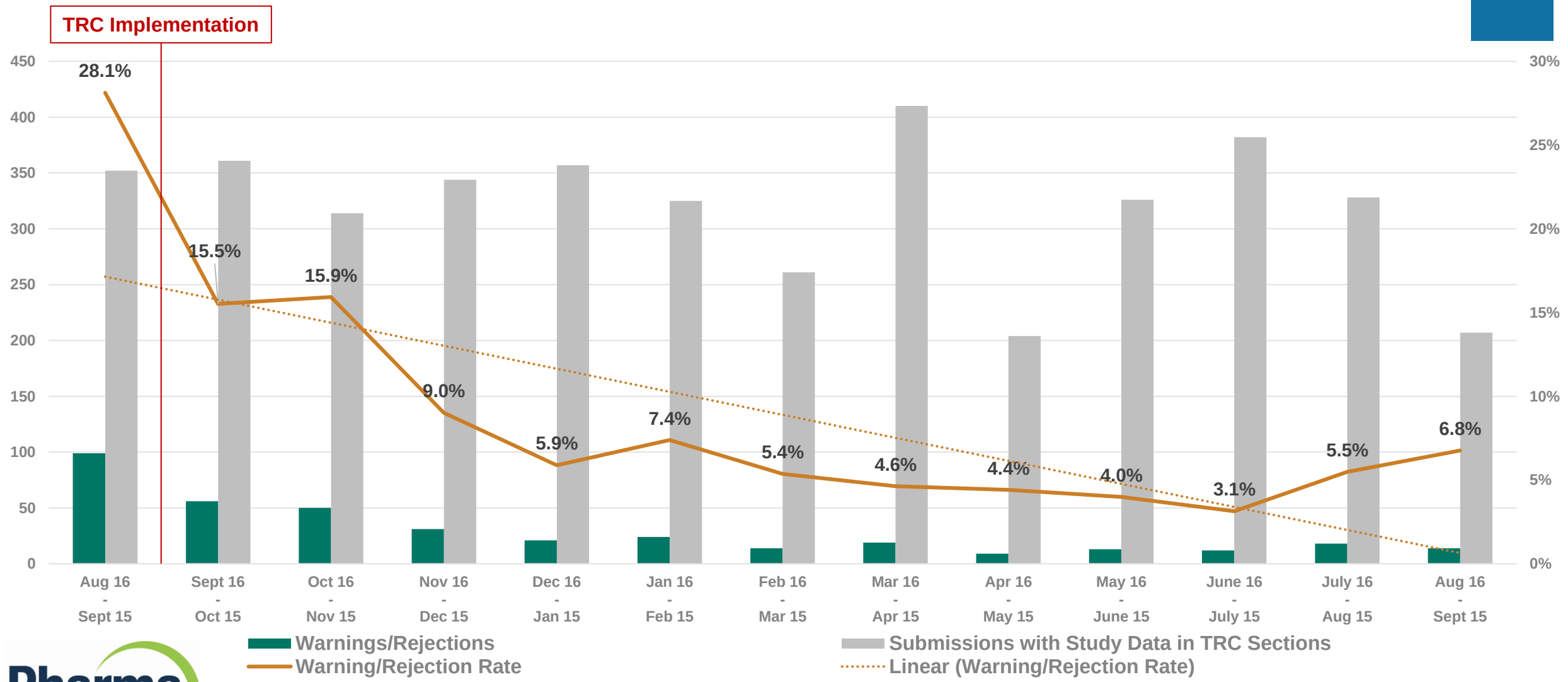
CDER Rejection Rate Trend



Notes: *Metrics generated from data between August 16, 2021 - September 15, 2022*
CDER began rejecting submissions with TRC errors on September 15, 2021
The Aug 16 – Sept 15, 2021 time period includes warnings for TRC errors, not rejections
Warnings/Rejections include submissions rejected due to TRC errors 1734, 1735, and 1736

Tools to Help Industry Pass TRC Validation

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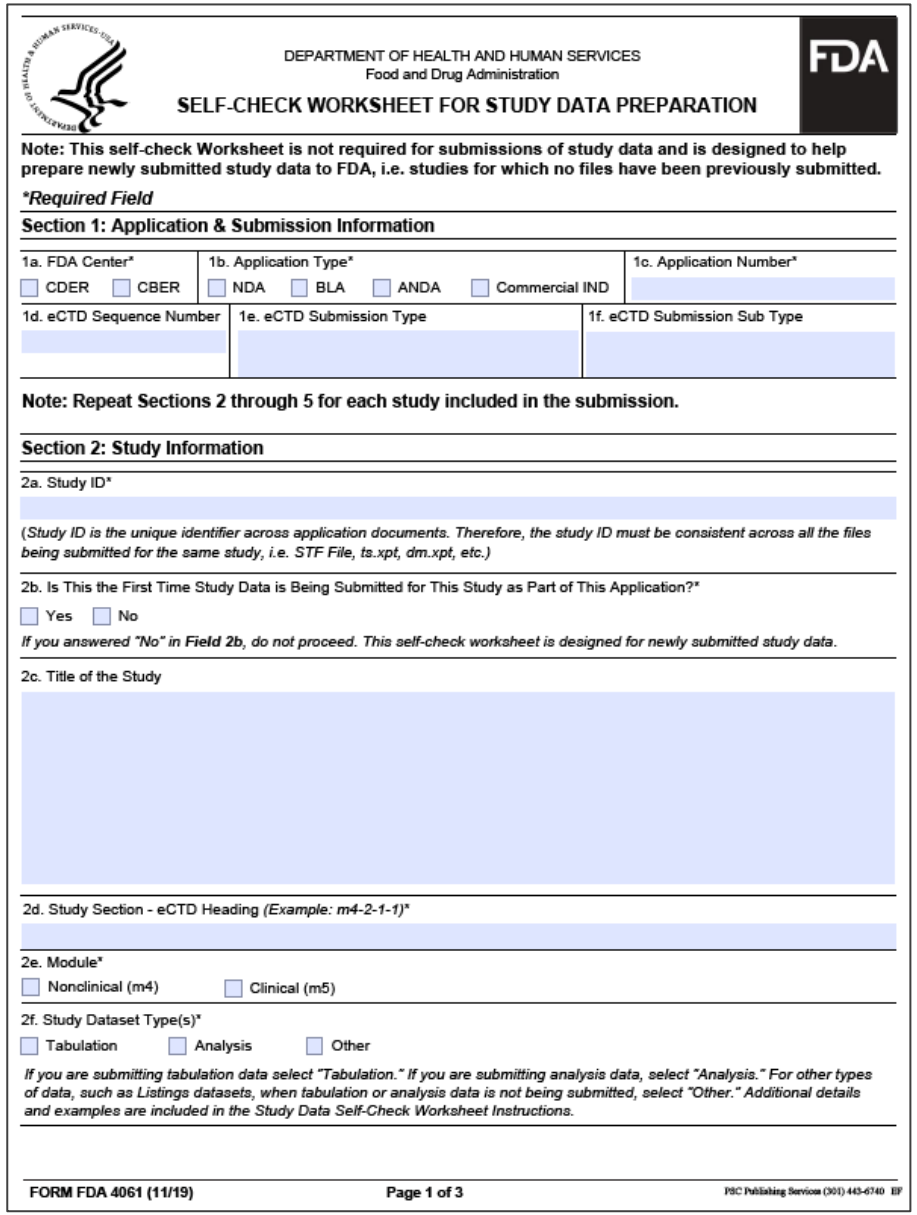
The Self-Check Worksheet

- Designed to walk sponsors through each step of the TRC validation process
- Dynamically guides sponsors through study data requirements based on study information entered
- Helps sponsors prepare study data to submit to the FDA for the first time

[Demonstration Videos & Other Supporting Material]

[Technical Rejection Criteria Self-Check Worksheet]

[Self-Check Worksheet Instructions]



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

SELF-CHECK WORKSHEET FOR STUDY DATA PREPARATION

Note: This self-check Worksheet is not required for submissions of study data and is designed to help prepare newly submitted study data to FDA, i.e. studies for which no files have been previously submitted.

Required Field

Section 1: Application & Submission Information

1a. FDA Center*	1b. Application Type*	1c. Application Number*
☐ CDER ☐ CBER	☐ NDA ☐ BLA ☐ ANDA ☐ Commercial IND	

1d. eCTD Sequence Number	1e. eCTD Submission Type	1f. eCTD Submission Sub Type

Note: Repeat Sections 2 through 5 for each study included in the submission.

Section 2: Study Information

2a. Study ID*

(Study ID is the unique identifier across application documents. Therefore, the study ID must be consistent across all the files being submitted for the same study, i.e. STF File, ts.xpt, dm.xpt, etc.)

2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?*

☐ Yes ☐ No

*If you answered "No" in **Field 2b**, do not proceed. This self-check worksheet is designed for newly submitted study data.*

2c. Title of the Study

2d. Study Section - eCTD Heading *(Example: m4-2-1-1)**

2e. Module*

☐ Nonclinical (m4) ☐ Clinical (m5)

2f. Study Dataset Type(s)*

☐ Tabulation ☐ Analysis ☐ Other

If you are submitting tabulation data select "Tabulation." If you are submitting analysis data, select "Analysis." For other types of data, such as Listings datasets, when tabulation or analysis data is not being submitted, select "Other." Additional details and examples are included in the Study Data Self-Check Worksheet Instructions.

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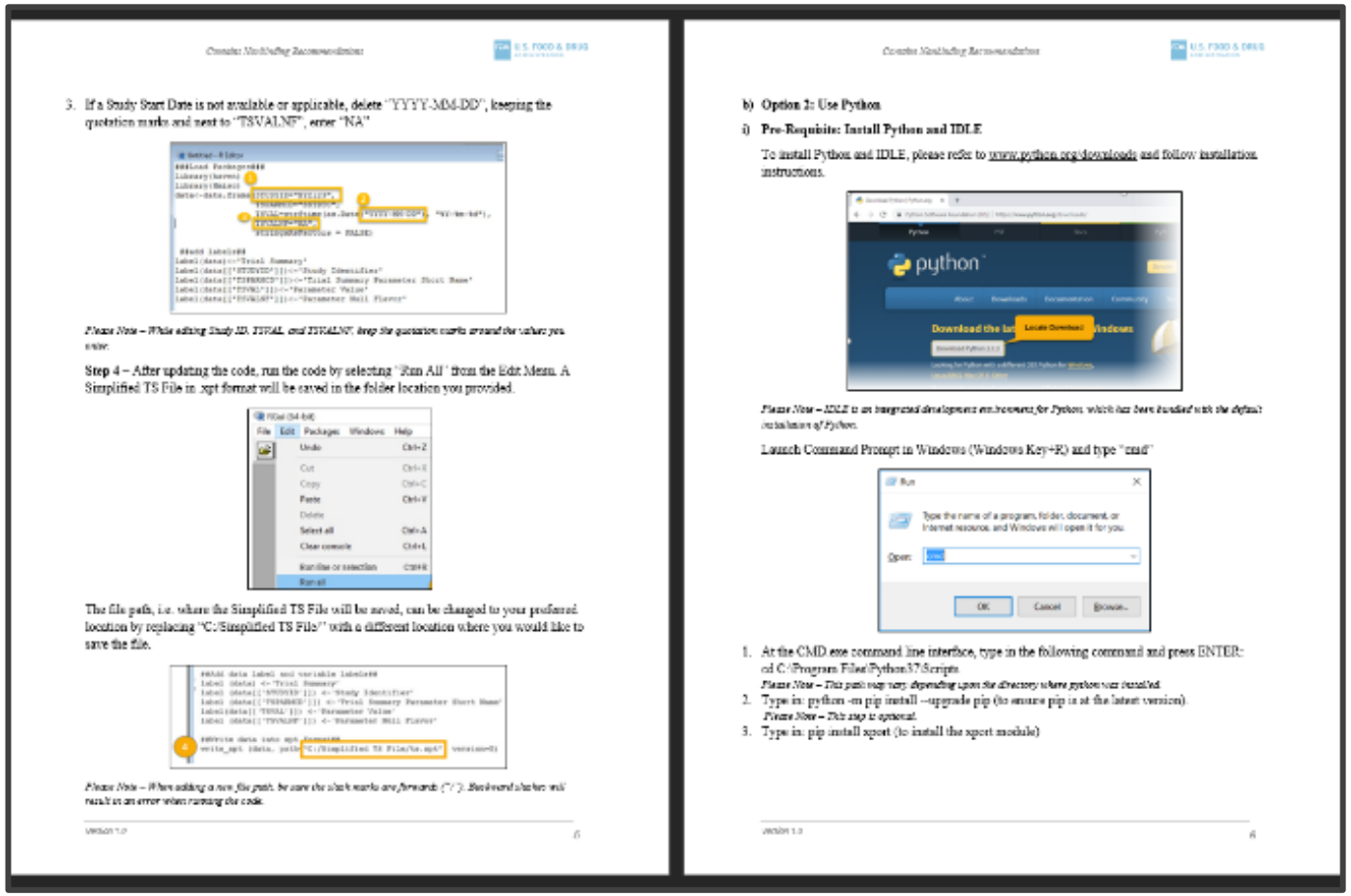
The Simplified ts.xpt Creation Guide

- Helps industry create simplified TS files using free and open-source software, R and Python
- Provides step by step instructions to install the necessary software
- Users can copy and paste code samples from the guide into R or Python
- Available on FDA's web page, *Study Data for Submission to CDER and CBER*
- Demonstration video also available at *Study Data for Submission to CDER and CBER*
- Additionally, a publicly available tool was developed by PHUSE:
  Simplified ts.xpt File Generator (*https://geotiger.shinyapps.io/07_genTS/*)



3. If a Study Start Date is not available or applicable, delete "YYYY-MM-DD", keeping the quotation marks and next to "TSVALNF", enter "NA"

Please Note – While editing Study ID, TSVAL, and TSVALNF, keep the quotation marks around the values you enter.

Step 4 – After updating the code, run the code by selecting "Run All" from the Edit Menu. A Simplified TS File in .xpt format will be saved in the folder location you provided.

The file path, i.e. where the Simplified TS File will be saved, can be changed to your preferred location by replacing "C:/Simplified TS Files/" with a different location where you would like to save the file.

Please Note – When adding a new file path, be sure the slash marks are forwards ("/"). Backward slashes will result in an error when running the code.

b) **Option 2: Use Python**

i) **Pre-Requisite: Install Python and IDLE**

To install Python and IDLE, please refer to www.python.org/downloads and follow installation instructions.

Please Note – IDLE is an integrated development environment for Python, which has been bundled with the default installation of Python.

Launch Command Prompt in Windows (Windows Key+R) and type "cmd"

1. At the CMD exe command line interface, type in the following command and press ENTER:
   cd C:\Program Files\Python37\Scripts
   Please Note – This path may vary, depending upon the directory where python was installed.
2. Type in: python -m pip install --upgrade pip (to ensure pip is at the latest version).
   Please Note – This step is optional.
3. Type in: pip install xport (to install the xport module)

Study Data Validation Overview

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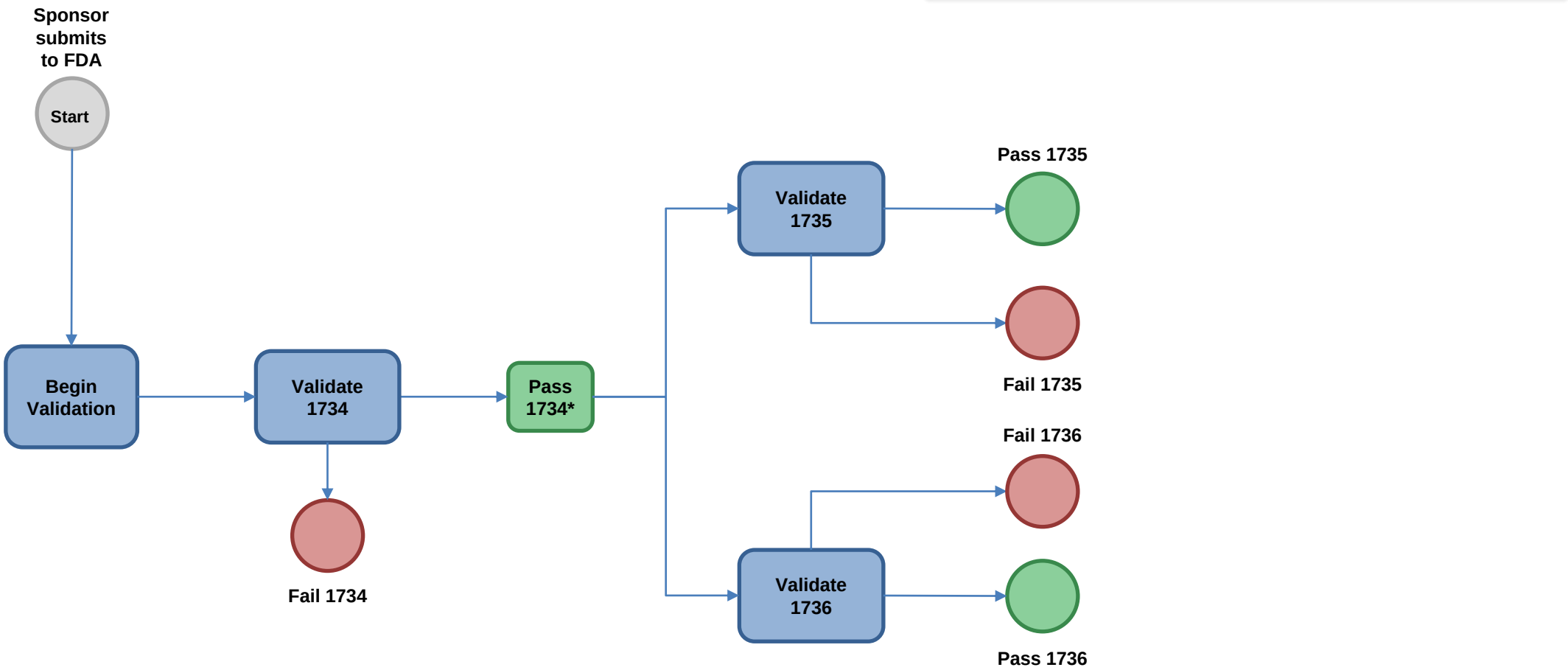
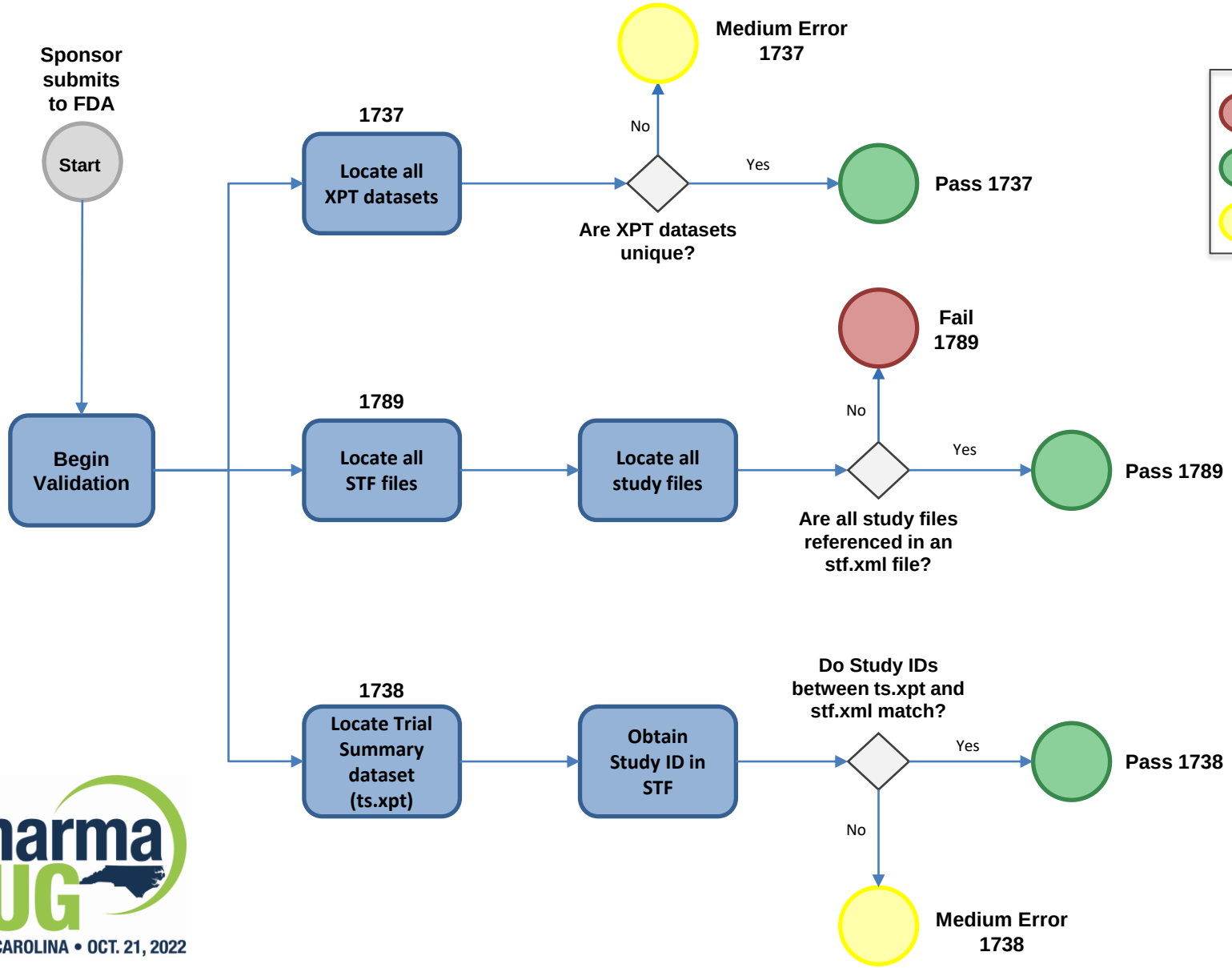
TRC Validation Rule Flow



** Not every submission will proceed beyond 1734 to 1735 and 1736, depending on the Study Start Date (SSD)*

Validation Rule Flow: 1737, 1738, & 1789



Legend

- High validation errors lead to rejection of the submission
- Validation passes
- Medium severity errors do not lead to a rejection

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Addressing Common TRC Errors

Error 1734

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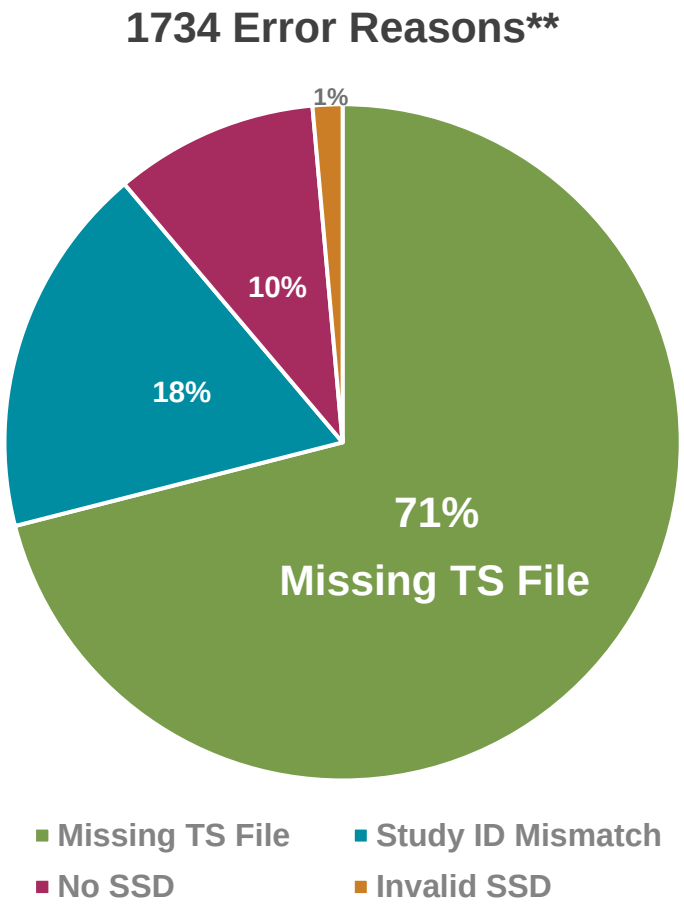
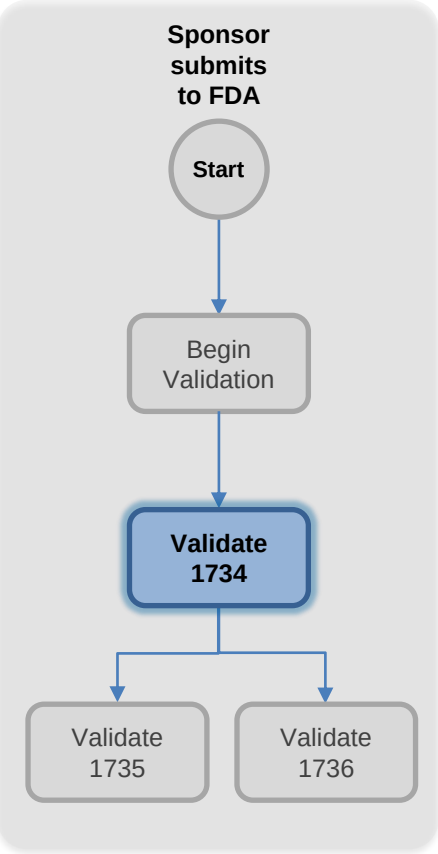
Validation Rule 1734

A dataset named ts.xpt with information on study start date must be present for each study in required sections*

- ✓ Trial Summary Dataset (ts.xpt) is present
- ✓ Study ID (or SPREFID) matches STF Study ID^
- ✓ Study start date is provided (or TSVALNF = NA)
- ✓ Study start date is in a valid format

^Moving to Rule 1738, effective 3/16/2023





*Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4, Module 5 sections: 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

***421 studies from September 15, 2021 – September 15, 2022*

Addressing 1734 Errors for Missing TS File

Providing a TS File for non-clinical studies which require a Simplified TS will address the biggest root cause of Error 1734.

Over 70% of Missing TS File Errors are for non-clinical studies with study reports and no .xpt datasets*

	M4	M5
Studies with only study reports	73%	N/A
Studies with only study data	0%	8%
Studies with study data and reports**	17%	NA

Out of 230 studies profiled between September 15, 2021 – September 15, 2022

Option 1

Use the Simplified ts.xpt Creation Guide to generate a simplified ts.xpt in R or Python:

Option 2

Use publicly available tool developed by PHUSE to generate simplified ts.xpt files:

Example of a Simplified TS file for a non-clinical study:

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	S107	STSTDTC	2014-10-26	

Addressing Common TRC Errors

Error 1735

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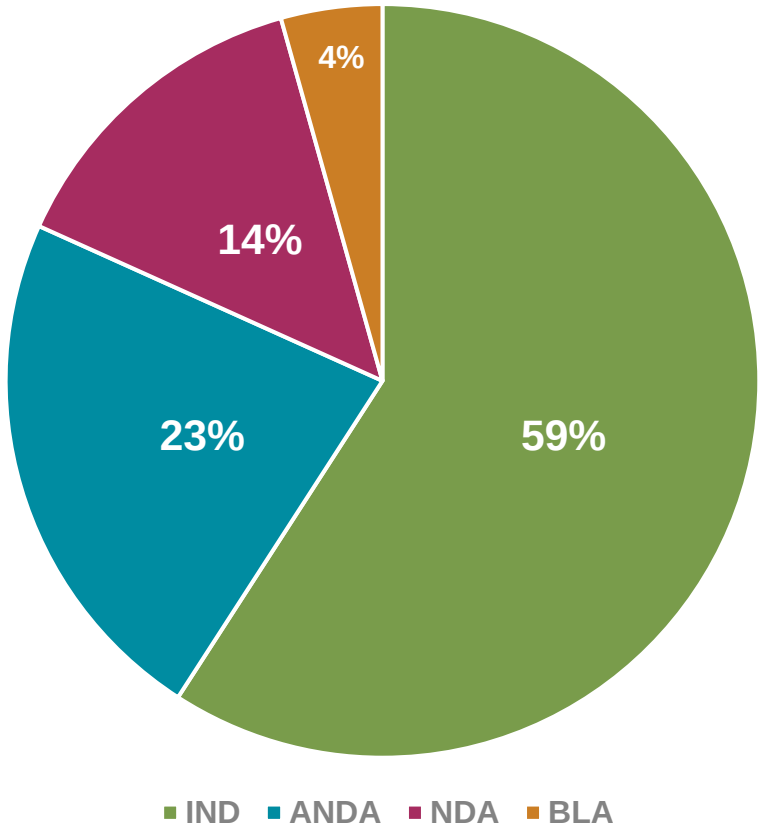
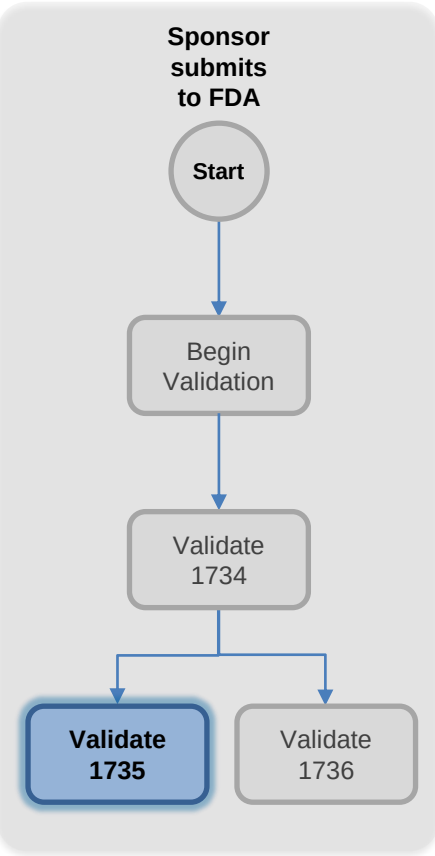
Validation Rule 1735

The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*

- ✓ Valid file tags for XPT files (e.g., adsl.xpt, dm.xpt) are tagged as:
  - "data-tabulation-dataset-sdtm" for SDTM
  - "analysis-dataset-adam" for ADaM
  - "data-tabulation-dataset-send" for SEND
- ✓ Valid file tags for corresponding define.xml files:
  - "data-tabulation-data-definition" for SDTM & SEND
  - "analysis-data-definition" for ADaM

IND submissions have the highest number of 1735 errors**





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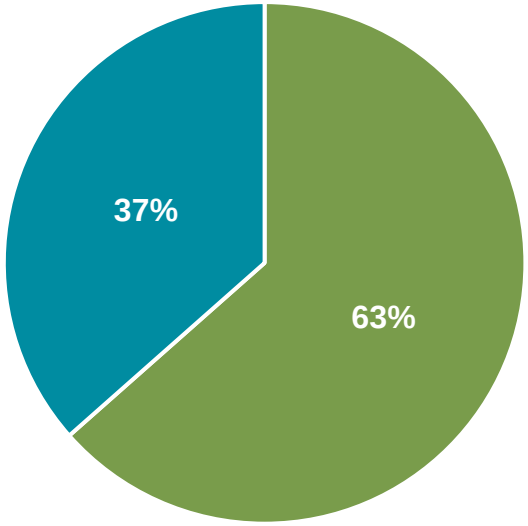
*Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4, Module 5 sections: 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

**115 studies from September 15, 2021 – September 15, 2022*

Addressing the Most Common 1735 Error

- **The most common cause of 1735 errors is incorrectly tagged define.xml files**
- **When preparing STF files, ensure files are tagged properly**

1735 Error Reasons*



Example Study Tagging File (STF) for SDTM:

Sponsors commonly apply the same file tags as datasets or other files for all files submitted, including define.xml files

Standardized dataset domains (e.g. dm.xpt)

Define.xml

```
<doc-content
    xlink:href="../../../../../../0001/index.xml#adf5f97a527ef1507a6db8fca2f8b4867" xlink:type="simple">
    <file-tag info-type="us" name="data-tabulation-dataset-sdtm"/>
</doc-content>
<doc-content
    xlink:href="../../../../../../0001/index.xml#ab54f98276616b94d1d30fa071ffffc36" xlink:type="simple">
    <file-tag info-type="us" name="data-tabulation-dataset-sdtm"/>
</doc-content>
<doc-content
    xlink:href="../../../../../../0001/index.xml#a7794eaba0442a7c66cbf122fb66ff932" xlink:type="simple">
    <file-tag info-type="us" name="data-tabulation-dataset-sdtm"/>
</doc-content>
<doc-content
    xlink:href="../../../../../../0001/index.xml#a57bb2ed13e2d2feb7606e65d59586355" xlink:type="simple">
    <file-tag info-type="us" name="data-tabulation-dataset-sdtm/>
```

File tag for define.xml needs to be corrected to: "data-tabulation-data-definition"

Correct File Tags

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**115 studies from September 15, 2021 – September 15, 2022*

Addressing Common TRC Errors

Error 1736

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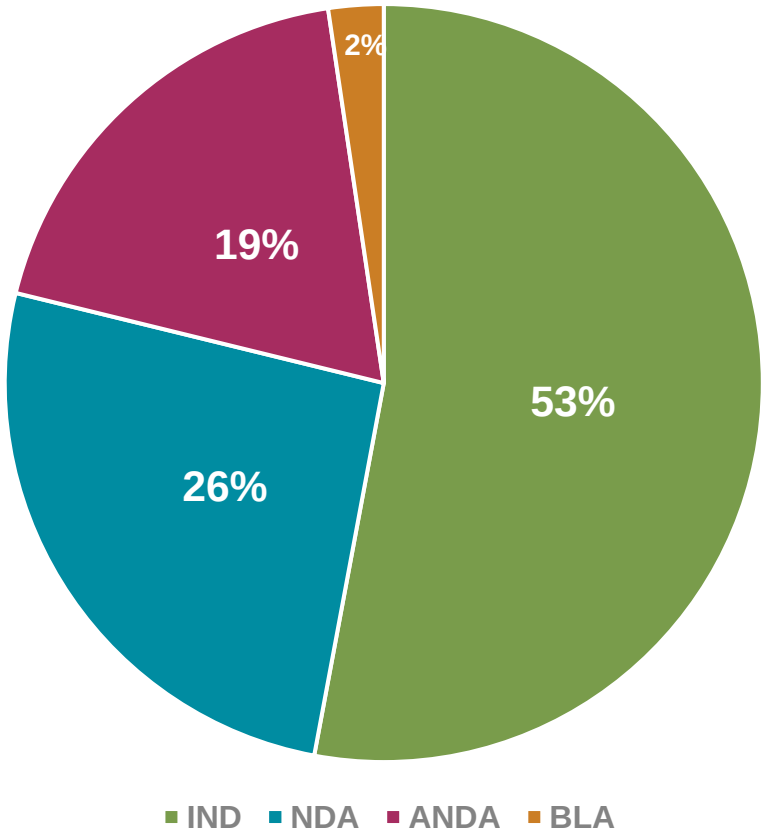
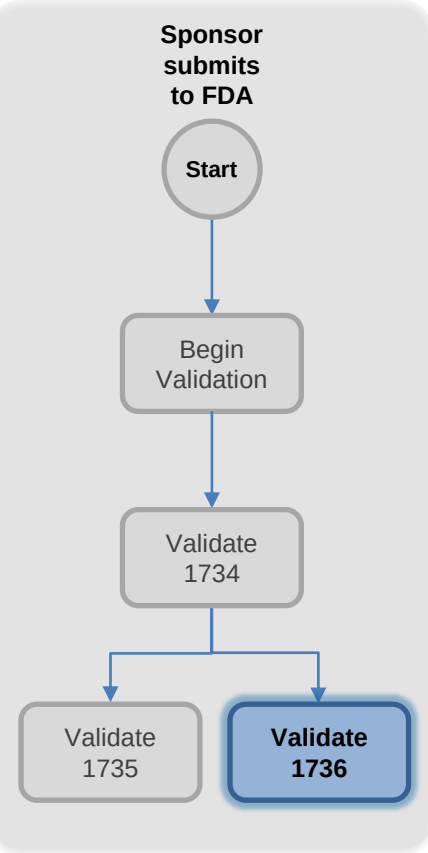
Validation Rule 1736

DM datasets and define.xml files are submitted with SDTM and SEND (tabulations) data and an ADSL dataset and define.xml file are submitted with ADaM (analysis) data.

- ✓ For SEND, a DM dataset and define.xml must be submitted in module 4*
- ✓ For SDTM data, a DM dataset and define.xml must be submitted in module 5*
- ✓ For ADaM data, an ADSL dataset and define.xml must be submitted in module 5*

IND submissions have the highest number of 1736 errors**





*Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4, Module 5 sections: 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

***85 studies from September 15, 2021 – September 15, 2022*

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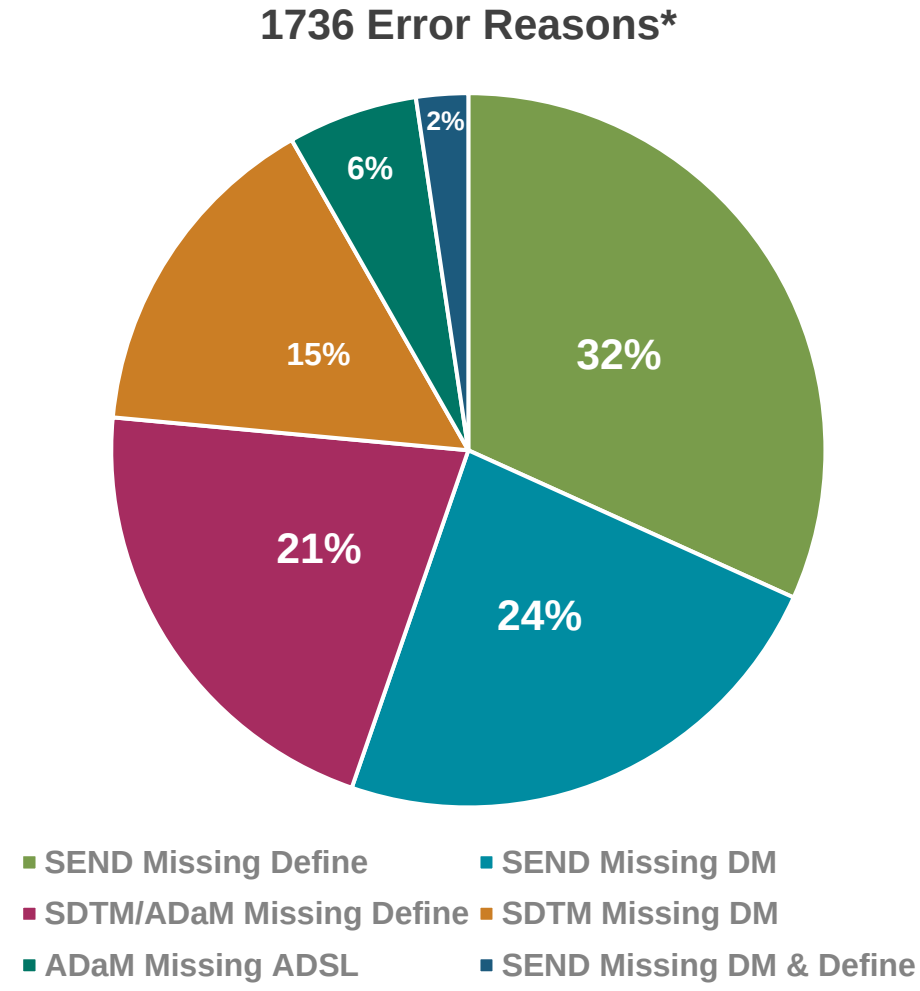
Addressing the Most Common 1736 Error

The most common cause of 1736 errors is missing define.xml and/or dm.xpt files for non-clinical studies requiring SEND standardized datasets

	SEND	SDTM/ADaM
Missing Datasets	20	18
Missing Define	27	18
Both	2	-
Total	**49 (58%)**	**36 (42%)**



*85 studies from September 15, 2021 – September 15, 2022

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Summary

Summary: Addressing Top 3 Causes of TRC Errors

	1734		1735	1736
Impact	**All 1734** 71% of Rejections	**Comm. IND** 52% of Rejections	17% of Rejections	12% of Rejections
Rule Summary	A dataset named ts.xpt with information on study start date must be present for each study in required sections		The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files	Checks that DM datasets and define.xml files are submitted with SDTM and SEND (tabulations) data and an ADSL dataset and define.xml file are submitted with ADaM (analysis) data
1. Check if your study has an error	Self-Check Worksheet Sections 3 & 4		Self-Check Worksheet Section 5	Self-Check Worksheet Section 5
2. Correct the errors	If a Simplified TS file is required, utilize the *Simplified ts.xpt Creation Guide* or online PHUSE Utility		Ensure the correct STF file-tags for standardized datasets and define.xml files are used	Ensure that DM, ADSL datasets, and define.xml files are submitted with corresponding data

Notes: *Metrics generated from data between September 15, 2021 - September 15, 2022*
CDER began rejecting submissions with TRC errors on September 15, 2021

Frequently Asked Questions

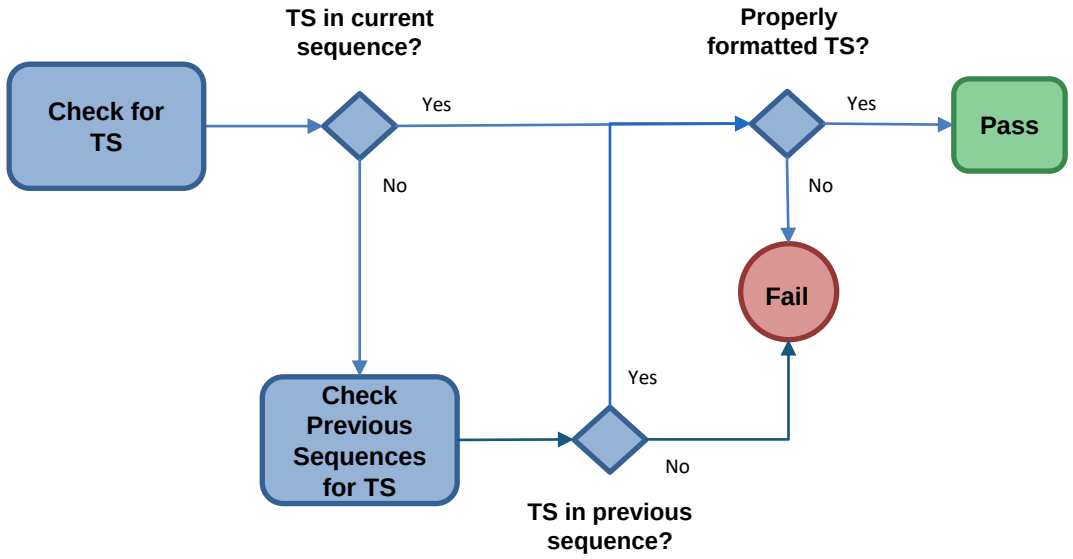
Do I have to submit a ts.xpt with every submission to meet TRC requirements?

- It is not required to submit a ts.xpt with every submission
- Previously submitted ts.xpt must be standardized and properly formatted
- Validations check previously submitted files for Rule 1734 (ts.xpt) and Rule 1736 (dm.xpt, adsl.xpt, and define.xml)

Properly Formatted TS:

- ✓ Study ID (or SPREFID) matches STF Study ID^
- ✓ Study start date is provided (or TSVALNF = NA)
- ✓ Study start date is in a valid format

^Moving to Rule 1738, effective 3/16/2023



How can multiple sets of data be submitted for the same study?

- Option 1: Submitting multiple sets of data under the same STF
  - Creating sub-folders for each set of data
  - Assigning different leaf titles for each set of data
- Option 2: Submitting multiple sets of data under different STFs
  - Using different STFs for each sets of data – treat each set of data as different studies

References

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
  - FDA Data Standards Catalog [August 2022]
  - Study Data Technical Conformance Guide [March 2022]
  - Link: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources
- **Study Data for Submission to CDER and CBER**
  - Technical Rejection Criteria Self-Check Worksheet
  - Technical Rejection Criteria Self-Check Worksheet Instructions
  - Link: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
- **Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry**
  - Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents