U.S. FOOD & DRUG ADMINISTRATION

Study Data Technical Rejection Criteria

SEND F2F Spring 2021
Public Meeting

April 27, 2022

FDA Disclaimer

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Agenda

- Technical Rejection Criteria for Study Data (TRC)
- TRC Conformance Statistics and Trends
- Addressing the Most Common TRC Error
- Importance of Standardized Study Data

Technical Rejection Criteria for Study Data (TRC)

Electronic Submission Guidance

Study Data Guidance - *Providing Regulatory Submissions in Electronic Format -- Standardized Study Data (last updated June 2021)*

- Sponsors must conform to standards in the FDA Data Standards Catalog:
  - CDER & CBER Clinical Studies
    - NDA, BLA, ANDA studies that started after December 17th, 2016
  - CDER Non-clinical Studies
    - NDA, BLA, ANDA studies that started after December 17th, 2016
    - Commercial IND studies that started after December 17th, 2017
  - CBER Non-clinical studies
    - NDA, BLA, ANDA, and Commercial IND studies that started after March 15, 2023
- **FDA uses eCTD validations (1734, 1735, 1736)** to confirm Sponsors are conforming to the FDA Data Standards Catalog. This subset of eCTD validations are described in detail in the Specification for eCTD Validation Criteria.

For more information on how to submit and what will be validated, see the documents below:

- Study Data Technical Conformance Guide – Latest update March 2022
- Study Data for Submission to CDER and CBER website

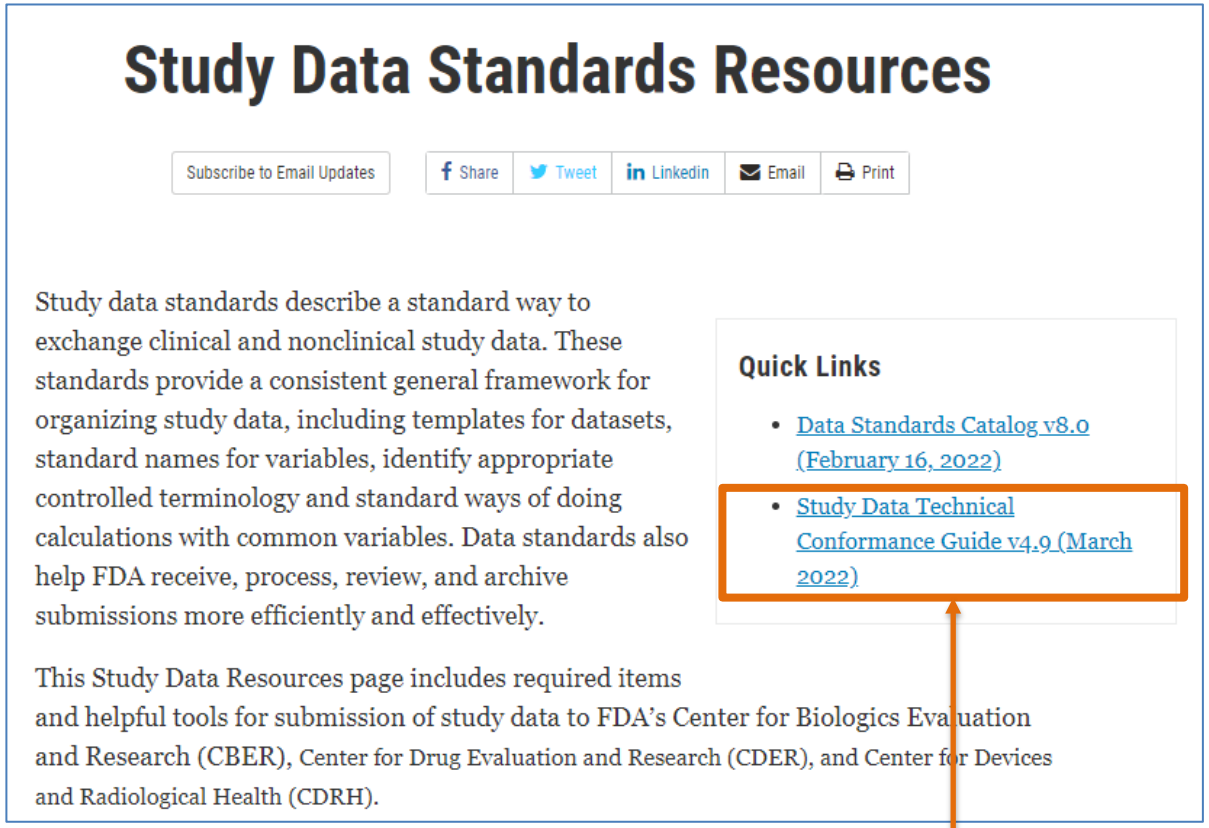
What's New

- CDER and CBER began rejecting submissions that fail eCTD study data validations on September 15, 2021
- FDA Data Standards Catalog was updated (February 2022)
  - Added SENDIG v3.1.1 with the Date Support begins and the Date Requirement begins
- CBER Non-clinical studies requirements will start after March 15, 2023
- Technical Rejection Criteria for Study Data (TRC) document was incorporated into the Study Data Technical Conformance Guide (March 2022)

Electronic Submission Guidance

- The Study Data Technical Conformance Guide is available on the Study Data Standards Resources web page

- All links to the TRC now redirect to this web page



Study Data Standards Resources

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Study data standards describe a standard way to exchange clinical and nonclinical study data. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, identify appropriate controlled terminology and standard ways of doing calculations with common variables. Data standards also help FDA receive, process, review, and archive submissions more efficiently and effectively.

Quick Links

- Data Standards Catalog v8.0 (February 16, 2022)
- Study Data Technical Conformance Guide v4.9 (March 2022)

This Study Data Resources page includes required items and helpful tools for submission of study data to FDA's Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH).

The Technical Rejection Criteria for Study Data document has been incorporated into the Study Data Technical Conformance Guide. The Study Data Technical Conformance Guide is located here: https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources

eCTD Validation Updates

- Study Data Validation Effective Date updated:

  9/15/2021 (CBER module 4 sections, 03/16/2023)

Error	Description
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections*
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*
1736	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*
1737	For each study in required sections, no more than one dataset of the same name should be submitted as new*

** 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

eCTD validation rule 1789 has different expectations than 1734, 1735, and 1736.

Error	Description
1789	A file has been submitted in a study section without providing an STF file. STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports

- 1789 applies to all subsections of modules 4 and 5 except:

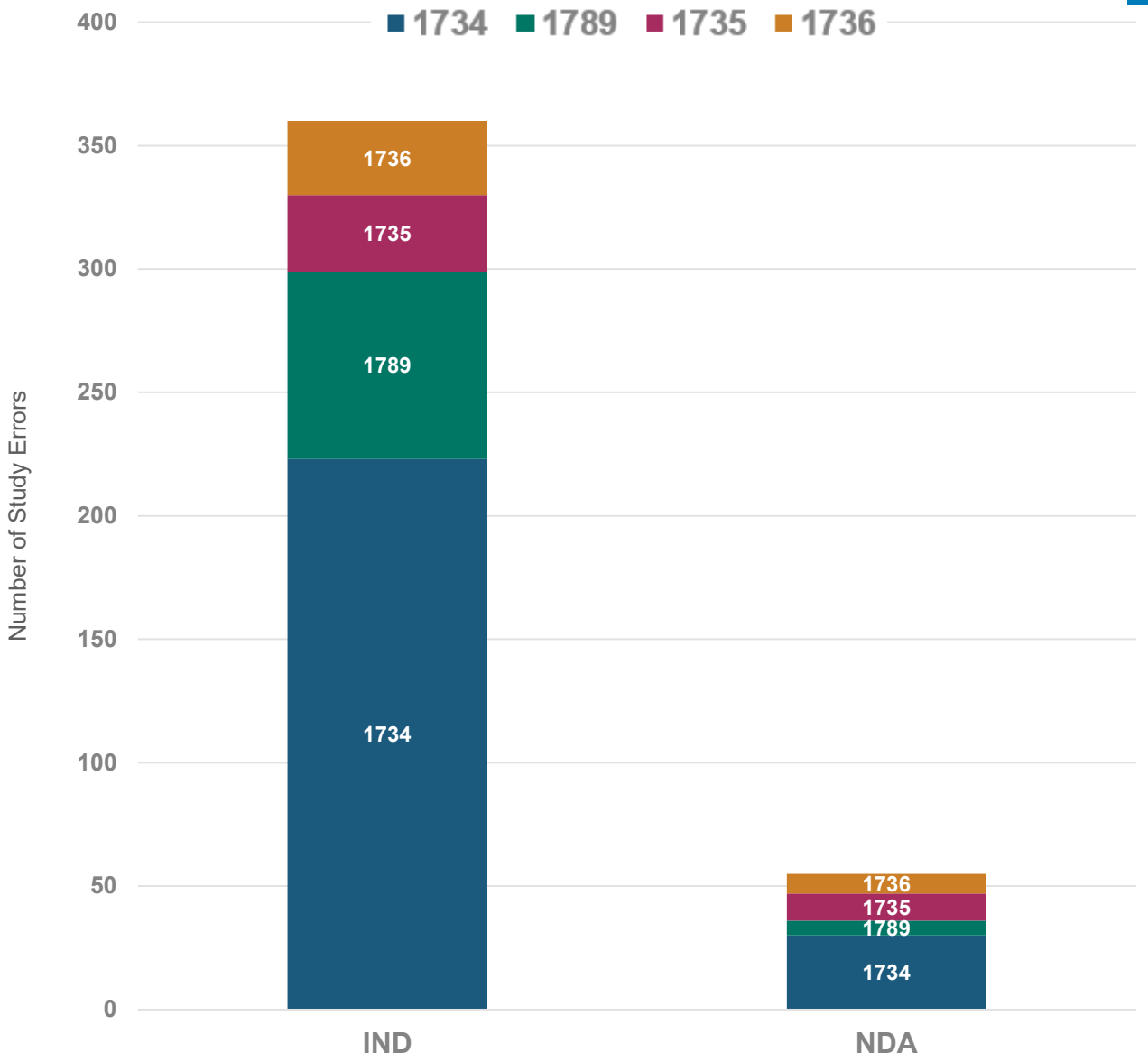
  Sections 4.3, 5.2, 5.4, and 5.3.6

- An STF must be provided for all applications and data types for both CDER and CBER regardless of study start date

TRC Conformance Statistics and Trends

Rejected Submissions: September 15, 2021 – March 15, 2022

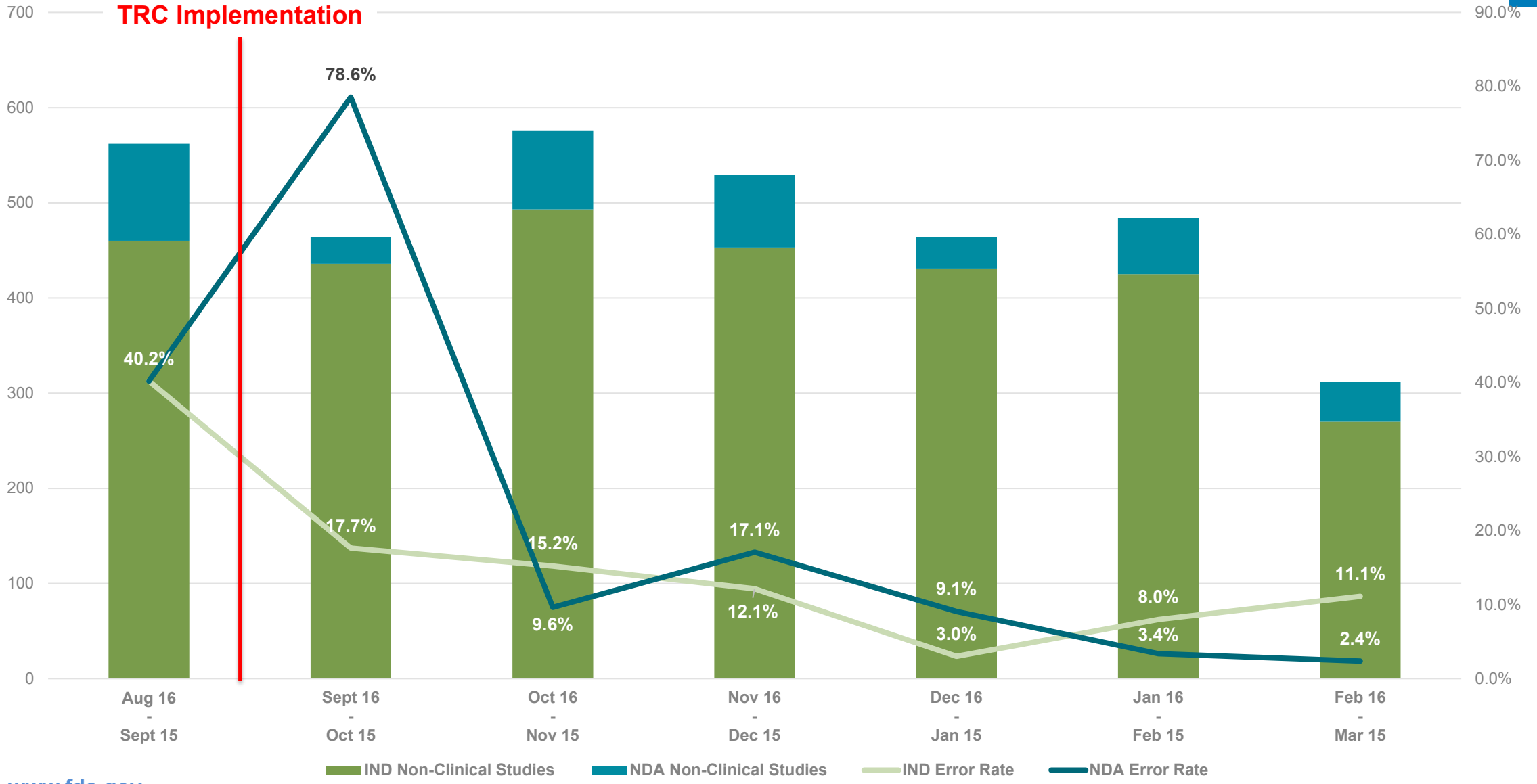
- 1734 is the most common error and rejection reason for a missing ts.xpt
- Commercial IND submissions have highest number of errors and rejections overall



Notes: *Metrics generated from data between September 15, 2021 and March 15, 2022.*

1789 severity elevated to high 9/15/21 but not specific to standardized study data requirements.

Trend of Non-Clinical Study Errors



www.fda.gov

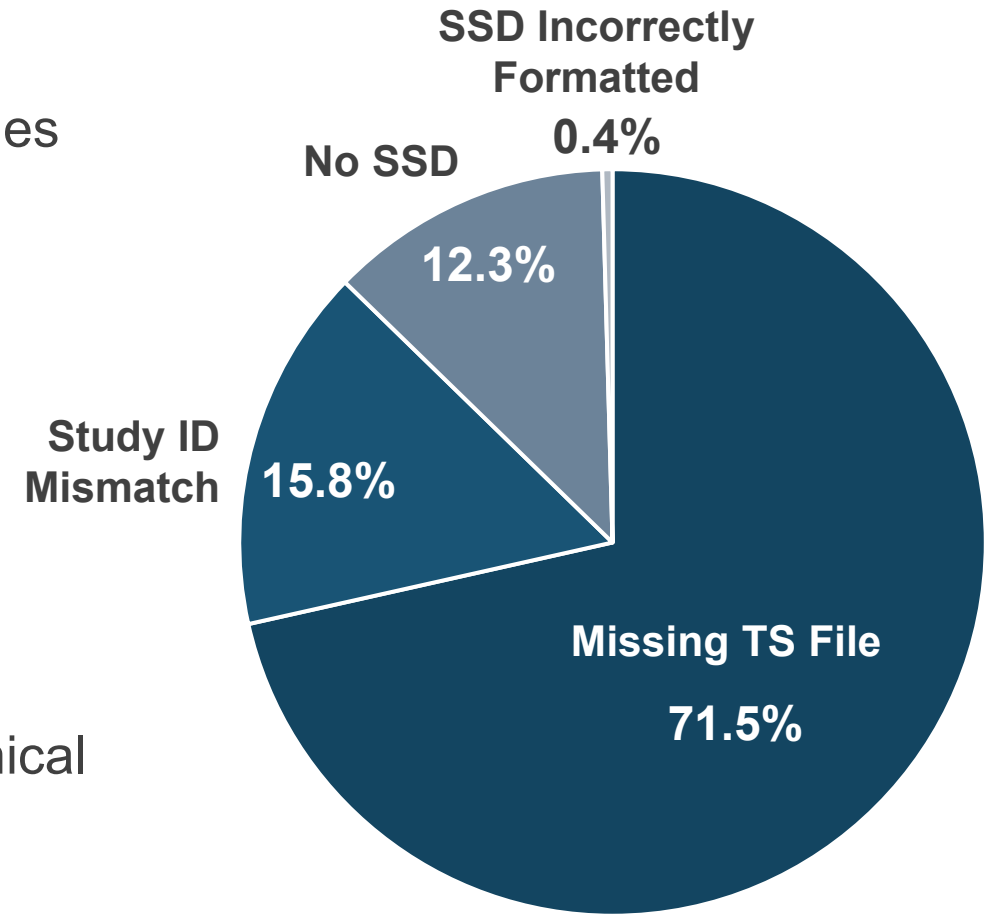
Timeframe: September 15, 2021 – March 15, 2022

1734 Error Reasons: September 15, 2021 – March 15, 2022

- 228 IND & NDA non-clinical studies failed Rule 1734
- 71.5% (163 of 228) failed due to a missing ts.xpt
- 64.0% (146 of 228) were Repeat Dose Toxicology studies

Toxicology Sections	Count
Repeat dose toxicology (m4.2.3.2)	146
Single dose toxicology (m4.2.3.1)	61
Carcinogenicity (m4.2.3.4)	21
	228

228 Non-clinical Studies with Error 1734:



- Submitting a simplified ts.xpt for many of these non-clinical studies will greatly reduce the 1734 error rate
- SEND datasets require a full ts.xpt

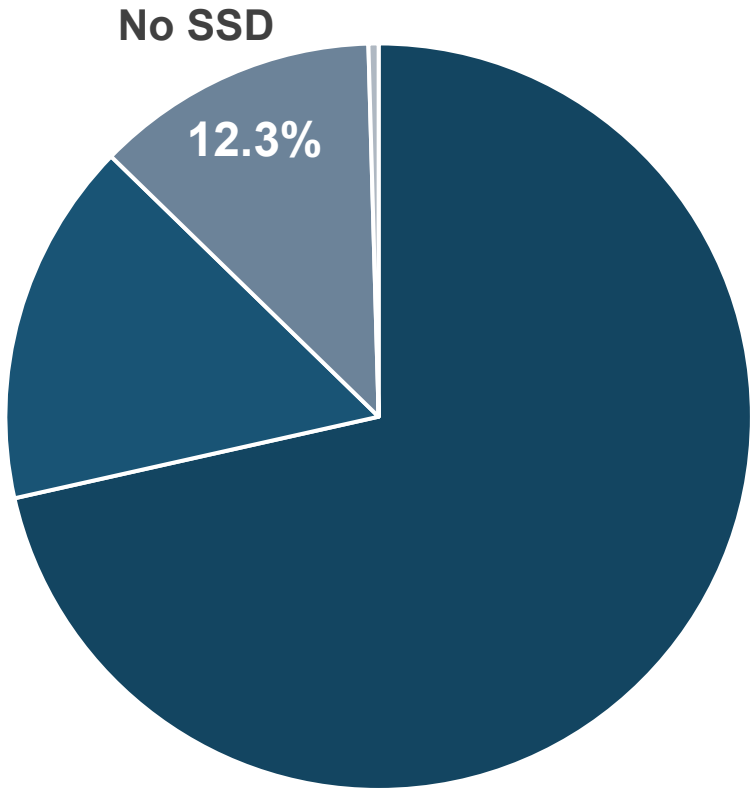
Timeframe: September 15, 2021 – March 15, 2022

Addressing 1734 Errors: Missing TS File

CDER and CBER expectations for standardized data:

Application Type	Data Type	Modules & Sub-Modules	Expectation by CDER	Expectation by CBER
NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: On or prior to 2016-12-17* Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	***Study Start Date: On or prior to 2023-03-15*** **Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)**
NDA, BLA, ANDA	Clinical	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	*Study Start Date: On or prior to 2016-12-17* Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)	
Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: On or prior to 2017-12-17* Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	***Study Start Date: On or prior to 2023-03-15*** **Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)**
Comm. INDs	Clinical	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	*Study Start Date: On or prior to 2017-12-17* Rejection criteria will not be applied	
NDA, BLA, ANDA	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: After 2016-12-17* Rejection criteria will be applied; submit a full TS	***Study Start Date: After 2023-03-15*** **Rejection criteria will be applied; submit a full TS**
NDA, BLA, ANDA	Clinical	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	*Study Start Date: After 2016-12-17* Rejection criteria will be applied; submit a full TS with standardized data	
Comm. INDs	Non-Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	*Study Start Date: After 2017-12-17* Rejection criteria will be applied; submit a full TS	***Study Start Date: After 2023-03-15*** **Rejection criteria will be applied; submit a full TS**
Comm. INDs	Clinical	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	*Study Start Date: After 2017-12-17* Rejection criteria will not be applied	

Addressing 1734 Errors: No Study Start Date



No ts.xpt with value for SSD found (and no null flavor value)

Simplified ts.xpt referenced by the study causes a 1734 failure for missing study start date:

STF
.xml

TS
.xpt

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	90-day-oral-tox-s...			NA

Causes of 1734 Missing Study Start Date:

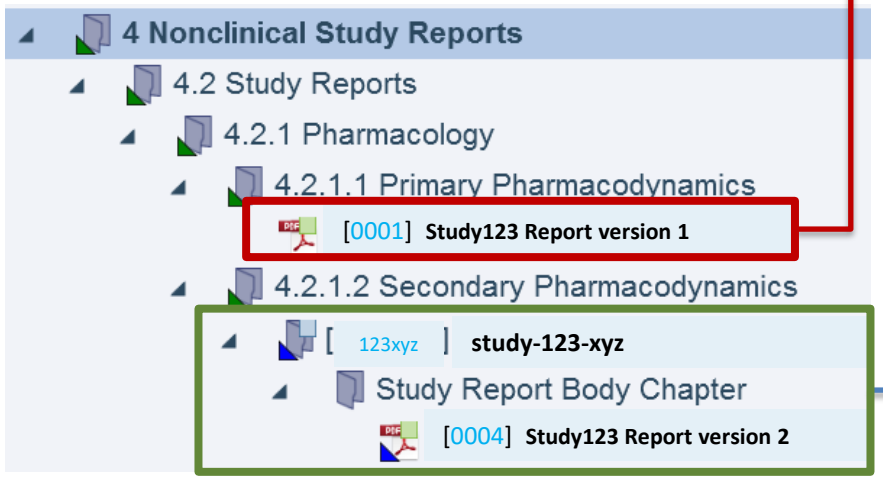
- **Missing Value for SSD**
- **Missing Parameter Code**
- **Incorrect Parameter Code**

Importance of Standardized Study Data

Why is 1789 important?

Each study has its own stf.xml file with a unique study id and study title. When files are not referenced in a study tagging file they will not be connected to a specific study and may lead to reviewers not being able to find or review the data.

eCTD Viewer:

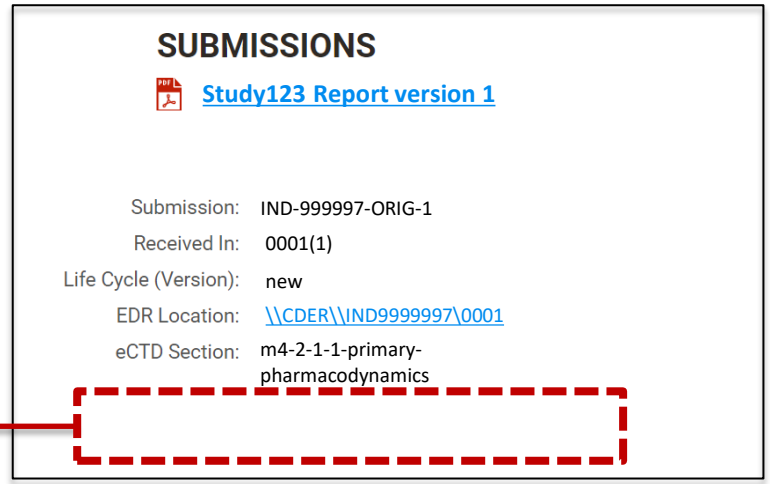


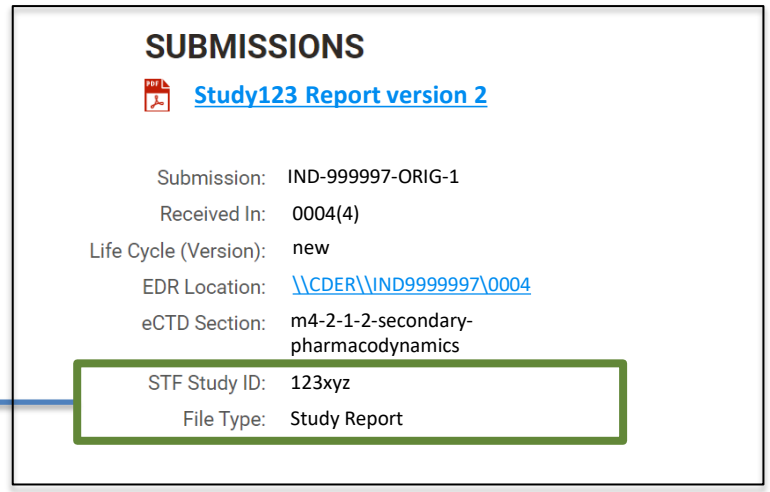
Unorganized and not connected to a study

Organized by Study Title and ID

File Tags indicate file types

Search:



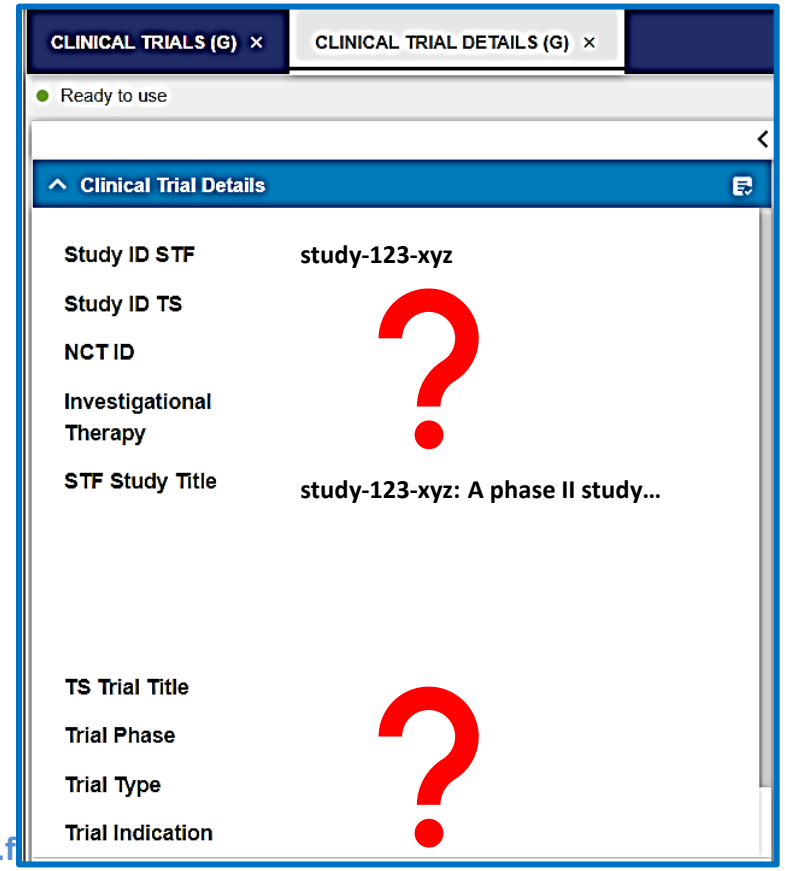


Why is 1734 important?

Missing ts.xpt:

X Can't determine the study start date, if TRC applies and whether standardized datasets are required

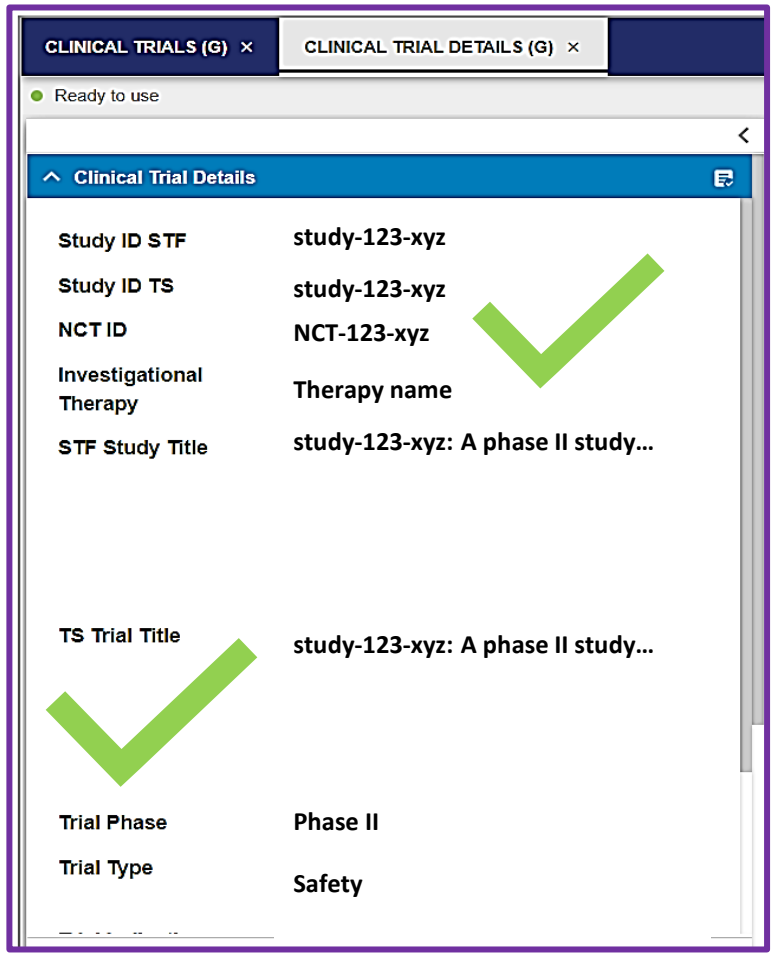
X Cannot connect to other clinical trial data and limits details available to reviewers



When a ts.xpt is included:

✓ Enables detailed searches

✓ Enables connections between data sources, such as ClinicalTrials.gov using NCT number



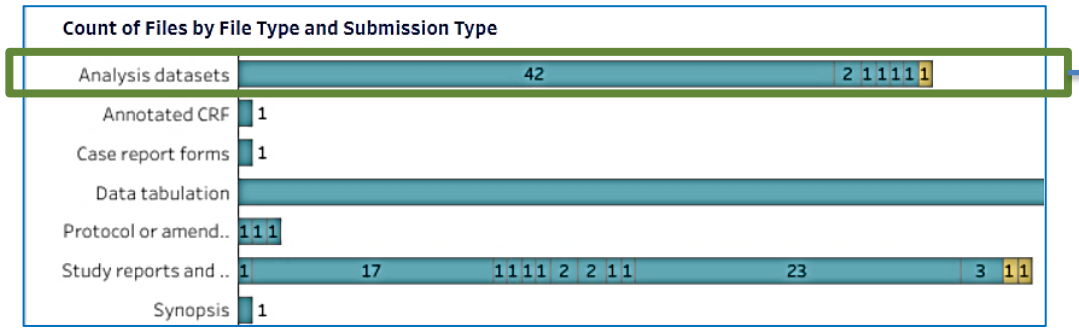
Why are 1735 & 1736 important?

File tags act as standardized sub-headings within a study to help distinguish and group files based on content.

When datasets are provided and tagged correctly:

- ✓ Enables detailed searches by file type
- ✓ Enables filtering by file type
- ✓ Enables locating essential study files, including dm.xpt, adsl.xpt, and define.xml
- ✓ Enables automated loading into analysis applications

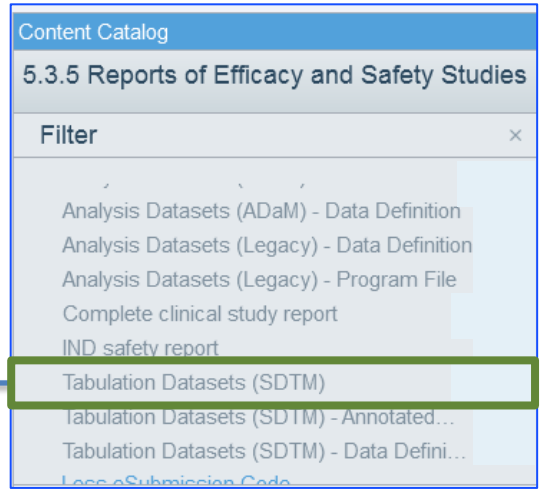
Reports & Filtering:

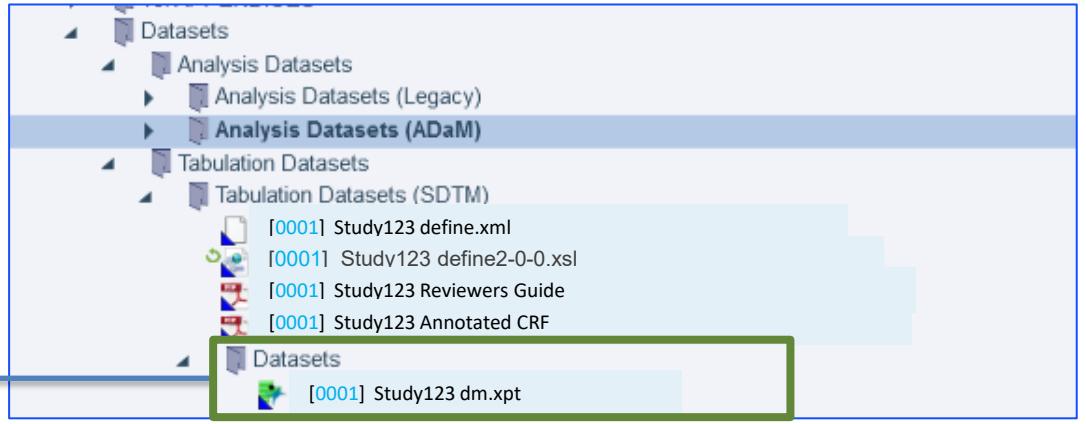


ADaM Datasets Grouped

SDTM Datasets Grouped

eCTD Viewer:





References

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
  - FDA Data Standards Catalog [February 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

Questions

For questions please contact:

CDER

Study Data Questions:
edata@fda.hhs.gov

eCTD Questions:
esub@fda.hhs.gov

CBER

Study Data Questions:
cber-edata@fda.hhs.gov

eCTD Questions:
esubprep@fda.hhs.gov

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