Regulatory Submissions, Information, and Document Management Forum

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Technical Rejection Criteria for Study Data

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Agenda

- Benefits of Standardized Data
- Study Data Validations – What's New
- Technical Rejection Criteria for Study Data (TRC)
  - Overview
  - Trends
  - Top Errors
- Impacts & Improvements from Standardized Study Data

Benefits of Standardized Data

Purpose of eCTD and Study Data Requirements

- Reviewing study data in a timely manner is critical for FDA's review process (e.g. Reviewers have 30 days to review an IND application)
- When sponsors submit data to the FDA in a reliable and accessible format, it improves efficiency and consistency of review decisions
- CDISC Standards enable FDA to streamline the review process:
  - Reduce time for reviewers to locate and identify study data
  - Reduce the burden on sponsors and reviewers from IRs (Information Requests)
  - Reduce review time by enabling the use of COTS reviewer's tools such as JMP, JMP Clinical, etc. to automate review analyses
  - Support data driven decisions by applying data mining and data analytic techniques

"The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities."

Source: https://www.ich.org/products/ctd.html

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:**
  - NDA, BLA, ANDA studies that started after December 17th, 2016
  - Commercial IND studies started after December 17th, 2017
- **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 Technical Rejection Criteria for Study Data (TRC).

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

- Study Data Technical Conformance Guide – Latest update October 2022
- Electronic Common Technical Document (eCTD) website
- Study Data for Submission to CDER and CBER website
- SBIA Webinar, FDA Study Data Technical Rejection Criteria (TRC): What you need to know!

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Study Data Validations – What's New

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

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

TRC Updates

1. **CBER SEND Date Requirements**
   - CBER now requires SEND datasets for non-clinical studies with a Study Start Date after 3/15/2023
   - Date applies to all application types
2. **1734 – Remove Study ID Matching**
   - 1734 no longer validates for STUDYID mismatch between ts.xpt and STF file
   - New validation rule 1738 now validates STUDYID matching
3. **1735 – Allow define.xml Files to be Tagged as "data-listing-data-definition"**
   - A Define.xml file tagged as "data-listing-data-definition" no longer triggers a 1735 error

Other Study Data Validation Updates

4. **1737 – Apply Rule to All Sections Except 4.3, 5.2, 5.4, & 5.3.6 Postmarketing reports**
   - 1737 now applies to same sections as validation rule 1789
   - Medium severity error
   - 1737 is not currently included in the Self-Check Worksheet
5. **1738 – New Study ID Matching Rule**
   - 1738 is not currently included in the Self-Check Worksheet
   - 1738 now validates for STUDYID mismatch between ts.xpt and STF file
   - Medium severity error
   - Applies to all sections except 4.3, 5.2, 5.4, & 5.3.6 Postmarketing reports

Technical Rejection Criteria for Study Data (TRC)

Technical Rejection Criteria for Study Data

- eCTD Validations 1734, 1735, and 1736 are in effect (as of Sept. 15th, 2021)

- If a submission contains study information and fails eCTD validations in listed in Technical Rejection Criteria for Study Data, CDER and CBER will reject the submission
- Sponsors will receive a rejection notice if a submission fails eCTD validations

Validation Rule 1734 in the *Specifications for eCTD Validation Criteria*:

Number:	1734
Group:	General
Description:	A dataset named ts.xpt with information on study start date must be present for each study in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in 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
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	9/15/2021
Problem:	You have not submitted a dataset named ts.xpt with information on study start date for each study in Module 4, section 4.2, or in Module 5, section 5.3
Corrective Action:	Resubmit, including a dataset named ts.xpt with information on study start date for each study in Module 4, section 4.2, and Module 5, section 5.3
Guidance Source:	Providing Regulatory Submissions in Electronic Format – Standardized Study Data; Study Data Technical Conformance Guide.

Addressing Top Errors: 1734

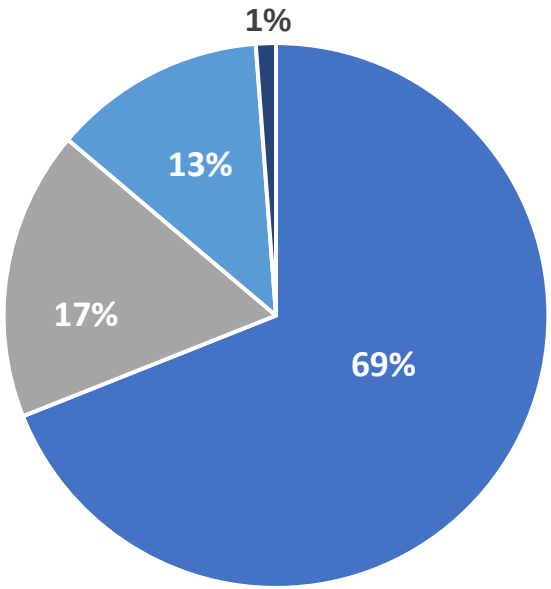
❖ **76% of all 1734 errors are from studies in IND Applications**

1734 Validation

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



69% due to Missing ts.xpt

83% of Missing ts.xpt 1734 Errors are for Non-Clinical Studies in M4

- No ts.xpt found for this study
- Study ID in ts.xpt does not match study ID from STF
- No ts.xpt with value for SSD found (and no null flavor value)
- Study start date is incorrectly formatted and TSVALNF has no null flavor value

Note: 506 1734 Study Errors between Sept. 15 – Dec. 31, 2022

Verifying Study Data Expectations for Rules 1734, 1735, & 1736

Table 6: eCTD Technical Rejection Criteria for Study Data Expectations

Application Type	Data Type	Modules and Submodules	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)	**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) commercial INDs
Commercial 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)
Commercial 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 Study	**Start Date:** ***On or prior to 2017-12-17*** Rejection criteria will not be applied

Table 6 found in [Study Data Technical Conformance Guide_v5.0_October 2022 (fda.gov)]

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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	**Study Start Date:** ***After 2016-12-17*** Rejection criteria will be applied; submit a full TS
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Table 6 found in Study Data Technical Conformance Guide_v5.0_October 2022 (fda.gov)

Verifying Rule 1734 Using Self-Check Worksheet

✓ Trial Summary Dataset (ts.xpt) is present

Section 3 helps check if non-clinical studies without .xpt datasets require a TS file:

3f. Are XPT Datasets (other than the ts.xpt File) Included?*	3g. If the Study is Nonclinical (m4), are any Study Files Tagged as "pre-clinical-study-report," "legacy-clinical-study-report," or "study-report-body"?*
☐ Yes ☒ No	☒ Yes ☐ No

Section 4 helps check if a Full or Simplified TS file is required:

Section 4: TS File Information

4a. If the Study is for a Commercial IND Application, Is the Study Start Date:

☐ Prior to or on **17-Dec-2017** ☒ After **17-Dec-2017**

4b. If the Study Is for an NDA, BLA, or ANDA Application, Is the Study Start Date:

☐ Prior to or on **17-Dec-2016** ☐ After **17-Dec-2016**

4e. If TS File is Required, What Type of TS File is Required?

☐ Full TS ☒ Simplified TS

Refer to guidelines in chart above. See the Study Data Technical Conformance Guide for more information on submitting a Simplified TS for nonclinical data.

***Field 4f-4k** are applicable if a Full TS File is submitted, **Fields 4l-4p** are applicable if a simplified TS file is submitted.*

✓ Self-Check Worksheet and tools for creating a simplified ts.xpt can be found: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

Note: TS files must be named *ts.xpt* and cannot be customized or changed (other standardized datasets, such as dm.xpt and adsl.xpt, must also be named correctly)

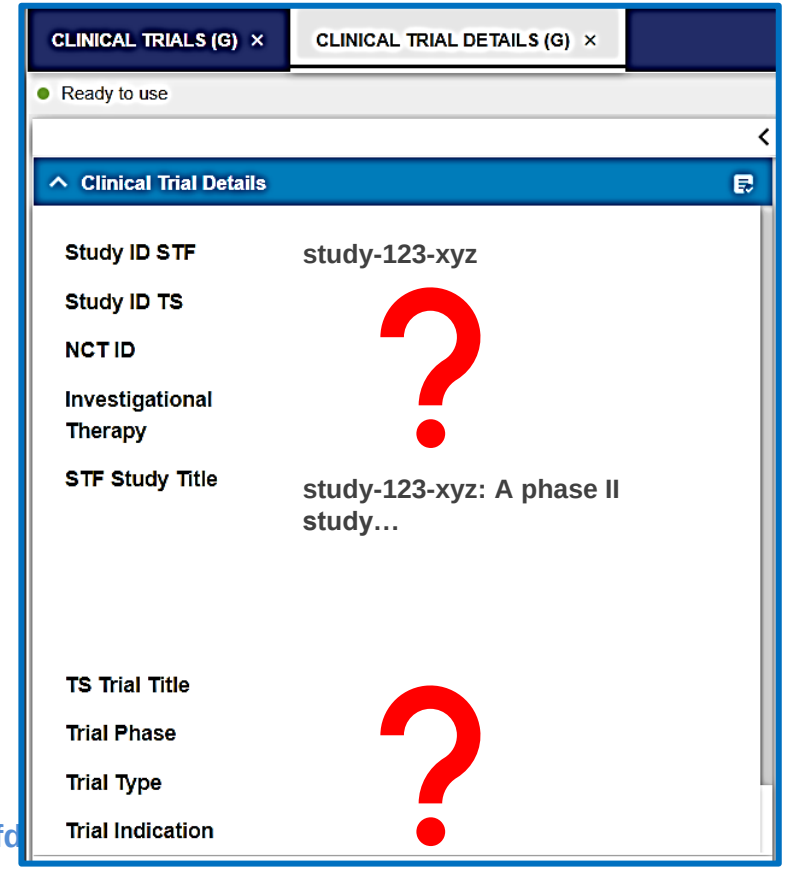
Impacts & Improvements from Standardized Study Data

Why is 1734 important?

Missing ts.xpt:

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

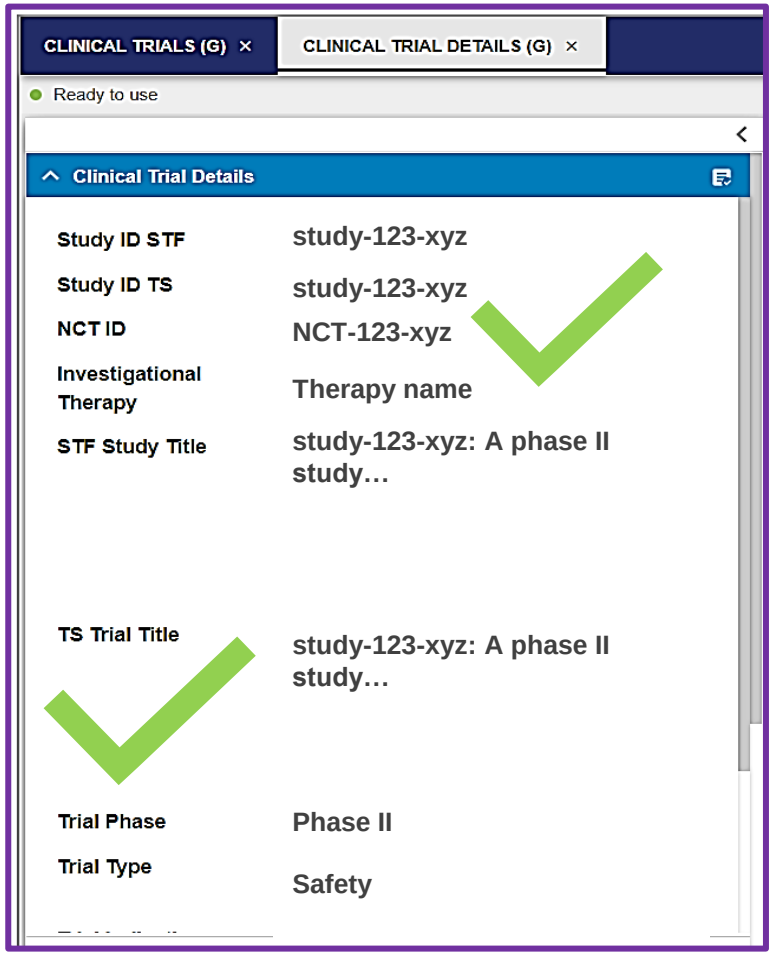
X Cannot connect to other clinical trial data and limits details available to reviewers



When a ts.xpt is included:

✓ Enables detailed searches

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



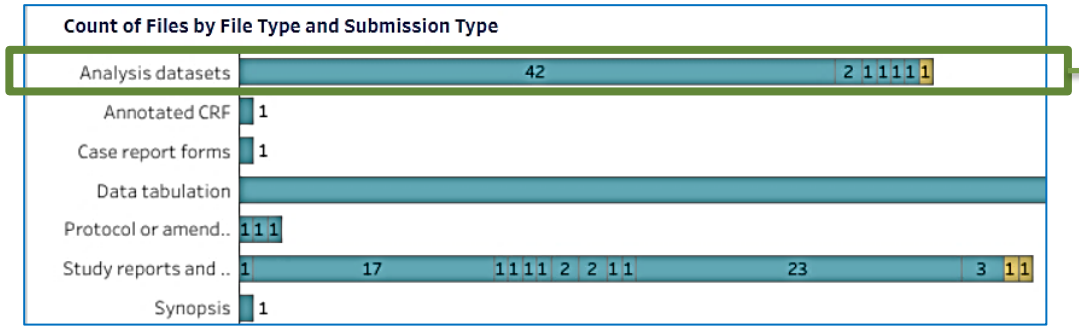
Why are 1735 & 1736 important?

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:

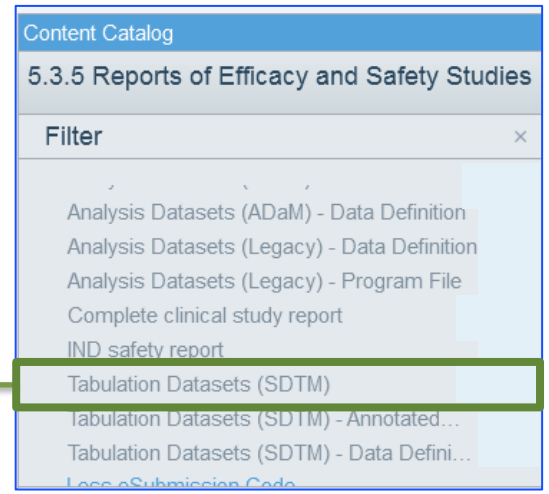
- ✓ Enables detailed searches by file type
- ✓ Enables filtering by file type
- ✓ Enables locating essential study files, including dm.xpt, adsl.xpt, and define.xml
- ✓ Enables automated loading into analysis applications

Reports & Filtering:

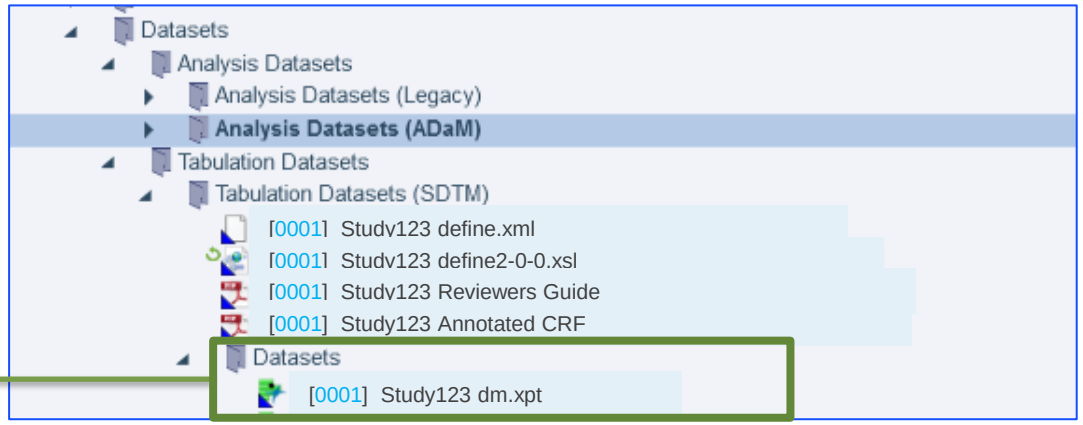


ADaM Datasets Grouped

eCTD Viewer:



SDTM Datasets Grouped



References

- **Study Data Standards Resources**
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [April 2022]
  - Study Data Technical Conformance Guide [October 2022]
  - FDA Data Standards Catalog [August 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

- **Electronic Common Technical Document (eCTD)**
  - Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications: Guidance for Industry [February 2020]
  - eCTD Submission Standards [December 2022]
  - Specifications for eCTD Validation Criteria [May 2022]
  - Link: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd

- **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

Thank You

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Questions?

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