FDA Study Data Technical Rejection Criteria (TRC): What you need to know!

For Submissions to CBER and CDER

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Learning Objectives

- Review the background of the Technical Rejection Criteria (TRC) and updates
- List and review the most common TRC errors
- Describe the importance of Standardized Study Data
TRC Background & Updates
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
Study Data Technical Conformance Guide

- 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.
### eCTD Validation Updates

- **Study Data Validation Effective Date updated:**
  
  9/15/2021 (CBER module 4 sections, 03/16/2023)

<table>
<thead>
<tr>
<th>Error</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1734</td>
<td>A dataset named ts.xpt with information on study start date must be present for each study in required sections*</td>
</tr>
<tr>
<td>1735</td>
<td>Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*</td>
</tr>
</tbody>
</table>
| 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.

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<td>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</td>
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- 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
Challenge Question #1

When does CBER's SEND requirement begin?

A. Studies started after December 17th, 2017
B. Studies started after December 17th, 2016
C. Studies started after March 15th, 2023
D. CBER will not require SEND standardized data
Most Common Errors
Monthly TRC Warning & Rejection Trend (CDER)

**Warning Rate**
- Aug 15 - Sept 15: 39.9%
- Sept 16 - Oct 15: 22.9%
- Oct 16 - Nov 15: 28.3%
- Nov 16 - Dec 15: 13.5%
- Dec 16 - Jan 15: 12.3%
- Jan 16 - Feb 15: 13.7%
- Feb 16 - Mar 15: 13.0%
- Mar 16 - Apr 15: 6.6%

**Rejection Rate**
- Average Rejection Rate After Implementation: 15.8%

**Notes:**
- Metrics generated from data between Aug. 15, 2021 and April 15, 2022.
- Error 1789 applies to all application types.
- Warning and rejection rates calculated as total warnings/rejections as a percentage of submissions with study data in TRC-applicable sections.
CDER TRC Rejections

- 1734 is the most common error and failure reason for all application types for a missing ts.xpt

- 1789 is the second most common error and failure reason

- Commercial IND submissions the have highest number of failures overall and have particularly high numbers of 1734 and 1789 errors

Notes: Metrics generated from data between September 15, 2021 and April 30, 2022. 1789 severity elevated to high 9/15/21 but not specific to standardized study data requirements.
Addressing Top Errors: 1734

58% of errors across Application Types

62% of errors for 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

71% due to Missing ts.xpt

90% 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: 280 1734 Study Errors for IND, NDA, BLA submissions between Sept. 15 – Apr. 30, 2022
# Addressing 1734 Errors: Missing TS File

**CDER and CBER expectations for standardized data:**

<table>
<thead>
<tr>
<th>Application Type</th>
<th>Data Type</th>
<th>Modules &amp; Sub-Modules</th>
<th>Expectation by CDER</th>
<th>Expectation by CBER</th>
</tr>
</thead>
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<tr>
<td>NDA, BLA, ANDA</td>
<td>Non-Clinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>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)</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>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</td>
<td>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)</td>
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<td>Comm. INDs</td>
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<td>Study Start Date: On or prior to 2017-12-17 Rejection criteria will be applied; submit a full TS</td>
<td>Study Start Date: On or prior to 2023-03-15 Rejection criteria will be applied; submit a full TS</td>
</tr>
<tr>
<td>NDA, BLA, ANDA</td>
<td>Non-Clinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>Study Start Date: After 2016-12-17 Rejection criteria will be applied; submit a full TS</td>
<td>Study Start Date: After 2023-03-15 Rejection criteria will be applied; submit a full TS</td>
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<tr>
<td></td>
<td>Clinical</td>
<td>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</td>
<td>Study Start Date: After 2016-12-17 Rejection criteria will be applied; submit a full TS with standardized data</td>
<td>Study Start Date: After 2023-03-15 Rejection criteria will be applied; submit a full TS</td>
</tr>
<tr>
<td>Comm. INDs</td>
<td>Non-Clinical</td>
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<td>Study Start Date: After 2017-12-17 Rejection criteria will be applied; submit a full TS</td>
<td>Study Start Date: After 2017-12-17 Rejection criteria will not be applied</td>
</tr>
</tbody>
</table>

The Study Data Technical Conformance Guide can be found here: [https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources](https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources)
Addressing Top Errors: 1789

- 20% of errors across Application Types
- 22% of errors for IND Applications

1789 Validation:

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).

87% of all 1789 Errors for IND Applications
9% of all 1789 Errors for NDA Applications
4% of all 1789 Errors for BLA Applications

When placing files in applicable sections within Modules 4 and 5, they should also be referenced within an STF for the study to which they belong.

Note: 96 1789 Submission Errors for IND, NDA, BLA submissions between Sept. 15 – Apr. 30, 2022
Study Tagging Files:

- Identify and link together all files associated with a study
- The index.xml and us-regional.xml do not contain enough information on the subject matter of several documents (e.g., study report documents) to support certain regulatory uses
- An STF must be provided with the submission of any file or group of files belonging to a study in Modules 4 and 5.
- The STF provides for additional heading elements, file-tags, and heading attributes not currently provided by the eCTD DTD

ICH Study Tagging File Specification
Challenge Question #2

What is the most common reason for a 1734 error?

A. No ts.xpt found for the study
B. Study ID in ts.xpt does not match study ID from STF
C. No ts.xpt with value for SSD found
D. Study start date is incorrectly formatted
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.
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:

<table>
<thead>
<tr>
<th>Count of Files by File Type and Submission Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis datasets: 42</td>
</tr>
<tr>
<td>Annotated CRF: 1</td>
</tr>
<tr>
<td>Case report forms: 1</td>
</tr>
<tr>
<td>Data tabulation:</td>
</tr>
<tr>
<td>Protocol or amend.:</td>
</tr>
<tr>
<td>Study reports and...</td>
</tr>
<tr>
<td>Synopsis:</td>
</tr>
</tbody>
</table>

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]
  - Study Data Technical Conformance Guide [March 2022]
  - FDA Data Standards Catalog [February 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)**
  - eCTD Submission Standards [May 2022]
  - Specifications for eCTD Validation Criteria [May 2022]

- **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
Summary

- FDA uses eCTD validations (1734, 1735, 1736) to confirm Sponsors are conforming to the FDA Data Standards Catalog
- CBER’s SEND requirement for module 4 begins March 16, 2023
- Commercial IND submissions have the highest number of failures related to TRC errors
- Missing ts.xpt is the most common error reason for 1734
- 1789 is the second most common error and failure reason
- Standardized data helps FDA to streamline the review process by organizing files and data and enabling search and automation capabilities
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: esub-prep@fda.hhs.gov