

# Submitting Data to CDER: Requirements for your Application

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# Agenda

- ❖ Electronic Submissions to CDER
- ❖ eCTD Requirements
- ❖ Study Data Requirements
- ❖ Addressing the Most Common Error Reason



## Electronic Submissions to CDER

# Requirements for Electronic Submissions

- ❖ Electronic submissions to CDER must conform to standards in the [FDA Data Standard Catalog](#)
- ❖ **Section 745A(a)** of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that submissions under section 505(b), (i), or (j) of the FD&C Act and submissions under section 351(a) or (k) of the Public Health Service Act (PHS Act) be submitted in electronic format
- ❖ Submissions to NDA, BLA, ANDA, Commercial IND and Master Files\* must be in eCTD format

### 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.

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).

#### Quick Links

- [Data Standards Catalog v7.3 \(September 14, 2021\)](#)
- [Study Data Technical Conformance Guide v4.8 \(September 2021\)](#)

#### 1. FDA Data Standards Catalog

FDA accepts electronic submissions that provide study data using the standards, formats, and terminologies described in the FDA Data Standards Catalog.

- [FDA Data Standards Catalog v7.3 \(XLS -73KB\) \(September 14, 2021\)](#)

Centers other than CDER and CBER may have additional supported standards, so please check with the Center in question. Where indicated in the FDA Data Standards Catalog, study data standards are recognized and supported by CDRH

# Electronic Submissions to CDER


Electronic submissions can be submitted to CDER in one of two ways:

## ❖ Electronic Submission Gateway (ESG)

- eCTD submission to NDA, BLA, ANDA, IND, DMF applications
- Non-eCTD submission to Research IND applications
- Non-eCTD submission to applications granted eCTD Waiver

## ❖ CDER NextGen

- Non-eCTD submission to Research IND applications
- Non-eCTD submission to applications granted eCTD Waiver
- Non-eCTD submission of EUA or Pre-submission Correspondence



***eCTD is the standard format for submitting applications, amendments, supplements, and reports to CDER***

## Electronic Common Technical Document (eCTD)

The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

### Important Dates

Reminder: Per [Providing Regulatory Submissions In Electronic Format – Standardized Study Data, Guidance for Industry](#), electronic submission of standardized study data is required for NDA, BLA, ANDA, and Commercial IND. FDA plans to implement eCTD validation checks when submissions contain content under modules 4 and 5 beginning **September 15, 2021**. Submissions which fail this validation will be subject to rejection. Please see the [Technical Rejection Criteria for Study Data](#) and the [eCTD Validation Criteria](#) (error code 1734, 1735, 1736, 1789) for details.

### Quick Links

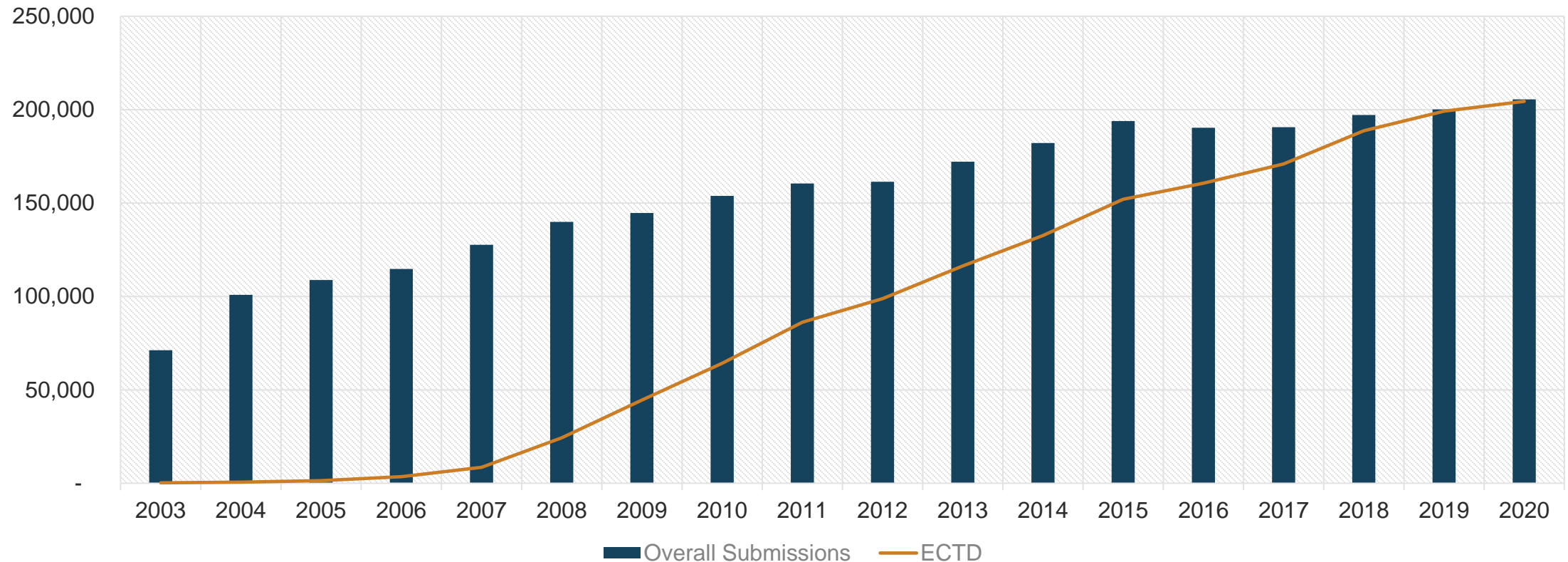
- [NDA to BLA eCTD Transition Instruction to Industry](#) (PDF - 90 KB)
- [eCTD Guidance \(Final, Rev 7\)](#) (PDF - 11 KB)
- [eCTD Submission Standards \(v4.3\)](#) (PDF - 130 KB) **NEW**
- [FDA Data Standards Catalog](#)
- [eCTD Technical Conformance Guide](#) (PDF - 303 KB)
- [Drug Master Files \(DMFs\)](#)
- [Technical Rejection Criteria for Study Data Information](#)
- [eCTD Submission Types and Sub-Types](#) (PDF - 630 KB)

# Electronic Submissions to CDER



CDER received approximately 205,000\* electronic submissions via ESG in FY 2020. Nearly all were in eCTD.

**Comparison: Overall Submissions vs. eCTD Submissions**





# Study Data Requirements



# Study Data Requirements

- ❖ [Study Data Guidance](#) specifies that study data submitted to CDER must be in standardized format:
  - For NDAs, BLAs, ANDAs, studies that started after Dec. 17th, 2016
  - For Commercial INDs, studies that started after Dec. 17th, 2017
- ❖ Clinical Data Interchange Standards Consortium (CDISC) study data standards:
  - Study Data Tabulation Model (SDTM) for clinical trial tabulations data
  - Standard Exchange for Nonclinical Data (SEND) for non-clinical trial tabulations data
  - Analysis Data Model (ADaM) for clinical trial analysis data
- ❖ Study datasets should be provided in .xpt format

## Electronic Common Technical Document (eCTD)

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The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

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### Quick Links

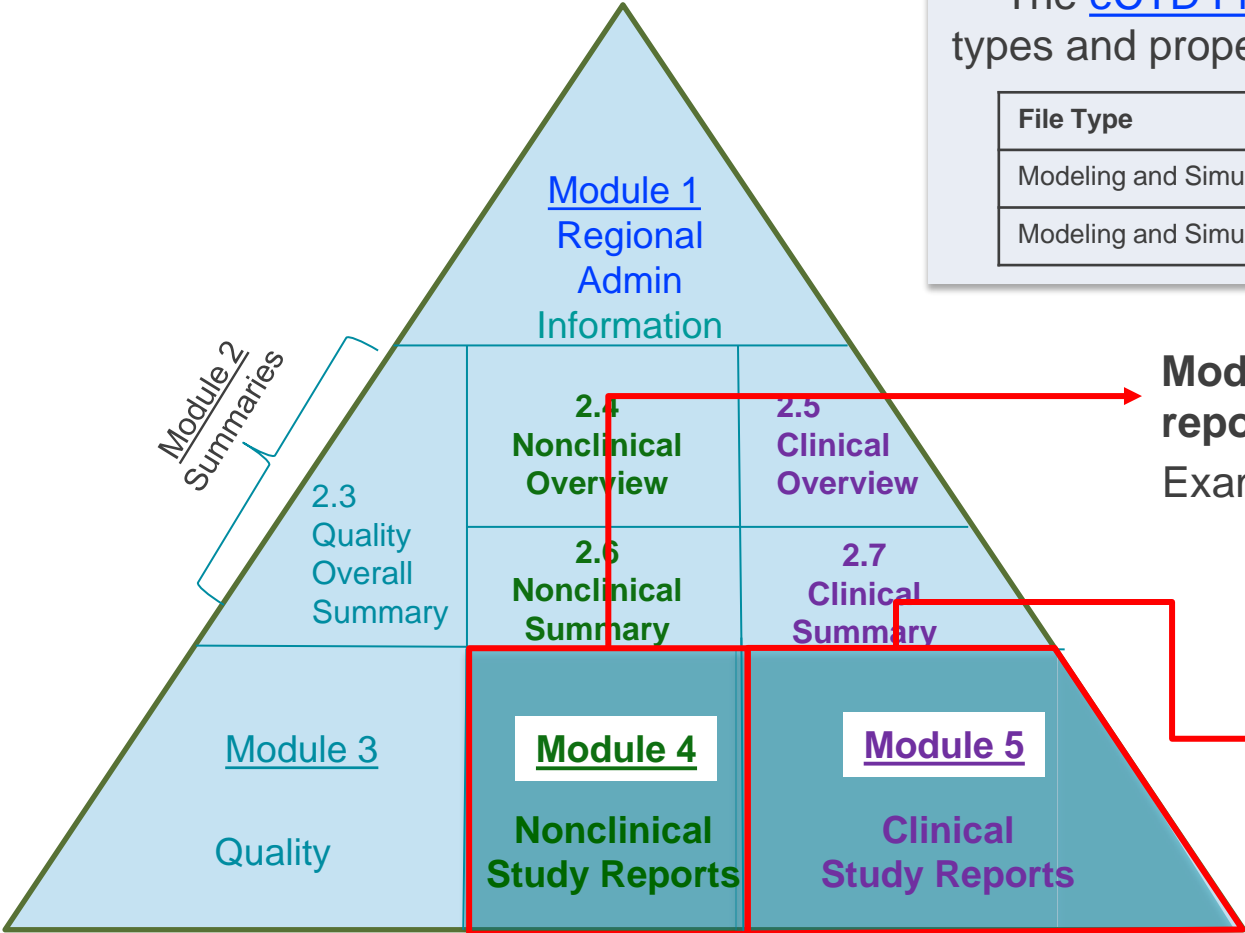
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# eCTD Placement of Study Data Files

- Most study data files should be submitted in eCTD Module 4 (non-clinical) and Module 5 (clinical)
- The proper placement of the datasets should follow the [Comprehensive Table of Headings and Hierarchy](#)

The [eCTD File Format Types Specifications](#) provides accepted file types and proper eCTD locations for those file types. Examples include:

File Type	File Format	Format Name	Accepted eCTD location
Modeling and Simulation	.rmd	R Markdown file	M5
Modeling and Simulation Reporting	.r	R Script file	M3 – M5



**Module 4 - Non-clinical studies and components such as reports, datasets, protocols, etc.**

Example:

- 4.2.3 Toxicology
  - 4.2.3.1 Single dose toxicity
  - 4.2.3.2 Repeat dose toxicity

**Module 5 - Clinical studies and components such as reports, datasets, protocols, etc.**

Example:

- 5.3.1 Biopharmaceutic Studies
  - 5.3.1.1 Bioavailability (BA) Study reports
  - 5.3.1.2 Comparative BA and bioequivalence (BE) Study reports

# eCTD & Study Data Resources

## Electronic Common Technical Document (eCTD)



The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

### Important Dates

Reminder: Per [Providing Regulatory Submissions In Electronic Format – Standardized Study Data, Guidance for Industry](#), electronic submission of standardized study data is required for NDA, BLA, ANDA, and Commercial IND. FDA plans to implement eCTD validation checks when submissions contain content under modules 4 and 5 beginning **September 15, 2021**. Submissions which fail this validation will be subject to rejection. Please see the [Technical Rejection Criteria for Study Data](#) and the [eCTD Validation Criteria](#) (error code 1734, 1735, 1736, 1789) for details.

After the dates listed below, eCTD requirements for submissions to CDER and CBER will go into effect and submissions that do not use eCTD

### Quick Links

- [NDA to BLA eCTD Transition Instruction to Industry](#) (PDF - 90 KB)
- [eCTD Guidance \(Final, Rev 7\)](#) (PDF - 11 KB)
- [eCTD Submission Standards \(v4.3\)](#) (PDF - 130 KB) **NEW**
- [FDA Data Standards Catalog](#)
- [eCTD Technical Conformance Guide](#) (PDF - 303 KB)
- [Drug Master Files \(DMFs\)](#)
- [Technical Rejection Criteria for Study Data Information](#)
- [eCTD Submission Types and Sub-Types](#) (PDF - 630 KB)

- ❖ [eCTD Technical Conformance Guide](#) (eCTD TCG) provides technical recommendations for submitting files in eCTD
- ❖ [Technical Rejection Criteria for Study Data](#) (TRC) provides the conditions under which FDA will not accept submissions with study data
- ❖ [Study Data Technical Conformance Guide](#) (SD TCG) provides technical recommendations for submitting study data according to CDISC standards
  - Planning and Providing Standardized Study Data
  - Exchange Format: Electronic Submissions
  - Study Data Submission Format: Clinical and Nonclinical
  - Therapeutic Area Standards
  - Terminology
  - Electronic Submission Format
  - Study Data Validation and Traceability



# Overview of Technical Rejection Criteria

The TRC are eCTD validation criteria to determine compliance with requirements for submitting standardized study data in required sections in Modules 4 and 5, including:

- ❖ 4.2.3.1, 4.2.3.2, 4.2.3.4
- ❖ 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

Error	Description (Reference to FDA Study Data Technical Rejection Criteria <u>March 2021 version</u> )	Severity Level	Effective Date
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections	High	Sept. 15, 2021
1735	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections	High	
1736	For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4 required sections For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in Module 5 required sections	High	

- ❖ **Between September 15th and October 15th, 2021, 65% of TRC related rejections were caused by 1734 errors**



## Addressing the Most Common Error Reason

# Causes of 1734 Errors

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

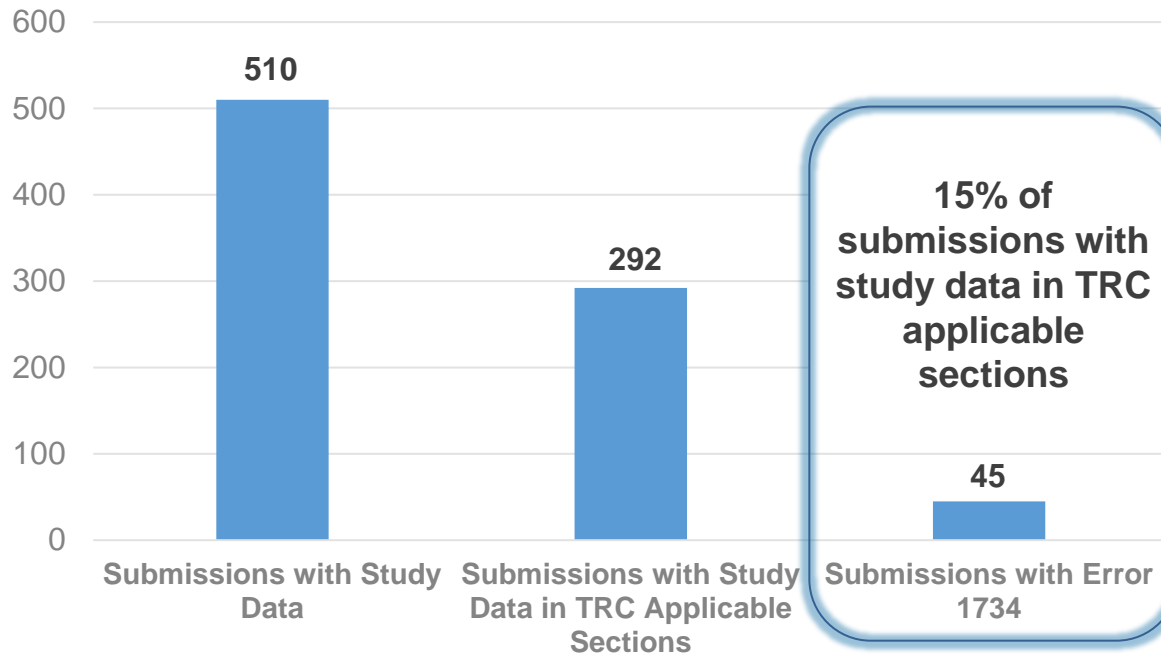
✓ Trial Summary Dataset (ts.xpt) is present

✓ Study ID (or SPREFID) matches STF Study ID

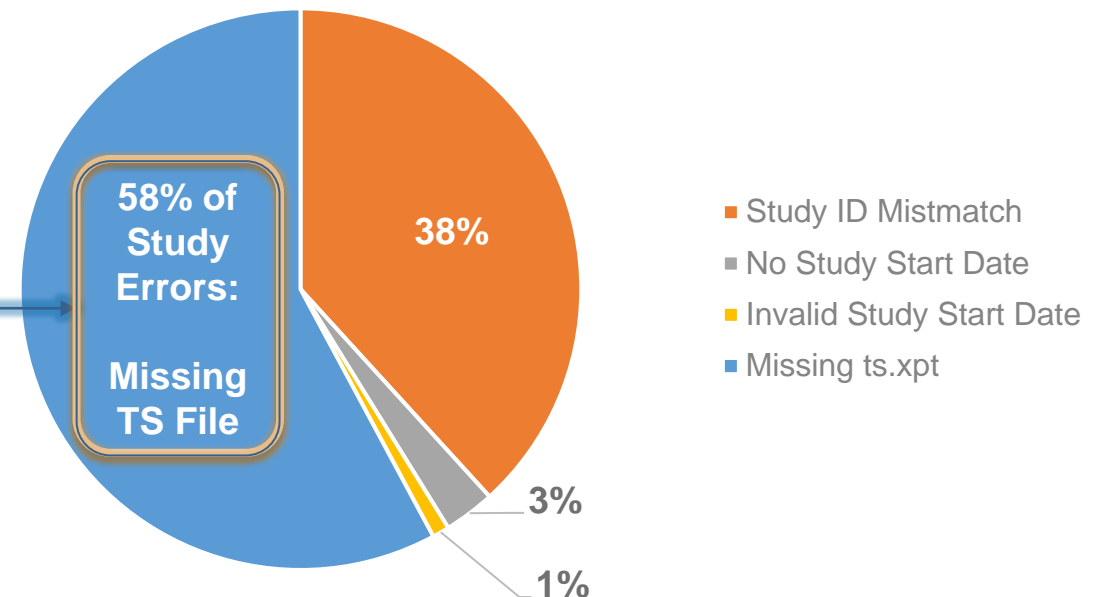
✓ Study start date is provided (or TSVLNF = NA)

✓ Study start date is in a valid format

CDER Submissions: September 15<sup>th</sup> – October 15<sup>th</sup> 2021



1734 Error Reasons\*\*



# 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 \(https://geotiger.shinyapps.io/07\\_genTS/\)](https://geotiger.shinyapps.io/07_genTS/)

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

```

#R Script - R Code
##Load Packages##
library(tidyverse)
library(dplyr)
library(stringr)
library(readr)

##Data Source##
#Data Source (see Date "YYYY-MM-DD")
#Data Source (see Date "YYYY-MM-DD")
#Data Source (see Date "YYYY-MM-DD")

##Data Labels##
label(data) <- "Trial Summary"
label(data) %>% summarise() <- "Study Identifier"
label(data) %>% summarise() <- "Trial Summary Parameter Short Name"
label(data) %>% summarise() <- "Parameter Value"
label(data) %>% summarise() <- "Parameter Value"
label(data) %>% summarise() <- "Parameter Value"
  
```

**Please Note** – While editing Study ID, TRTVAL, and TRTVALNF, drop the question 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.

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

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

- At the CMD use command line interface, type in the following command and press ENTER: cd C:\Program Files\Python37\Scripts
- Type in: python -m pip install --upgrade pip (to ensure pip is at the latest version).
- Type in: pip install export (to install the export module)



# Option 1: Use the Simplified ts.xpt Creation Guide



## 1. Copy and paste code from the Guide into R Editor to create a script

Table 2: Code for Creating ts.xpt Using R : Option B - Using the SASxport Package

R Package	Clinical Study	Non-clinical Study
<b>Option B:</b> Using the SASxport Package	<pre>##Load package## library(SASxport) library(Hmisc)  ##Create data file## abc&lt;-data.frame(STUDYID="XYZ123",                 TSPARMCD="SSTDTC",                  TSVAl=strftime(as.Date("YYYY-MM-DD"), "%Y-%m-%d"),                 TSVAlNF="NA",                 stringsAsFactors = FALSE)  ##Add labels##  label(abc) &lt;- 'Trial Summary' label(abc\$STUDYID) &lt;- 'Study Identifier' label(abc\$TSPARMCD) &lt;- 'Trial Summary Parameter Short Name' label(abc\$TSVAL) &lt;- 'Parameter Value' label(abc\$TSVALNF) &lt;- 'Parameter Null Flavor'  ##Write data into xpt format## write.xport(abc, file="C:/Simplified TS File/ts.xpt")</pre>	<pre>##Load package## library(SASxport) library(Hmisc)  ##Create data file## abc&lt;-data.frame(STUDYID="XYZ123",                 TSPARMCD="STSTDTC",                  TSVAl=strftime(as.Date("YYYY-MM-DD"), "%Y-%m-%d"),                 TSVAlNF="NA",                 stringsAsFactors = FALSE)  ##Add labels##  label(abc) &lt;- 'Trial Summary' label(abc\$STUDYID) &lt;- 'Study Identifier' label(abc\$TSPARMCD) &lt;- 'Trial Summary Parameter Short Name' label(abc\$TSVAL) &lt;- 'Parameter Value' label(abc\$TSVALNF) &lt;- 'Parameter Null Flavor'  ##Write data into xpt format## write.xport(abc, file="C:/Simplified TS File/ts.xpt")</pre>

Simplified TS File

[www.fda.gov](http://www.fda.gov) Creation Guide



```
RGui (64-bit)
File Edit Packages Windows Help

R Console
C:\Users\Ryan.Olivett\OneDrive - FDA\Documents\Sim...
##Load package##
library(SASxport)
library(Hmisc)

##Create data file##
abc<-data.frame(STUDYID="XYZ123",
                TSPARMCD="STSTDTC",

                TSVAl=strftime(as.Date("YYYY-MM-DD"), "%Y-%m-%d"),
                TSVAlNF="NA",
                stringsAsFactors = FALSE)

##Add labels##
label(abc) <- 'Trial Summary'
label(abc$STUDYID) <- 'Study Identifier'
label(abc$TSPARMCD) <- 'Trial Summary Parameter Short Name'
label(abc$TSVAL) <- 'Parameter Value'
label(abc$TSVALNF) <- 'Parameter Null Flavor'

##Write data into xpt format##
write.xport(abc, file="C:/Simplified TS/ts.xpt")
```

R Application

2. Edit the Study ID

3. Edit the Study Start Date and TSVAlNF Value

4. Edit where to save the file



# Option 2: Use the PHUSE Utility

Example using the online PHUSE Utility to generate a Simplified TS File:

The screenshot shows the 'Creating TS Domain' interface. It includes a 'Show/Hide sidebar' button, 'Create' and 'View' tabs, and four main input fields: 'Study ID (STUDYID) \*', 'Study Type Parameter (TSPARMCD) \*' (with 'Nonclinical (STSTDTC)' selected), 'Study Start Date (TSVAL)', and 'Exception Code (TSVALNF)' (with '\_\_Blank\_\_' selected). A 'Download' button is at the bottom. Four numbered callouts point to these fields: 1. Enter the Study ID, 2. Select the TSPARMCD Code, 3. Enter the Study Start Date or TSVALNF Value, and 4. Download the file.



**Thank you!**

# References

## ❖ Study Data Standards Resources

- Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [Jun 2021]
- Study Data Technical Conformance Guide [Sep 2021]
- FDA Data Standards Catalog [Sep 2021]
- 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 For Study Data [August 2021]
- 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: [Providing Regulatory Submissions in Electronic Format](#)



# Questions

For Questions Please Contact:

- ❖ Study Data Questions:  
[edata@fda.hhs.gov](mailto:edata@fda.hhs.gov)
- ❖ eCTD Questions:  
[esub@fda.hhs.gov](mailto:esub@fda.hhs.gov)

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