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Study Data Technical Rejection Criteria (TRC) Considerations for Multiple Data Packages in a Single Submission

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ABSTRACT

The Study Data Technical Conformance Guide (TCG) provides technical recommendations to sponsors for the submission of animal and human study data and related information in a standardized electronic format in INDs, NDAs, ANDAs, and BLAs. Study datasets and their supporting files should be organized into a specific file directory structure. Submission files within the appropriate folders allows automated systems to detect and validate the presence of expected data and datasets for review and minimizes the need for manual processing. Effective September 15, 2021, the FDA implemented the Study Data Technical Rejection Criteria (TRC) validation which can reject a submission if criteria are not met through the automated inbound process, Electronic Submission Gateway (ESG). This paper will share the challenges and successful approaches that were considered when preparing multiple data packages for submission. This paper will include best practices and insights gained from submitting data packages for an interim analysis and final analysis; supportive studies; integrated analysis and meta-analysis.

INTRODUCTION

Electronic submission package (eSub) to FDA is a critical deliverable in a drug development lifecycle. Submission effort requires careful planning upfront. It involves many functional teams. In this paper, the focus is on the datasets packages supporting eCTD module 5 folder.

Study datasets and their supportive files are organized in accordance with Study Data Technical Conformance Guide.

[module]	1	Refers to the eCTD module in which clinical study data is being submitted.
datasets	2	Resides within the module folder as the top-level folder for clinical study data being submitted for m5.
[study]	3	Study identifier or analysis type performed
analysis	4	Contains folders for analysis datasets and software programs; arrange in designated level 6 subfolders
adam	5	Contains subfolders for ADaM datasets and corresponding software programs
datasets	6	Contains ADaM datasets, analysis data reviewer's guide, analysis results metadata and define files
programs	6	Contains software programs for analysis datasets, tables, and figures
tabulations	4	Contains subfolders for SDTM datasets
sdtm	5	Contains SDTM datasets, SDTM data reviewer's guide, SDTM annotated CRF and define files

We will share a complex submission experience which includes multiple data packages for a single study within one submission. With limited resources and tight deadlines, detailed planning and organization are required to ensure high quality deliverables. Understanding the regulatory requirements and electronic submission standards will help streamline the process and minimize the re-work and rejection.

Key preparation steps are outlined below:

• Understand the submission strategy
• Plan the submission components
• Check the latest standards
• Set-up kick off meeting to cover roles and responsibilities
• Generate and validate the submission packages
• Review the final packages before submission

UNDERSTAND THE SUBMISSION STRATEGY

As a team, it is critical to collectively identify the reporting needs that support analyses. Defining the submission strategy should be discussed in advance during submission preparations. For example,

- What are the pivotal and supportive studies?
- Is there a plan to include study data from multiple cutoff dates?
- Is meta-analysis required?
- What studies are included for integrated summary of safety (ISS)?
- Will the study be submitted to other countries (e.g., China extension study)?

In this paper, the submission example includes one pivotal (study A) and one supportive study (study B). These two studies have similar designs, including, but not limited to similar eligibility criteria, same key endpoints (i.e. Overall Survival (OS), Progression-Free Survival (PFS), and Objective Response Rate (ORR)), similar treatment groups, and similar statistical methods with stratified Cox regression, stratified log-rank test for OS and PFS and stratified Miettinen and Nurminen's method for ORR. Therefore, pre-specified meta-analysis is performed on all three endpoints for these two studies. Per pre-specified interim analyses strategy for each study, endpoints may be analyzed from different cutoff dates (the below package names and cutoff dates were made-up for illustration purpose) within each study.

For PFS meta-analysis, Study A's second interim analysis (IA2) and Study B's first interim analysis (IA1) data were combined. However, for OS meta-analysis, Study A's final analysis and Study B's final analysis data were combined. Refer to Table 1 and Table 2 for details.

Study A: (Pivotal)

Analyses	Key Endpoints	Primary Purpose of Analysis
IA1 Cutoff Date: 30Jan2018	ORR, PFS, OS	Descriptive ORR analysis; consistency evaluation with global data.
		OS Interim
IA2 Cutoff Date: 30Jan2020	OS, PFS, ORR	PFS Final ORR Final
FA Cutoff Date: 30Jan2021	OS	OS Final

Table 1: Summary of Interim and Final Analysis for Study A

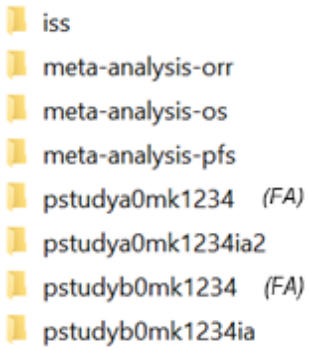
Study B: (Supportive)

Analyses	Key Endpoints	Primary Purpose of Analysis
IA1 Cutoff Date:26Jan2018	ORR, PFS, OS	PFS Final ORR Final OS Interim
IA2 Cutoff Date: 26Jun2018	OS	OS Interim
FA Cutoff Date: 26Jan2019	OS	OS Final

Table 2: Summary of Interim and Final Analysis for Study B

PLAN THE SUBMISSION COMPONENTS

Based on the strategy planning from the prior step, the team identified 8 submission packages that are traceable from source to TLF. This includes: two eSUB packages from each study using two different database locks (IA2 and FA for Study A, IA1 and FA for Study B); three eSUB packages to support each efficacy meta-analysis (ORR, PFS, OS) containing different cutoff dates; and one ISS package. The following folders illustrate the folders containing the analyses.



Module 5.3.5.3 Reports of Analyses of Data from More than One Study	**Module 5.3.5.1 Study Reports of Controlled Clinical Studies**
meta-analysis-os meta-analysis-pfs meta-analysis-orr iss	pstudya0mk1234 *(Study A FA)* pstudya0mk1234ia2 (*Study A IA2*) pstudyb0mk1234 *(Study B FA)* pstudyb0mk1234ia (*Study B IA1)*

Study Package Plan

In table 3 below, Study A (pivotal) FA eSUB package includes all submission components needed for the US filing, whereas Study B (supportive study) eSUB package includes all the same submission components, except for CDER's Bioresearch Monitoring (BIMO) deliverables, which are only required for the pivotal study. The content inside of the package (excluded BIMO package) is outlined in a later part of the paper.

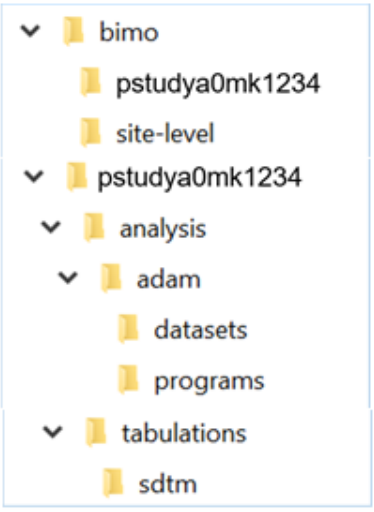
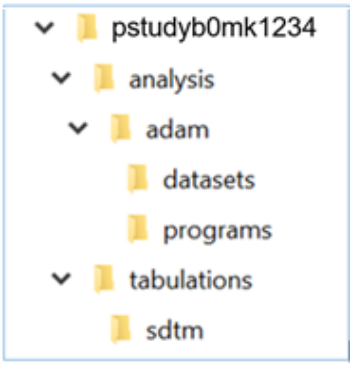
Pivotal FA (Final Analysis)	Supportive FA (Final Analysis)
	

Table 3: Submission package folder for FA

The Analysis Result Metadata (ARM), which identifies the key TLFs in the CSR, programs and input data, is included in the FA package for Study A and Study B. In this example, the ARM was prepared for the FA package only, but it referenced both IA2 and FA outputs. The corresponding data source and programs (.txt format) contained hyperlinks to the IA2 or FA package folder. During the assembly of the eCTD, it is important to perform quality checks to ensure that correct links are attributable to the correct package source for SAS programs and analysis data. Both FA and IA2 define.xml should be provided under Analysis Data Definitions for reference. Below is a sample of ARM:

Analysis Results Metadata

1. Analysis Define and Data Reviewers Guide

Program & Protocol Number	MK 1234 Protocol STUDYA
Protocol Title	A Phase III Randomized Double-blind Study of …….
Analysis Data Definitions	[PSTUDYA0MK1234: adam-define.xml] [PSTUDYA0MK1234IA2: adam-define.xml]
Analysis Data Reviewers Guide	[PSTUDYA0MK1234: adam-adrg.pdf]

The Analysis Results Metadata describes the key results and analysis datasets found in the pstudya0mk1234\analysis\adam and pstudya0mk1234ia2\analysis\adam subfolder. The ADaM datasets are the source data used to support the analysis.

2. Analysis Results Metadata Summary

Table Reference	Table Title	SAS Program Name (programs)	Input File Name
			Analysis (datasets)
[Ref 5.3.5.1: PSTUDYA0MK1234: Table 10-1]	Disposition of Participants (ITT Population)	ds0rand0tgen.txt	adsl.xpt
[Ref 5.3.5.1 PSTUDYA0MK1234: Table 11-2]	Analysis of Overall Survival (ITT Population)	e0or0tte0tot0osgen.txt	adsl.xpt, adtte.xpt
[Ref 5.3.5.1: PSTUDYA0MK1234IA2 Table 11-4]	Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 at IA2 (Primary Censoring Rule) (ITT Population)	e0or0tte0tot0pfsircgen.txt	adsl.xpt, adtte.xpt

Meta-Analysis Plan

Efficacy endpoints are summarized together from study A and B based on pre-specified corresponding cutoff dates in each study, as outlined in Table 4 below. There are three different combinations of cutoff

dates to support the analysis endpoints. Three separate packages were organized into their own meta-analysis folder to provide clear traceability back to the correct data source. These descriptions and the use of the data was included in the Analysis Data Reviewer's Guide (ADRG) of each meta-analysis folder.

	Study A	Study B	Pooled Datasets
OS	FA (30Jan2021)	FA (26Jan2019)	adsl, adtte
PFS	IA2 (30Jan2020)	IA1 (26Jan2018)	adsl, adtte
ORR	IA2 (30Jan2020)	FA (26Jan2019)	adsl, adrs

Table 4: Meta-analysis by endpoint

ISS Plan

ISS setup followed the standard process for pooled safety analysis supporting the indication.

CHECK THE LATEST STANDARDS

As a best practice, teams must reference the latest standards found in Industry Guidance, Study Data Technical Conformance Guides, sponsor's SOPs, and sponsor's training to ensure the eSUB data deliverables are prepared according to the FDA Data Standards Catalog and comply with regulatory requirements. Below listed some resources available on the FDA sites.

Study Data Standards Resources | FDA includes required items and helpful tools for the submission of study data to the FDA's Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH). There are additional links on the site to the following topics:

- *FDA Data Standards Catalog*
- *FDA Guidance*
- *Technical Guides*
- *FDA Business and Validation Rules*

Data Standards Catalog v9.0 (January 25, 2023) at the time of writing describes certain format, standards and terminologies which are required by the FDA for regulatory submission. It includes *the date the requirements begin, and, as needed, the date the requirements end, as well as information sources. The submission of data using standards or terminologies not listed in the Catalog should be discussed with the Agency in advance.*

Study Data Technical Conformance Guide v5.0.(October, 2022) *provides specifications, recommendations, and general considerations on how to submit standardized study data using FDA-supported data standards located in the FDA Data Standards Catalog.* Information on eCTD study data validation rules is included in section 8 and Appendix F.

During the development of multiple clinical data packages, the FDA enforced 4 TRC Validation Rules (1734, 1735, 1736, 1789). These rules require sponsors to provide ts.xpt, dm.xpt, define.xml for SDTM and adsl.xpt and define.xml for ADaM for clinical studies that started after December 17, 2016. In addition, the files must contain the correct study tagging file (STF), otherwise, incomplete or missing deliverables could lead to delays. Rule 1734 and 1736 are more relevant to the programming team responsible for preparing the data package. As part of the planning exercise, the team had to carefully examine the FDA Study Data Technical Conformance Guide and the eCTD modules against which the TRC validations would be applied.

SET UP KICK-OFF MEETING

Suggest using an eSUB planner to help facilitate the kick-off meeting.

eSUB Planner

An eSUB planner was created and maintained to capture the submission details that were defined in the submission strategy. Once the study statisticians agreed to the content, the submission programming lead from each study held a kick-off meeting to align on the deliverables and managed an eSUB planner, a crucial tracker that enabled success for the filing preparation. It served two purposes. First, the team used the eSUB planner as a checklist to describe the details and effort required to prepare the final submission packages. Second, it helped reviewers outside of the study team, who had limited knowledge to the study and decisions, to have a guide that oriented the information and background to the complex package.

The eSUB planner also provides a list of QC tools/macros/checklists required to sign off on the package. Each QC tool checked the expected output and listed all issues from the QC step that required cleaning or documentation to support unresolved rationales. The owner and author for each package were expected to perform their own due diligence and quality confirmations before final reviews initiated. A snapshot example of the required components for a study planner is listed below for reference. The eSUB planner allows stakeholders to add comments, clarify requirements and align on expectations.

Description	Package # 1 IA	Package # 2 FA	Package # 3 ISS
SDTM Version	SDTM32	SDTM32	N/A
COVID Related TFL/ Setup (e.g., ADPDEV2)	No	Yes	No
Labeling Requirement Available (e.g.: KM Plot), part of RTOR package	No	Yes	N/A
SDSP	Yes	Yes	Yes
RTOR Required?	Yes	Yes	N/A
ADaM Package in Scope?	Yes, partial (ADSL, ADRS, ADINTDT, ADTTE, Define, .XPT, GEN.SAS for efficacy outputs) Need to confirm which efficacy tables to include, and which ones are for RTOR.	Yes (Define, ADRG, ARM, .XPT, GEN.SAS)	Yes (Define, ADRG, .XPT, GEN.SAS)
ARM (Analysis Result Metadata) in Scope? References to multiple folders (e.g., different locks)?	No	Yes (Including both IA and FA)	No

Kick-off Meeting

The programming manager and anyone who contributes to the submission package should be invited to the kick-off meeting and understand the submission strategy, required components/resources, and expected milestones to avoid delays to the downstream process. Study-specific items such as protocol deviations, PK/PD and COVID related reports should be noted upfront if they need input or support from clinical or other functional groups. The eSUB planner contains all the submission details, timeline expectations, as well as roles and responsibilities.

GENERATE AND VALIDATE THE SUBMISSION PACKAGES

Types of Validation Rules

There are three sets of validation rules to support regulatory review of study data:

- eCTD Validation Criteria
- FDA Business Rules
- Validator Rules

According to eCTD Submission Standards for eCTD v3.2.2 and Regional M1 | FDA, current validation tools and electronic submission validation criteria in use are depicted below:

Tool Name	Standards Being Validated	Validation Criteria
Lorenz eValidator	eCTD	Specifications for eCTD Validation Criteria
Pinnacle 21 Enterprise	SDTM, SEND, ADaM, ASCII, Define, XML	FDA Business Rules and FDA Validator Rules

Packages for Main Pivotal Study

Pinnacle 21 Enterprise version was used to validate ADaM and SDTM compliance and to generate the define.xml for ADaM and SDTM packages.

A complete eSUB package for the pivotal FA folder contains: ADaM, SDTM and BIMO packages. BIMO package was not created for the FA supportive study.

ADaM package includes:

- ADaM datasets (.xpt)
- Define.xml and style sheet
- Analysis data reviewer's guide (pdf)
- Analysis results metadata (pdf) ← CSR key analysis from FA and IA2
- Programs (.txt format, including ADaM creation programs and TLF programs documented in the ARM)
- Supplemental documents which added supporting information

SDTM package includes:

- SDTM datasets (.xpt)
- Define.xml and style sheet
- Clinical study data reviewer's guide (pdf)
- Annotated case report form (pdf)

Any unresolved data issues identified from the Pinnacle 21 issue report are documented in the ADRG and cSDRG Data Conformance section and they provide context to the issues.

In addition, programming teams execute Pinnacle 21 tool to generate and validate the define.xml to identify any metadata discrepancies. The define.xml provides dataset and variable metadata, origin and derivation algorithms.

Special Solution for Combining Multiple Locks

Table 1 and Table 2, shown above, depict two studies' statistical design and the desire to include key OS, PFS and ORR endpoints from both studies. Study teams created 4 packages from two studies with two different interim and final analysis database locks. To avoid redundancy in explaining the same study data design between interim analysis and final analysis, a single ARM, ADRG and cSDRG was created and stored in the final analysis folder (pstudya0mk1234; pstudyb0mk1234).

For the interim analysis folder, the team included the define.xml and ADaM datasets used to generate the PFS and ORR results. Since the SDTM Trial Summary (ts.xpt) date cutoff was different between the interim analysis and final analysis, a minimal SDTM package (ts.xpt, dm.xpt, suppdm.xpt, define.xml) was created to avoid any TRC error.

ADaM package includes:

- ADaM datasets (.xpt)
- Define.xml and style sheet
- Programs (.txt format, including ADaM creation programs and TLF programs documented in the Main CSR ARM)

SDTM package includes:

- SDTM datasets (.xpt) ← ts.xpt, dm.xpt and suppdm.xpt
- Define.xml and style sheet
- Annotated case report form (pdf)

TRC Validations

When the clinical study deliverables were developed for each interim and final analysis, the tabulations SDTM folder minimally contained: ts.xpt, define.xml, dm.xpt and suppdm.xpt supporting Module 5.3. As expected, the presence of these datasets and define files did not trigger any TRC errors during a simulation exercise which involved executing the same validation rules when data is received through the FDA electronic submission gateway (ESG).

Meta-Analysis Solution

Meta-analysis is more complicated than analysis on a single study. Meta-analysis requires attention to combine ADaM data from different studies to present combined efficacy endpoints. In the example provided in this paper, both the pivotal study and supportive study have similar ADaM structures, which is convenient to set two studies' ADaM together.

In the meta-analysis submission folder, we only include ADaM packages. No SDTM package is required for meta-analysis since this is not a study-level deliverable.

ADaM package includes:

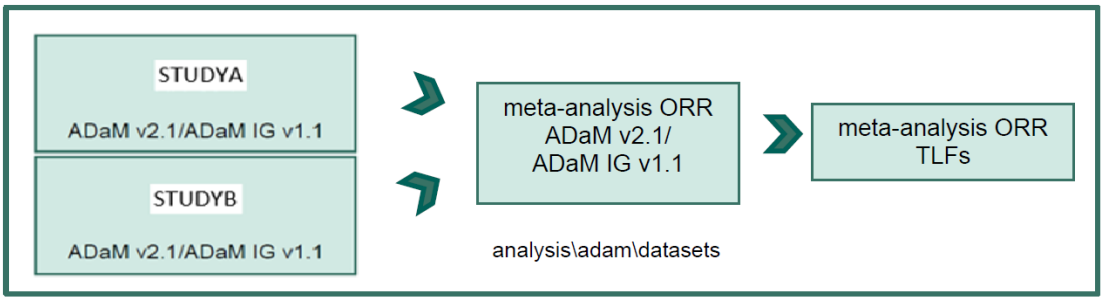
- ADaM datasets (.xpt) ← ADSL and efficacy datasets
- Define.xml and stylesheet
- Analysis data reviewer's guide (pdf)
- Programs (.txt format, including ADaM creation programs and TLF programs)

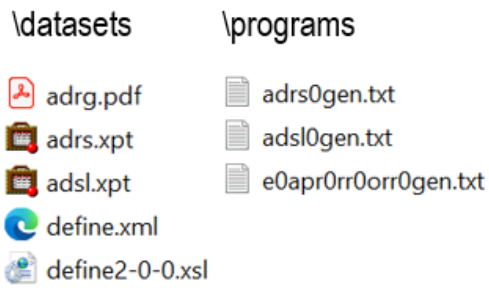
Below is an example of data flow map from ADRG of the meta-analysis for the ORR endpoint. It clearly indicates the cutoff date from STUDYA and STUDYB and it matches to the information provided in the eSUB planner. There is no separate analysis result metadata since only a handful of datasets and analysis tables are included. The analysis outputs are detailed in the ADRG Section 7.

1.4 Source Data Used for Analysis Dataset Creation

The ADaM datasets for meta-analysis ORR were pooled from STUDYA ADaM datasets with a cutoff date of 30JAN2020 and STUDYB with a cutoff date of 26JAN2019.

Data Flow Approach





REVIEW THE FINAL PACKAGES BEFORE SUBMISSION

This section focuses on the overall review process used to review the 8 eSUB packages. Due to the complexity introduced in this example, the team involved:

- **Individual study eSUB programming lead** who has responsibilities for the study level deliverables
- **Indication submission lead** who has responsibilities to check that all components in each package are provided according to the eSUB planner and standards and to verify consistency across 8 authored documents.
- **Consultant from eSUB standards team** who has responsibilities to review and provide feedback based on the latest industry standards and to ensure compliance is not violated.

Reviewer's guides must be written to clearly describe the data source, data flow, datasets, cutoff date, and purpose. Consistencies such as data citations, dictionary version, protocol text and expected external references in the define.xml should be reviewed. Reviewer will also check if all QC outputs are free of error, read and cross-check all the reviewer's guides and provide feedback if they need additional clarifications. The PARAM/PARAMCD listed in ADRG will be checked against the actual ADaM datasets. It is important to check each document header for consistency to link back to the correct submission folder.

CONCLUSION

It is critical to plan submission activities early, especially if multiple packages are involved in one submission. Close collaboration is required to ensure the success of the deliverables to support regulatory submission. It is important to work proactively with the study statistician, indication lead or programming manager to gain support to collect the required submission details. Having an official kick-

off meeting prior to the implementation helps all stakeholders understand their responsibilities and expected timeline for each package and deliverable. An eSUB planner helps to identify all submission components, standards and their details in a central document. This eSUB planner helps minimize email exchanges, tracks team discussions and decisions, which leads to an organized document authoring and review of the packages. It's important to schedule the eSUB planning meeting well in advance of the database lock date, typically around 2 months prior, to ensure that most if not all details are finalized in time. A lessons learned session is recommended after a complex submission effort to identify area of improvements and challenges to increase efficiency in future submissions.

REFERENCES

Study Data Standards Resource:
Study Data Standards Resources | FDA
Data Standards Catalog
Data Standards Catalog v9.0
Study Data Technical Conformance Guide:
https://www.fda.gov/media/153632/download
eCTD:
Electronic Common Technical Document (eCTD) | FDA
Specifications for eCTD validation criteria:
https://www.fda.gov/media/87056/download
eCTD Submission Standards for eCTD:
eCTD Submission Standards for eCTD v3.2.2 and Regional M1 | FDA
eSUB Gateway:
Electronic Submissions Gateway | FDA

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