

Plan for Success: Strategies for Efficient Development of a High Quality Study Data Reviewer's Guide

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- History
- Content review
- Proactive development
- FDA thoughts
- Rebuttal to recent presentation @ CDISC Interchange
- Future consideration: Legacy Data Conversion Plan & Report

Study Data Reviewer's Guide

PharmaSUG Development Corp
Study DLN2016-12-18

Study DLN2016-12-18

Study Data Reviewer's Guide

4. Data Conformance Summary

4.1 Conformance Inputs

Was OpenCDISC used to evaluate conformance?

If yes, specify the versions of OpenCDISC and the OpenCDISC validation rules:
(Text here)

Were sponsor-defined validation rules used to evaluate conformance?

If yes, describe any significant sponsor-defined validation rules:
(Text here)

Were the SDTM datasets evaluated in relation to defnc.xml?

Was defnc.xml evaluated?

Provide any additional compliance evaluation information:
(Text here)

4.2 Issues Summary

Dataset	Diagnostic Message	Severity	Count	Explanation

Page 7 of 10

Inspiration for Study Data Reviewer's Guide

- In 2011 FDA engaged in an effort to perform a legacy data conversion on 300 +/- studies
- Motivation – Cross product analysis with focus on safety signals
- Pain point – Had agreed on a target, but had trouble documenting study level migration strategy & decisions
- Solution – a Study Data Reviewer's Guide!

FDA / PhUSE Development

- Initiated in 2012
- 1st version published in 2013
- Subsequently updated twice in 2014
- Soon to be revised again...

Related Products

- ADRG – Analysis Data Reviewer's Guide
- nSDRG – Non-clinical Study Data Reviewer's Guide

Study Data Reviewer's Guide

Study Metadata	
Trial Design Deployment	
Details of Domain Usage	
Standards Conformance	
Inclusion/Exclusion Details	

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1.2 Acronyms

Acronym	Translation

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	
Controlled Terminology	
Data Definitions	
Medications Dictionary	
Medical Events Dictionary	
Other standards (optional)	

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number:

Protocol Title:

Protocol Versions:

(Note here changes in protocol amendments that affected data collection or interpretation)

2.2 Protocol Design

(Graphic or text here, or delete this section)

Observations

- Most everything on this page could be taken from the Protocol or Statistical Analysis Plan (SAP)... if it were included in one of those documents... hint hint...
- Pay close attention to expectations for study standards and dictionary usage based on Data Standards Catalog
- Only this part of this section requires you to consider content once the study is (near) complete

2.3 Trial Design Datasets

~~Are Trial Design datasets included in the submission?~~

~~(If no, delete the remainder of this section. If yes, refer to SDRG Completion Guidelines Section 2.3 and provide additional information below.)~~

The only correct answer at this point is “yes”!

2.3.1 TA – Trial Arms

(Text here)

2.3.2 TE – Trial Elements

(Text here)

2.3.3 TV – Trial Visits

(Text here)

2.3.4 TI – Trial Inclusion/Exclusion Criteria

(If criteria are not fully described in TI, complete [Appendix I: Inclusion/Exclusion Criteria](#) or hyperlink to the pages in blankcrf.pdf that contain the full criteria text. Delete these instructions.)

2.3.5 TS – Trial Summary

(Text here)

Observations

- Note: this section immediately follows a description of the study design in the document...
- I have frequently seen links out to all of the SAS transport files plus preserving the link to Appendix I.
- IMPORTANT: your CDMS must be able to track which version of a protocol a subject was enrolled under
- What’s missing? (hint: TD)

3.1 Overview

Are the submitted data taken from an ongoing study?

If yes, describe the data cut or database status:

(Text here)

Were the SDTM datasets used as sources for the analysis datasets?

If no, what were the sources of analysis datasets?

(Text here)

Do the submission datasets include screen failures?

If yes, which datasets include screen failure data?

(Text here)

Were any domains planned, but not submitted because no data were collected?

If yes, list domains not submitted:

(Text here)

Are the submitted data a subset of collected data?

If yes, describe the reason that all collected data were not provided:

(Text here)

Additional Content of Interest

(See SDRG Completion Guidelines for additional content of interest, and include text here).

Observations

- This is where you place answers to questions the balance of the submission data package cannot
- The information provided in this section is typically uniquely defined and presented here for the first time

3.3 SDTM Subject Domains

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
AE – Adverse Events		X				Events
DM – Demographics			X			Special Purpose
DS – Disposition			X			Events
EX – Exposure			X			Interventions

3.3.1 AE – Adverse Events

(Text and/or supplemental qualifier inventory here)

3.3.2 DS – Disposition

(Text and/or supplemental qualifier inventory here)

3.3.3 EX – Exposure

(Text and/or supplemental qualifier inventory here)

3.3.4 Dataset – Dataset Label

(Text here)

QNAM	Description

Observations

- Each entry in the top table should link out to the define.xml location for the table, from there they can open the transport file
- IMPORTANT: This is where you get to add all the explanation needed by a reviewer for domains that are not that obvious
 - Custom domains
 - Domains that have a flexible structure to hold various types of data

Efficiency Steps – Data Conformance Summary

4. Data Conformance Summary

4.1 Conformance Inputs

Pinnacle21

~~Was OpenCDISC used to evaluate conformance?~~

~~If yes, specify the versions of OpenCDISC and the OpenCDISC validation rules:~~

~~(Text here)~~

~~Were sponsor-defined validation rules used to evaluate conformance?~~

~~If yes, describe any significant sponsor-defined validation rules:~~

~~(Text here)~~

Were the SDTM datasets evaluated in relation to define.xml?

Was define.xml evaluated?

Provide any additional compliance evaluation information:

(Text here)

Best Practice:

**Validate define.xml
& SDTM domains at
the same time...**

4.2 Issues Summary

Dataset	Diagnostic Message	Severity	Count	Explanation

Observations

- If define.xml is not correct / not functional it will bring your review to a halt until fixed
- FDA is looking for high quality, clear comments and rationalizations for the presence of errors and warnings in this section
 - ~~“Company Convention”~~
 - ~~“That was the data”~~
 - ~~“Can’t determine how data should be formatted”~~

Appendix I: Inclusion/Exclusion Criteria

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion

Goals of Section

- Opportunity to present full set of inclusion/exclusion criteria values
 - Full text of criteria
 - Paired with IETESTCD information
 - Broken down by protocol / amendment version
- Viewed by agency as the primary source of this data, used as the starting point to go back towards the protocol and forward into the data to validate

Highlights from Helena Sviglin's presentation at CDISC International Interchange 2016

- A Reviewer's Guide is...
 - Human readable
 - Essential to the review
 - Offers explanations not available elsewhere
- A Reviewer's Guide is not...
 - Define+
 - An expanded validation report
 - Meant to be machine readable
- Make the Reviewer's Guide even better / more useful
 - Don't delete sections, just mark them as "not used"
 - Provide meaningful, clear explanations for nonconformance / errors
- FDA developing criteria to evaluate Reviewer Guide quality
 - Response to increase in vague / incomplete explanations for validation errors
 - Could become metric to reject study data / halt review timeline in future

FDA Technical Conformance Guide

(July 2016)

8.2.2 Support on Data Validation Rules

The Standards Web page provides links to the currently available validation rules, i.e. **both conformance rules and quality checks**.

Sponsors should **validate their study data before submission using the most recently published validation rules** and either correct any validation errors or explain in the Reviewer's Guide (SDRG or ADRG) why certain validation errors could not be corrected. The recommended pre-submission validation step is intended to minimize the presence of validation errors at the time of submission.

FDA Technical Conformance Guide

(July 2016)

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Why?!?

- Clinical and non-clinical data should not be a moving target
 - Errors/warning and their rationales should be developed at the time the set of SEND/SDTM & ADaM data are finalized
 - Revisiting quality & conformance @ time of submission could result in inconsistencies between error reporting and actual results
 - Puts submission data package development & publishing on the critical path

Update Coming Soon: Legacy Data Conversion Plan & Report



- From the Study Data Technical Conformance Guide, v3.1
 - “During the transition period to required study data standards, FDA recognizes that some study data (i.e., legacy data) submissions may not conform to FDA-supported study data standards and may need to be converted.”
[\[Section 8.3.1, 3rd paragraph\]](#)
 - “Sponsors should use processes for legacy data conversion that account for traceability.... there should be an explanation in the SDRG as to why certain data elements could not be fully standardized or were otherwise not included in the standardized data submission.”
[\[Section 8.3.2, 1st paragraph\]](#)
 - “Sponsors should evaluate the decision involved in converting previously collected non-standardized data (i.e., legacy study data) to standardized data (i.e., SDTM, SEND, and ADaM). Sponsors should provide the explanation and rationale for the study data conversion in the SDRG.”
[Section 8.3.2.2, 1st paragraph](#)

Nonclinical & Clinical	Legacy Data	Study data that does not conform to the standards by the date of requirement specified in the published Data Standards Catalog ² .
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Update Coming Soon: Legacy Data Conversion Plan & Report



- “To mitigate traceability issues when converting legacy data, FDA recommends the following procedures:
 1. Prepare and Submit a Legacy Data Conversion Plan and Report
 - The plan should describe the legacy data and the process intended for the conversion.
 - The report should present the results of the conversions, issues encountered and resolved, and outstanding issues.
 - The plan and report should be provided in the SDRG.
 2. Provide an aCRF, for clinical data, that maps the legacy data elements.
 - Sponsors should provide two separate CRF annotations, one based on the original legacy data, and the other based on the converted data (i.e., SDTM) when legacy datasets are submitted. The legacy CRF tabulation data should include all versions and all forms used in the study.
 3. Record significant data issues, clarifications, explanations of traceability, and adjudications in the SDRG. For example, data were not collected or were collected using different/incompatible terminologies, or were collected but will not fit into, for example, SDTM format.
 4. Legacy data (i.e., legacy aCRF, legacy tabulation data, and legacy analysis data) may be needed in addition to the converted data.”

[\[Study Data Technical Conformance Guide, v3.1, Section 8.3.2.2 less 1st 2 sentences\]](#)

Update Coming Soon: Legacy Data Conversion Plan & Report

5. Legacy Data Conversion Plan & Report

5.1 Purpose

Data for this study was converted from a non-standardized format to SDTM.

<Insert Data Flow Diagram here>

5.2 Legacy Data Summary

Describe the conversion approach used for each study:

Study Number	Conversion method
ABC-123	Legacy to SDTM only
ABC-456	Legacy to SDTM and ADaM independent / parallel
ABC-789	Legacy to SDTM then ADaM in sequence

5.3 Converted Data Summary

For each study and legacy data conversion method summarize the issues observed relative to conversion.

Legacy to SDTM only

When legacy study data are converted to SDTM and submitted with legacy analysis and/or source datasets used to create the SDTM and legacy analysis

- Was the CRF re-annotated to support the SDTM conversion?
- What was the impact of the SDTM conversion on the traceability to the legacy analysis data?
 - o No impact because can trace SDTM variables to legacy analysis data
 - o Some impact because SDTM variables cannot be traced to legacy analysis data
 - o Some impact because legacy analysis variables cannot be traced to SDTM
- Can the legacy analysis data be confirmed by the SDTM data?
 - o Are there key efficacy safety and/or efficacy domains that have complex mappings from the source data to SDTM?
 - o Are there key differences between values in the legacy analysis datasets versus the SDTM datasets (i.e. RACE has 10 values in legacy analysis datasets and SDTM has 6)
- Were the derivations or imputations needed for analysis fully confirmed with SDTM as the source?
 - o If custom domains or intermediate analysis datasets were needed describe the impact

Legacy to SDTM and ADaM Independent / Parallel

When legacy study data and legacy analysis data are independently converted to SDTM and ADaM formats, respectively, rather than ADaM datasets being created directly from the SDTM datasets (converted from legacy study data).

- Was the CRF re-annotated to support the SDTM conversion?
- What was the impact of the SDTM conversion on the traceability to the legacy analysis data as well as ADaM?
- Can the legacy analysis data be confirmed by the SDTM data?
- Were the derivations or imputations needed for analysis fully confirmed with SDTM as the source?
 - o If custom domains or intermediate analysis datasets were needed describe the impact
- What were the issues relating to the ability to confirm the Tables, Figures and Clinical Study Report as originally created?

Legacy Data to SDTM and ADaM in sequence

When legacy data are converted to SDTM and ADaM formats in sequence (i.e., converting legacy study data to SDTM and then creating ADaM from the SDTM).

- Was the CRF re-annotated to support the SDTM conversion?
- What was the impact of the SDTM conversion on the traceability to the legacy analysis data as well as ADaM?
- Can the legacy analysis data be confirmed by the SDTM data?
- Were the derivations or imputations needed for analysis fully confirmed with SDTM as the source?
 - o If custom domains or intermediate analysis datasets were needed describe the impact
- What were the issues relating to the ability to confirm the Tables, Figures and Clinical Study Report as originally created?

1.2 Conversion Results / Summary

Record significant data issues, clarifications, explanations of traceability, and adjudications in the SDRG. For example, data were not collected or were collected using different/incompatible terminologies, or were collected but will not fit into, for example, SDTM format.

Takeaways

- Features of LDCP
 - Starting point
 - Motivation for conversion
 - Relationship of converted data to other sets of data
 - Challenges encountered
 - Results
- Graphics / visuals well received
- New information only!

Final Words: End-to-End -- A True Transition



From Steve Wilson's
presentation at 2016 CDISC
International Interchange


- At the following location on the PhUSE web site...
http://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer%27s_Guide
- ...you will find a number of resources and tools to support SDRG development


Study Data Reviewer's Guide

Study Data Reviewer's Guide Final Work Package

Version	Release Date	Downloadable Work Package	Changes from Previous Version
Clinical Study Data Reviewer's Guide			
v1.2	26-Jan-2015	SDRG Package v1.2 2015-01-26	<ul style="list-style-type: none"> • Removed Trial Design Dataset navigation table from Section 2.3 • Improved SDRG Template usability • Minor revisions to instructions in SDRG Completion Guidelines • SDRG Examples updated to match revised SDRG Template
v1.1	03-May-2013	SDRG Package v1.1 2013-05-13	Initial Version
Nonclinical Study Data Reviewer's Guide			
v1.0	03-Mar-2016	Nonclinical SDRG Package v1.0 2016-03-03	v1.0 for Federal Register Notice Docket No. FDA-2016-N-0701 -Public Review

Applicable Federal Register Notices:

FR Notice 2015-18027  **applies to the Clinical SDRG only.** The public review period on this notice has ended.

FR Notice 2016-04791  **applies to the Nonclinical SDRG only** The public review period on this notice **opens 4 March 2016**. Click on the FR Notice link to find out how to comment.



Questions? Thank you!

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