Study Data Reviewer's Guide Completion Guidelines

Version 1.2

Revision History

Version	Date	Summary
0.9	2013-02-22	Draft for public comment
1.0	2013-03-18	Updated based on public comments
1.1	2013-05-13	Changed blue headers in template and sample documents to black to conform to FDA's PDF specifications. No changes were made to this Completion Guidelines document.
1.2	2015-01-26	Changed header formats and dropped the TDM dataset navigation table in the template, updated instructions in this Completion Guidelines document, and updated the sample SDRG documents to reflect the changes to the template.

Contents

Study Data Reviewer's Guide Completion Guidelines Overview

1. Study Data Reviewer's Guide Purpose

The Study Data Reviewer's Guide (SDRG) provides FDA Reviewers with additional context for SDTM datasets received as part of a regulatory submission. The SDRG is intended to describe SDTM data submitted for an individual study in the Module 5 clinical section of the eCTD. The SDRG purposefully duplicates information found in other submission documentation (e.g. the protocol, clinical study report, define.xml, etc.) in order to provide FDA Reviewers with a single point of orientation to the SDTM datasets.

2. SDRG Overview

The SDRG has four main sections and two optional appendices - Introduction, Protocol Description, Subject Data Descriptions, Data Conformance Summary, Appendix I: Inclusion/Exclusion Criteria, and Appendix II: Conformance Issues Details. The Introduction provides an overview and inventory of standards used on the study. The Protocol Description provides a brief orientation to the study and, if necessary, provides additional context about the Trial Design Datasets. The Subject Data Descriptions section provides additional context for subject-level SDTM domains that are not adequately documented in define.xml or the SDTM Implementation Guide and its supplements. Additionally, the Subject Data Descriptions section describes sponsor-specific annotated CRF conventions as needed. The Data Conformance Summary documents the validation inputs used to evaluate SDTM conformance and summarizes conformance findings.

If the inclusion/exclusion criteria cannot be fully documented in the Trial Inclusion/Exclusion Criteria (TI) dataset due to SAS v5 limitations, the criteria can either be provided in Appendix I, or as a hyperlink to the full criteria in an annotated CRF. All significant conformance findings should be documented in the Data Conformance Summary; however, a detailed record-level description of conformance issues may be included in Appendix II. Sponsors are strongly discouraged from including Appendix II due to its limited usefulness for FDA Reviewers.

3. SDRG Completion Guidelines Purpose

The purpose of this document is to provide sponsors with a clear, concise set of instructions that facilitates the consistent development of the SDRG from the Study Data Reviewer's Guide Template. In addition to the SDRG Completion Guideline, SDRG examples are available as an additional reference.

4. Organization of This Document

This document has three sections: a Guidelines overview, SDRG Template Completion Instructions, and SDRG Finalization Instructions. The section number in the SDRG Template Completion Instructions corresponds directly to the SDRG Template. Section headings in *italics* do not contain any content and serve to organize the SDRG. These have been included in the instructions for completeness. The SDRG Finalization Instructions describe how to create the document for submission after completing the SDRG Template.

Study Data Reviewer's Guide Template Completion Instructions

This section provides companion instructions for the SDRG Template. The section numbering corresponds directly to the SDRG Template. Section headings in *italics* (e.g., *1. Introduction*) do not contain any content and are included for completeness. **Note: Certain SDRG Sections include a series of questions intended to aid FDA Reviewers. Provide complete answers to all questions. Do not delete the primary questions from the final document. Sub-questions may be removed at the discretion of the sponsor.**

1. Introduction

1.1. Purpose

This required section states the purpose of the SDRG. The SDRG Template includes standard text.

1.2. Acronyms

This optional section documents any sponsor-specific or non-industry standard acronyms used in the SDRG. Standard industry acronyms (e.g. MedDRA, LOINC, CDISC, SDTM, ADaM, etc.) do not need to be documented.

1.3. Study Data Standards and Dictionary Inventory

This required section documents the SDTM version(s), controlled terminology version(s), and dictionary version(s) used in the study. Conformance inputs and version(s) are documented in Section 4.

Example:

	Version
SDTM	SDTM v1.2/SDTM IG v3.1.2 including Amendment 1. Oncology Domains, TU, TR, and RS, have been submitted according to the version released for public comment dated 30-Jan-2011
Controlled Terminology	CDISC Controlled Terminology dated 22-Jul-2011 has been used for all domains except for LB. LBTESTCD and LBTEST use terminology from the 29-Jun-2012 CDISC Controlled Terminology package.
Data Definitions	define.xml v1.0
Medications Dictionary	WHODrug December 2012
Medical Events Dictionary	MedDRA v14.1

End of Example

2. Protocol Description

2.1. Protocol Number and Title

This required section provides the protocol number or identifier, title, and versions included in the submission. For protocol amendments, note changes that affected data collection or interpretation, if any.

2.2. Protocol Design

This optional section provides a visual representation or brief textual description of the protocol design. This can be taken directly from the protocol or developed specifically for the SDRG. If this section is removed, correct the numbering for the Trial Design datasets in the next section.

2.3. Trial Design Datasets

This required section provides additional context for the Trial Design datasets. Additional context may not be required for simple protocol designs that are adequately documented in define.xml or self-evident in the Trial Design Dataset content.

The following question must be answered:

- Are Trial Design datasets included in the submission?

If Trial Design datasets are not included, or if no additional explanations are called for, the rest of section 2.3 should be deleted.

Additional content may include, but is not limited to the following:

- If Trial Design Datasets were submitted, list the dataset name and dataset label only for datasets that benefit from additional explanation.
- Description of the modeling of Trial Arms, Trial Elements, and Trial Visits.
- If inclusion/exclusion criteria are not fully described in TI, complete Appendix I: Inclusion/Exclusion Criteria, or create a hyperlink to the pages in blankcrf.pdf that contain the full criteria text. (See Finalization Instructions at the end of this document for detailed instructions. Also note that an example hyperlink has been provided in the template from heading 2.3.4 TI – Trial Inclusion/Exclusion Criteria to Appendix I for inclusion/exclusion criteria not fully described in the TI dataset.)
- Method for identifying cross-over or open-label extension periods.
- Explanation of sponsor-defined Trial Summary parameters.

Note that the **dataset section headers are not automatically numbered** in the Trial Design Datasets section, so **check and correct the numbering** when you use this section. Be aware that if the optional Section 2.2 above is left out, the Trial Design Datasets section is renumbered to 2.2, and the dataset description headings should reflect that.

Example:

2.3.1 TA – Trial Arms

The primary analysis compares Drug A to Drug B; however, as depicted in Section 2.2, subjects may receive one of three different therapies after a response evaluation at Week 24. ARMCD uses the convention randomized treatment underscore post-Week 24 treatment (e.g. A_A, A_D, A_X, B_A, B_D, or B_X).

End of Example

3. Subject Data Description

3.1. Overview

This required section provides a summary orientation to the datasets containing subject data.

Answers to the following questions must be provided:

- Are the submitted data taken from an ongoing study?
- Were the SDTM datasets used as sources for the analysis datasets?
- Do the submission datasets include screen failures?
- Were any domains planned, but not submitted because no data were collected?
- Are the submitted data a subset of collected data?

Additional content may include, but is not limited to the following:

- Description of any study history or timing relevant to the submitted data (e.g. interim data cutoff, data differences due to protocol amendments, etc.).
- Location of key safety, efficacy, or other data of special interest.
- Explanation of the mapping of death information in the subject level datasets. Explain any differences in the occurrences (frequencies) of death across the datasets.
- Document the location of adjudication data and the method used to differentiate these data from data collected at the investigational site.
- Document any notable subjects of interest within the context of the study.
- Description of the reference start date including any differences in the definition across subjects and description of the calculation of study days. These should align with the definitions in define.xml.
- If you are documenting an extension study, include description(s) of any data that have been copied from or are located in another study in the submission.

3.2. Annotated CRFs

This optional section describes the sponsor-specific annotated CRF conventions. Content may include but is not limited to the following:

- Organization of bookmarks if different from what is specified in the SDTM Metadata Submission Guidelines v1.0, section 4.2 (by time points and CRF topics).
- Explanation of content organization when blankcrf.pdf includes multiple sources (e.g. primary CRF, secondary forms for PRO, format of central laboratory data, etc.).
- Description of the representation for amended or updated CRF (e.g. does blankcrf.pdf include all versions of amended CRFs or only the last version?).
- Description of notable annotation conventions.
- Explanation of data that were not submitted.

3.3. SDTM Subject Domains

This required section provides an overview of the subject-related SDTM domains. Provide hyperlinks to domains that merit additional explanation within the context of the study.

- List all subject-related datasets included in the submission alphabetically by domain code.
  - Include a separate row for each split dataset and describe the method for splitting in the domain-specific section.
  - Include a row for each Findings About (FA or FA--) dataset.
  - Do not include a row for RELREC, as related records are indicated in a column and described in the associated domain-specific section.
  - Do not list SUPP-- datasets. The presence of a SUPP-- dataset is indicated in a column.
  - Do not list Trial Design datasets. Do include SE and SV.
  - Provide a hyperlink from the Dataset – Dataset Label cell to the domain description below for any domain that requires additional explanation within the context of the study. Do not provide a hyperlink or domain description section for standard datasets that do not have supplemental qualifiers and do not need additional explanation.
- Specify the functional category or categories for each domain.
  - Include categories of Efficacy, Safety, and Other.
  - Additional categories may be defined at the discretion of the sponsor.
- Indicate if a Supplemental Qualifiers dataset is submitted for the domain.
  - Include a Supplemental Qualifiers inventory table in the domain-specific section.
- If relationships between the domain and other domains have been described in RELREC, specify the related domains.
  - Explain a domain's key relationships to other domains in the domain-specific section. Provide the explanation of the relationship within the context of a one of the related domains. Do not create a separate section for RELREC.
- Specify the SDTM Observation Class.

Example:

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP--	Related Using RELREC	Observation Class
AE - Adverse Events		X		X	CM, DS	Events
CE - Clinical Events	X					Events
CM - Concomitant Medications	X	X		X	AE, FA	Interventions
CO - Comments			X			Special Purpose
DM - Demographics			X	X		Special Purpose
DS - Disposition			X		AE	Events
EX - Exposure			X	X		Interventions
FA - Findings About	X	X			CM, MH	Findings
LB - Laboratory Test Results	X	X				Findings
LB1 - Hematology		X				Findings
LB2 - Chemistry		X				Findings
LB3 - Biomarkers	X					Findings
MH - Medical History				X	FA	Events
. . .						
SE - Subject Elements			X			Special Purpose
SV - Subject Visits			X			Special Purpose
. . .						

End of Example

3.3.x Dataset – Dataset Label

Provide explanation beyond that which is documented in define.xml or the SDTM Implementation Guide and its supplements. This section is required for datasets for which hyperlinks have been provided in the Section 3.3 table. Provide a section number for each dataset requiring additional explanation (e.g. 3.3.1, 3.3.2, 3.3.3, etc.). This section describes the subject-related SDTM domains that benefit from additional description. **Note: to easily add another dataset, copy and paste an existing dataset heading and text prompt. The headings in this section are NOT automatically numbered, so be sure to verify and correct the numbering for the dataset descriptions.** Be aware that if the optional

Section 2.2 above is left out, the SDTM Subject Domains section is renumbered to 3.2, and the dataset description headings should reflect that.

Content should include the following, where applicable:

- Description of custom domains or organization of content (e.g. Findings About [FA]) for which the content is very specific to the study. **All custom domains must have a description.**
- A table of all Supplemental Qualifiers for a given domain.
- Descriptions of relationships to other domains that are documented in RELREC.
- Description of criteria used to split datasets and the content of the split datasets.
- Descriptions of derivations that may benefit from additional detail beyond that included in define.xml.

Content may also include, but is not limited to the following:

- Description of notable, sponsor-defined uses of category and sub-category.
- Description of notable sponsor extensions to CDISC Controlled Terminology.
- Descriptions of notable mapping of legacy sponsor terminology to CDISC Controlled Terminology.
- General validation issues resulting from data collection (e.g., missing start date for prior medications due to start date not being collected).
- Description of the representation of disposition information in the Disposition (DS) domain especially for submissions where the study is ongoing.
- Description of the representation of collected treatment administration data in the Exposure (EX) domain (e.g., describe what data were collected and what data were derived).
- If all protocol-specified medications (e.g. "companion" or "background" medications) are not in then Exposure (EX) domain, document the domain(s) that contain these medications and how to identify them.

Example:

3.3.1 AE – Adverse Events

A relationship has been defined in RELREC between the disposition event and the primary adverse event leading to discontinuation. The observations are related by AEGRPID and DSGRPID. A relationship has also been defined between the adverse events and concomitant medications used to treat the AE. The observations are related by AEGRPID and CMGRPID. The MedDRA coding hierarchy is located in SUPPAE.

QNAM	Description
AELLT	MedDRA Lowest Level Term
AELLTCD	MedDRA Lowest Level Term Code
AEPTCD	MedDRA Preferred Term Code
AEHLT	MedDRA High Level Term
AEHLTCD	MedDRA High Level Term Code
AEHLGT	MedDRA High Level Group Term
AEHGLTCD	MedDRA High Level Group Term Code

End of Example

4. Data Conformance Summary

4.1. Conformance Inputs

This required section describes the validation checks and inputs used to evaluate conformance.

Answers to the following questions must be provided:

- Was OpenCDISC used to evaluate conformance?
    - If yes, specify the versions of OpenCDISC and the OpenCDISC validation rules (for example, OpenCDISC 1.3, SDTM 3.1.2 Amendment 1).
    - If software other than OpenCDISC was used to assess compliance, describe under "Provide any additional compliance evaluation information."
- Were sponsor-defined validation rules used to evaluate conformance?
- Were the SDTM datasets evaluated in relation to define.xml?
- Was define.xml evaluated?
- Provide any additional compliance evaluation information.

4.2. Issues Summary

This required section summarizes findings from OpenCDISC validation rules and/or corresponding sponsor-defined validation rules.

- Insert findings from an SDTM conformance report (e.g., the OpenCDISC report's Issues Summary tab or similar) into the table provided.

- Annotate issues with a brief, non-technical explanation of the findings.
- Do not include skipped validation checks or validation checks for which datasets do not exist.
- If you are using an SDTM conformance checker *other than* OpenCDISC, report only the diagnostic messages for validation rules that overlap with the OpenCDISC rules.
- If your conformance diagnostics do not include severity, leave that column blank.

Example:

Dataset	Diagnostic Message	Severity	Count	Explanation
LB	Missing Units on Value	Error	22	**Not an error:** Lab results for pH and Specific Gravity have no units

End of Example

4.3. Additional Conformance Details

This optional section documents summary findings from validation rules other than the ones reported by OpenCDISC, which in the sponsor's opinion merit explanation. Fill in the table in this section as you would the one in section 4.2. Leave columns blank where not applicable.

This section is not intended to contain the full OpenCDISC Details report. Sponsors are discouraged from submitting the full report, but if the sponsor considers it necessary, the full report may be submitted as SDRG Appendix II.

Appendix I: Inclusion/Exclusion Criteria

This optional Appendix provides the complete set of inclusion/exclusion criteria when they cannot be fully documented in the Trial Inclusion/Exclusion Criteria (TI) dataset. For example, if inclusion/exclusion criteria are too long to be fully described in the TI dataset, include the full text in Appendix I. This section is not necessary if a hyperlink is supplied (in section 2.3.x) to the full inclusion/exclusion criteria contained in an annotated CRF. If criteria are provided in this Appendix I, there is no need to include a separate document in the submission as described in the SDTM Metadata Submission Guideline v1.0, Section 5.1.3. We recommend that you provide a link from define.xml to the SDRG.

Appendix II: Conformance Issues Details

A detailed record-level description of conformance issues (e.g., the OpenCDISC report Details tab or similar) may be included in this optional Appendix. Sponsors are strongly

discouraged from including this appendix due to its limited utility for FDA Reviewers. All significant findings should be described in Sections 4.2 or 4.3.

Study Data Reviewer's Guide Finalization Instructions

This section describes how to create the document for submission after completing the SDRG Template.

1. Create hyperlinks from dataset names in section 3.3 to descriptions in 3.3.x

Select the text in the first column of Table 3.3 that needs a hyperlink. **Right click the selected text** and choose "**Hyperlink**" from the menu. In the left panel of the Hyperlink window, make sure that "**Place in this document**" is selected. Then, in the list of document places select the dataset name's header under SDTM Subject Domains (e.g. AE – Adverse Events) and click **OK**. Ctrl+click the hyperlink to test it.

2. Remove unused sections from the document

Before converting the document to PDF format, remove any optional sections that were not used. Highlight the section heading, text prompt and any trailing blank lines then press the Delete key. Required sections should be left in, even if they are blank.

3. Update the Table of Contents, document header and version date

After all edits have been completed, update the table of contents at the top if the document. **Right click on any line in the table** and select "**Update Field**." In the dialog window, select "**update entire table**," then click **OK**.

Do not edit the document header or footer. The study number in the header references the study number on the title page. When you edit the study number on the title page, the study number in the header is updated automatically. To update the version date on the title page and the PDF creation date in the document footer, **save and close the document**, then **re-open it**. All necessary fields will be updated.

4. Convert the document to PDF format

These instructions are for Microsoft Word 2003 or newer, using either the Adobe Acrobat plug-in or the MS Office PDF creation feature.

4.1 Using the Adobe Acrobat plug-in for Microsoft Office:

Click the **Acrobat tab** in the Word menu at the top of the screen. Select "**Create PDF**." If a dialog window pops up asking you to save and continue, click **Yes**. In the second dialog window, **navigate to the directory** in which you want to save the PDF, **name the file** "**study-data-reviewers-guide.pdf"**, and click **Save**.

4.2 Conversion without Adobe Acrobat plug-in:

Click the **Office button** at the top left of your screen. Select "**Save As**," then "**PDF or XPS**". **Navigate to the directory** in which you want to save the PDF, name **the file** "**study-data-reviewers-guide.pdf"**, and click **Save**.

4.3 Formatting and verifying the PDF

Open the PDF. Go to the **File menu** and select **"Properties**." Navigate to the **Initial View tab**. In the drop-down menu for **Navigation tab**, select "**Bookmarks Panel and Page**." In the drop-down menus for both **Page Layout** and **Magnification**, select "**Default**." Click **OK**.

Still in the "**Document Properties**" window, navigate to the **Description tab** and delete the information in the **Title**, **Author**, **Subject** and **Keywords** boxes. Click **OK** and then **save the file**. While there, verify at the bottom of the dialog window that the **PDF version is 1.7** or lower.

If the version is too high, go to the **Document menu** and select "**Reduce File Size**." In the drop-down list select "**Acrobat 8.0 and later**." Click **OK**, then **navigate to the directory** in which you want to save the PDF, **name the file** "**study-data-reviewers-guide.pdf"**, and click **Save**.

Go to **File**, and select "**Properties**." Verify at the bottom of the dialog window that the **PDF version is 1.7** or lower.

5. Create a hyperlink to full inclusion/exclusion text in blankcrf.pdf

If you need to link to the full inclusion/exclusion criteria in blankcrf.pdf: **open both the study-data-reviewers-guide.pdf and the blankcrf.pdf** in separate windows. In the top menu of **study-data-reviewers-guide.pdf**, click **Tools,** then **Advanced Editing,** and finally the **Link Tool. Draw a box around the text that you want you turn into a hyperlink** in section 2.3.x. Under **Link Action**, make sure **"Go to a page view"** is selected, then click **Next**. While the next dialog box is still open, **navigate to the page in blankcrf.pdf** that you would like to hyperlink to. **While still in the blankcrf.pdf window,** click **Set Link.**