Study Data Reviewer's Guide
Completion Guideline: Nonclinical (nNSDRG)

V1.1

Revision History

Date	Version	Summary
03 March 2016	1.0	First Public Version: posted for Public Comment
17 March 2017	1.1	Update from Public Review and FDA Comments from Fit for Use Pilot

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Study Data Reviewer's Guide Purpose

The Nonclinical Study Data Reviewer's Guide (nSDRG) provides FDA Reviewers and Data Managers with additional context for Standard for Exchange of Nonclinical Data (SEND) datasets received as part of a regulatory submission. The nSDRG is intended to describe SEND data submitted for an individual study in the Module 4 nonclinical section of the eCTD. The nSDRG may duplicate information found in other submission documentation (e.g. the protocol, nonclinical study report, define.xml, etc.) in order to help the Reviewer understand the relationship between the study report and the data.

It is strongly recommended to review this nSDRG Completion Guideline and the Technical Conformance Guide in their entirety before embarking on your first nSDRG!

nSDRG Overview

The nSDRG has six main sections. These main sections (numbers 1 – 6) are mentioned in the FDA Technical Conformance Guide. Additional subsections were added based on the interpretation of the aforementioned guidance by the PhUSE Nonclinical nSDRG Team.

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I. nSDRG Completion Guideline Purpose

The purpose of this document is to provide Sponsors with recommendations to facilitate the consistent development of an nSDRG from the Nonclinical Study Data Reviewer's Guide Template. In addition to this Completion Guideline, nSDRG examples are available as an additional reference.

This document is organized into three sections: a guideline overview, nSDRG Template Completion Instructions, and nSDRG Finalization Instructions. The headings and their numbers under Section II in these instructions correspond directly to the nSDRG Template. The nSDRG Finalization Instructions describe how to create the document for submission after completing the nSDRG Template.

II. Study Data Reviewer's Guide Template Completion Instructions

This section provides instructions to complete the nSDRG Template. The section numbering here corresponds directly to the nSDRG Template.

Note: Certain nSDRG Sections in the template might include 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 Author.

Any Sponsor specific or non-industry standard acronyms used in the n SDRG should be spelled out when first used. Standard industry acronyms (e.g. CDISC, SEND etc.) do not need to be documented.

Critical note to nSDRG authors: consider that the template and instructions have sufficient flexibility to focus on what is important to convey for a particular study's datasets. This is the purpose of an nSDRG.

1. nSDRG Introduction

The nSDRG is intended to be a tool for a Data Manager to explain to the Reviewer, important narrative information about the SEND submission which may, or may not be in other submission information. The decision about what is "important" may vary study to study. Remember, the nSDRG is intended for a different customer: the Reviewer, differing from the Define file, which is used by people who load the data into tools.

1.1 Study Title, Number, and Report Version

This section provides, in a tabular format, the study title, number or identifier and report version included in the submission.

Study Title	*<Enter the study title here>*
Study Number	*<Enter the study number here>*
Report Version	*<Include here any amendments issued to the final report>*

It is highly recommended that the Study# used in the table is consistent across the submission (i.e., study report/nSDRG/SEND dataset/Electronic Document Room (EDR)). Either the CRO's study# or Sponsor's study# can be used, as long as it is the same number used throughout the submission to ensure proper cross-referencing.

1.2 Summary of SEND Dataset Creation Process

This section is a high-level summary of the process by which the SEND dataset was created from study data. Below is a text example. Another option for summarizing the SEND dataset creation process is to use a visual flow chart.

An example of a summary is:

"All in-life, clinical pathology, postmortem and TK blood collection data were collected with LIMS 1 by Provider A. Bioanalytical analysis was determined with LIMS 2 by Provider B, with electronic transfer of in-life TK blood collection data from LIMS 1. Toxicokinetic calculations were determined using LIMS 3 by the sponsor. Input (raw data extracts) from each of the LIMS via LIMS-specific adaptors was processed by SEND Solution XX to produce one integrated SEND dataset with a define.xml, a validation report and LIMS terms mapped to controlled terminology.

1.3 SEND Dataset Verification

Appropriate verifications need to be done to ensure that data in the SEND datasets are an accurate representation of study data. A positive statement needs to be included in this section. In the event of a directed audit of the data set integrity, the actual verification documentation would most likely be helpful to the auditor.

An example of a statement is:

"Data in the SEND datasets are an accurate representation of the data for Study No. 12345. Any differences between the data sets and the report are described in section 6.2. Verification procedures and documentation supporting this are available upon request."

2. Study Design

This section provides a brief orientation to the study and additional context about the Trial Design datasets.

2.1 Study Design Summary

This section provides a brief textual description and/or visual representation of the protocol design. The study design table can be included, taken directly from the protocol or developed specifically for the nSDRG. It is recommended that the textual description be very brief, no longer than a few sentences. Include changes from protocol amendments that affected the study design. (e.g., premature termination of a dose group)

2.2 Trial Design Domain Overview

This section provides additional context for the Trial Design datasets. It should describe whether Trial Design domains are submitted, include a diagram of the Trial Design. Also include a subsection describing any nonstandard Trial Design domains included in the study data package.

The following question must be answered:

Are all Trial Design domains described in the SEND Implementation Guide (SENDIG) included in the submission?

In this section, a diagram such as the one following or as shown in SENDIG should be included to illustrate the Trial Design. The following diagrams are suggestions on how to illustrate the Trial Design. Select a representation of the study for the nSDRG.

Example 1: The text in <*italics*> should be replaced by the study specific Trial Design items. Keep the bold text as column headings. If desired, the user may color individual elements to a specific color to aid a fast overview.

Depending on the Trial Design, the user can add and delete rows and EPOCH columns as needed.

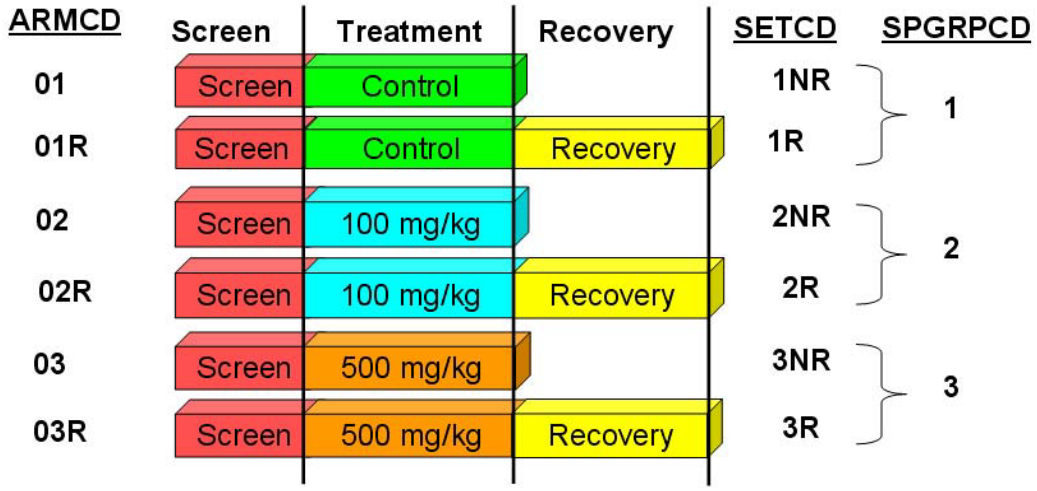
- The first row represents a way to describe one Sponsor defined group with two Arms and three Sets.
- The second row represents a way to describe one Sponsor defined group with one Arm and two Sets.
- The last row of the example table represents a way to describe one Sponsor defined group with one Arm and one Set.

Example 1 Trial Design Overview 1

Study Group	Trial Arms		Element in each Epoch			Trial Set	
SPGRPCD	ARMCD	ARM	*<EPOCH name 1>*	*<EPOCH name 2>*	*<EPOCH name 3>*	SETCD	SET
<Sponsors group no.>							*<Set name 1>*
							<Set name 2>
							<Set name 3>

Example 2:

Example 2 is an alternate Trial Design diagram, similar to those used in SEND Implementation Guide (refer to this resource for further instruction).



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.

Any nonstandard study design domains that need additional explanation, or are sponsor specific, should be described in Section 6.1 of this document.

3. Standards, Formats, and Terminologies and their Versions

This section documents the versions of standards used for the study. SEND version, controlled terminology version, and any relevant dictionary version (more likely in clinical than nonclinical) used in the study and the rationale for the selection are included.

3.1 Standards Used

Provide a tabular overview of all standards used in the submitted study data package.

Example:

Component	Standard or Dictionary	Versions Used
Tabulation Datasets	CDISC SEND Implementation Guide	3.0
Controlled Terminology	CDISC SEND Controlled Terminology	2016-12-16
Data Definition file formats provided: .xml and .pdf	CDISC DEFINE	2.0

3.2 Rationale for Standards Selection

A likely rationale for standards and versions selection is that they were the most current ones listed in FDA's Study Data Standards Catalog and supported by the Sponsors' production systems at the time of dataset creation. This is also the place to state if a waiver was granted to use an earlier or different standard.

3.3 Nonstandard Terminology

For variables requiring use of a Controlled Terminology Codelist, any use of nonstandard terminology should be explained in the nSDRG as shown below. Be sure to provide explanations that help reviewers understand the meaning of the nonstandard terminology. Avoid using lots of acronyms without sufficient explanations.

Example:

Dataset Name	Variable	Codelist	Term Used	Meaning
LB	LBTEST	LBTEST	Melamine abutyltransferfree	A measurement of the melamine abutyltransferfree in a biological specimen.
LB	LBTESTCD	LBTESTCD	MELTRFRE	A measurement of the melamine abutyltransferfree in a biological specimen.

Alternatively, if only standard terms were used, indicate so in a statement and delete the table.

4. Description of Study Datasets

This section provides additional context for SEND domains that is not adequately addressed in define.xml or SENDIG. To help determine if content is needed in this section, answers to the following questions may be helpful:

1. Are the submitted data taken from an ongoing study? If so, what was the cut point? Indicate when the rest of the data should be expected.

2. Were the SEND datasets used as sources for the analysis?

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

4. Are the submitted data a subset of collected data? (The answer will be "yes" if data were collected but not included in the submission.) Explanation can be provided in Section 6.2 of this document.

5. If an extension study is being documented, include description(s) of any data that have been copied from or are located in another study in the submission, such as the use of one control group for multiple studies.

4.1 Dataset Summary

This section provides an overview of all domains included in the SEND dataset including the Trial Design datasets. Additional text in Section 4.2 should be provided for any domains that require additional explanation. Any custom domains should be included in this section.

- Add only those datasets in the table that are included in submission.
- Indicate with an 'X' in the "Supplemental Qualifiers?" column if a Supplemental Qualifiers dataset is submitted for the domain. Do not include separate rows for each Supplemental dataset. The use of any Supplemental Qualifiers should be explained in Section 4.3.
- If relationships between the domain and other domains have been described in RELREC, specify the related domains in the "Related Using RELREC? "column with an 'X'. Do not include a row for the RELREC dataset. If considered necessary to explain a domain's key relationships to other domains, this should be done in the domain-specific section. Provide the explanation of the relationship within the context of one of the related domains. Do not create a separate section for RELREC.
- Specify the domain Observation Class from the SENDIG for all included datasets.

Example:

Dataset	Dataset Label	Supplemental Qualifiers?	Related Using RELREC?	Observation Class
TA	Trial Arms			Special Purpose
TE	Trial Elements			Special Purpose
TS	Trial Summary			Special Purpose
TX	Trial Sets			Special Purpose
CO	Comments			Special Purpose
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
EX	Exposure			Interventions
DS	Disposition			Events
BW	Body Weight			Findings
BG	Body Weight Gain			Findings
CL	Clinical Observations			Findings
DD	Death Diagnosis			Findings
EG	ECG Test Results			Findings
FW	Food and Water Consumption			Events
LB	Laboratory Test Results			Findings
MA	Macroscopic Findings	X	X	Findings
MI	Microscopic Findings	X	X	Findings
OM	Organ Measurements			Findings
PM	Palpable Masses			Findings
PC	Pharmacokinetics Concentrations			Findings

Dataset	Dataset Label	Supplemental Qualifiers?	Related Using RELREC?	Observation Class
PP	Pharmacokinetics Parameters			Findings
SC	Subject Characteristics			Findings
TF	Tumor Findings			Findings
VS	Vital Signs			Findings
POOLDEF	Pooled Definitions			Special Purpose

4.2 Dataset Explanation

If necessary, provide explanation beyond that which is documented in define.xml or the SENDIG and its supplements. It is optional to hyperlink domain names in Section 4.1, to subsections needed for additional explanations.

Provide a numeric subheading for each dataset and ensure that is appears in the Table of Contents (e.g. 4.2.1, 4.2.2, 4.2.3).

Examples:

4.2.1 Comments

The comments domain reports comments from LIMS1 only.

4.2.2 LB domain

The times presented in the LBDTC do not represent the time of sample collection; instead, they represent the time of sample analysis.

To aid in the review and analysis of the datasets, the dataset explanation may include, but is not limited to the following:

- Previous agreements with regulatory agencies on specific representation of study data not specified in current implementation guides (e.g. SEND IG v. 3.0).
- Organization of content (e.g. custom endpoints) for which the content is very specific to the study.
- Inclusion of important non-standard variables supporting key analysis, apprearing in an associated supplemental qualifier dataset.
- Description of notable, Sponsor defined uses of category and subcategory.
- Descriptions of derivations/deviations/amendments that may benefit from additional detail beyond that included in define.xml.

- Description of criteria used to split datasets and the content of the split datasets. (Splitting datasets is expected to be very rare.)

4.3 Use of Supplemental Qualifiers

This section is recommended in the event supplemental qualifiers are used. It should include a list and explanation of all Supplemental Qualifiers used in the dataset package. See section 4.1.3.3 of the Technical Conformance Guide.

Example:

Dataset Name	Associated Dataset	Qualifiers Used
SUPPMA	MA Macroscopic Findings	Modifiers that were part of MAORRES for which SEND variables have not yet been developed
SUPPMI	MI Microscopic Findings	Modifiers that were part of MIORRES for which SEND variables have not yet been developed

5. Data Standards Validation Rules, Versions, and Conformance Issues

This section describes the validation checks and inputs used to evaluate conformance of the datasets to standard rules.

5.1 Validation Outcome Summary

All significant conformance findings should be documented in Section 5 to a detail that will provide a Reviewer or Data Manager a quick and clear overview of any issues with the data package and the rationale for their presence.

It is not necessary to include all detailed record-level descriptions of conformance issues (e.g. the Pinnacle21 report Details tab or similar) due to its limited utility for reviewers. All significant findings should be described in Sections 5.3 – 5.5.

5.2. FDA SEND Validation Rules Version

This section focuses on FDA rule conformance issues, as these are expected to be the main rules of interest for submitted data.

FDA Validation Rules are maintained in the Study Data Standards Resources website on FDA.gov.

There is a standard statement in the template to define which validation resource is used (as there are several possibilities) and a reference to the correct version of the FDA rules applied at the time of the validation.

5.3. Errors

This section summarizes findings from validation. Insert errors from the SEND conformance report into the table provided; or, indicate no errors were found.

- 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.
- Explain why validation errors could not be corrected
- If you are using a SEND conformance checker other than FDA rules, at minimum, report the diagnostic messages for validation rules that overlap with the FDA rules.

Example:

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

5.4. Warnings

Describe any relevant validation warnings that could not be corrected similar to description of errors in Section 5.3 above, or indicate no warnings were found.

Add an example to accommodate extensible term warnings and reference section 3 for meanings of those terms (objective to make warning list less redundant.)

6. Sponsor Decisions Related to Data Standard Implementations

6.1 Sponsor Defined Standardization Descriptions

This section describes Sponsor defined decisions related to data standardization that are important for review and interpretation of the datasets.

There may be instances in which current implementation guides (e.g. SDTMIG, SENDIG) do not provide specific instruction as to how certain study data should be represented. In these instances, sponsors should discuss their proposed solution with the review division and submit supporting documentation that describes these decisions or solutions in the nSDRG at the time of submission (taken from Section 4.1 of Technical Conformance Guide).

In some instances, it may not be possible to represent a collected data element as a standardized data element. In these cases, there should be an explanation in the nSDRG as to why certain data elements could not be fully standardized or were otherwise not included in the standardized data submission (taken from Section 8.3.2 of Technical Conformance Guide).

The following are example topics that should be included in this section:

- Descriptions of any custom domains
- Comment as to whether a dataset contains derived values in addition to raw data values. (Derived values are linked to raw data values within the same dataset).

- 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. One such example is the use of one control group for multiple studies.

6.2 Differences between SEND Datasets and Study Report

This section describes differences that are present between the SEND datasets and the Final Study Report (the .pdf report) which are important to point out to the reviewer(s). Differences which are technical in nature (such as differences between SENDIG and the e-data set) should be recorded in the define file and probably are not needed here.

The following are examples topics for this section:

- Explain multiple study numbers, if existing in study datasets
- Include justification of why reference start date is different from first day of dosing, including any differences in the definition across subjects and description of the calculation of study days.

It is recommended to include a table mapping study days in the report to SEND study days if/where they appear different.

6.3 Nonstandard Electronic Data Submitted

This section is for recording significant data issues, clarifications, explanations where traceability is not obvious, and adjudications in the nSDRG. For example, data were not collected or were collected using different/incompatible terminologies, or were collected but will not fit into, for example, SEND format. In some instances, where not possible to represent a collected data element as a standardized data element, explain why these data elements could not be fully standardized or were otherwise not included in the standardized data submission.

6.4 Legacy Data Conversion

This section describes any legacy data conversion required to transform collected data to standard format, if a conversion was performed. Refer to Section 8.3.2.2 of FDA's Study Data Technical Conformance Guide.

Sponsors should evaluate the decision involved in converting previously collected non-standardized data (i.e. legacy study data) to standardized data (i.e. SEND). Sponsors should provide the explanation and rationale for the study data conversion in the nSDRG.

Studies which will contain previously collected non-standard data subsequently converted to a standard format should be listed in the overall *Study Data Standardization Plan (SDSP).* Refer to Section 2.1 of FDA's Study Data Technical Conformance Guide.

Legacy data (i.e. legacy tabulation data) may be needed in addition to the converted data.

III. Study Data Reviewer's Guide Finalization Instructions

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

1. 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.

Do not edit the document header. The study title and 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.

2. Convert the document to PDF format

- Name the file "nsdrg.pdf", or current name requirement defined in the FDA Technical Conformance Guide.
- Verify the PDF version is current to the FDA Study Data Standards Catalog requirement.

End of Document