50008

The Nonclinical Study Data Reviewer's Guide: An Update from PhUSE

FDA/PhUSE Nonclinical Study Data Reviewer's Guide Working Group

Abstract

According to FDA's Study Data Technical Conformance Guide, preparation of a Study Data Reviewer's Guide (SDRG) is recommended as an integral part of a CDISC standards-compliant study data submission. The PhUSE / FDA Nonclinical SDRG Working Group, with representation from Pharma, CROs, and SEND solution vendors, has developed an SDRG for nonclinical studies with inputs and feedback from the FDA. The nonclinical SDRG should describe for each study any special considerations that may facilitate review of the dataset by FDA reviewers and data managers. These include clarification of any differences between study report and SEND datasets; identification of SEND standards, controlled terminologies and versions used in the datasets; a summary of included domains; conformance observations relating to FDA SEND validator rules; and decisions related to data standards implementations including deviations and errors where applicable. The SDRG should include a high-level summary of the process by which the SEND datasets were created from study data. Each SDRG should be specific to a particular study to enable effective use by FDA reviewers and data managers. Highlights of recommendations for authoring a nonclinical SDRG form the basis of this poster presentation.

SDRG Table of Contents

The SDRG Table of Contents comes from recommendations in FDA's Study Data Technical Conformance Guide (most recent version, March 2016).

1. Introduction

The Introduction should include high-level information for a reviewer to become familiarized with the study submission package:

- Study ID Information
- SEND dataset creation process
- Statement that SEND datasets accurately represent data in the study report and, if needed, where in the SDRG any differences are noted

Example

1.Introduction

This document provides context for the SEND tabulation datasets and terminology for Study 54321, in addition to what is provided in the define.xml file, to facilitate the FDA reviewer's and data manager's use of the datasets.

1.1 Study Protocol Title, Number, and Report Version

Study Title	A 13-week Oral Toxicology Study in Dogs with C1234 followed by an 8-week Recovery Period
Study Number	54321
Report Version	Final. There have been no report amendments.

1.2 Summary of SEND Dataset Creation Process

All in-life, clinical pathology, and postmortem data were collected using LIMS 1 (Vendor). Bioanalytical data were determined using LIMS 2 (Vendor). Toxicokinetic parameters were calculated using LIMS 3 (Vendor). Input from the each of the LIMS via LIMS-specific adaptors was processed by SEND solution XXX (Vendor) to produce one integrated SEND dataset, define.xml and PDF files, and a validation report. SEND solution XXX and the LIMS-specific adaptors are Part 11 compliant.

1.3 SEND Dataset Verification

Data in the SEND datasets are an accurate representation of data in the study report for Study No. 54321. Any differences between the datasets and the report are described in section 6.2.

2. Study Design

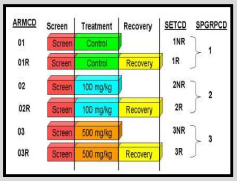
This section provides a brief orientation to the study and additional context about the Trial Design Datasets.

Example

2.1 Study Design Summary

In study 54321, 6 dogs/sex/group were dosed by oral gavage once daily for 13 weeks at doses of 0, 100, and 500 mg/kg C1234. At the end of the treatment period, 4 dogs/sex/group underwent terminal sacrifice. The remaining 2 dogs/sex/group were placed on an 8-week recovery period followed by sacrifice.

2.2 Trial Design Domain Overview



3. Standards, Formats, Terminologies, and their Versions

This section documents the SEND version, controlled terminology version, validation rule version and dictionary version used in the study and the rationale for the selection.

Example

3.1 Standards Used

Dataset Component	Standard or Dictionary	Version
Tabulation Datasets	CDISC SEND	3.0
Data Definition File	CDISC DEFINE.XML	1.0
Controlled Terminology (CT)	CDISC SEND CT	2015-6-24

3.2 Rationale for Standards Selection

The versions listed were the most current ones defined in FDA's Study Data Standards Catalog and supported by the company at the time the study started.

3.3 Nonstandard Terminology

Nonstandard terminology was used in the EG domain as shown following:

Dataset Abbreviation	Variable	Term Used	Meaning
EG	EGTEST	Beat-to-beat QT/TQ ratio	A measure of the ability of the heart to recover from one beat to the next by examining the relationship between action potential duration (QT interval) and diastolic interval (TQ)

4. Description of Study Datasets

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.

Example

4.1 Dataset Summary

Dataset	Dataset Label	Supplemental Qualifiers?	Related using RELREC?	Observation Class
TA	Trial Arm			Trial Design
TE	Trial Elements			Trial Design
TS	Trial Summary			Trial Design
TX	Trial Sets			Trial Design
DS	Disposition			Events
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
EX	Exposure			Interventions
EG	ECG Test Results			Findings
LB	Laboratory Test Results			Findings
MA	Macroscopic	X	X	Findings
MI	Microscopic	X	X	Findings

4. Description of Study Datasets (continued)

Example

4.2 Dataset Explanations

4.2.1 DS Domain

The DSDECOD of UNPLANNED TERMINAL SACRIFICE was used for animals in the high-dose treatment group that were terminated early by protocol amendment. Other animals in that group were terminated prior to issuance of the protocol amendment and were assigned a DSDECOD of MORIBUND SACRIFICE.

4.3 Supplemental Qualifiers

Dataset Name	Associated Dataset	Qualifiers Used
SUPPMI	MI (Microscopic Findings)	Modifiers from MIORRES for which SEND 3.0 variables have not yet been developed
SUPPMA	MA (Macroscopic Findings)	Modifiers from MAORRES for which SEND 3.0 variables have not yet been developed

5. Data Standards Validation Rules, Versions, & Conformance

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.

Example

5.1 Validation Outcome Summary

Of a total of 31,682 records, there were 0 errors and 1807 warnings. None of the Warnings had an impact on the SEND submission for reasons provided in Section 5.4.

5.2. FDA SEND Validation Rules Version

OpenCDISC Validator version 2.0.1, which includes FDA SEND validation rules Version 2.0, was used to evaluate conformance to SEND 3.0.

5.3 Errors

No errors were reported.

5.4 Warnings

The Warnings for Study 54321 resulted from a small number of FDA SEND validation rules as shown in the table following.

FDA Rule	Message	Domain	Count	Explanation
FDAN212	Duplicate Records	MI	1347	FDAN212 determines record uniqueness based on --TESTCD, USUBJID, and --DTC. These variables are insufficient to determine uniqueness for MI records.
FDAN169	Missing value for LBSTRESU when LBSTRESC is provided	LB	79	The value for LBSTRESC is albumin / globulin ratio, which is not associated with units. Accordingly, LBSTRESU should not be populated, and the validation rule is incorrectly configured.

6. Sponsor Decisions Related to Data Standards Implementations

6.1 Sponsor-Defined Standardization Descriptions, such as:

- Explanation for why certain data elements could not be fully standardized, if applicable
- Comments on inclusion of any derived values

6.2 Differences Between SEND Datasets and Study Report, such as:

- Data included in report but not datasets or vice versa
- Differences in study day numbering

6.3 Nonstandard Electronic Data Submitted, such as:

- Data collected using different terminologies
- Electronic data that do not conform to SDTM

6.4 Legacy Data Conversion

If data was not collected with a specific standard in mind, this section should outline the legacy data conversion plan for such data.

Status of Nonclinical SDRG Package

- Public review, announced through PhUSE, ended October 30, 2015 – All comments were addressed. FDA informal review of Nonclinical SDRG Package was positive: no comments.
- Federal Register Notice of public review period ended May 3, 2016.
- The current nonclinical SDRG template, User Guide, and examples can be found at: http://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer%27s_Guide

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