

The State of Data Reviewer Guides *

** For this presentation a Reviewer Guide
refers to the document in the m4 or m5
(not m1) in eCTD*

Helena Sviglin, MPH
Office of Computational Science, CDER, FDA
March 2016

Definitions

- SDRG = Study Data Reviewer Guide
- ADRG = Analysis Data Reviewer Guide
- NSDRG = Nonclinical SDRG (*acronym may change*)
- JumpStart = an OCS service to help Reviewers jump start their review
- OCS = Office of Computational Science

Brief History

- SDRG development started in 2012 as part of an FDA/PhUSE collaboration
- Early and consistent FDA participation
- **WAS WILDLY SUCCESSFUL**
- Soon followed by the ADRG
- Then the nonclinical SDRG debuted last month

Thank you

What *is* a Reviewer Guide?

It's a human readable document meant to convey details about a study's data that are:

- Relevant to the review
- Not contained elsewhere (has no good home in the Define, Statistical Analysis Plan (SAP), or other reports)
- Essential to understanding why data is presented a certain way
- Conveys clarifying information on things that may appear to be discrepancies between reports and various datasets that could result in an information request

Reviewer Guides

☀ Help both Sponsors and Reviewers

☀ *Help tell rest of the story*

*(because we all know it can get
pretty complicated)*

What a Reviewer Guide is *not*

- Define plus
- Expanded validation report
- Meant to be machine readable

Reports have been favorable



SDRG (the clinical one)

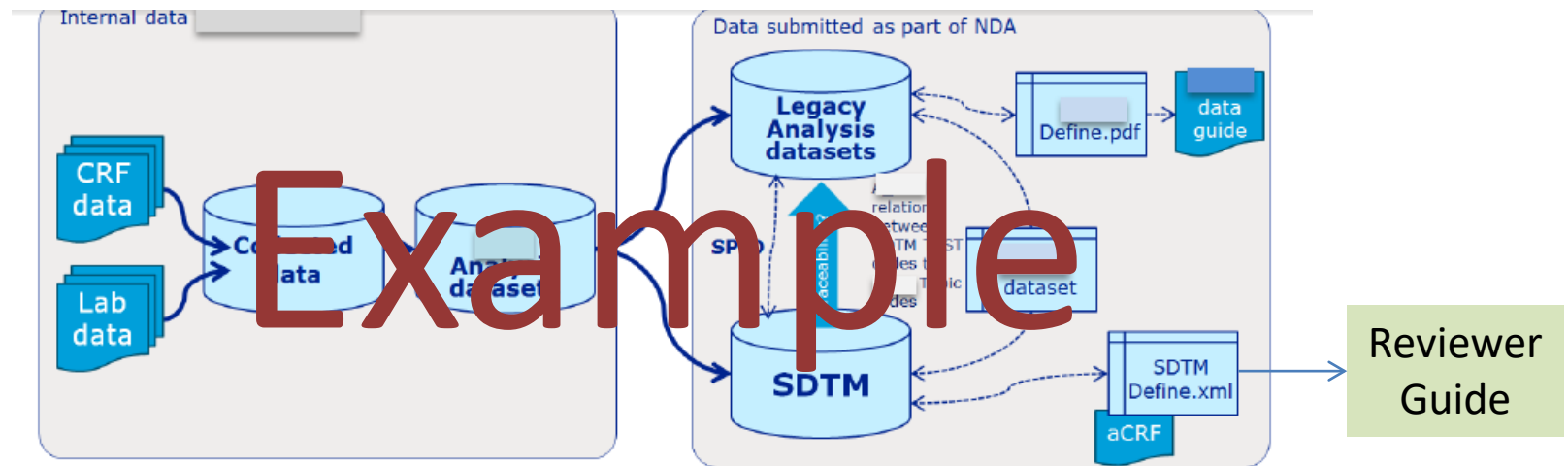
- PhUSE/FDA collaboration started in 2012
- FDA folks invested heavily in development by providing content and leadership
- V1.1 released at PhUSE CSS in March 2013
- In the Technical Conformance Guide in January 2014
- V1.2 released in January 2015
- 80 FR 43779 Intent to Review in July 2015
- We reviewed and considered each one carefully

SDRG in action

- When its good - it's REALLY good
- The content is working great for JumpStart Analysts
- Reviewers feel the same way
- 38% of JumpStart services in 2015/16 were missing an SDRG or sections for at least one of the studies in the application.

SDRG in action

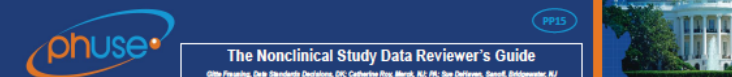
Sometimes you guys surprise us with something we wish we thought of...



traceability flow diagram

NSDRG (aka Nonclinical SDRG)

- FDA liaisons involved in early development
- In the Technical Conformance Guide in 2015
- FR notice published February 29, 2016
 - **60 day comment period**
- Will evaluate the NSDRG using Pharm/Tox input
 - Team assembled and currently evaluating:
 - Is it useful to Reviewers?
 - Is it applicable across many scenarios?
- Input will be vetted with Pharm/Tox leadership
- Planning to educate Pharm/Tox Reviewers on the utility of NSDRG



phuse

The Nonclinical Study Data Reviewer's Guide

Offit Planning, Data Standards Definition, DQC Collection Registry, R2C, R2A, R2B, Data Definitions, Standard, Identification, R2J

Abstract

According to FDA Study Data Technical Content Guide (v2 June 2015), preparation of a Study Data Reviewer's Guide (SDRG) is recommended as an integral part of a CDISC standards-based study data submission. As SDRG templates, completion guidelines, and examples for clinical studies have been available since May 2013. Recently, the PhUSE / FDA Nonclinical SDRG Working Group, with representation from Pharms, CDISC, and SEND validation vendors, has developed an SDRG for nonclinical studies with inputs and feedback from the FDA.

These materials can be found at:

- PhUSE website: [http://nonclinical.sdrg.phuse.org](#)
- Nonclinical SDRG should describe for each study any special considerations that may influence review of the dataset by FDA reviewers and data managers. These include identification of any differences between study report and SEND standard; identification of SEND standards, controlled terminologies and classifiers used in the datasets; a summary of included datasets, information observations relating to FDA SEND validation rules, and decision related to data standards implementation including deviations and errors when applicable. The SDRG should indicate 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 the poster presentation.
- Note: It is critical for an SDRG author to have sufficient flexibility to focus on what is important for a particular study.

SDRG Table of Contents

- Introduction
- Study Design
- Standards, Formats, Terminologies, and Test Statistics
- Description of Study Datasets
- Data Standards, Validation Rules, Versions, and Conformance
- Sponsor Decisions Related to Data Standards Implementation

The SDRG Table of Contents comes from recommendations in FDA Study Data Technical Content Guide (current version, October 2015).

1. Introduction

This section 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 the SDRG references are noted

Example

1.1 Introduction
This document provides context for the SEND Submission details and terminology for Study S4521. In addition to what is provided in the definition file, it facilitates the FDA reviewer's and data manager's view of the datasets.

Study Title, Number, and Report Version

Study Name	Study Number	Report Version
Study Name	S4521	1.0

Summary of SEND Dataset Creation Process

All in-lab, clinical pathology, and pre-clinical data were collected using LIMS 1 (Vendor). Statistical data were observed using LIMS 2 (Vendor). Toxicological parameters were calculated using LIMS 2 (Vendor). Input from the rest of the LIMS was LIMS-specific outputs was processed by SEND Validation XCL. Similar to products are Integrated SEND datasets, COC and PDF files, and a validation report. SEND Validation COC and the LIMS-specific products are Part 11 compliant.

SEND Dataset Verification

Data in the SEND datasets are an accurate representation of data in the study report for Study No. S4521. Any difference between the datasets and the report are described in section B.2.

2. Study Design

This section provides a brief introduction to the study and additional context about the Trial Design Details.

Example

2.1 Study Design Summary

In Study S4521, 6 developmental groups were divided by test groups once daily for 7 weeks at doses of 0, 10L and 500 mg/kg CDNA. At the end of the treatment period, 4 developmental endpoints were measured. The remaining 2 developmental groups were placed on an 8-week recovery period followed by sacrifice.

2.2 Trial Design Details Overview

Group	Treatment	Recovery	CDNA	Endpoint
G1	0	No	Yes	1
G2	10L	No	Yes	1
G3	10L	Yes	Yes	1
G4	500	No	Yes	1
G5	500	Yes	Yes	1

3. Standards, Formats, Terminologies, & their Versions

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

3.1 Standards Used - Example

Standard	Version	Source
SEND Validation Rule	SEND Validation Rule V2.1	SEND
SEND Format	SEND Format V2.1	SEND
SEND Terminology	SEND Terminology V2.1	SEND

3.2 Platform for Standards Selection

The vendor Brand was the most current one defined in the FDA Study Data Standards Catalog and supported by the agency at the time the dataset was submitted.

3.3 Normalized Terminology

Normalized terminology was used in the SEND domain as shown below:

Domain	Variable	Term	Meaning
CO	COTEST	TEST	A measure of the ability of the test material to detect the presence of the substance being tested.
CO	COTEST	TEST	A measure of the ability of the test material to detect the presence of the substance being tested.

4. Description of Study Datasets

This section provides an overview of all domains included in the SEND dataset including the Trial Design Categories. Additional detail in section 4.2 should be provided for key domains that require additional explanation.

4.1 Dataset Summary - Example

Dataset	Date	Frequency	Number of Subjects	Number of Events
SEND	2015-01-01	Daily	100	1000
SEND	2015-01-01	Daily	100	1000
SEND	2015-01-01	Daily	100	1000
SEND	2015-01-01	Daily	100	1000
SEND	2015-01-01	Daily	100	1000
SEND	2015-01-01	Daily	100	1000
SEND	2015-01-01	Daily	100	1000
SEND	2015-01-01	Daily	100	1000
SEND	2015-01-01	Daily	100	1000
SEND	2015-01-01	Daily	100	1000

4. Description of Study Datasets (continued)

Example

4.2 Dataset Descriptions

4.2.1 DE Domain

The DISPOSITION OF UNPAIRED TERMINAL SACRIFICE was used to record the disposition of the terminal group that was terminated early by protocol amendment. Other animals in that group were terminated prior to issuance of the practical amendment and were assigned a DISPOSITION OF UNPAIRED TERMINAL SACRIFICE.

4.3 Supplemental Qualifiers

Qualifier	Qualifier Code	Qualifier Value
Qualifier	Qualifier Code	Qualifier Value
Qualifier	Qualifier Code	Qualifier Value
Qualifier	Qualifier Code	Qualifier Value
Qualifier	Qualifier Code	Qualifier Value

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 processes.

Example

5.1 Validation Outcome Summary

Of a total of 15,000 records, there were 0 errors and 100 warnings. None of the warnings were related to the SEND submission for the reasons provided in Section 5.4.

5.2 FDA SEND Validation Rule Version

Operational Validation version 2.1.1, which includes all FDA SEND validation rules version 2.1, was used to evaluate conformance to SEND 2.1.

5.3 Errors

No errors were reported.

5.4 Warnings

The warnings for Study S4521 resulted from a small number of FDA SEND validation rules as shown in the table below:

Rule ID	Message	Count	Severity
RULEID <td>Message</td> <td>Count</td> <td>Severity</td>	Message	Count	Severity
RULEID <td>Message</td> <td>Count</td> <td>Severity</td>	Message	Count	Severity
RULEID <td>Message</td> <td>Count</td> <td>Severity</td>	Message	Count	Severity
RULEID <td>Message</td> <td>Count</td> <td>Severity</td>	Message	Count	Severity

6. Sponsor Decisions Related to Data Standards Implementations

6.1 Sponsor-Defined Standardization Descriptors such as:

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

6.2 Differences Between SEND Datasets and Study Report such as:

- Differences in input data or data sources
- Nonstandard Electronic Data Submissions
- Data collected using different terminologies
- Electronic data that do not conform to SDTM

6.3 Legacy Data Conversion

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

Status of Nonclinical SDRG Package

- Public review announced through PRIDE, ended October 30, 2016 – All comments have been addressed
- FDA Internal review of Nonclinical SDRG Package was positive
- A Federated Register announcement is expected for broader public review of the Nonclinical SDRG Package

PHUSE Nonclinical SDRG Working Group (in addition to authors)

Offit Planning, Data Standards Definition, DQC Collection Registry, R2C, R2A, R2B, Data Definitions, Standard, Identification, R2J

Cellular Ray
Nancy Williams, Bristol Myers Squibb

Jeffrey Feldman, Ipsen
Debra Ostrom, Janssen
William Hovine, Bristol Myers Squibb

Christy Kuhn, MP Research
John Polley, Chondria Oncology
Michelle Robinson, GlaxoSmithKline

Margaret Rossi, Roche
Lisa Kofron, Pfizer
Tina Springer, Cytos

Note: The opinions expressed in this poster are those of the authors and do not necessarily represent the opinions of their respective companies.

ADRG

- Scoped here at this meeting in March 2013
- Two different versions:
 - V1.01, May 2014
 - V1.1, January 2015
- Added to Technical Conformance Guide in June 2015
- Intent to Review, projected 2016

ADRG in action

- *JumpStart Team uses it to help clarify complex derivations (ex. treatment emergent)*
- *We used information from the ADRG See how Major Adverse Cardiac Events (MACE) events are flagged in diabetes data*
- *ADRG lives up to the expectation set by SDRG*

In closing...

- Reviewer Guides are here to stay
 - Reviewer Guides are useful
 - Every study should have them
 - Stay tuned!
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- Tell us about your experience (good and bad)
Helena.sviglin@fda.hhs.gov