Study Data Reviewer's Guide (SDRG): Recommendations on Use of the Clinical SDRG Model for Nonclinical Data Submission

Nonclinical Working Group, SDRG Project – PP09

Abstract

The FDA draft guidance, "Providing Regulatory Submissions in Electronic Format – Standardized Study Data" (Feb 2012) refers to the Reviewer's Guide [Study Data Reviewer's Guide or SDRG] as an "integral part of a standards-compliant submission". SDRGs are needed to provide supplemental information that may not be covered by a SEND dataset and its associated define.xml, such as decisions used to represent a study in SEND format, sponsor-defined CT, differences between the report and SEND files, or explanations for validator warnings. The FDA/PhUSE Clinical Working Group, Optimizing the Use of Data Standards, developed an SDRG template for clinical studies. The Nonclinical SDRG Project Team is evaluating this to determine: 1) Is the clinical SDRG template appropriate for nonclinical? 2) If not, can it be modified? 3) Is a new nonclinical SDRG template needed? We plan to address these questions by piloting the use of the clinical SDRG using model SEND datasets and define files. The poster presents accomplishments to date.

Why is an SDRG Needed for Nonclinical?

A module 4 submission package for a study includes the final study report, the SEND datasets with the associated define file, and an SDRG.

The SDRG's primary objective is to aid in the navigation between and review of items in the submission package by providing information not found elsewhere in the submission, i.e. building bridges where needed for clarification and review.

The nonclinical SDRG group believes that the current need for a nonclinical SDRG reflects the early stages of implementation of electronic data standards. It is expected that as IT systems, procedures, and science adapt to the end-to-end use of standards in the conduct of nonclinical studies, the content of the SDRG will diminish

The SDRG is not a "carte blanche" to disregard regulatory guidances, but rather a tool to communicate how the implementation of a standard for a study may have not quite reached its full potential. The examples of such supplemental information provided below should be interpreted in this spirit. It may be productive in some instances to discuss such issues with FDA in advance of submission of standard electronic datasets.

- Clarification of the modelling of Trial Design datasets, as flexibility of SEND will support different correct interpretations
- Mapping decisions and any necessary data transformations
- Rationale for use of extensible terminology
- SEND datasets fail to account for how conclusions were reached in the final report
- Specification of any collected data included in the final report but not submitted electronically
- Difficulties meeting target standards – SEND, CDISC terminology, define.xml
- Clarification of validation warnings
- Standards/dictionaries other than SEND/CDISC terminology
- The define file is not able to fully reflect the content and structure of the datasets

Relationship Between Define File and SDRG

The define file is used for validation and for storing the define information with the data. Define information, according to the define standards, includes a list of domains, variables and terminology (controlled, extensible, sponsor defined) included in the submission. The reviewer guide (SDRG) is for the reviewer. r. Another way to express this is that the define file always lives with the dataset, the reviewer guide always lives with the submission as a whole.

There are several items in clinical SDRG template and examples on the PhUSE wiki page that are already included in the Define.xml file. Some of these include a list of domains included in the submission and an explanation of the Trials domains. This apparent redundancy is deemed to have an advantage as it provides reinforcement of points particularly important for a reviewer's full understanding. In fact, as highlighted in the middle section of this poster, the STUDY DATA TECHNICAL CONFORMANCE GUIDE (draft, February 2014) specifically recommends documentation of some items in both places.

SDRG Highlights from Feb 2014 Draft Data Technical Conformance Guide

Note: this draft guidance is currently in the comments phase. To ensure that the Agency considers comments before it begins work on the final version of the guidance, submit electronic or written comments by May 7, 2014. For further information on this process, please see:

http://www.regulations.gov/#!documentDetail;D=FDA-2012-D-0097-0021

2.2. Study Data Reviewer's Guide

Some data standards may not require the use of all data elements defined by the standard to be collected in any given study. For example, the Study Data Tabulation Model (SDTM) classifies variables as required, expected, or permissible. *What* data are collected and submitted is the subject of science, regulation, and discussions with the review division. However, all study-specific data necessary to evaluate the safety and efficacy of the product should be submitted with the highest level of standardization possible.

When using a data standard, there may be occasional ambiguity resulting in more than one way to implement the standard. Instances in which a standard allows for more than one implementation should be discussed with the appropriate review division or the data resource team (CBER and CDER products) before data submission. Sponsors and applicants should ensure their data conform to the required standard. Sponsors and applicants should **describe their use of study data standards and their conformance validation** in a *Reviewer's Data Guide (Data Guide).*

The *Data Guide* should describe, for each study, any special considerations or directions that may facilitate an FDA reviewer's use of the submitted data and may **help the reviewer understand the relationships between the study report and the data.** The *Data Guide* is recommended as an integral part of a standards-compliant study data submission. The *Data Guide* should be placed in the electronic Common Technical Document (eCTD) in Module 5. *(Module 4 for nonclinical studies.)*

For each study, the *Data Guide* should include, but is not limited to the following:

1. **Study protocol title, number, and version**
2. **Study design**
3. **Standards, formats, and terminologies and their versions**
4. **Description of study datasets**
5. **Data standards conformance validation rules, versions, and issues**

3.3.5.1 Split data should be noted **in the define.xml (see section 4.1.9.1)** and the *Data Guide*, clearly identifying **the method used for the dataset splitting.**

4.1.1 There may be instances in which the current implementation guides 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 Data Guide at the time of submission.

4.1.5 Conversions to one standardized version should be described in the Data Guide, including the rationale for the conversion

4.1.6 SDTM General Considerations
(This appears to be focused on clinical studies.)

4.1.6.3 Until standards for adjudication data are developed, it is advised that sponsors discuss their proposed approach with the review division and also include details about the presence, implementation approach, and location of adjudication data in the Data Guide.

4.1.7.3 Further, primary and secondary [efficacy and safety] variables and their derivations (as applicable) should be provided, as well as **documented in the define file and Data Guide.**

6.1 The use of a **dictionary that is sponsor-defined or an extension of a standard dictionary** should be **documented in the define.xml file and the *Data Guide*.**

6.1.2 If custom terms cannot be avoided, the submitter should clearly identify and define them within the submission, reference them in the *Data Guide*, and use them consistently throughout the application. …. Sponsors should clearly reference in the *Data Guide* **which terminologies and versions are used** for every study within a submission.

6.2.1.1 For variables for which no standard terminology exists, or if the available terminology is insufficient the sponsor should propose its own terminology. The sponsor should provide this **information in the define.xml file and in the Data Guide.**

8.2.3 Sponsors should validate their study data before submission using the published validation rules and either correct any validation errors or explain in the *Data Guide* **why certain validation errors could not be corrected.**

8.3.2 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 *Data Guide* as to **why certain data elements could not be fully standardized or were otherwise not included in the standardized data submission**. In cases where the data were collected on a Case Report Form (CRF) or electronic CRF but were not included in the converted datasets, the omitted data should be apparent on the annotated CRF and described in the *Data Guide*.

8.3.4 Sponsors should provide the **explanation and rationale for the study data conversion** in the *Data Guide*.

8.3.4 point 3. Record significant data issues, clarifications, explanations of traceability, and adjudications in the *Data Guide*. 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.

Red highlight and italics indicate Nonclinical SDRG Working Group emphasis within FDA guidelines

Comparison Between Clinical SDRG Template and Nonclinical Needs

Clinical SDRG Template[(a)]		2014 FDA Draft Guidance	Nonclinical Analysis	
Clinical SDRG Section	Include?	"Should Include"?	Include?	Observations/ Comments
1. Introduction				The Introduction is similar for clinical & nonclinical, although SEND & CT versions included in TS.
1.1 Purpose	Yes		Yes	
1.2 Acronyms	Optional		Yes	
1.3 Study Data Standards & Dictionary Inventory	Yes	Yes	Yes	
2. Protocol Description				This section is similar for clinical and nonclinical, although some of the domains differ.
2.1 Protocol No. & Title	Yes	Yes	Yes	
2.2 Protocol Design	Optional	Yes	Yes	
2.3 Trial Design Datasets	Yes	Should include "description of data sets"	Yes	
2.3.1 TA	Yes		Yes	
2.3.2 TE	Yes		Yes	
2.3.3 TV	Yes		N/A	
2.3.4 TI	Yes		N/A	
2.3.5 TS	Yes		Yes	
3. Subject Data Description				List domains included in submission. Further information can be added if explanation is needed, i.e. nonconformance.
3.1 Overview	Yes		Yes	
3.2 Annotated CRFs	Optional		N/A	
3.3 SDTM Subject Domains	Yes		Yes	
3.3.1 AE	Yes	Should include "description of data sets"	N/A	
3.3.2 DS	Yes		Yes	
3.3.3 EX	Yes		Yes	
3.3.4 Dataset – Dataset Label	Yes		Yes	
4. Data Conformance Summary				Identify validation approach used. Provide explanations for warnings as needed.
4.1 Conformance Inputs	Yes	Yes	Yes	
4.2 Issues Summary	Yes	Yes	Yes	
4.3 Additional Conformance Details	Optional	As necessary	As necessary	
Appendix 1: Inclusion/ Exclusion Criteria	Required		N/A	N/A
Appendix 2: Conformance Issues Details	Optional		Optional	

Abbreviations: AE: Adverse Event; CRF: Case Report Form; DS: Disposition; N/A: Not Applicable; TA: Trial Arm; TE: Trial Element; TS = Trial Summary; TV = Trial Visits.

[(a)] Clinical SDRG template analyzed is from PHUSE Wiki: http://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer%27s_Guide

Discussion and Conclusions

In these early days of standards implementation in the industry, the SDRG can be a tool for communicating the rationale behind implementation decisions that will impact interpretation of electronic data. Going forward, as SEND "awareness" increases in the industry and nonclinical study designs incorporate SEND requirements, creating an SDRG will likely become simpler.

Observations on Suitability of Clinical SDRG Template for Nonclinical Studies: Both clinical and nonclinical studies share the need to clearly convey how the design and results of a study are presented as SDTM datasets. In its current form, the clinical SDRG template requires significant knowledge of the differences between clinical and nonclinical data types, SDTM domains, and handling; we expect persons populating SDRGs would have clinical OR nonclinical expertise and likely not both. With minor adjustments, though, we feel the clinical template could be easily adapted for nonclinical authors. A collaborative and parallel lifecycle for the templates would maintain similarity between the two and allow knowledge and experience obtained from the clinical use of the SDRG to benefit nonclinical use and vice versa.

Future Plans of Nonclinical SDRG Working Group: We plan to continue meeting to complete our analysis and to pilot the use of an SDRG adapted for nonclinical using model SEND data sets and define files.

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