

Achieving Clarity through Proper Study Documentation: An Introduction to the Study Data Reviewer's Guide (SDRG)

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ABSTRACT

With the ever-growing standardization requirements of FDA submissions, it can be difficult to understand where exactly you place non-conformant, essential information that does not have a home within other submission documentation. Now, with the Study Data Reviewer's Guide (SDRG), this information has a home and can be effectively communicated. The SDRG provides reviewers with key details they will need to perform a thorough review of the data, along with a space to answer questions from the reviewer before they are asked, expediting the review of the full documentation package of your trial. PhUSE has provided a step-by-step template that helps you understand what to report, where to report it, and makes sure nothing is lost so that traceability is clear. This paper will help you understand why it is important to think about the SDRG from the start, how to use these documents to your advantage, and provide examples of their flexibility and utilization.

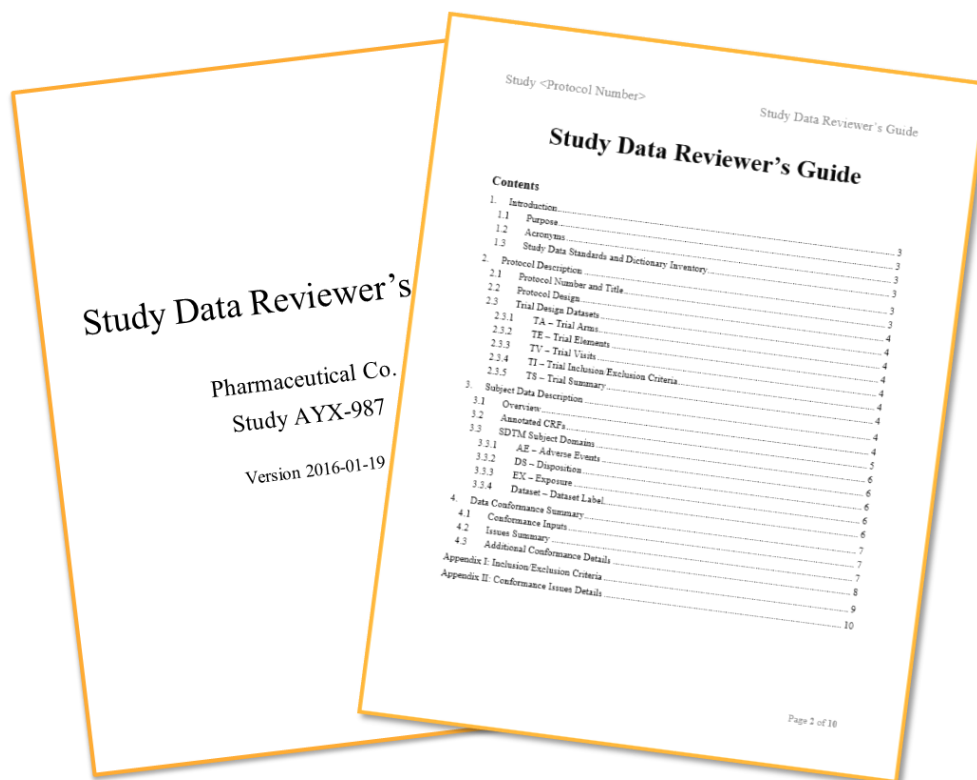
INTRODUCTION

The Study Data Reviewers Guide (SDRG) is recommended as an integral part of a standards-compliant study data submission per the FDA's Study Data Technical Conformance Guide. It is intended to describe SDTM data submitted for an individual study in the Module 5 clinical section of the eCTD. Thanks to the great work by the PhUSE Work Group, in a very short period of time, "Reviewer's Guides" went from every company - and frankly every study team - having their own format to a highly standardized document with completion instructions in a consistent and understood structure. Though not strictly required, the SDRG provides clarity to the FDA reviewer when using the submitted data.

The FDA's expectation of a reviewer's guide is that it describes any special considerations or directions that may facilitate a reviewer's use of submitted data, and may help a reviewer understand the relationships between the study report and data. The SDRG purposefully duplicates information found in other submission documentation (e.g. the protocol, clinical study report, define.xml, etc.) to provide FDA Reviewers a single point of orientation. Per section 2.2 of the Study Data Technical Conformance Guide, the SDRG should include, but is not limited to:

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 validation rules, versions, and issues
6. Description of all sponsor decisions related to data standard implementations

The template built by PhUSE has been developed around exactly these expectations. PhUSE's template walks you through step by step, with instructions, so that all you need to worry about is the content. Prebuilt tables are already placed in the document to aid in creation. From the description of your protocol to the explanation of Pinnacle 21 conformance issues, the document is laid out and has the sections waiting.



WHEN DO I START CREATING IT? THE EARLIER, THE BETTER

The SDRG can be a living document throughout the life of the study. Decisions are constantly being made throughout the course of a trial. Does it not make sense to build the document and add the content while the decisions are being made, rather than trying to remember every choice at the end of a trial? With the SDRG template, you can populate corresponding sections as each step of a study is started.

WHEN YOU HAVE A PROTOCOL

Section 1: Introduction

From the moment a protocol is finished you can start the introduction. The introduction provides an overview of the study data standards and an inventory of the dictionaries used. At this point, you may already know which SDTM and define.xml version you will use, planned MedDRA or WHODrug dictionaries, or other standards planned. Additionally, you can already start building a list of acronyms that will be used throughout the course of the document.

Section 2: Protocol Description

The protocol description provides a brief orientation to the study and, if necessary, provides additional context about the Trial Design Datasets. This is a great place to put content like graphics from the protocol that elaborate on the design of the study, such as process flows that map out each treatment arm. In this section, you also have the opportunity to expand on the content of your Trial Design datasets and explain anything that was not sufficiently described within the metadata in define.xml.

Appendix I: Inclusion Exclusion Criteria

With the SAS V5 Export file limitations, your Inclusion/Exclusion criteria may not play nicely with the IE or TI domains, and the Define.xml may not even be the most elegant place to represent this. The SDRG template provides an additional table where you may enter your full text, carriage returns, bullet points, and more as needed.

WHEN YOU HAVE CRF ANNOTATIONS AND SDTM MAPPING

Section 3: Subject Data Description

Section 3 provides additional context for subject-level SDTM domains that will not be adequately documented in define.xml or the SDTM Implementation Guide and its supplements. The overview prompts basic questions about your trial with which the reviewer will be interested. These questions include topics such as whether the study is currently ongoing, whether screen failures were included in the submission, if any planned domains were not submitted due to lack of data, and more. Additionally, here you may describe sponsor-specific annotated CRF conventions as needed. It is important for the reviewer to understand if annotation conventions deviate from the recommended process and how the annotations should be interpreted, as this may answer questions before they are asked.

WHEN SDTM PROGRAMMING IS COMPLETE

Section 4: Data Conformance Summary

You should already be running compliance checks on your data – hopefully using the Pinnacle 21 Community Validator (formerly OpenCDISC Validator). Section 4 prompts some questions about whether OpenCDISC was used, what version was used, which version of SDTM Controlled Terminology was used, whether the compliance report was evaluated against the define.xml – all extremely important topics directly relevant to the validation findings that you will be justifying.

The Issue Summary section allows you to justify your findings. The format of the pre-entered table for this section is very similar to that of the OpenCDISC validator report Issue Summary tab, making it very simple to get information from the report to your SDRG. All you need to do is add a justification for the found issues.

FLEXIBILITY AND CUSTOMIZABILITY

The SDRG has a set and logical structure, but it still allows for flexibility and customizability. Certain sections of the SDRG are expected to be populated and other sections are subject to removal if they do not add value, which are noted within the template. If you do not see a section that suits information that you need to communicate, you can always add one. Additionally, if your trial offers no information to support a section, then it may also be removed. For instance, if you are not providing Trial Domains, then there is no reason to populate section 2.3 (Trial Domain Datasets).

PRACTICAL USE: USING THE SDRG DYNAMICALLY

At this point, we have shown that building the SDRG from the beginning of your trial instead of the end is a logical decision, keeping you from struggling to find all of that important information at the end of your trial. But why can’t your team use it dynamically throughout the project for their *own* benefit? This is where a reviewer is going to look for information, so why not your team? Trials may often have team members shifting on and off the project or changing roles, and many of the sections of the SDRG can be a quick reference to answer questions and ramp new team members up to speed – saving your entire team time.

Another simple yet useful section to add into your SDRG is a decision log – a simple spreadsheet of issues encountered, decisions made and resolutions that give you, your team and a reviewer the answers to many of the questions they are going to have. The items captured in this log could include from data issues encountered throughout to the course of a trial to decisions, decisions about how to utilize a variable, use of custom domains – anything noteworthy.

Decision Log

| Domain | Variable | Issue | Resolution |
|-------------------|---------------------|------------------------|-----------------------------|
| <Impacted domain> | <Impacted Variable> | <Description of Issue> | <Description of Resolution> |

Table 1. Decision Log

Maintaining multiple trackers can easily build a lot of clutter in your project directories. Keeping too many documents to track study information is an easy way to lose traceability, lose consistency, and create confusion. Having a decision log within the SDRG while you are developing it is just another way to consolidate your important information into one logical and transparent location. When the time comes to create the final SDRG, you can clean out anything

that is no longer relevant, such as mapping discussions that have been resolved, and move what is left to logical sections of the SDRG.

THE SDRG IN ACTION: A REAL EXAMPLE

So far, we have discussed how the SDRG can aid not only your reviewer, but your team in understanding and communicating important decisions made or issues found throughout a trial. Now let us take a look at how this can be put to use using real examples.

The SDRG provides an appropriate place to document data issues encountered throughout a study. This informs the reviewer of the issue and creates clarity and transparency. For example, in section 3.1 (Overview), you have the space to detail if a subject was accidentally randomized twice.

3.1 (Overview):

| |
|---|
| <p>Additional Content of Interest</p> <p>In Part B, subject 9999 completed the multiple-dose phase but discontinued during the DDI phase due to an AE on Day 10. The subject subsequently rejoined the study and completed the DDI phase as subject 9998. Records for this subject are captured under one unique subject identifier (USUBJID=ZJ123-1234-999-9999). Only one record is kept in DM with first and last dates computed using combined subject records.</p> |
|---|

Under section 3.3.X (SDTM Subject domains), explanations of this data issue may be detailed for the impact to individual domains. For example:

| |
|--|
| <p>USUBJID ZJ123-1234-999-9999 represents SUBJID=9999 and SUBJID 9998 who is a subject that was randomized twice. The two records in this domain for these two SUBJID's were combined into one record under one USUBJID. Start and end dates were used from both records to compute RFSTDTC, RFENDTC, RFXSTDTC, RFENDTC. Age is from the first record. ARM and ARMCD were different for each record. The first randomized ARM was used for this subject. The second set of information for SUBJID = 9998 was placed in SUPPDM.</p> |
|--|

In section 4.2 (Issue Summary), the explanation column allows you to justify Pinnacle 21 Community conformance issues that remain.

Issue Summary

| Dataset | Diagnostic Message | Severity | Count | Explanation |
|---------|---------------------------|----------|-------|--|
| LB | SD11117-Duplicate records | Warning | 9 | USUBJID ZJ123-1234-999-9999 was randomized twice and entered the study twice so has duplicate records. |
| PC | SD11117-Duplicate records | Warning | 9 | USUBJID ZJ123-1234-999-9999 was randomized twice and entered the study twice so has duplicate records. |

Table 2. Issue Summary

As you can see, there are multiple locations throughout the SDRG where important information like this can be communicated, and multiple locations that it should be communicated. An issue like a subject accidentally being randomized twice will be prevalent throughout multiple aspects of your data and surface in many different ways. Therefore, it is very important that you communicate this in a way that a reviewer will quickly find the explanation or justification. With no clear or obvious place within the other documents involved in a submission, the SDRG is exactly the place where these type of issues should be documented and explained.

CONCLUSION

It is very easy to lose track of important issues found or decisions made throughout the course of a clinical trial and the last thing that you or your team wants is for an FDA reviewer to ask a question that you do not have the answer to during a submission. Even if you have the answers, it is imperative that they are documented somewhere easy to find for your reviewer. This is one reason why the FDA recommends the Study Data Reviewer's Guide as an integral part of a standards-compliant study data submission per the Study Data Technical Conformance Guide. With PhUSE's SDRG template, this job is made easy. By following the template, not only will your SDRG be easy to navigate and interpret, but it will also have all of the information that the FDA wants to see in an SDRG.

Not only is the SDRG a great tool for a reviewer – it is a great tool for your team. By offering a single point of reference for standards used, domains provided, issues found and more, your team can stay in communication and not let the small things slip through the cracks. Don't let the SDRG be a crisis at the end of your project – let it be a tool that helps you get there faster.

REFERENCES

- SDRG Package v1.2 2015-01-26 Study Data Reviewer's Guide Final Work Package
[http://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer%27s_Guide]
- Study Data Technical Conformance Guide v2.3
[<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>]
- Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format – eCTD Specifications
[<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/>]

CONTACT INFORMATION

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