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The Importance of Work Instructions When Creating Reviewer's Guides

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ABSTRACT

Creating a submission document is no small task – there are many steps and checks that should be performed to ensure a smooth delivery in tight timelines. Unexpected issues inevitably arise throughout a project. When time is short, consistency is needed to ensure the Reviewer's Guides are of highest quality. It is invaluable to have a Work Instruction detailing each task to be performed that is encompassing enough to apply to all studies, especially when creating highly consistent Reviewer's Guides. It is imperative to have a clear list of instructions on place documenting necessary steps to create comprehensive documents that adhere to CDISC standards and PhUSE templates. Good work instructions help reduce the shifting of workload to the documentation team and allow for less experienced staff to contribute to these tasks. This paper will explore the advantages of enforcing the use of Work Instructions to the author of Reviewer's Guides.

INTRODUCTION

Reviewer's Guides provide the Food and Drug Administration (FDA) Reviewers with additional context for datasets received as part of a regulatory submission. The Reviewer's Guide is intended to describe data submitted for an individual study in the Module 5 (clinical) section of the Electronic Common Technical Document (eCTD). These guides purposefully duplicate information found in other submission documents in order to provide FDA Reviewers with a single point of orientation to the datasets. Due to the information in the reviewer's guides being so standardized, it is possible to develop instructions and processes for completion in a more efficient manner and use them to improve production time of submissions.

A successful work instruction for creating reviewer's guides should include a template of the document. In practice, with many programmers involved in a study, it's realistic for multiple people to update or edit the working copy of the reviewer's guide simultaneously. Multiple authors can easily lead to an asynchronization in terms of fonts, formatting, etc. that will detract from the final product. Having a template in place at the start of the reviewer's guide creation can help address these issues before they occur. This will ensure that when the document is finalized to the FDA-required PDF version, it will look clean and professional. Furthermore, when the template is adhered to rather than starting from scratch, it can lead to a more efficient creation of links to other sections of the document. An additional advantage is the high level of consistency that can be achieved across multiple studies, which is especially valuable when submitting a large volume of similar packages to the same sponsor.

By creating a reviewer's guide template, the author(s) will have a clear starting point for writing the guide. Within the template employed at Covance, all possible document sections are included. The work instruction denotes them as either a required or optional section. This proves especially helpful at a Contract Research Organization (CRO) where work is closely catered to client needs. For example, the work instruction cites *Acronyms* as an optional section. One Functional Service Provider (FSP) may request a full acronym section while another may choose to exclude it entirely. Having a clear layout of what is flexible to client needs and conversely, what is a submission requirement, is a valuable tool. As the author reads through, in addition to whether the section is required or optional, there is a brief description of what explanatory text belongs there. Having a template and further explanation creates even more clarity about exactly what should be in each section, which in turn generates consistency within studies, and additionally within all submissions coming from the sponsor.

The documents are intended to be utilized as a pair; reading through the work instruction while populating the necessary fields in the template. The work instruction is written in a manner that corresponds directly to the sections in the template. This is done to help it work as an efficient tool in conjunction with the template. Because of the core

differences between Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) studies, Covance has separate work instructions and templates for creating the Study Data Reviewer's Guides (SDRGs) versus an Analysis Data Reviewer's Guides (ADRGs). Explore the SDRG template and work instruction as an example to understand the benefits of implementing these documents.

WALKING THROUGH THE WORK INSTRUCTION

Reviewer's guides vary depending on what kind of study is being submitted. Guides associated with SDTM studies, as a standard, are required by the FDA to include different information than those associated with ADaM studies, as well as any other data standards that may be adhered to. For clarity, the following paper will be specifically discussing guides related to SDTM studies submitted to the FDA. With that said, no matter the data standard, documents can be developed for applying similar instructions to simplify the work in the same manner and would allow an analogous standardization of the process.

The SDRG template associated with the work instruction is 10 pages long, and includes all possible sections of the reviewer's guide. It opens with a cover page, where the author need only to update the *Sponsor Name* and *Protocol Number*, unless otherwise indicated by the client. The template is useful in this section, because when the title page is correctly formatted and populated, the protocol number on each page of the document is automatically populated throughout the headers of the document. This decreases the chance of typing inconsistencies in the text.

The title page is followed by the *Contents*. Creating a template for this has drastically decreased errors with linking within the document. Covance uses a word processing software to edit the working document before finalizing it to a PDF. When the capabilities of the software are being efficiently utilized and the table of contents is set up correctly (as it is in the template) the author does not need to make any changes to this page. The author can populate the rest of the guide with all necessary information, updating the appropriate headers, etc. without concern for keeping track of the order, phrasing of titles, or page numbers. Once the document is ready to be finalized, this page simply needs to be right clicked and "updated" which will adjust it to include all sections of the document appropriately. Again, this decreases the chance of typing inconsistencies between the table of contents entries and the actual titles of sections. It is also a more accurate and easier way to ensure the page numbers are correct. Finally, the table of contents automatically creates links to the corresponding sections, so it simplifies that work as well. Before the template is edited and the table of contents is updated, it looks like the following:



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Following the introductory pages, the study-specific content begins with the *Introduction*. This section aims to provide an overview and information about the inventory standards used on the study. The first subsection, *Purpose*, is populated with brief, entirely standardized, explanatory text that would be applicable to most SDTM studies, describing what an SDRG is used for. The purpose is immediately followed by two unpopulated tables, *Acronyms* and *Study Data Standards and Dictionary Inventory*, respectively. Because the acronyms section is not required, the work instruction suggests deleting this table unless sponsor-specific or non-industry standard acronyms are used elsewhere in the SDRG. It need not explain industry standard acronyms that an FDA Reviewer will already be familiar with. Conversely, the study data standards and dictionary inventory is a required section. This table prompts for the SDTM, Controlled Terminology, and Define.xml versions, as well as multiple specific dictionaries. The author simply needs to populate the versions used, and delete any non-applicable dictionary rows.

Protocol Description is the next section. This section provides a brief orientation to the study and, if necessary, provides additional context about the Trial Design Datasets (TDMs). The template requests *Protocol Number*, *Title*, and each *Protocol Version* in the first, required subsection. This can be followed by the optional subsection for *Protocol Design*. Each of these sections requires information or graphics that should be taken directly from the protocol documents provided with the study, as the work instruction notes. However, they are followed by questions concerning the TDMs, which may require more complex thinking to populate. It asks if TDMs will be included in the submission – if not, this section can be answered negatively and it is complete. However, when included, this is where the FDA Reviewer can find descriptive text of what is in each trial design dataset. The author is requested to provide this descriptive text. This information can again be taken from the protocol, as well as the existing datasets. However this section requires more synthesis from the author than the previous ones. The advantage to noting the complexity of a section is that this information can be utilized to further standardize the creation process. A less experienced team member, possibly an entry-level programmer or an intern, could use the work instruction and template to successfully fill out any straight-forward sections of the document. This allows a team member with more

industry- and project-experience to only review this document, paying additional attention to areas of the guide that might require more expertise to populate.

Subject Data Description begins with an *Overview* that provides additional context for subject-level SDTM domains that are not adequately documented in the define.xml or the Study Data Tabulation Model Implementation Guide (SDTMIG) and its supplements. It is comprised of questions prompting for some information about whether the study is ongoing, if it will be accompanied by further analysis, screen failures, and other related information. Additionally, in the following *Annotated CRFs* section, the template describes sponsor-specific annotated Case Report Form (CRF) conventions as needed. However, this subsection should only be populated when sponsor-specific annotation conventions need to be explained. As long as the Study Data Technical Conformance Guide (TCG) conventions are being followed, this optional section can be removed. This is followed by the *SDTM Subject Domains* section, which tend to be the bulk of these guides. It includes a table that needs to be populated with an inventory of the SDTM datasets being submitted.

This list (below) should not include any datasets noted in Section 3.1 as a domain that was planned, but not submitted because no data were collected. All subject-related datasets should be listed alphabetically by domain code, each appearing on a separate row. Split datasets should each have a separate row, however RELREC and TDMs should not be presented here. The explanation of TDMs in Section 2.3 is sufficient, and if relationships between any domains have been described in RELREC, this can be specified in the 'Related Using RELREC' column of the table. Using the appropriate columns, the functionality of each dataset needs to be denoted as Efficacy, Safety, or Other. The Observation Class, which can be retrieved from the SDTMIG, should also be populated in the appropriate column. It should also be specified if a Parent domain has an associated Supplemental domain in the appropriate column. Any domains that do have an associated supplemental domain, in addition to any datasets that have an additional explanation within the document, need to include this text in a subsection of Section 3.3.

3.3 SDTM Subject Domains

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
AE – Adverse Events		X				Events
DM – Demographics			X			Special Purpose
DS – Disposition			X			Events
EX – Exposure			X			Interventions

In addition to the explanatory text, the dataset entered in the table needs to be hyperlinked to the page where the description is found. The usefulness of the template in this section is again related to consistency and accuracy. The template is populated with a handful of example domains (AE, DM, DS, and EX) and the related subsections (shown below). Because authors are populating this existing table rather than creating it on their own, it is harder to make some technical mistakes. For example, it is unlikely that any author would enter RELREC into its own row when a column specifying this relationship already exists. Similarly, having a template table for the QNAM and description that is required of the supplemental datasets present leaves less room for mistakes as well.

3.3.1 AE – Adverse Events

(Text and/or supplemental qualifier inventory here)

3.3.2 DS – Disposition

(Text and/or supplemental qualifier inventory here)

3.3.3 EX – Exposure

(Text and/or supplemental qualifier inventory here)

3.3.4 Dataset – Dataset Label

(Text here)

QNAM	Description

The fourth and final numerical section of the SDRG is the *Data Conformance Summary*, which documents the validation inputs used to evaluate SDTM conformance and summarizes conformance findings. *Conformance Inputs* begins with a subsection asking questions related to validation processes and versions, or if any sponsor-defined validation rules were used. It also contains some information about the define.xml. The questions in the template clearly lay out what information the author must provide, which eases the creation of this section. This is followed by the *Issues Summary*. In case the sponsor requires a different form of data validation, this work instruction does not require that Pinnacle21 software is used to validate the data. However, when used, population of this section is simpler. This is because it provides instructions for transferring information from the report document into the actual reviewer's guide. At this point, only an explanation for the messages needs to be populated. Similar to *Protocol Design* above, this is another section worth exploring the complexity of for standardization purposes. The unpopulated table is shown below.

4.2 Issues Summary

Dataset	Diagnostic Message	Severity	Count	Explanation

Most information required by this table, as previously explained, can easily be reformatted from a validation report output. However, the importance of providing a clear, accurate explanation for why the message is occurring and furthermore why it can be left in the data is cannot be understated. To an FDA reviewer, these explanations are one of the most significant sections of the document, because they determine the difference between a data issue, and an allowable deviation from standards. These explanations can require in-depth, study-specific knowledge from the author, and should be carefully reviewed for accuracy. However, based on the nature of these reports, diagnostic messages can be repetitive, and thus reasons for the explanation can be repetitive as well.

To ease the creation of this table, it is helpful for studies to have a repository of explanations that can be referenced. This can ensure consistency within phrasing – for example, a study completed at Covance once used standardized text as an example for every domain with the message “SD1078: Permissible variable with missing value for all records”. The reason this message was generating was straightforward enough and there is a simple, programmatic solution to remedy this. However, after discussions with the sponsor, they requested to keep certain permissible variables present in all studies for consistency purposes. (This was a case of submitting 30+ very similar SDTM studies for FDA approval, so unless a permissible variable was missing for all values in every study being submitted, they did not want it to be dropped.) An explanation was authored describing this: “It is a sponsor decision to include variable for all studies.” This is simple enough, but could be phrased in a multitude of ways depending on who is saying it. It's especially important to have a process to achieve consistency in a case where this many studies are

being submitted together – a project that spans that long could easily have team members moving on and off of it. Because of this, a repository of explanations was collected, so it could be referred to when populating this table. It's recommended to keep this repository on a smaller scale for CRO purposes. The suggestion is to keep it within studies, stored in a place that can be accessed by all the Reviewer's Guides authors.

It's clear to see that this explanation might be insufficient on a study for a different sponsor who might simply choose to drop the variables. However, having these repositories can aid in assigning this work to a less-experienced member. Again, similar to *Protocol Design*, having a list of common explanations can transition this from being a time-consuming section for a project expert to complete into a task that can be assigned to an intern. This standard text for common issues can be referred to and utilized to create more cohesive study packages. Then it need only be carefully reviewed and updated by a Senior Reviewer.

Additional Conformance Details is the final, optional, subsection of the data conformance summary. This is only necessary when there exist summary findings other than the ones reported by the conformance report, which the sponsor deems to merit explanation. When this needs to be populated, the template specifies to do it in a similar manner to Section 4.2.

The appendices are the final, optional, sections of the Reviewers Guide. *Appendix I* should only be included when the complete set of inclusion/exclusion criteria cannot be fully documented in the Trial Inclusion/Exclusion Criteria (TI) dataset. This section must be included when a hyperlink is supplied (in Section 2.3) to the full inclusion/exclusion criteria contained in the annotated CRF. *Appendix II* should only be included when specifically requested by the sponsor, and should include a detailed record-level description of conformance issues. Each of these sections are described in the work instruction, with unpopulated tables provided in the template. This helps facilitate the accuracy with which they are populated in situations when they are necessary for the submission.

FINALIZING, STANDARDIZING, AND APPLYING THE PROCESS

As this paper has alluded to, no parts of completing a reviewer's guide should be terribly complicated. Ideally, programmers or team members on the study with project-specific knowledge should know most of the information that will be immediately present. Because of this, with a template and instructions, the task at hand should not be terribly pressing. Without a template, however, teams can run into inconsistencies within header labels, the syntax for explaining issues, and lots of other formatting issues on top of any content that needed to be reviewed.

Due to the nature of information contained in a Reviewer's Guide, while some pre-work can be done to prepare for the creation, it does need to be completed near the end of a study. With dynamic data, information that is included in the guide, such as the labels of QNAM variables in the supplemental datasets, may still change. If entered into the guide too early, it can either misrepresent the data, or need to be updated again anyway. For these reasons, communication is key in developing a quality work instruction. The documentation team and programming team, if separate, need to have a clear understanding of the status of the datasets. However, once communication and a process is achieved, the work is easier to shift elsewhere, which can be helpful for allowing more people to contribute and achieving earlier deadlines.

If a clear and consistent process is developed early on, it becomes easy to apply and teach to others. At Covance, after working to achieve a clear process, the use of global teams was possible to help improve speed of production. This would not have been possible without a template that laid out what information belonged where and with what instructions. The sections were clearly laid out, so it was possible to communicate with the global team in a way that they could populate the document and others could read, review, and finalize this document, rather than creating it from scratch. Additionally, having templates and instructions to point global team members to proved to be invaluable when working in different time zones. If a team member encountered a question about the work, they could explore these instructions and templates rather than needing to email a question and wait for an answer.

Along with using global teams, having very standardized instructions allows lower-level programmers who might be assigned to contribute to a document like this, or interns in a company that still have much to learn, get familiar with looking at a study and taking a first pass at populating this kind of document. Working on an SDRG is an excellent place for team members to get their feet wet with SDTM studies—getting experience with the data standard while remaining a low-risk addition to the project deadlines. In practice, it helped speed up production greatly on the documentation-side of the team, who were now beginning work with a document that needed to be reviewed and verified rather than developed. This allows the documentation team to complete and submit the entire package in a much more quick and efficient manner.



ACKNOWLEDGING ISSUES AND MOVING FORWARD

Of course, even with instructions problems can still arise. The most pressing ones at hand in this situation were communication-related. After laying out the instructions and template and resourcing the work to a team located in Bangalore, they started producing draft SDRGs for multiple studies at an incredible rate. Their valuable work allowed the all 30+ SDRGs to be completed in a preliminary state before the US documentation team was reviewing them for the first time. While this helped develop useful drafts that just needed to be updated, rather than a document that needed to be completed, because of the location and expertise of the team, problems still existed. There very reasonably existed a language barrier that extended past the standardized text in some sections. The document still needed to be reviewed for clarity and cohesiveness because that could be lost, even with rules laying out how to populate certain sections. Although having instructions and a template helped assuage the time-zone barrier slightly, it did not remove the issue. Though these issues did exist, the transfer of SDRG work was ultimately a success, one which would not have been possible without a clear work instruction and template.

The same sponsor has contracted further analysis for the aforementioned studies. This will mean the creation of another 30+ packages for submission to the FDA – this time for ADaM datasets. As stated above, Covance has separate templates and work instructions for authors of SDRGs and ADRGs due to the differing content. Now that project teams have utilized these documents to facilitate SDTM package creation, it will be simple to use the ADaM-related documents for similar ADRG work. Addressing the problems run into on the SDTM packages will be integral to further improving the process on this second pass. A more clear line of communication needs to be developed. Perhaps weekly status meetings at a time that is convenient for all time zones could be useful for keeping all team members on the same page, and allow a forum for asking questions and getting quick responses. This could possibly help lower the language barrier a bit as well, though it is unlikely it will remove it entirely. However, consistent conversations with all team members create an understanding of how everyone thinks and speaks, which would certainly ease some of the language-related problems. Another step to further standardization could be implementing programmatic retrieval of some of this information from the datasets. This would add a layer of quality assurance as well – for example, programmatically checking the dataset labels would ensure that the datasets are labelled correctly in both the data and the guide. Developing these could be an exciting next step to improving the process.

CONCLUSION

In conclusion, a reviewer's guide explains a lot of information about a study that the team of people most invested in a project need to understand in order to complete their work. Because of this, the content populated in these documents does not tend to be terribly complicated. However, it can be difficult to provide exactly what is needed for the reviewer in a useful layout, in a time-efficient manner, on top of working on other project-related tasks. In many cases this can include multiple teams of people, potentially traversing hurdles like different time zones and language barriers in addition to any study-related issues. A line of communication should be established and adhered to – this will ensure that information is disseminated to the team in time-appropriate manners. If plans are established and a work instruction is clearly laid out, then the project team should have the confidence to trust the process in creating this product. Having a template and instructions explaining what information belongs where in the document in a clear manner facilitates this process and allows for standardization of creation, outsourcing of specific responsibilities, and ultimately quicker and more efficient development and finalization of higher-quality documents.

REFERENCES

[Study Data Technical Conformance Guide](#)

Internal Document: Creation and Quality Control of Study Data Reviewer's Guide

Internal Document: Creation and Quality Control of Analysis Data Reviewer's Guide

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