How Can I Put This? - Using a pre-defined spreadsheet to explain your Pinnacle 21 Enterprise Issues

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INTRODUCTION

Pinnacle 21 Enterprise compliance issues are going to happen on every study. Whether validating SDTM or ADaM, or using the tool to create Define.xml documents, the odds are almost 100% that some compliance issues will be identified and almost equally high odds that some of those issues cannot or will not be resolved. Even in the very rare occasions that a sponsor might be using a different compliance tool, the regulatory agencies (FDA, PMDA, etc.) are still going to run the data through Pinnacle 21 Enterprise as part of their review process. It is given that at least some Pinnacle 21 Enterprise compliance issues will exist. And for every compliance issue that remains unsolved, the clinical study team is required to provide an explanation in the Data Conformance Summary of the appropriate reviewer’s guide (Section 4.2 in the cSDRG and Section 6.2 in the ADRG).

Lilly has taken a novel approach in our issue resolution process to provide clear, appropriate, and consistent explanations using a pre-defined spreadsheet that is uploaded directly into Pinnacle 21 Enterprise and is available for all our studies. This spreadsheet contains fix tips and suggested wording for most of the Pinnacle 21 Enterprise issues that would require explanations. These fix tips and explanations are more specific to our clinical trials and data standards than those already provided in the Pinnacle 21 Enterprise tool. While it is understood that the suggested wording won’t work in every case, they do cover the most frequently encountered situations. Even in the cases where the suggested text isn’t an exact fit, its format and wording usually provide the clinical study teams with a good starting point to help provide the appropriate explanation.

This paper will explore the background on why we felt this approach was valuable. How the fix tips and explanations were developed, and how the spreadsheet is maintained. It will also address what clinical study teams should do when a particular issue is not included in the spreadsheet or when the provided fix tip or explanation is not relevant for their situation.

BACKGROUND

As was previously stated, Pinnacle 21 Enterprise compliance issues are going to happen. Clinical study teams can certainly take steps to reduce the number of issues. But no matter how much attention is given to quality and data integrity; no matter how close the entire clinical study team adheres to CDISC standards; no matter how diligent the investigator sites are at collecting the data, situations are going to arise during the study that either create inconsistencies in the data or just don’t fit well into the CDISC structure.

Both the FDA and PMDA have set their expectation for sponsors to provide meaningful explanations in their respective Technical Conformance Guides for all unresolved issues:
FDA Technical Conformance Guide

8.2.2 Support on Data Validation Rules

Sponsors should evaluate their study data before submission against the conformance rules published by an SDO, the eCTD Technical Rejection Criteria for Study Data, and the FDA business rules. Sponsors may also wish to use the FDA validator rules to understand what is available to the FDA reviewer. The FDA validator rules also represent the latest understanding of what best supports regulatory review. Sponsors should either correct any discrepancies between study data and the standard or the business rules or explain meaningful discrepancies in the relevant Reviewer Guide (RG).

PMDA Technical Conformance Guide

4.1.2.3 Reviewer’s guide

To promote the understanding of the content and characteristics of the dataset by reviewers during the review and enable the applicant to explain about the utilization status of and conformance to the data standards when creating the datasets, a dataset definition document as well as a data guide must be created for each of the SDTM and ADaM datasets, which, in principle, should be stored in the same folder as their corresponding dataset prior to submission.

At least the following items should be included in the data guide for the SDTM dataset.

- Clinical study name, protocol number
- Explanation of the clinical study design
- Standards, controlled terminologies, and dictionaries used and their versions
- Explanation of the annotated CRF
- List of datasets to be submitted
- Explanation of the subject data

- **Information on conformance to the data standards**
  - Validation tool used for the validation and its version
  - Version of the validation rules used for validation
  - Explanation on conformance to the data standards (explanation of the validation results)

In principle, the following items should be included in the reviewer’s guide for the ADaM dataset.

- Clinical study name, protocol number
- Explanation of the clinical study design related to the analysis dataset
- Standards, controlled terminologies, and dictionaries used and their versions
- Considerations related to multiple analysis datasets
- Considerations on creating the analysis datasets
- List of datasets to be submitted
- Explanation of the datasets

- **Information on conformance to the data standards**
  - Validation tool used for the validation and its version
  - Version of the validation rules used for validation
While the expectation and direction for providing issue explanations is clear, the execution can be challenging. What often happens when trying to explain Pinnacle 21 Enterprise compliance issues is the clinical study teams struggle with providing an explanation that is concise, appropriate, and transparent to what caused the compliance issue to fire. The teams also tend to provide explanations that lack consistency with the study’s data or metadata or with similar issues, whether within the same study or in other studies being submitted. These types of explanations risk creating confusion for the data reviewers which can hurt their confidence in the data integrity of the submission and often lead to more regulatory questions.

Resolving or explaining Pinnacle 21 Enterprise issues is seldom someone’s primary job. The clinical study team is comprised of many people who are knowledgeable and well trained in their specific areas. And while they know and understand the data very well, they don’t always understand why a Pinnacle 21 Enterprise issue is firing or what the issue description really means. This results in explanations that might not get down to the root cause of the problem, or explanations that are over-simplified and don’t provide any meaningful information such as “per sponsor’s standard”, “this is our standard”, “data is as collected” or the more-often-than-not incorrect “false positive”.

Other times, the issue explanation can be written using terms or sponsor-specific acronyms that might be very clear and common to members of the clinical study team, but not to anyone outside of that specific sponsor.

And one final example of a common non-optimal type of explanation is one that is long and convoluted. Most often this type of explanation is overloaded with too much information in too few sentences.

Doing a bad job of explaining issues hurts the integrity and credibility of the study data. We can’t assume that the reviewer is just going to know what we are talking about. Being vague, long-winded, or abstract fails to achieve the goal of providing a clear, understandable explanation. Over explaining can raise more questions than it answers, especially if it leads the reviewer down paths that they were not originally on.

DEVELOPMENT OF THE FIX TIPS AND EXPLANATION SPREADSHEET

Since its initial rollout, Lilly has looked to utilize the features in Pinnacle 21 Enterprise to optimize data delivery and the user experience. With the version 4.0 release, we recognized the benefit and usefulness that having suggested explanations would have for both the clinical study teams and the reviewers. In 2019, the Subject Matter Experts (SMEs) that supported Pinnacle 21 Enterprise for all the clinical study teams came together to develop a template for this purpose. Whereas the members of the clinical study teams often struggled to understand why some of the issues were firing, the SMEs were much more familiar with the common issues and had several years of experience in helping teams resolve some of the more complex issues (including REJECTS and issues that resulted from uncommon situations that should not have occurred). We also were able to obtain metrics on how often issues were firing by study and could analyze them to see if certain issues were more likely to fire for certain types of studies or
in certain therapeutic areas.

The SMEs established a set of assumptions and rules to guide our definitions of the suggested explanations including:

- We could not always anticipate or provide final wording for every situation. Teams would have to tweak the suggested explanation or create a new explanation as appropriate.
- Fix tips and/or issue descriptions would help guide the user on why the issue was firing and/or how to fix the issue.
- Comments on how to use the suggested explanation or provide an alternative explanation would be included in bold text in explanation column of the spreadsheet with instructions to discard the comment from the final explanation wording.
- Many explanations would provide more clarity with information included that was specific to that study and situation (e.g. values, protocol specifications, variable names). To indicate that a change was needed, pointy brackets were used in the suggested explanation as a place holder (e.g. for AD0148: Non integers are used for parameters <List the parameters> to assist the TFL Programming sequence.)
- Many issues had multiple conditions that would make them fire. If more than one suggested explanation was required to cover all of the conditions, each condition would be paired with the suggested explanation (e.g. for SD1096: [If the original value was greater than 200 characters:]). Instructions would be included to drop the condition text from the final explanation wording
- Some issues had multiple conditions that would make it fire but fixing the issue rather than providing an explanation was the appropriate action for one or more of the conditions. When this situation occurred, the only suggested explanations included in the spreadsheet would be for those conditions the SMEs felt were appropriate.

The template was created using an excel spreadsheet. We approached the issues by initially grouping them by the tasked performed that would be most likely to cause them to fire:

- Validating SDTM
- Validating ADaM
- Creating a Define.XML

Knowing that some issues could fire for two or all three tasks, we looked at each one for each task and adjusted conditions and explanation wording as appropriate.

CREATING THE ISSUES EXPLANATION FILE FOR PINNACLE 21 ENTERPRISE VERSION 4.0

As previously stated, Lilly first started to define custom explanations to use in release 4.0. The original spreadsheet was vertically organized whereas the current spreadsheet is horizontal. If an issue had more than one possible suggested explanation, a new row in the spreadsheet was added. Lilly also used the vertical approach to provide descriptions for different scenarios which would later be the basis for the company-defined fix tips in version 5.0
Layout of the Issues Explanation File used for Pinnacle 21 Enterprise version 4.0

CONVERTING THE SPREADSHEET TO PINNACLE 21 ENTERPRISE VERSION 5.0

When Pinnacle 21 Enterprise version 5.0 was being implemented, many of the Pinnacle 21 Enterprise fix tips that were provided with the release were very similar to the ones Lilly had established in 4.0. The SMEs decided to keep both with the Lilly fix tips appearing first. Our reasoning was we didn’t find any risk or harm to have both, and that going through another evaluation process to determine which ones to keep or modify wasn’t value added at the present time.

Populating the Issues Metadata Spreadsheet

Pinnacle 21 Enterprise provides the ability to manage the issues metadata spreadsheet through the ISSUE METADATA menu option.
Clicking on + Import Issues Metadata will allow you to download a blank template or the existing explanations metadata already loaded.

One important note: If you have previously imported a template with custom fix tips, you will want to keep that as your master copy on file somewhere outside of the tool. Downloading your existing template out of the tool will provide your custom explanations, but not the custom fix tips.

Another reason to keep a master copy is it will save a little bit of time by eliminating the need to...
format or wrap the spreadsheet cells every time you want to make a modification.

Example of the downloaded Issues Metadata file

Example of a Master Copy Issues Metadata file
Example of a rule (SD0058) with both Lilly and Pinnacle 21 Enterprise fix tips

Version 5.0 also only allowed a maximum of five pre-defined explanations and fix tips where version 4.0 allowed us to set as many as needed. For most rules, this was not an issue, but Lilly did have a handful of rules in the 4.0 template that had more than five unique explanation choices. Most of the differences between them were minor points of clarification, having to do with different domains or domain classes. To stay within the maximum limit set in version 5.0, several of these explanations were combined by modifying the fixed text with pointy bracket placeholders so the user would know to insert the appropriate text to match the situation.

It was also discovered that once uploaded into Pinnacle 21 Enterprise 5.0, the explanations did not always display in the same order as in the spreadsheet. This would sometimes cause a mismatch between the fix tip and the explanation. To work around this issue, an integer prefix was used in the explanation before the explanation comments. We chose to only do this for rules that had multiple explanations.
Example of a rule (SD0058) with multiple explanations

1. Information between [ ] provides condition. Select the explanation based on the condition, then delete this line and the condition */ [Select when variable is APID, domain is a SQAP—] As per the Associate Persons IG, APID is a key variable and it is added to maintain relationships between data in AP— and SQAP—.

2. Information between [ ] provides condition. Select the explanation based on the condition, then delete this line and the condition */ [Select when variable is SSTUDYID, domain is a trial design domain, and study is a master protocol] This protocol in a master protocol. The non-standard variable (SSTUDYID) was added to trial design domains in order to differentiate information across the various sub-protocols that are part of the master protocol.

Found 4 records
Example of a rule (SD0058) with multiple explanations scrolled down

SD0058 as it appears in the Master Copy of the Issues Metadata File
ONGOING MAINTENANCE OF THE ISSUES METADATA FILE

We work completely from our Master Copy of the Issues Metadata File. Uploading the Master Copy back into Pinnacle 21 Enterprise just overwrites the previous copy so we have found no benefit to downloading the current version out of the tool. In fact, the amount of reformatting and adding our custom fix tips makes it inefficient to use the exported copy after the initial upload.

Adding, deleting, and modifying fix tips and issue explanations is an activity that is shared across almost every function involved in data delivery. While the Pinnacle 21 Enterprise SMEs stay on top of new or modified rules in the tool, most of the changes are suggested from clinical study team members using the tool. They provide valuable feedback on existing fix tips and explanations and let us know when and why new explanations are needed.

Once it is established that a fix tip or an issue explanation needs to be added or modified, one of the Pinnacle 21 Enterprise SMEs will compose a draft for review. The Pinnacle 21 Enterprise SMEs approve and add the final wording to the Master Copy and upload it into Pinnacle 21 Enterprise.

The final scenario to discuss is when the issue does not have suggested wording because it should not be left unresolved. Some examples of this would be anything that causes a REJECT message, missing required variables or values, or situations that would be considered protocol violations. In these instances, the SMEs do not provide suggested explanation text. The reasoning is that the study team should make every effort to resolve the issue. REJECT issues are always resolved. For other issues of this nature, if resolution is impossible, each occurrence must be addressed on a case-by-case basis. The Pinnacle 21 Enterprise SMEs work with the clinical study team to ensure the explanation and any additional documentation is transparent and appropriate to the circumstances that caused the issue to fire.

CONCLUSION

Lilly’s approach to provide teams with custom fix tips and suggested wording for issue explanations has been a great success. Clinical study teams are more engaged in the issue resolution process which has led to issues being addressed sooner and more issues being resolved before final data lock. For those issues that aren’t resolved, the explanations provided to the reviewers are more consistent, concise, and appropriate to the root cause of what made the issue fire in the first place. Study teams are experiencing fewer post-production changes due to missed or incorrectly documented Pinnacle 21 Enterprise issues, therefore saving time on the back end of the submission process when it is most critical. Spending less time on Pinnacle 21 Enterprise issue resolution has allowed team members to focus on other submission tasks.

The overall effect of addressing issues earlier, having fewer unresolved issues, and having more suitable explanations has resulted in higher quality submissions and a reduced number of questions from regulatory reviewers.
REFERENCES


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