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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[1]

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 bests 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[2]

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*

    - ***Explanation on conformance to the data standards (explanation of the validation results)***
- *Information on the program*

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:

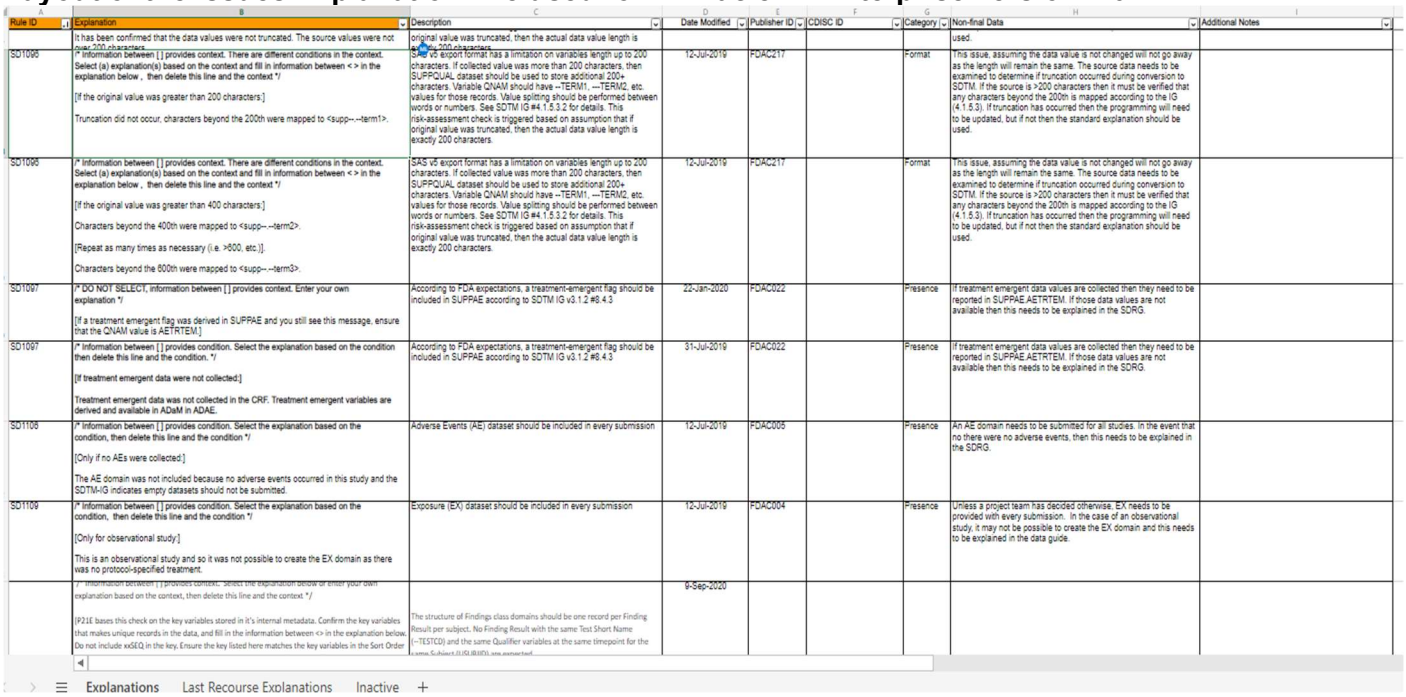
- Validating SDTM
- Validating ADaM
- Creating a Define.XML

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 EXPLANATON 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



Rule ID	Explanation	Description	Date Modified	Publisher ID	CDISC ID	Category	Non-final Data	Additional Notes
	It has been confirmed that the data values were not truncated. The source values were not over 200 characters.	original value was truncated, then the actual data value length is exactly 200 characters.					used.	
SD1095	/* Information between [ ] provides context. There are different conditions in the context. Select (a) explanation(s) based on the context and fill in information between < > in the explanation below , then delete this line and the context */ [If the original value was greater than 200 characters:] Truncation did not occur, characters beyond the 200th were mapped to <supp--.--term1>.	SAS v5 export format has a limitation on variables length up to 200 characters. If collected value was more than 200 characters, then SUPPQUAL dataset should be used to store additional 200+ characters. Variable QNAM should have --TERM1, ---TERM2, etc. values for those records. Value splitting should be performed between words or numbers. See SDTM IG #4.1.5.3.2 for details. This risk-assessment check is triggered based on assumption that if original value was truncated, then the actual data value length is exactly 200 characters.	12-Jul-2019	FDAC217		Format	This issue, assuming the data value is not changed will not go away as the length will remain the same. The source data needs to be examined to determine if truncation occurred during conversion to SDTM. If the source is >200 characters then it must be verified that any characters beyond the 200th is mapped according to the IG (4.1.5.3). If truncation has occurred then the programming will need to be updated, but if not then the standard explanation should be used.	
SD1096	/* Information between [ ] provides context. There are different conditions in the context. Select (a) explanation(s) based on the context and fill in information between < > in the explanation below , then delete this line and the context */ [If the original value was greater than 400 characters:] Characters beyond the 400th were mapped to <supp--.--term2>. [Repeat as many times as necessary (i.e. >600, etc.)]. Characters beyond the 800th were mapped to <supp--.--term3>.	SAS v5 export format has a limitation on variables length up to 200 characters. If collected value was more than 200 characters, then SUPPQUAL dataset should be used to store additional 200+ characters. Variable QNAM should have --TERM1, ---TERM2, etc. values for those records. Value splitting should be performed between words or numbers. See SDTM IG #4.1.5.3.2 for details. This risk-assessment check is triggered based on assumption that if original value was truncated, then the actual data value length is exactly 200 characters.	12-Jul-2019	FDAC217		Format	This issue, assuming the data value is not changed will not go away as the length will remain the same. The source data needs to be examined to determine if truncation occurred during conversion to SDTM. If the source is >200 characters then it must be verified that any characters beyond the 200th is mapped according to the IG (4.1.5.3). If truncation has occurred then the programming will need to be updated, but if not then the standard explanation should be used.	
SD1097	/* DO NOT SELECT, information between [ ] provides context. Enter your own explanation */ [If a treatment emergent flag was derived in SUPPAE and you still see this message, ensure that the QNAM value is AETRTEM.]	According to FDA expectations, a treatment-emergent flag should be included in SUPPAE according to SDTM IG v3.1.2 #8.4.3	22-Jan-2020	FDAC022		Presence	If treatment emergent data values are collected then they need to be reported in SUPPAE.AETRTEM. If those data values are not available then this needs to be explained in the SDRG.	
SD1097	/* Information between [ ] provides condition. Select the explanation based on the condition then delete this line and the condition. */ [If treatment emergent data were not collected:] Treatment emergent data was not collected in the CRF. Treatment emergent variables are derived and available in ADaM in ADAE.	According to FDA expectations, a treatment-emergent flag should be included in SUPPAE according to SDTM IG v3.1.2 #8.4.3	31-Jul-2019	FDAC022		Presence	If treatment emergent data values are collected then they need to be reported in SUPPAE.AETRTEM. If those data values are not available then this needs to be explained in the SDRG.	
SD1108	/* Information between [ ] provides condition. Select the explanation based on the condition, then delete this line and the condition */ [Only if no AEs were collected:] The AE domain was not included because no adverse events occurred in this study and the SDTM-IG indicates empty datasets should not be submitted.	Adverse Events (AE) dataset should be included in every submission	12-Jul-2019	FDAC005		Presence	An AE domain needs to be submitted for all studies. In the event that no there were no adverse events, then this needs to be explained in the SDRG.	
SD1109	/* Information between [ ] provides condition. Select the explanation based on the condition, then delete this line and the condition */ [Only for observational study:] This is an observational study and so it was not possible to create the EX domain as there was no protocol-specified treatment.	Exposure (EX) dataset should be included in every submission	12-Jul-2019	FDAC004		Presence	Unless a project team has decided otherwise, EX needs to be provided with every submission. In the case of an observational study, it may not be possible to create the EX domain and this needs to be explained in the data guide.	
	/* Information between [ ] provides context. Select the explanation below or enter your own explanation based on the context, then delete this line and the context */ [P21E bases this check on the key variables stored in it's internal metadata. Confirm the key variables that makes unique records in the data, and fill in the information between <> in the explanation below. Do not include xxSEQ in the key. Ensure the key listed here matches the key variables in the Sort Order	The structure of Findings class domains should be one record per Finding Result per subject. No Finding Result with the same Test Short Name (--TESTCD) and the same Qualifier variables at the same timepoint for the same Subject (USUBJID) are reported.	9-Sep-2020					

Explanations | Last Recourse Explanations | Inactive

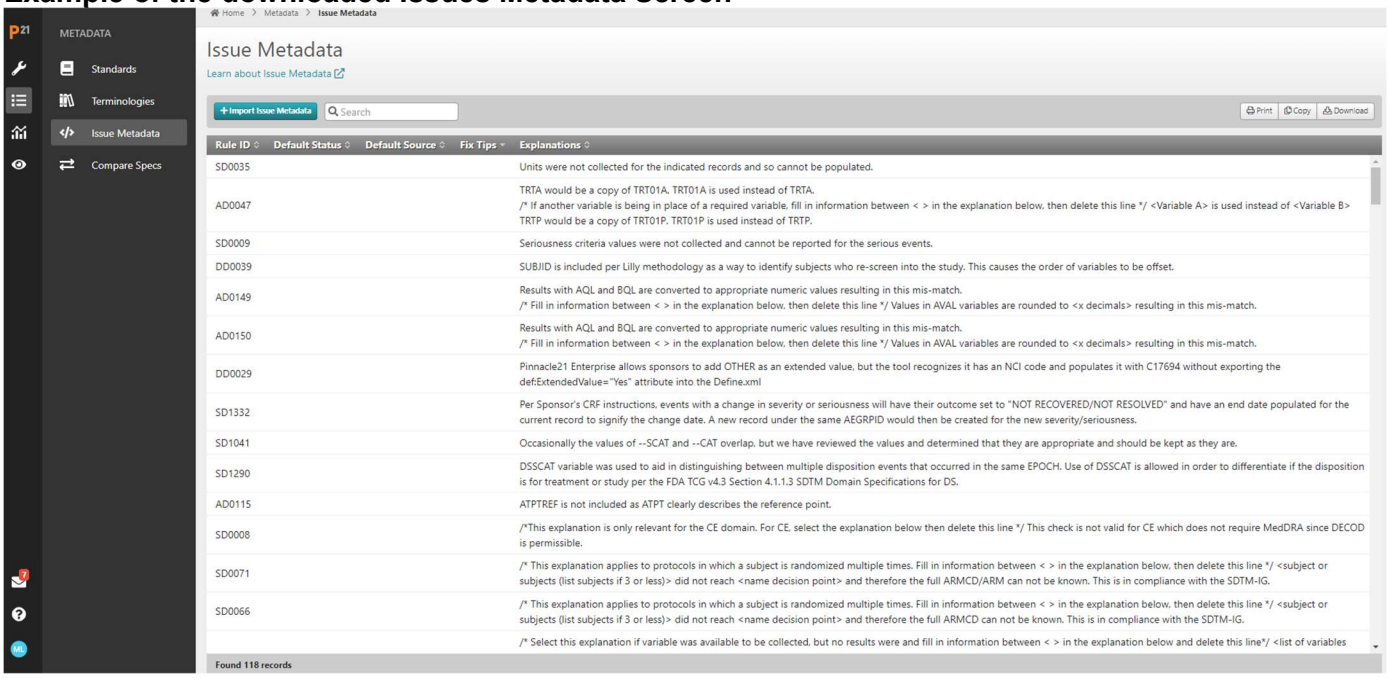
CONVERTING THE SPREADSHEET TO PINNACLE 21 ENTERPRISE VERSION 5.0

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.

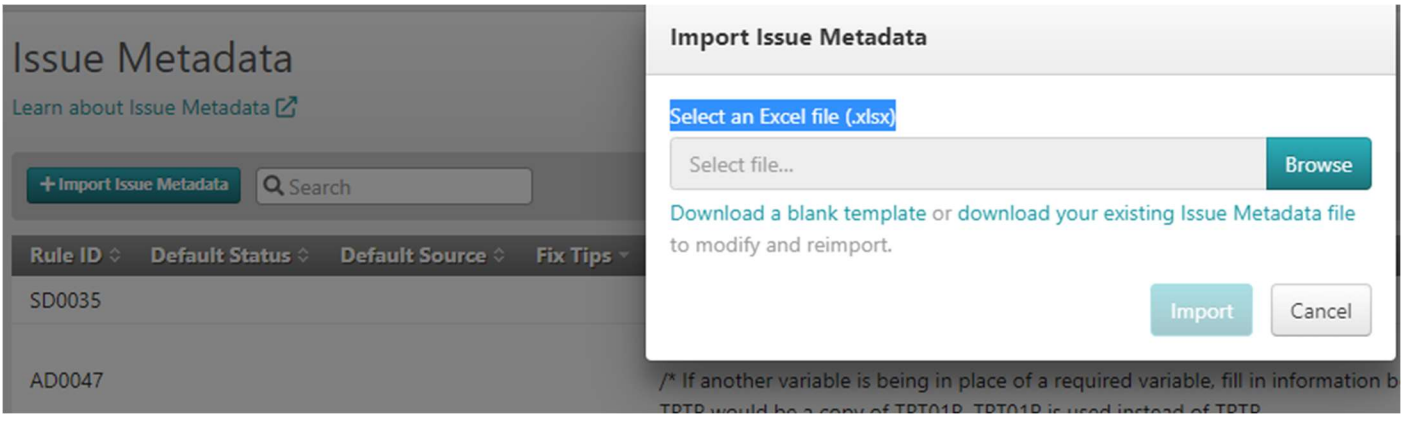
Populating the Issues Metadata Spreadsheet

Pinnacle 21 Enterprise provides the ability to manage the issues metadata spreadsheet through the ISSUE METADATA menu option.

Example of the downloaded Issues Metadata Screen



Clicking on + Import Issues Metadata will allow you to download a blank template or the existing explanations metadata already loaded.

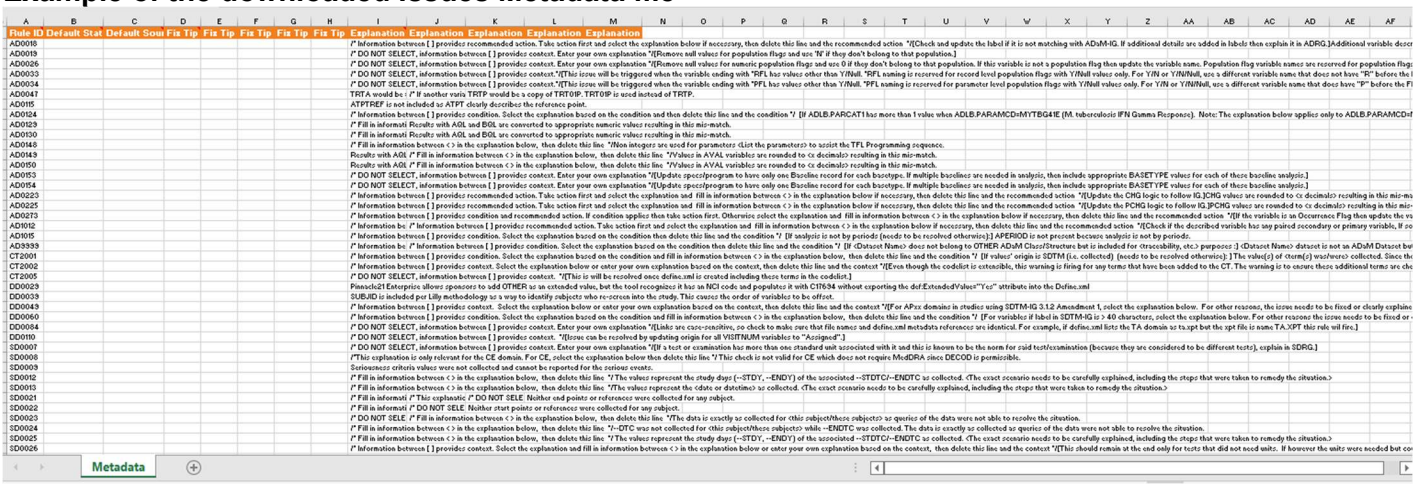


One important note: If you have previously imported a template with custom fix tips, you will want to keep that as your master copy on file somewhere outside of the tool. Downloading your existing template out of the tool will provide your custom explanations, but not the custom fix tips.

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



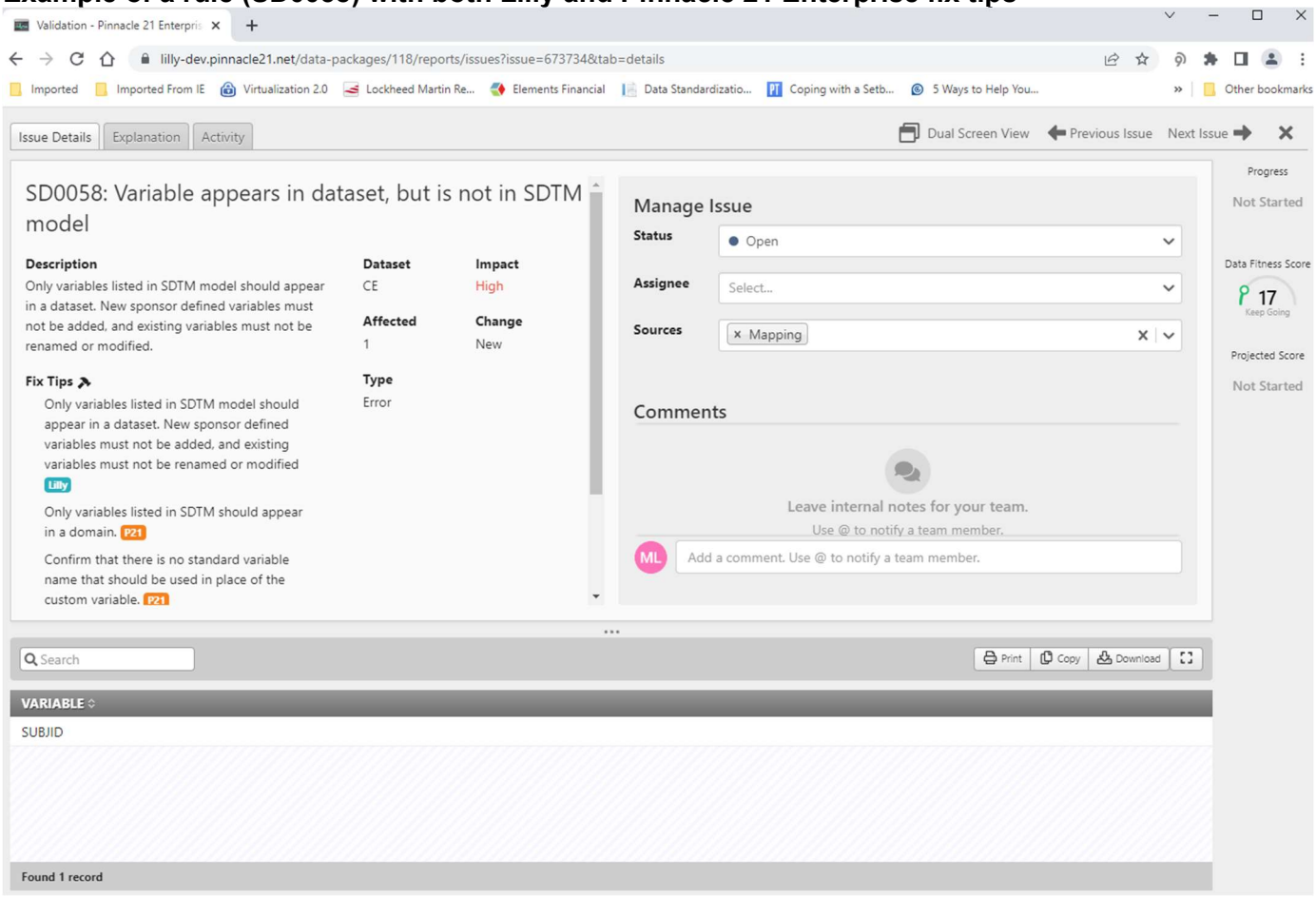
Rule ID	Default Stat	Default Sou	Fix Tip	Fix Tip	Fix Tip	Fix Tip	Fix Tip	Explanation	Explanation	Explanation	Explanation	Explanation
AD0016								/* Information between [ ] provides recommended action. Take action first and select the explanation below if necessary, then delete this line and the recommended action */[Check and update the label if it is not matching with ADaM-IG. If additional details are added in labels then explain it in ADRG.]Additional variable descr				
AD0019								/* DO NOT SELECT, information between [ ] provides context. Enter your own explanation */[Remove null values for population flags and sets 'N' if they don't belong to that population.]				
AD0026								/* DO NOT SELECT, information between [ ] provides context. Enter your own explanation */[Remove null values for numeric population flags and sets 0 if they don't belong to that population. If this variable is not a population flag then update the variable name. Population flag variable names are reserved for population flags				
AD0033								/* DO NOT SELECT, information between [ ] provides context.*/[This issue will be triggered when the variable ending with "RFL has values other than Y/Null. "RFL naming is reserved for record level population flags with Y/Null values only. For Y/N or Y/N/Null, use a different variable name that does not have "R" before the l				
AD0034								/* DO NOT SELECT, information between [ ] provides context.*/[This issue will be triggered when the variable ending with "PFL has values other than Y/Null. "PFL naming is reserved for parameter level population flags with Y/Null values only. For Y/N or Y/N/Null, use a different variable name that does have "P" before the F				
AD0047								TRTA would be : /* If another varia TRTP would be a copy of TRTO1P, TRTO1P is used instead of TRTP.				
AD0115								ATPTREF is not included as ATPT clearly describes the reference point.				
AD0124								/* Information between [ ] provides condition. Select the explanation based on the condition and then delete this line and the condition */ [If ADLB.PARCAT1 has more than 1 value when ADLB.PARAMCD=MYTBG41E (M. tuberculosis IFN Gamma Response). Note: The explanation below applies only to ADLB.PARAMCD=				
AD0129								/* Fill in informati Results with AOL and BOL are converted to appropriate numeric values resulting in this mic-match.				
AD0130								/* Fill in informati Results with AOL and BOL are converted to appropriate numeric values resulting in this mic-match.				
AD0148								/* Fill in information between <> in the explanation below, then delete this line */Non integers are used for parameters <List the parameters> to assist the TFL Programming sequence.				
AD0149								Results with AOL /* Fill in information between <> in the explanation below, then delete this line */Values in AVAL variables are rounded to <x decimals> resulting in this mic-match.				
AD0150								Results with AOL /* Fill in information between <> in the explanation below, then delete this line */Values in AVAL variables are rounded to <x decimals> resulting in this mic-match.				
AD0153								/* DO NOT SELECT, information between [ ] provides context. Enter your own explanation */[Update <pecs/program> to have only one Baseline record for each basetypes. If multiple baselines are needed in analysis, then include appropriate BASETYPE values for each of these baseline analysis.]				
AD0154								/* DO NOT SELECT, information between [ ] provides context. Enter your own explanation */[Update <pecs/program> to have only one Baseline record for each basetypes. If multiple baselines are needed in analysis, then include appropriate BASETYPE values for each of these baseline analysis.]				
AD0223								/* Information between [ ] provides recommended action. Take action first and select the explanation and fill in information between <> in the explanation below if necessary, then delete this line and the recommended action */[Update the CHG logic to follow IG.]CHG values are rounded to <x decimals> resulting in this mic-ma				
AD0225								/* Information between [ ] provides recommended action. Take action first and select the explanation and fill in information between <> in the explanation below if necessary, then delete this line and the recommended action */[Update the PCHG logic to follow IG.]PCHG values are rounded to <x decimals> resulting in this mic-				
AD0273								/* Information between [ ] provides condition and recommended action. If condition applies then take action first. Otherwise select the explanation and fill in information between <> in the explanation below if necessary, then delete this line and the recommended action */[If the variable is an Occurrence Flag then update the va				
AD1012								/* Information be /* Information between [ ] provides recommended action. Take action first and select the explanation and fill in information between <> in the explanation below if necessary, then delete this line and the recommended action */[Check if the described variable has any paired secondary or primary variable, If so				
AD1015								/* Information between [ ] provides condition. Select the explanation based on the condition then delete this line and the condition */ [If analysis is not by periods (needs to be resolved otherwise):] APERIOD is not present because analysis is not by periods.				
AD3333								/* Information be /* Information between [ ] provides condition. Select the explanation based on the condition then delete this line and the condition */ [If <Dataset Name> does not belong to OTHER ADaM Class/Structure but is included for traceability, etc.> purposes:] <Dataset Name> dataset is not an ADaM Dataset but				
CT2001								/* Information between [ ] provides condition. Select the explanation based on the condition and fill in information between <> in the explanation below, then delete this line and the condition */ [If values' origin is SDTM (i.e. collected) (needs to be resolved otherwise):] The value(s) of <term(s) was/were> collected. Since th				
CT2002								/* Information between [ ] provides context. Select the explanation below or enter your own explanation based on the context, then delete this line and the context */[Even though the codelist is extensible, this warning is firing for any terms that have been added to the CT. The warning is to ensure these additional terms are ch				
CT2005								/* DO NOT SELECT, information between [ ] provides context. */[This will be resolved once define.xml is created including these terms in the codelist.]				
DD0029								Pinnacle21Enterprise allows sponsors to add OTHER as an extended value, but the tool recognizes it has an NCI code and populates it with C17634 without exporting the def:ExtendedValue="Yes" attribute into the Define.xml				
DD0039								SUBJID is included per Lilly methodology as a way to identify subjects who re-screen into the study. This causes the order of variables to be offset.				
DD0049								/* Information between [ ] provides context. Select the explanation below or enter your own explanation based on the context, then delete this line and the context */[For APxx domains in studies using SDTM-IG 3.1.2 Amendment 1, select the explanation below. For other reasons, the issue needs to be fixed or clearly explaine				
DD0060								/* Information between [ ] provides condition. Select the explanation based on the condition and fill in information between <> in the explanation below, then delete this line and the condition */ [For variables if label in SDTM-IG is > 40 characters, select the explanation below. For other reasons the issue needs to be fixed or				
DD0084								/* DO NOT SELECT, information between [ ] provides context. Enter your own explanation */[Links are case-sensitive, so check to make sure that file names and define.xml metadata references are identical. For example, if define.xml lists the TA domain as ta.xpt but the xpt file is name TA.XPT this rule will fire.]				
DD0110								/* DO NOT SELECT, information between [ ] provides context. */[Issue can be resolved by updating origin for all VISITNUM variables to "Assigned".]				
SD0007								/* DO NOT SELECT, information between [ ] provides context. Enter your own explanation */[If a test or examination has more than one standard unit associated with it and this is known to be the norm for said test/examination (because they are considered to be different tests), explain in SDRG.]				
SD0008								/*This explanation is only relevant for the CE domain. For CE, select the explanation below then delete this line */ This check is not valid for CE which does not require MedDRA since DECOD is permissible.				
SD0009								Seriousness criteria values were not collected and cannot be reported for the serious events.				
SD0012								/* Fill in information between <> in the explanation below, then delete this line */The values represent the study days (--STDY, --ENDY) of the associated --STDTC/--ENDTC as collected. <The exact scenario needs to be carefully explained, including the steps that were taken to remedy the situation.>				
SD0015								/* Fill in information between <> in the explanation below, then delete this line */The values represent the <date or datetime> as collected. <The exact scenario needs to be carefully explained, including the steps that were taken to remedy the situation.>				
SD0021								/* Fill in informati /* This explanatic /* DO NOT SELE Neither end points or references were collected for any subject.				
SD0022								/* Fill in informati /* DO NOT SELE Neither start points or references were collected for any subject.				
SD0023								/* DO NOT SELE /* Fill in information between <> in the explanation below, then delete this line */The data is exactly as collected for <this subject/these subjects> as queries of the data were not able to resolve the situation.				
SD0024								/* Fill in information between <> in the explanation below, then delete this line */--DTC was not collected for <this subject/these subjects> while --ENDTC was collected. The data is exactly as collected as queries of the data were not able to resolve the situation.				
SD0025								/* Fill in information between <> in the explanation below, then delete this line */The values represent the study days (--STDY, --ENDY) of the associated --STDTC/--ENDTC as collected. <The exact scenario needs to be carefully explained, including the steps that were taken to remedy the situation.>				
SD0026								/* Information between [ ] provides context. Select the explanation and fill in information between <> in the explanation below or enter your own explanation based on the context, then delete this line and the context */[This should remain at the end only for tests that did not need units. If however the units were needed but co				

Metadata

Example of a Master Copy Issues Metadata file

Rule ID	Default Sour	Fix Tip 1	Fix Tip 2	Fix Tip 3	Fix Tip 4	Fix Tip 5	Explanation 1	Explanation 2	Explanation 3	Explanation 4	Explanation 5
		not to create these flags.					and AOCCzzFL naming convention is not used because <explain>.				
AD0314		MedDRA variables DECDORGy, BDSYORGy, HLGTORGy, HLTORGy, LLTORGy, LLTNORGy (Original or Prior MedDRA Coding) should have the suffix 'y' which represents an integer [1-9] corresponding to a previous version.					/* Information between [ ] provides recommended action. Take action first and select the explanation below if necessary, then delete this line and the recommended action */ [If the suffix y is equal to 0 and less than 9 MedDRA coding versions are needed for the study, re-sequence the variable names starting with y equal to 1. If more than 9 MedDRA coding versions:] More than 9 MedDRA coding versions were needed for analysis.				
AD1012		1. In a pair of corresponding character and numeric variables, the primary or most commonly used variable must be present if its secondary version describing it (*N or *C) is present. This is the generic rule to capture all instances of custom variables. Specific rules 64,66,70,75,97,201 exist for some standard ADaM variables. AD1012A rule covers all other standard ADaM variable.	2. In a pair of corresponding character and numeric variables, the primary or most commonly used variable must be present if its secondary version describing it (*N or *C) is present. This is the generic rule to capture all instances. Specific rules 64,66,70,75,97,201 exist for other variables. PARAM and TRTP are required regardless of the presence of their N variable. Exceptions: [AVAL,AVALC] (refer to AD0198) and [BASE,BASEC]. This rule is expected to be added to CDISC ADaM Validation checks in v1.3. ADaM IG v1.0 p.10.				1. /* Information between [ ] provides context. Select the explanation below or enter your own explanation based on the context, then delete this line and the context */ [For ADAE SMQzz(NAM,CD,SC,SCN) variables, with zz in [01-99], select the explanation below if the records reported in the Issue Details only display SMQzzS. For other reasons the issue needs to be fixed or clearly explained here.] This is a false positive. The variable SMQzzSC (scope) is the parent variable to the secondary variable SMQzzSCN (scope (N)) and were correctly created and populated in accordance with the ADaM-IG for OCCDS v1.0.	2. /* Information between [ ] provides recommended action. Take action first and select the explanation and fill in information between <> in the explanation below if necessary, then delete this line and the recommended action */ [Check if the described variable has any paired secondary or primary variable, If so add the primary/secondary paired variable, If not explain in ADRG.] <Variable> does not have any paired primary variable.			
AD1015		APHASE generally is a higher-level categorization of APERIOD. APHASE Does not replace APERIOD because APERIOD provides the indexing for the TRxx and APxx variables. ADaM IG v1.0 p.25.					/* Information between [ ] provides condition. Select the explanation based on the condition then delete this line and the condition */ [If analysis is not by periods (needs to be resolved otherwise):] APERIOD is not present because analysis is not by periods.				
AD9999		Validation is defined only for ADSL, BDS, BDS-TTE and ADAE datasets. Other dataset structures are not currently supported. The ADaM team is working on a specification for a more general structure supporting analysis of incidence data, such as interventions					1. /* Information between [ ] provides condition. Select the explanation based on the condition then delete this line and the condition */ [If <Dataset Name> belongs to OTHER ADaM Class/Structure :]	2. /* Information between [ ] provides condition. Select the explanation based on the condition then delete this line and the condition */ [If <Dataset Name> does not belong to OTHER ADaM Class/Structure but is			

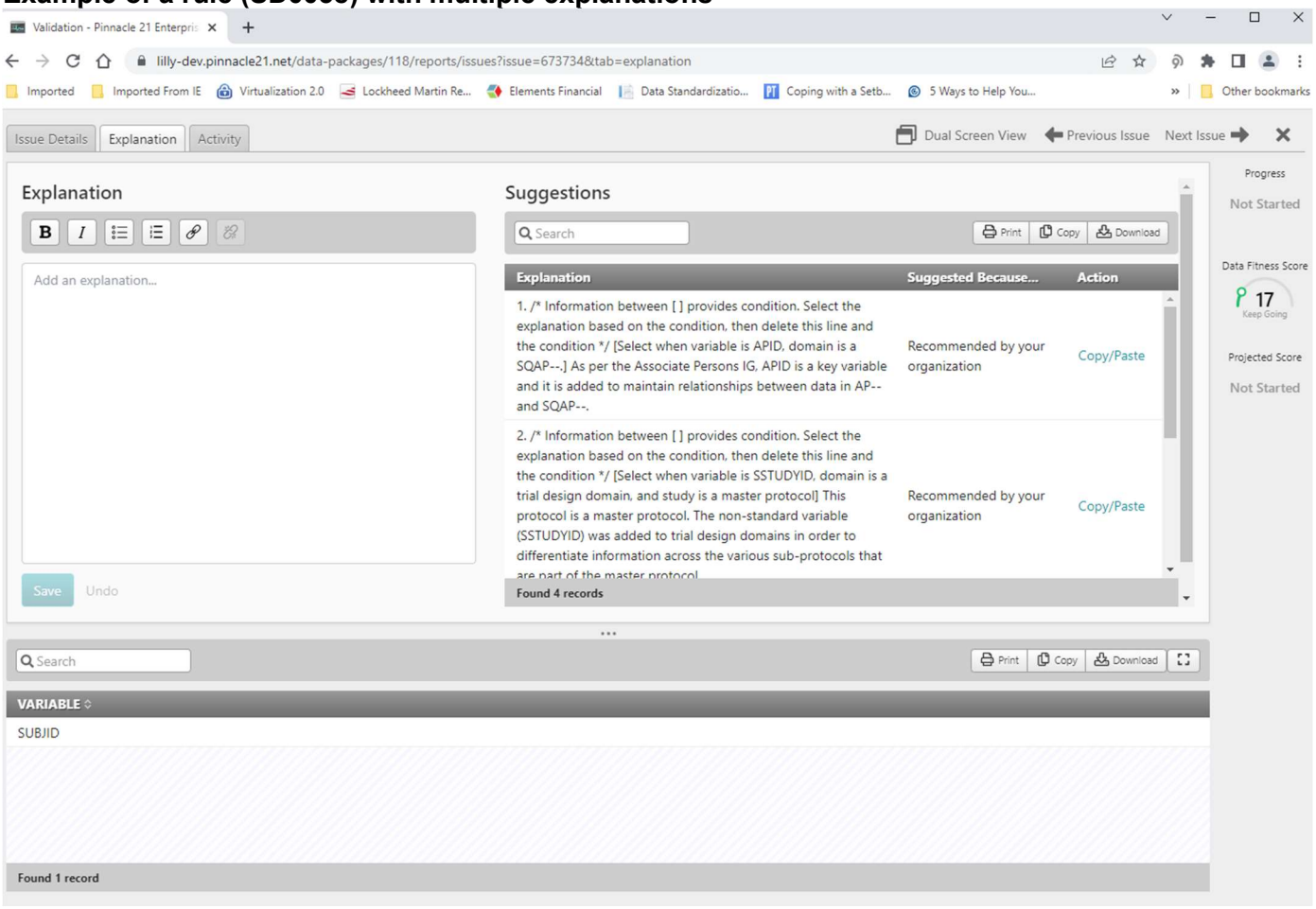
Example of a rule (SD0058) with both Lilly and Pinnacle 21 Enterprise fix tips



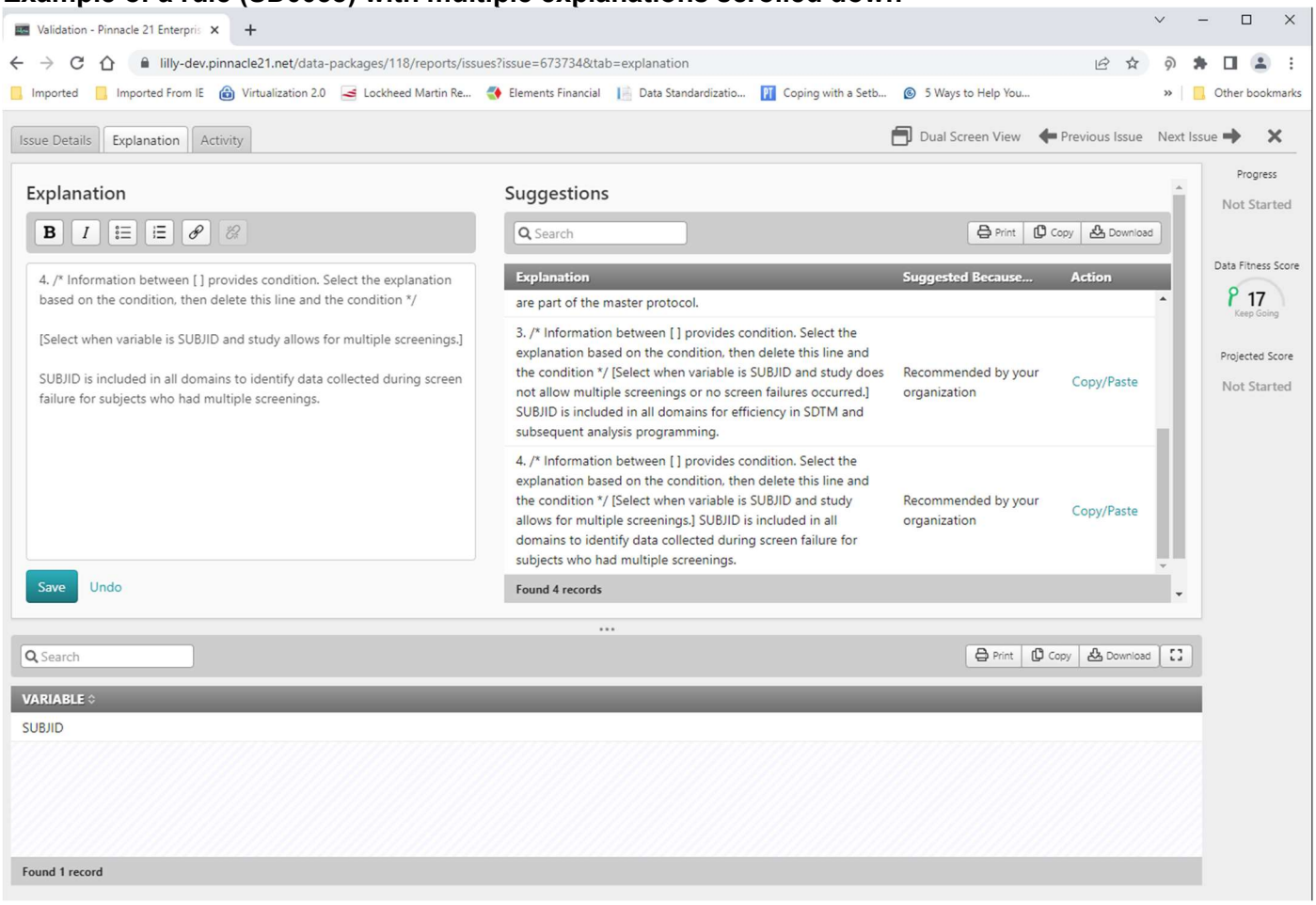
Version 5.0 also only allowed a maximum of five pre-defined explanations and fix tips where version 4.0 allowed us to set as many as needed. For most rules, this was not an issue, but Lilly did have a handful of rules in the 4.0 template that had more than five unique explanation choices. Most of the 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.

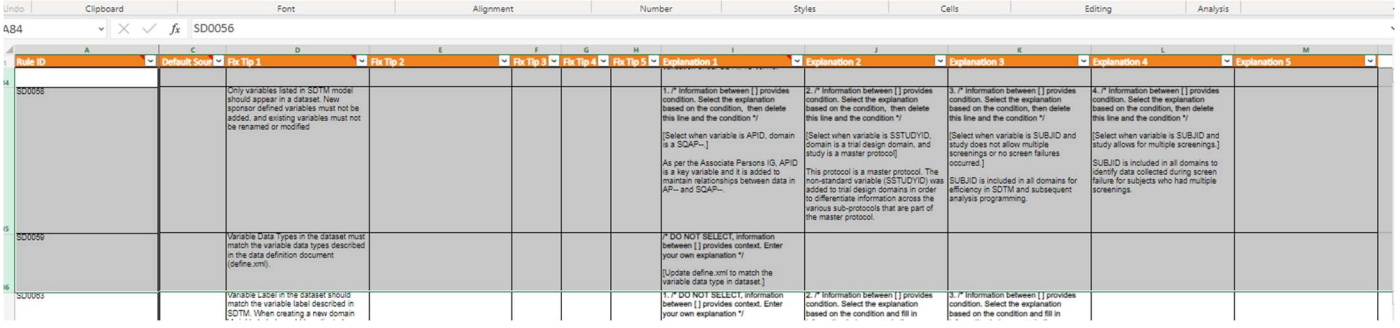
Example of a rule (SD0058) with multiple explanations



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 be 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

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Study Data Technical Conformance Guide: Technical Specifications Document. October 2022. Available at https://www.fda.gov/media/162867/download.

[2] Technical Conformance Guide on Electronic Study Data Submissions (PMDA/CPE Notification No. 0401003 and PMDA/CRS Notification No. 0401001, by the Director of Center for Product Evaluation and the Director of Center for Regulatory Science, Pharmaceuticals and Medical Devices Agency, dated April 1, 2022). Available at 000247157.pdf (pmda.go.jp)

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