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Proposal for New ADaM Paired Variables: PARQUAL/PARTYPE

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ABSTRACT

For more than a decade, producers have struggled to create unique PARAM values to fully describe each analysis parameter. Even when it is less efficient to have fully unique PARAMs, it has been the requirement.

With ADaM IG v3.0 this is expected to change. PARQUAL (and the paired variable PARTYPE) are expected additions that will allow PARAM to identify multiple analysis parameters.

These are special purpose variables that are intended to be an exception, not a common occurrence. In most cases they will be unnecessary. However, when the meaning of PARAM essentially remains unchanged except for a single qualifier (such as 'Investigator' or 'Central Reader'), PARQUAL can be a useful tool to simplify PARAM.

This paper will summarize the current requirements of PARAM and PARCATy. It will review the history of past proposals for PARQUAL and its existence in Therapeutic Area User's Guides (TAUGs) and other documents. The new requirements for PARQUAL and PARTYPE will be introduced, along with examples of correct usage. Examples of not allowed usage will also be discussed. Finally, the status of the associated controlled terminology will be presented.

INTRODUCTION

The ADaM variable PARAM is not synonymous with the SDTM variable --TEST. In SDTM, this is a properly constructed dataset:

STUDYID	USUBJID	OESEQ	OETESTCD	OETEST	OESTRESN	OESTRESU	OELAT	OEDTC
AB-12	AB-12-01	1	IOP	Intraocular Pressure	18	mmHg	LEFT	2014-01-01
AB-12	AB-12-01	2	IOP	Intraocular Pressure	12	mmHg	RIGHT	2014-01-01

Table 1 SDTM Dataset

A similarly constructed dataset in ADaM, though, is not allowed.

STUDYID	USUBJID	ASEQ	PARCAT1	PARAMCD	PARAM	AVAL	ADT
AB-12	AB-12-01	1	Left	IOP	Intraocular Pressure (mmHg)	18	01Jan2014
AB-12	AB-12-01	2	Right	IOP	Intraocular Pressure (mmHg)	12	01Jan2014

Table 2 Incorrect use of PARCATy

To follow ADaM Implementation Guide v1.3[1], a separate PARAMCD/PARAM must be used to distinguish the laterality.

STUDYID	USUBJID	ASEQ	PARCAT1	PARAMCD	PARAM	AVAL	ADT
AB-12	AB-12-01	1	Left	LIOP	Left Intraocular Pressure (mmHg)	18	01Jan2014
AB-12	AB-12-01	2	Right	RIOP	Right Intraocular Pressure (mmHg)	12	01Jan2014

Table 3 Correct use of PARAMCD/PARAM with PARCATy

The rules surrounding the population of the ADaM Basic Data Structure variable PARAM require that PARAM uniquely and fully describe the contents of AVAL/AVALC, and no additional information is needed to further qualify PARAM.

There are certain cases, though, where a single qualifier would greatly simplify the values of PARAM. For many years, the ADaM community has struggled with the idea of allowing a qualifier for PARAM, and possible qualifier variables PARQUAL or PARCATy have been considered. However, many people have been reluctant to open the definition of PARAM to allow for any possible qualifier, as it would change the basic intent and usage of PARAM.

HISTORY OF PARAMETER QUALIFIERS

There are currently two published uses of PARQUAL in industry documents.

In the Therapeutic Area User's Guide for Breast Cancer (v1.0 Provisional)[2] published in 2016, the variable PARQUAL was used. The TAUG used a specific limited list of controlled terms for PARQUAL (INVESTIGATOR, CENTRAL, PATHOLOGIC, PROTOCOL). This TAUG defines PARQUAL as this: "This identifies the source of the Parameter. Investigator for investigator-based assessments; Central for central imaging assessments; Pathologic for an assessment by biopsy; and Protocol for events affecting assessment."

The following table shows how it was used:

Row	STUDYID	USUBJID	ASEQ	ASTDT	ASTDY	PARQUAL	PARAMCD	AVALC
1	AB-12	AB-12-01	1	01JAN2014	20	INVESTIGATOR	ASSESS	SD
2	AB-12	AB-12-01	2	01JAN2014	20	CENTRAL	ASSESS	PR

Table 4 Breast Cancer TAUG

The second published use is in the FDA's Pilot OCE/OOD Standard Safety Data Requests v1.3[3]. This document is a part of the FDA "Real-Time Oncology Review (RTOR)", which is an FDA project started in 2018 to facilitate earlier submission of topline results and datasets to support an earlier start to the FDA application review. The webpage with details about the Real-Time Oncology Review contains this Standard Safety Data Request document, which details expected ADaM datasets and dataset contents.

Here's a portion of the FDA's requested dataset ADEXSUM (Exposure Summary Analysis Dataset).

PARQUAL	PARAMCD	PARAM	OCE/OOD Notes
<each value of EXTRT>	DOSRED	Any Dose Reductions	Y if there were any dose reductions
<each value of EXTRT>	NDOSRED	Number of Dose Reductions	Number of dose reductions
<each value of EXTRT>	DOSINT	Any Dose Interruptions	Y if there were any dose interruptions
<each value of EXTRT>	NDOSINT	Number of Dose Interruptions	Number of dose interruptions
ALL	TRTDTC	Treatment Discontinued	Y if treatment permanently discontinued for all drugs

Table 5 FDA's OCE/OOD

Neither of these use cases for PARQUAL is currently supported by the ADaM Implementation Guide v1.3.

PARQUAL IN DRAFT ADAM IMPLEMENTATION GUIDE V1.2

The draft version of this implementation guide that was released in 2018 included PARQUAL. After evaluating the public review comments regarding PARQUAL, there was concern that the current text regarding PARQUAL was not sufficiently clear. The ADaM team weighed different options:

(1) modifying the current text,

(2) restricting the use of PARQUAL to a small list of permissible use cases, or

(3) explore alternate ways to address the underlying issue PARQUAL was seeking to address.

Ultimately, the ADaM team decided that more time was required to evaluate PARQUAL and that ADaM IG v1.2 should move forward without it.

PROPOSED QUALIFIER VARIABLES

In ADaM IG v3.0, the ADaM team is using option 2 from above, allowing PARQUAL but restricting its permissible use cases through the addition of PARTYPE. PARTYPE will contain controlled terminology that restricts the use of PARQUAL to specific approved uses. Both of the examples in Tables 4 and 5 are expected to be allowed, where PARTYPE is 'EVALUATOR' and 'TREATMENT' respectively.

Repeating the example from the Breast Cancer TAUG, PARTYPE is now used.

Row	STUDYID	USUBJID	ASEQ	ASTDY	PARTYPE	PARQUAL	PARAMCD	AVALC
1	AB-12	AB-12-01	1	20	EVALUATOR	INVESTIGATOR	ASSESS	SD
2	AB-12	AB-12-01	2	20	EVALUATOR	CENTRAL	ASSESS	PR

Table 6 Breast Cancer TAUG including PARTYPE

The ADEXSUM example now looks like this:

PARTYPE	PARQUAL	PARAMCD	OCE/OOD Notes
TREATMENT	<each value of EXTRT>	DOSRED	Y if there were any dose reductions
TREATMENT	<each value of EXTRT>	NDOSRED	Number of dose reductions
TREATMENT	<each value of EXTRT>	DOSINT	Y if there were any dose interruptions
TREATMENT	<each value of EXTRT>	NDOSINT	Number of dose interruptions
TREATMENT	ALL	TRTDTC	Y if treatment permanently discontinued for all drugs

Table 7 FDA's OCE/OOD including PARTYPE

Since only the non-extensible codelist values of PARTYPE are allowed, in most cases PARAM/PARAMCD must be used alone. In cases where PARTYPE and PARQUAL are used, the combination of PARAM and PARQUAL must be sufficient to describe unambiguously the contents of AVAL. The Implementation Guide reference to PARAM will now also apply to the combination of PARQUAL PARAM. For example, when PARQUAL is present in a dataset, ABLFL should be defined for the unique combination of USUBJID PARQUAL PARAM.

It is also important to note that PARQUAL, designed to qualify parameters, is different from PARCATy, designed to group or categorize parameters.

PARTYPE

The possible values of PARTYPE are governed by the controlled terminology. Additions or changes to ADaM controlled terminology may be requested by users through the CDISC New Term Request Page[4].

PARTYPE is the current working name for the variable and is subject to change before it is finalized. Another alternative that is being considered is PQUALTYP to signify that it denotes a type of PARQUAL rather than a type of parameter.

INCORRECT USAGE

PARQUAL is only allowed when the data fit with the non-extensible controlled terminology values of PARTYPE. The following is an example where PARQUAL is not allowed, since it requires a value for PARTYPE that is not included in the controlled terminology.

PARTYPE	PARQUAL	PARAMCD	PARAM	AVALC
SEVERITY	MILD	AESI	Occurrence of AE of Special Interest	Y
SEVERITY	MODERATE	AESI	Occurrence of AE of Special Interest	Y
SEVERITY	SEVERE	AESI	Occurrence of AE of Special Interest	N

Table 8 Incorrect use of PARQUAL/PARTYPE

Another tempting use of PARQUAL/PARTYPE is for lab tests that are from different lab panels. Again, this is not allowed, because the value of PARTYPE does not appear in the non-extensible controlled terminology.

PARTYPE	PARQUAL	PARAMCD	PARAM	AVAL
LBCAT	CHEMISTRY	GLUCOSE	Glucose (mmol/L)	5.48
LBCAT	URINALYSIS	GLUCOSE	Glucose (mmol/L)	0.6

Table 9 Incorrect use of PARQUAL/PARTYPE

Even with an allowed value of PARTYPE, PARQUAL cannot be used if PARAM is not the same across records. In the following example, since there is a single PARAMCD of TOTDOSE, the PARAM must be the same on both records, including units. The records have different units, so different PARAMCD must be used.

PARTYPE	PARQUAL	PARAMCD	PARAM
TREATMENT	Sirolimus	TOTDOSE	Total dose across the study (mg)
TREATMENT	Gemcitabine	TOTDOSE	Total dose across the study (mg/m2)

Table 10 Incorrect PARAMCD/PARAM

DOCUMENTATION

A dataset that uses PARQUAL should include an explanation in the Analysis Dataset Reviewer's Guide (ADRG). The Analysis Dataset section of the ADRG can provide specific details of how PARQUAL is used and highlight the variables that make a record unique. For example, the Breast Cancer TAUG dataset presented in Table 6 could benefit from additional explanation.

5.2 ADEVENT – Event Analysis Dataset
ADEVENT is a sponsor-defined analysis dataset following the ADaM Basic Data Structure (BDS). It's used as an intermediate dataset to support the primary efficacy analysis. The PARAMCD 'ASSESS' applies to different evaluators, with the variable PARQUAL used to differentiate the evaluators (INVESTIGATOR, CENTRAL). Variables that make a record unique for this dataset are USUBJID, PARQUAL, PARAMCD.

Table 11 ADRG Section

Here's an example of define.xml that documents the variables PARQUAL/PARTYPE. *(Note that not all rows or columns for the define.xml are shown.)*

Variable	Label/ Description	Type	Codelist/ Controlled Terms	Origin / Source / Method / Comment
STUDYID	Study Identifier	text		Predecessor: ADSL.STUDYID
USUBJID	Unique Subject Identifier	text		Predecessor: ADSL.USUBJID

Variable	Label/ Description	Type	Codelist/ Controlled Terms	Origin / Source / Method / Comment
SUBJID	Subject Identifier for the Study	text		Predecessor: ADSL.SUBJID
ASEQ	Analysis Sequence Number	Integer		Derived: Sequential number for associating a record number in the dataset. Unique number per subject per parameter per parameter qualifier per analysis start date.
ASTDT	Analysis Start Date	integer		Derived: This is the date that the event occurred. RS.RSDTC when PARAMCD = 'ASSESS'. Convert –DTC variables to numeric date format.
ASTDY	Analysis Start Day	integer		Derived: RANDT – ASTDT + 1
PARTYPE	Parameter Qualifier Type	text		Assigned: Set to 'EVALUATOR'
PARQUAL	Parameter Qualifier	text		Predecessor: RS.RSEVAL
PARAMCD	Parameter Code	text		Assigned: Set to 'ASSESS'
PARAM	Parameter	text		Assigned: Set to 'Assessment'
AVALC	Analysis Value (C)	text		Predecessor: RS.RSSTRESC

Table 12 Example of define.xml

CONCLUSION

After many years of debate, limited use of PARAM qualifiers will soon be allowed. The use is restricted by the paired variable PARTYPE, where the controlled terminology is non-extensible.

REFERENCES

1. ADaM IG v1.3 https://www.cdisc.org/standards/foundational/adam/adamig-v1-3-release-package

2. CDISC: “Therapeutic Area Data Standards User Guide for Breast Cancer” https://www.cdisc.org/standards/therapeutic-areas/breast-cancer

3. FDA: “OOD Safety Team Standard Data Requests v1.3” https://www.fda.gov/media/133252/download

4. CDISC New Term Request Page https://nciterm form.nci.nih.gov/nitermform/?version=cdisc

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