

Introducing the ADaM Implementation Guide v1.2

Terek Peterson¹, Brian Harris², Alyssa Wittle¹, Nancy Brucken³ and Deb Goodfellow¹

¹Covance Inc., King of Prussia, PA ; ²Medimmune, Gaithersburg, MD; ³Syneos Health, Ann Arbor, MI

Overview

The ADaM team is proposing a minor version update of the IG to provide clarifications and to introduce three significant changes:

- **Addition of PARQUAL**
- **Addition of stratification variables**
- **Guidance for bi-directional toxicity grades**

PARQUAL

New Permissible Variable within Basic Data Structure (BDS)

In some cases, an analysis parameter is defined the same (and AVAL or AVALC is derived in the same way) within each level of a single, separate, categorical concept. In such cases, it is permissible to use PARQUAL in addition to PARAM as an alternative to creating a distinct value of PARAM for each level of that separate categorical concept. PARQUAL provides qualifying information pertaining to PARAM that does not affect the meaning of PARAM. When using PARQUAL, PARAM must still uniquely and sufficiently describe what is contained in AVAL or AVALC.

PARQUAL may contain null values for some parameters within a dataset. If it is used for a parameter, PARQUAL must be populated for all records for that parameter within a dataset. The PARQUAL value cannot be included in the PARAM value. Invalid uses of PARQUAL include SDTM qualifiers (e.g., units), timepoints, and any other qualifying information that results in a change in the interpretation of AVAL or AVALC. All statements throughout all ADaM documents pertaining to PARAM alone also apply to the combination of PARQUAL plus PARAM.

USUBJID	ADT	ADY	AVISIT	AVISITN	PARAMCD	PARAM	AVAL	BASE	CHG	PCHG	ABLFL
ABC-001-0001	2007-01-01	-1	SCREEN	1	INVSLDIA	Sum of Longest Diameter (mm) - Inv	168				Y
ABC-001-0001	2007-02-27	56	WEEK 8	3	INVSLDIA	Sum of Longest Diameter (mm) - Inv	125	168	-43.00	-25.60	
ABC-001-0001	2007-04-24	112	WEEK 16	5	INVSLDIA	Sum of Longest Diameter (mm) - Inv	72	168	-96.00	-57.14	
ABC-001-0001	2007-06-19	168	WEEK 24	7	INVSLDIA	Sum of Longest Diameter (mm) - Inv	56	168	-112.00	-66.67	
ABC-001-0001	2007-08-12	222	WEEK 32	9	INVSLDIA	Sum of Longest Diameter (mm) - Inv	66	168	-102.00	-60.71	
ABC-001-0001	2007-01-01	-1	SCREEN	1	INDSLDIA	Sum of Longest Diameter (mm) - Ind	165				Y
ABC-001-0001	2007-02-27	56	WEEK 8	3	INDSLDIA	Sum of Longest Diameter (mm) - Ind	127	165	-38.00	-23.03	
ABC-001-0001	2007-04-24	112	WEEK 16	5	INDSLDIA	Sum of Longest Diameter (mm) - Ind	80	165	-85.00	-51.52	
ABC-001-0001	2007-06-19	168	WEEK 24	7	INDSLDIA	Sum of Longest Diameter (mm) - Ind	60	165	-105.00	-63.64	
ABC-001-0001	2007-08-12	222	WEEK 32	9	INDSLDIA	Sum of Longest Diameter (mm) - Ind	66	165	-99.00	-60.00	

Figure 1. Tumor Measurement without PARQUAL

In Figure 1 an example is shown using PARAM prior to the implementation of PARQUAL. In this case, PARAM and PARAMCD are unique for Investigator and Independent Reviewer. This is a good illustration of when the interpretation of AVAL does not change based on the individual who recorded the measurement.

USUBJID	ADT	ADY	AVISIT	AVISITN	PARAMCD	PARAM	AVAL	BASE	CHG	PCHG	ABLFL
ABC-001-0001	2007-01-01	-1	SCREEN	1	INVESTIGATOR	SUMLDIAM	Sum of Longest Diameter (mm)	168			Y
ABC-001-0001	2007-02-27	56	WEEK 8	3	INVESTIGATOR	SUMLDIAM	Sum of Longest Diameter (mm)	125	168	-43.00	-25.60
ABC-001-0001	2007-04-24	112	WEEK 16	5	INVESTIGATOR	SUMLDIAM	Sum of Longest Diameter (mm)	72	168	-96.00	-57.14
ABC-001-0001	2007-06-19	168	WEEK 24	7	INVESTIGATOR	SUMLDIAM	Sum of Longest Diameter (mm)	56	168	-112.00	-66.67
ABC-001-0001	2007-08-12	222	WEEK 32	9	INVESTIGATOR	SUMLDIAM	Sum of Longest Diameter (mm)	66	168	-102.00	-60.71
ABC-001-0001	2007-01-01	-1	SCREEN	1	INDEPENDENT	SUMLDIAM	Sum of Longest Diameter (mm)	165			Y
ABC-001-0001	2007-02-27	56	WEEK 8	3	INDEPENDENT	SUMLDIAM	Sum of Longest Diameter (mm)	127	165	-38.00	-23.03
ABC-001-0001	2007-04-24	112	WEEK 16	5	INDEPENDENT	SUMLDIAM	Sum of Longest Diameter (mm)	80	165	-85.00	-51.52
ABC-001-0001	2007-06-19	168	WEEK 24	7	INDEPENDENT	SUMLDIAM	Sum of Longest Diameter (mm)	60	165	-105.00	-63.64
ABC-001-0001	2007-08-12	222	WEEK 32	9	INDEPENDENT	SUMLDIAM	Sum of Longest Diameter (mm)	66	165	-99.00	-60.00

Figure 2. Tumor Measurement with PARQUAL

Figure 2 shows an example using the new PARQUAL method. The source or evaluator is considered as qualifying information pertaining to a tumor measurement parameter. Therefore, a PARQUAL variable is created to contain this information. Table 4.9.1.2 in ADaM IG v1.2 provides a schematic example of the implementation of PARQUAL. With the use of PARQUAL, only one set of PARAM/PARAMCD for each tumor measurement is needed, and the combination of PARAM and PARQUAL is sufficient to describe unambiguously the contents of AVAL. PARQUAL cannot be null for any records where PARAMCD is SUMLDIAM in this example. Also note, each combination of PARAM and PARQUAL has a separate baseline value identified.

PARCAT1	PARCAT2	PARQUAL	PARAM
Efficacy parameters	Primary endpoint and components	Adjudicated	Time to MACE (days)
			Time to CV death (days)
			Time to stroke (days)
		Investigator	Time to MACE (days)
			Time to CV death (days)
			Time to MI (days)
			Time to stroke (days)
	Secondary endpoints	Adjudicated	Time to death (days)
		Investigator	Time to death (days)
			Time to hospitalization (days)
Safety parameters		Adjudicated	Time to major bleeding (days)
		Investigator	Time to major bleeding (days)
			Time to nausea (days)

PARCAT1	PARQUAL	PARAM
Compliance parameters	IV	Compliance rate (%)
		Number of doses omitted:
	Central line	Compliance rate (%)
		Number of doses omitted:
Exposure parameters	IV	Duration of therapy (weeks)
		Cumulative dose (mg)
	Central line	Duration of therapy (weeks)
		Cumulative dose (mg)

Figure 3. PARQUAL vs PARCATy

PARQUAL, designed to qualify parameters, is different from PARCATy, which is designed to group or categorize parameters. Figure 3 displays two examples of appropriate uses of PARCATy and PARQUAL. Note that the use of PARQUAL does not affect the meaning of the parameters.

Stratification Variables within ADSL

Nomenclature for Stratification Variables within Subject-Level Analysis Dataset (ADSL)

Stratified randomization is used to ensure balance of treatment assignments across one or more prognostic factors. A prognostic factor is an aspect of the disease or a characteristic of the subject that may influence treatment response. The analysis may need (1) As Randomized – the value used to randomize the subject and (2) As Verified – the actual value for the subject. Table 3.2.9 in the ADaM IG v1.2 provides a set of variables to allow maximum flexibility in representing the description of the prognostic factors as well as the values used for randomization and the values that were verified.

Variable Name	Variable Label	Type	Core	Example
STRATA	Randomized Strata	Char	Perm	STRATA=">50, Treatment experienced, N"
STRATAN	Randomized Strata (N)	Num	Perm	STRATAN="3" when STRATA=">50, Treatment experienced, N"
STRATwNM	Description of Stratum w	Char	Perm	STRAT3NM="Hypertension"
STRATw	Randomized Value of Stratum w	Char	Perm	TSTRAT3="N"
STRATwN	Randomized Value of Stratum w (N)	Num	Perm	STRAT3N=0 when STRAT3="N"
STRATAV	Verified Strata	Char	Perm	STRATAV=">=50, Treatment experienced, Y"
STRATAVN	Verified Strata (N)	Num	Perm	STRATAVN="3" when STRATAV=">=50, Treatment experienced, N"
STRATwV	Verified Value of Stratum w	Char	Perm	STRAT3V="Y"
STRATwVN	Verified Value of Stratum w (N)	Num	Perm	STRAT3VN-1 when STRAT3V="Y"

Figure 4. Stratification Variables Within ADSL

Bi-Directional Toxicity Grades

Recommended Approach for Bi-Directional Toxicity Grades

The ADaM team discussed many options for handling lab limits that need to be assessed in more than one direction with different meaning. Rather than creating additional records, the ADaM team agreed to add guidance around the variables proposed to handle bi-directional information. Toxicity grades are the most common example of this, but other bi-directional examples can be applied to these new variables as needed.

Variable Name	Variable Label	Type	Core	Comments
ATOXGRL	Analysis Toxicity Grade Low	Char	Perm	Used to assess when a subject's lab value falls within the low toxicity range.
ATOXGRLN	Analysis Toxicity Grade Low (N)	Num	Perm	Numeric version of ATOXGRL.
ATOXGRH	Analysis Toxicity Grade High	Char	Perm	Used to assess when a subject's lab value falls within the high toxicity range.
ATOXGRHN	Analysis Toxicity Grade High (N)	Num	Perm	Numeric version of ATOXGRH.
BTOXGRL	Baseline Toxicity Grade Low	Char	Perm	Used to establish the shift in toxicity level from baseline level when a subject shifts to lower readings.
BTOXGRLN	Baseline Toxicity Grade Low (N)	Num	Perm	Numeric version of BTOXGRL.
BTOXGRH	Baseline Toxicity Grade High	Char	Perm	Used to establish the shift in toxicity level from baseline level when a subject shifts to higher readings.
BTOXGRHN	Baseline Toxicity Grade High (N)	Num	Perm	Numeric version of BTOXGRH.
ATOXDSDL	Analysis Toxicity Description Low	Char	Perm	Used to describe the low end of the lab test criteria preferred term.
ATOXDSCH	Analysis Toxicity Description High	Char	Perm	Used to describe the high end of the lab test criteria preferred term.

Figure 5. Bi-directional Toxicity Grades

Figure 5 displays the bi-directional toxicity grading proposed in ADaM IG v1.2. The toxicity descriptions (ATOXDSDL and ATOXDSCH) can help to determine denominators. For example, if ATOXDSDL is populated then that record is counted for low toxicity grading tables, and if ATOXDSCH is populated then that record is counted in high toxicity grading. In some cases, a record can be counted for both since the record would be assessed in both directions.

Row	USUBJID	PARAMCD	VISITNUM	AVAL	ANRLO	ANRHI	ANRIND	BASE	ABLFL	ATOXGRL	ATOXGRH	BNRIND	BTOXGRL	BTOXGRH
1	001-0001	HGB	1	7.4	11	16.1	LOW	7.4	Y	Grade 3		LOW	Grade 3	
2	001-0001	HGB	2	20.5	11	16.1	HIGH	7.4	Y		Grade 3	LOW		Grade 3
3	001-0001	SGOT	1	33	5	25	HIGH	33			Grade 1	HIGH		Grade 1
4	001-0001	SGOT	2	55	5	25	HIGH	33			Grade 2	HIGH		Grade 1
5	001-0001	WBC	1	11.8	4.5	11.5	HIGH	11.8	Y			HIGH		
6	001-0001	WBC	2	5.6	4.5	11.5	NORMAL	11.8		Grade 0		HIGH		
7	001-0002	HGB	1	21.1	11	16.1	HIGH	21.1	Y		Grade 3	HIGH		Grade 3

Row	SHIFT1	SHIFT2	ATOXDSDL	ATOXDSCH
1			Anemia	Hemoglobin increased
2	Grade 3 to High	Low to Grade 3	Anemia	Hemoglobin increased
3				Aspartate aminotransferase increased
4		Grade 1 to Grade 2		Aspartate aminotransferase increased
5			White blood cell decreased	
6	High to Grade 0		White blood cell decreased	
7			Anemia	Hemoglobin increased

Figure 6. Bi-directional Lab Example

Figure 6 is an example of some of the variables in a dataset supporting bi-directional toxicity grades. *GRL and *GRH are included to indicate variables that pertain to low/high toxicity grades. In this example, hemoglobin is bidirectional (see red boxes), while SGOT and WBC are only in one direction (see orange box).