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Incremental Changes: ADaMIG V1.2 Update

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ABSTRACT

The ADaM Implementation Guide (ADaMIG) has now been available to industry since 2009, providing a standardized way to communicate and analyze study data. Improvements and clarifications were added in 2016 with the release of v1.1. Since that release, the ADaM team has been working on some items that were not yet ready for v1.1 but are now ready for another minor release, v1.2. These items include a new permissible variable within the Basic Data Structure (BDS) called PARQUAL, standard nomenclature for stratification variables within ADSL, and a recommended approach for bi-directional toxicity grades.

INTRODUCTION

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

- Addition of a new permissible variable within the BDS structure called PARQUAL
- Addition of standard nomenclature for stratification variables within ADSL
- Guidance for Bi-directional toxicity grades

PARQUAL – New Permissible variable within Basic Data Structure (BDS)

In some instances, an analysis parameter is defined the same within each level of a single, separate, categorical concept. For 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 that 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. Examples of correct uses of PARQUAL are provided below:

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) – Investigator	168				Y
ABC-001-0001	2007-02-27	56	WEEK 8	3	INVSLDIA	Sum of Longest Diameter (mm) – Investigator	125	168	-43.00	-25.60	
ABC-001-0001	2007-04-24	112	WEEK 16	5	INVSLDIA	Sum of Longest Diameter (mm) – Investigator	72	168	-96.00	-57.14	
ABC-001-0001	2007-06-19	168	WEEK 24	7	INVSLDIA	Sum of Longest Diameter (mm) – Investigator	56	168	-112.00	-66.67	
ABC-001-0001	2007-08-12	222	WEEK 32	9	INVSLDIA	Sum of Longest Diameter (mm) – Investigator	66	168	-102.00	-60.71	
ABC-001-0001	2007-01-01	-1	SCREEN	1	INDSLDIA	Sum of Longest Diameter (mm) – Independent	165				Y
ABC-001-0001	2007-02-27	56	WEEK 8	3	INDSLDIA	Sum of Longest Diameter (mm) – Independent	127	165	-38.00	-23.03	
ABC-001-0001	2007-04-24	112	WEEK 16	5	INDSLDIA	Sum of Longest Diameter (mm) – Independent	80	165	-85.00	-51.52	
ABC-001-0001	2007-06-19	168	WEEK 24	7	INDSLDIA	Sum of Longest Diameter (mm) – Independent	60	165	-105.00	-63.64	
ABC-001-0001	2007-08-12	222	WEEK 32	9	INDSLDIA	Sum of Longest Diameter (mm) – Independent	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	PARQUAL	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 this same example after the implementation of PARQUAL. 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. 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.

Figures 3 and 4 demonstrate another instance where PARQUAL can be of use.

USUBJID	PARAMCD	PARAM	AVAL
ABC-001-0001	NCYCLE1	Number of Cycles - Central Line	10
ABC-001-0001	DURWK1	Duration of Therapy (Week) - Central Line	6
ABC-001-0001	CUMDS1	Cumulative Dose (mg) - Central Line	3000
ABC-001-0001	DSINT1	Dose Intensity (%) - Central Line	90
ABC-001-0001	NDSOMT1	Number of Dose Omitted - Central Line	2
ABC-001-0001	NDELAY1	Number of Dose Delayed - Central Line	1
ABC-001-0001	NDSINC1	Number of Dose Increased - Central Line	2
ABC-001-0001	NDSDEC1	Number of Dose Reduced - Central Line	0
ABC-001-0001	COMPRT1	Compliance Rate (%) - Central Line	90
ABC-001-0001	NCYCLE2	Number of Cycles - IV	20
ABC-001-0001	DURWK2	Duration of Therapy (Week) - IV	40
ABC-001-0001	CUMDS2	Cumulative Dose (mg) - IV	20000
ABC-001-0001	DSINT2	Dose Intensity (%) - IV	87
ABC-001-0001	NDSOMT2	Number of Dose Omitted - IV	0
ABC-001-0001	NDELAY2	Number of Dose Delayed - IV	1
ABC-001-0001	NDSINC2	Number of Dose Increased - IV	0
ABC-001-0001	NDSDEC2	Number of Dose Reduced - IV	2
ABC-001-0001	COMPRT2	Compliance Rate (%) - IV	92

Figure 3. Exposure Content without PARQUAL

USUBJID	PARAMCD	PARAM	PARQUAL	PARQUALN	AVAL
ABC-001-0001	NCYCLE	Number of Cycles	Central Line	1	10
ABC-001-0001	DURWK	Duration of Therapy (Week)	Central Line	1	6
ABC-001-0001	CUMDS	Cumulative Dose (mg)	Central Line	1	3000
ABC-001-0001	DSINT	Dose Intensity (%)	Central Line	1	90
ABC-001-0001	NDSOMT	Number of Dose Omitted	Central Line	1	2
ABC-001-0001	NDELAY	Number of Dose Delayed	Central Line	1	1
ABC-001-0001	NDSINC	Number of Dose Increased	Central Line	1	2
ABC-001-0001	NDSDEC	Number of Dose Reduced	Central Line	1	0
ABC-001-0001	COMPRT	Compliance Rate (%)	Central Line	1	90
ABC-001-0001	NCYCLE	Number of Cycles	IV	2	20
ABC-001-0001	DURWK	Duration of Therapy (Week)	IV	2	40
ABC-001-0001	CUMDS	Cumulative Dose (mg)	IV	2	20000
ABC-001-0001	DSINT	Dose Intensity (%)	IV	2	87
ABC-001-0001	NDSOMT	Number of Dose Omitted	IV	2	0
ABC-001-0001	NDELAY	Number of Dose Delayed	IV	2	1
ABC-001-0001	NDSINC	Number of Dose Increased	IV	2	0
ABC-001-0001	NDSDEC	Number of Dose Reduced	IV	2	2
ABC-001-0001	COMPRT	Compliance Rate (%)	IV	2	92

Figure 4. Exposure Content with PARQUAL

PARQUAL, designed to qualify parameters, is different from PARCATy which is designed to group or categorize parameters. Figures 5 and 6 are separate examples that demonstrate appropriate use of PARCATy and PARQUAL. Note that the use of PARQUAL does not affect the meaning of the parameters.

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

Figure 5. PARQUAL vs PARCATy Example 1

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

Figure 6. PARQUAL vs PARCATy Example 2

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	STRAT3 = "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 experience, Y"
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 7. 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.
ATOXDSCL	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 8. Bi-directional Toxicity Grades Example 1

Figure 8 displays the bi-directional toxicity grading proposed in ADaM IG v1.2. The toxicity descriptions (ATOXDSCL and ATOXDSCH) can help to determine denominators. For example, if ATOXDSCL 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.

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

Figure 9. Bi-directional Toxicity Grades Example 2

Figure 9 displays another example of the bi-directional toxicity grading proposed in ADaM IG v1.2. Here, PARAMCD WBC has CTC grading only in the low direction, only BTOXGRL, ATOXGRL, and other toxicity variables in the low direction are populated. Note that no variables in the high direction can be populated for PARAMCD WBC. This is true even when the value is out of range in the opposite direction that is being tested (e.g., ANRIND = HIGH for PARAMCD WBC). Also note that ATOXGRH, ATOXGRL, BTOXGRH, and BTOXGRL can have numeric counterparts (ATOXGRLN, ATOXGRHN, BTOXGRLN, and BTOXGRHN).

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			Grade 3	LOW	Grade 3	
3	001-0001	SGOT	1	33	5	25	HIGH	33	Y		Grade 1	HIGH		Grade 1
4	001-0001	SGOT	2	55	5	25	HIGH	33			Grade 2	HIGH		Grade 1
5	001-0001	PLAT	1	250	150	450	NORMAL	250	Y			NORMAL		
6	001-0001	PLAT	2	100	150	450	LOW	250		Grade 1		NORMAL		
7	001-0002	HGB	1	21.1	11	16.1	HIGH	21.1	Y		Grade 3	HIGH		Grade 3

Row	SHIFT1	SHIFT2	ATOXDSCL	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			Platelet count decreased	
6	Normal to Grade 1		Platelet count decreased	
7			Anemia	Hemoglobin increased

Figure 10. Bi-directional Lab Example

Figure 10 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).

CONCLUSION

Since 2009, the ADaM Implementation Guide (ADaMIG) has provided the industry with a standardized way to communicate and analyze study data. The ADaM team is proposing the release of ADaM IG v1.2 as part of an ongoing commitment to improving the ADaM IG. Version 1.2 will include the addition of PARQUAL within BDS, the addition of stratification variables within ADSL, as well as guidance for bi-directional toxicity grades. These updates will make the implementation of ADaM standards more efficient while also improving the overall quality and legibility of ADaM datasets.

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RECOMMENDED READING

- ADaMIG v1.1
- FDA and PMDA Technical Conformance Guides (TCGs)

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