

INCREMENTAL CHANGES: ADaMIG V1.2 UPDATE

PhUSE US Connect - June 2018



History of ADaMIG Versions

- ▶ ADaMIG v1.0 released late 2009
 - Two structures outlined
 - ADSL
 - BDS
- ▶ Supplemental parameters added for ADaM analysis datasets
 - BDS TTE v1.0 released mid- 2012
 - ADAE v1.0 released mid-2012
- ▶ ADaMIG v1.1 released early 2016
 - Concurrently created is a third analysis data structure
 - OCCDS v1.0

Overview of updates for the version of ADaM IG v1.2 that was sent out for public review

- ▶ New Permissible variable within Basic Data Structure (BDS): PARQUAL
- ▶ Nomenclature for Stratification variables within Subject-Level Analysis Dataset (ADSL)
- ▶ Recommended approach for bi-directional toxicity grades
- ▶ Additional descriptions, clarification and refinement of text, and examples

New Permissible Variable in BDS: PARQUAL

- ▶ 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.
- ▶ PARAM must still uniquely and sufficiently describe what is contained in AVAL or AVALC.

PARQUAL (cont)

- ▶ PARQUAL can be missing for some parameters within a dataset.
- ▶ If used for a parameter, PARQUAL must be populated for all records for that parameter within the dataset.
- ▶ The PARQUAL value cannot be part of 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 about PARAM alone also apply to the combination of PARQUAL plus PARAM.

PARQUAL Example 1 – Tumor Measurement without PARQUAL

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	

- PARAMCD is unique for Investigator and Independent Reviewer.

PARQUAL Example 1 – Tumor Measurement with PARQUAL

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	

- ▶ With PARQUAL only one set of PARAM/PARAMCD for each tumor measurement
- ▶ Combination of PARAM and PARQUAL is sufficient to describe unambiguously the contents of AVAL.

PARQUAL Example 2 – Exposure Content without PARQUAL

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	COMPR1	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	COMPR2	Compliance Rate (%) - IV	92

PARQUAL Example 2 – Exposure Content with 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

PARQUAL vs PARCATy – Example 1

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)

- ▶ PARQUAL is designed to qualify parameters.
- ▶ PARCATy is designed to group or categorize parameters.
- ▶ PARQUAL and PARCATy can be null.

PARQUAL vs PARCATy – Example 2

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)

- ▶ PARQUAL is designed to qualify parameters.
- ▶ PARCATy is designed to group or categorize parameters.

Stratification variables within 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 prognostic factors used to stratify the randomization are specified in the protocol.
- ▶ For analysis, we may need
 - As Randomized (ie, the strata values entered into Interactive Randomization Technology System (IRT) at the time of randomization)
 - As Verified (ie, the strata values verified against the source documents at the site)
- ▶ Table 3.2.9 in the IG 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 & the verified values.

Stratification Variables Within ADSL

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"

Bi-directionality

- ▶ Lab limits often need to be assessed in more than one direction.
- ▶ Creating additional rows can create issues in summaries and analysis and is not an optimal solution
- ▶ The ADaM team decided to provide guidance around additional variables that can be added to handle bi-directional lab limits
- ▶ Examples included are based on CTC Toxicity Grades, but any bi-directional issues could apply these new variables as needed

Bi-directional toxicity grades

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.

- Variables for handling lab limits assessed in more than one direction.

Bi-directional toxicity grades

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

- ▶ PARAMCD WBC has CTC grading only in the low direction, only BTOXGRL, ATOXGRL, and other toxicity variables in the low direction are populated; 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).
- ▶ Note that ATOXGRH, ATOXGRL, BTOXGRH, and BTOXGRL can have numeric counterparts (ATOXGRLN, ATOXGRHN, BTOXGRLN, and BTOXGRHN).

Bi-directional Lab Example

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	ATOXDSC	ATOXDSC
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

- ▶ The above example has some of the variables in a dataset supporting bi-directional toxicity grades.
- ▶ Variables with suffixes *GRL and *GRH are included to indicate variables that pertain to low/high toxicity grades.
- ▶ Hemoglobin is bidirectional (see red boxes), while SGOT and PLAT are only in one direction (see orange box).

Appendix B

Table 3.3.4.1	New	Added new variables <u>PARQUAL</u> and <u>PARQUALN</u> .
Table 3.3.4.1	Modification	Modified last sentence in CDISC notes for BASETYPE from "If used for any PARAM within a dataset, should be non-null for all records of that dataset." to "If used for any PARAM within a dataset, should be non-null for all records for that PARAM within that dataset."
Table 3.3.4.1	New	Added 6 new variables corresponding to the concept of Change <i>to</i> Baseline (where BASE-AVAL is the desired direction): <u>BCHG</u> , <u>BCHGCATy</u> , <u>BCHGCAyN</u> , <u>PBCHG</u> , <u>PBCHGCAy</u> , and <u>PBCHGCyN</u> .
Section 3.3.4.1	Clarification	For the v1.1 sentence of "For example, for parameters corresponding to numeric tests in SDTM Findings class domains, it is not recommended to copy SDTM --STRESC into AVALC, because there is no analysis need for a character value", changed "not recommended" to "not necessary".
Table 3.3.4.2.1	New	Table 3.3.4.2.1 and description were added to clarify the use of new variable <u>PARQUAL</u> compared to existing <u>PARCATy</u>
Table 3.3.5.2	Modification	Modified CDISC notes for AWU from "Unit used for AWLO and AWHI" to "Unit used for AWTARGET, AWTDIFF, AWLO and AWHI".
Section 3.3.7	New	New variables and examples were added to Section 3.3.7 to take into consideration Bi-Directional Lab Toxicity

- Changes are classified as new, clarification, or modification.

Thank You!

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