

INCREMENTAL CHANGES: ADAMIG V1.2 UPDATE

DATA STANDARDS AND GOVERNANCE STREAM – DS10

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Agenda

- ▶ History of ADaM Implementation Guide (ADaMIG)
- ▶ Overview of Updates for ADaMIG v.1.2
- ▶ Stratification Variables within ADSL
- ▶ Bi-directionality Variables and Examples
- ▶ Clarification of Issues Raised on Previous Versions

ADAMIG V.1.2

History of ADaM Implementation Guide (ADaMIG)

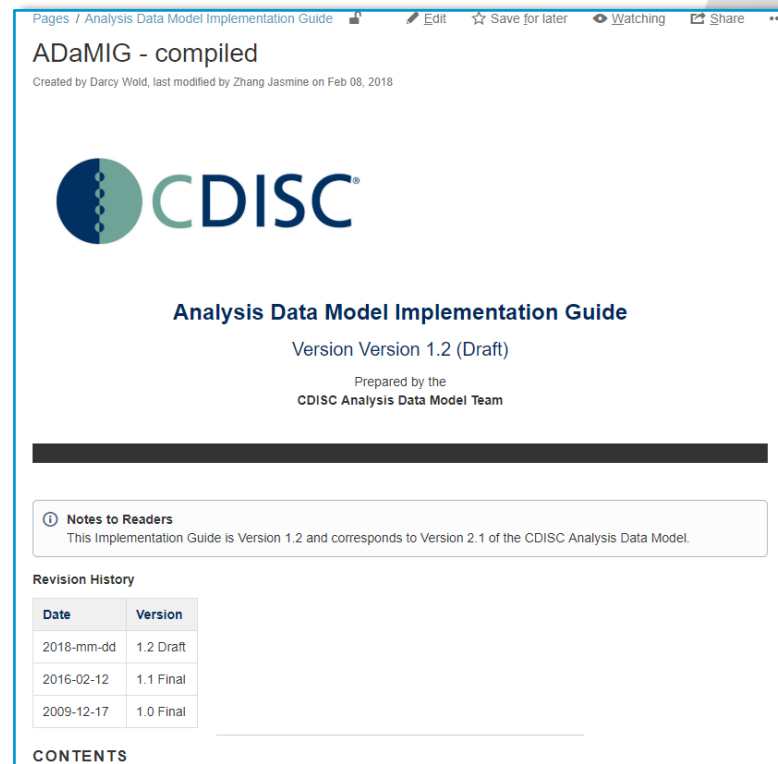
Overview of Updates for ADaMIG v.1.2

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 ADaMIG v1.2

- ▶ 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



ADAMIG V.1.2

Stratification variables within ADSL

Stratification Variables within ADSL

- ▶ A prognostic factor is an aspect of the disease or a characteristic of the subject that may influence treatment response
- ▶ Stratified randomization is used to ensure balance of treatment assignments across one or more prognostic factors
- ▶ The prognostic factors used to stratify the randomization are specified in the protocol
- ▶ For analysis, we may need
 - As Randomized
 - As Verified
- ▶ 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
STRATAR	Strata Used for Randomization	Char	Perm	STRATAR=">=50, Treatment experienced, N"
STRATARN	Strata Used for Randomization (N)	Num	Perm	STRATARN=3 when STRATAR=">=50, Treatment experienced, N"
STRATwD	Description of Stratification Factor w	Char	Perm	STRAT3D="Hypertension"
STRATwR	Strat Factor w Value Used for Rand	Char	Perm	STRAT3R="N"
STRATwRN	Strat Factor w Value Used for Rand (N)	Num	Perm	STRAT3RN=0 when STRAT3R="N"
STRATAV	Strata from Verification Source	Char	Perm	STRATAV=">=50, Treatment experienced, Y"
STRATAVN	Strata from Verification Source (N)	Num	Perm	STRATAVN=4 when STRATAV=">=50, Treatment experienced, Y"
STRATwV	Strat Factor w Value from Verif Source	Char	Perm	STRAT3V="Y"
STRATwVN	Strat Fact w Val from Verif Source (N)	Num	Perm	STRAT3VN=1 when STRAT3V="Y"

ADAMIG V.1.2

Bi-directionality Variables and Examples

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

VARIABLES FOR HANDLING LAB LIMITS ASSESSED IN MORE THAN ONE DIRECTION

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.
ATOXDSC	Analysis Toxicity Description Low	Char	Perm	Used to describe the low end of the lab test criteria preferred term.
ATOXDSC	Analysis Toxicity Description High	Char	Perm	Used to describe the high end of the lab test criteria preferred term.

Bi-directional Lab Example

Row	USUBJID	PARAMCD	AVISITN	AVAL	BASE	ABLFL	ANRLO	ANRHI
1	001-0001	HGB	1	7.4	7.4	Y	11	16.1
2	001-0001	HGB	2	20.5	7.4		11	16.1
3	001-0001	AST	1	33	33	Y	5	25
4	001-0001	AST	2	55	33		5	25
5	001-0001	AST	3	60	33		5	25
6	001-0001	AST	4	77	33		5	25
7	001-0001	PLAT	1	250	250	Y	150	450
8	001-0001	PLAT	2	100	250		150	450
9	001-0001	PLAT	3	99	250		150	450
10	001-0001	PLAT	4	75	250		150	450
11	001-0001	PLAT	5	49	250		150	450
12	001-0002	HGB	1	21.1	21.1	Y	11	16.1
Row	ATOXDSC		ATOXGRL	BTOXGRL	ATOXDSCH		ATOXGRH	BTOXGRH
1	Anemia		Grade 3	Grade 3	Hemoglobin increased		Grade 0	Grade 0
2	Anemia		Grade 0	Grade 3	Hemoglobin increased		Grade 3	Grade 0
3					Aspartate aminotransferase increased		Grade 1	Grade 1
4					Aspartate aminotransferase increased		Grade 1	Grade 1
5					Aspartate aminotransferase increased		Grade 1	Grade 1
6					Aspartate aminotransferase increased		Grade 2	Grade 1
7	Platelet count decreased		Grade 0	Grade 0				
8	Platelet count decreased		Grade 1	Grade 0				
9	Platelet count decreased		Grade 1	Grade 0				
10	Platelet count decreased		Grade 1	Grade 0				
11	Platelet count decreased		Grade 3	Grade 0				
12	Anemia		Grade 0	Grade 0	Hemoglobin increased		Grade 3	Grade 3

12 Incremental Changes: ADaMIG v1.2 Update

Bi-directional Lab Example

- ▶ Example on previous slide has variables supporting bi-directional toxicity grades
- ▶ Variables with suffixes *GRL and *GRH included to indicate variables that pertain to low/high toxicity grades
- ▶ The Orange box demonstrates the following:
 - ATOXDSCL is populated whenever AVAL is not null and grading is in the LOW direction, even if ATOXGRL is null
 - ATOXDSCH is populated whenever AVAL is not null and grading is in the HIGH direction, even if ATOXGRH is null
- ▶ The Red box demonstrates the following:
 - PARAMCD PLAT has toxicity grading only in the low direction, only BTOXGRL, ATOXGRL, and other toxicity variables in the low direction are populated
 - None of the high direction toxicity variables for PARAMCD PLAT are ever populated, even if the value is out of range in the high direction (ANRIND=HIGH)

Bi-directional Shift Variables Example

USUBJID	AVAL	BASE	ABLFL	ATOXGRL	BTOXGRL	ATOXGRH	BTOXGRH	SHIFT1	SHIFT2
001-0001	7.4	7.4	Y	Grade 3	Grade 3	Grade 0	Grade 0		
001-0001	20.5	7.4		Grade 0	Grade 3	Grade 3	Grade 0	Grade 3 to Grade 0	Grade 0 to Grade 3
001-0001	33	33	Y			Grade 1	Grade 1		
001-0001	55	33				Grade 1	Grade 1		Grade 1 to Grade 1
001-0001	60	33				Grade 1	Grade 1		Grade 1 to Grade 1
001-0001	77	33				Grade 2	Grade 1		Grade 1 to Grade 2
001-0001	250	250	Y	Grade 0	Grade 0				
001-0001	100	250		Grade 1	Grade 0			Grade 0 to Grade 1	
001-0001	99	250		Grade 1	Grade 0			Grade 0 to Grade 1	
001-0001	75	250		Grade 1	Grade 0			Grade 0 to Grade 1	
001-0001	49	250		Grade 3	Grade 0			Grade 0 to Grade 3	
001-0002	21.1	21.1	Y	Grade 0	Grade 0	Grade 3	Grade 3		

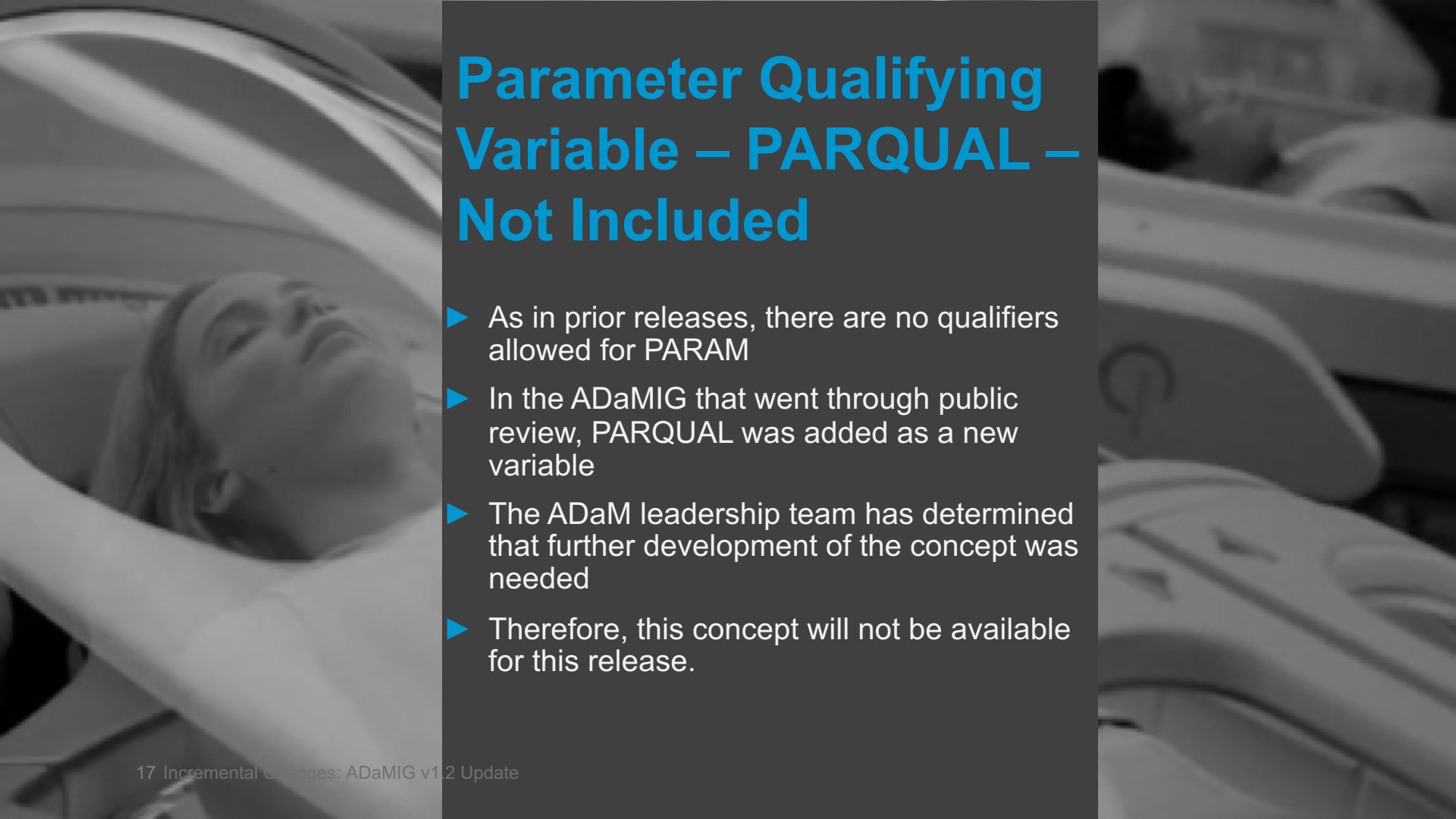
Bi-directional Shift Variables Example

- ▶ ATOXGRL, ATOXGRH, and the corresponding baseline toxicity variables were used to derive shift in toxicity grade
- ▶ SHIFT1 represents the shift from baseline in the low direction and is derived from BTOXGRL and ATOXGRL
- ▶ SHIFT2 represents the shift from baseline in the high direction and is derived from BTOXGRH and ATOXGRH



ADAMIG V.1.2

Clarification of Issues Raised on Previous Versions



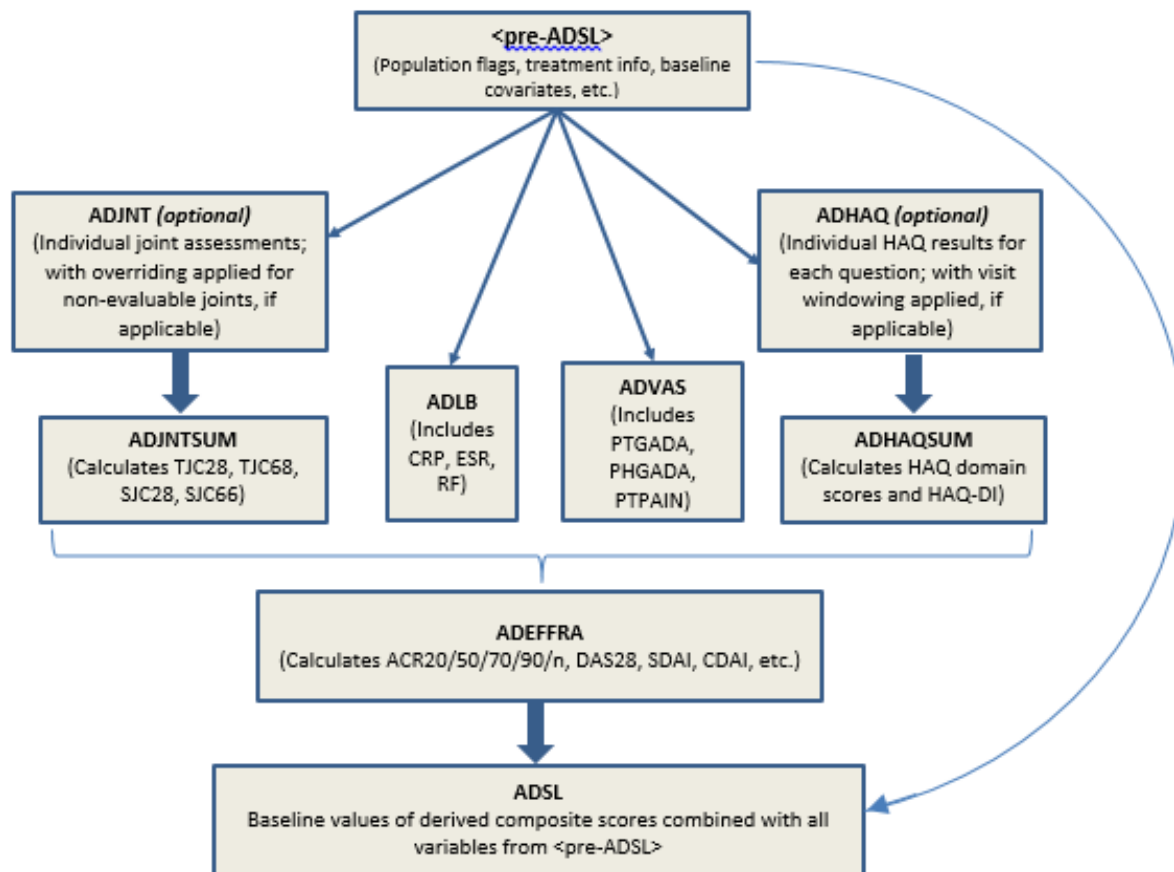
Parameter Qualifying Variable – PARQUAL – Not Included

- ▶ As in prior releases, there are no qualifiers allowed for PARAM
- ▶ In the ADaMIG that went through public review, PARQUAL was added as a new variable
- ▶ The ADaM leadership team has determined that further development of the concept was needed
- ▶ Therefore, this concept will not be available for this release.

ADSL Timing Variables

- ▶ Clarification of ADSL Subject-Level Period, Subperiod, and Phase Timing Variables and BDS Period, Subperiod, and Phase Start and End Timing Variables was added regarding when these variables can be defined in ADSL
- ▶ Timing variables include all the start and end dates within each of phase, period or sub-period (If a set of start variables are included, the set of corresponding end variables should also be included)
- ▶ Phase timing variables are independent of period and sub-period, while sub-period is dependent on period timing variables
- ▶ If the set is defined at the subject-level, then the dataset level assignment must be consistent with the subject-level (e.g. ADSL)
- ▶ Sub-period timing variables may only be included in ADSL if the period timing variables are included

Preparatory Partial ADSL Concept – <pre-ADSL>



Preparatory Partial ADSL Concept – <pre-ADSL>

- ▶ Where derivations for variables in ADSL are extremely complex or rely on imputed or derived values not available in SDTM datasets
- ▶ Create an intermediate dataset on the way to a complete ADSL which contains a partial set of ADSL variables
- ▶ Followed by additional processing to derive the required additional variables
- ▶ Final step to merge those variables back into ADSL
- ▶ Since <pre-ADSL> is a subset of ADSL, it is the sponsor's decision whether to include <pre-ADSL> in a regulatory submission

Deprecation of PARAMTYP Variable

- ▶ As promised in ADaMIG v1.1, PARAMTYP has been deprecated in ADaMIG v1.2
- ▶ There was confusion regarding the differences between DTYPE and PARAMTYP
- ▶ Metadata contains information describing variable derivations, there really was no need to explicitly flag derived parameters with a separate variable whose only possible values were DERIVED or null
- ▶ PARAMTYP may still be used if required by analysis needs.



BASETYPE Should be Populated for a PARAM if Used

USUBJID	PARAMCD	AVISIT	AVAL	BASE	ABLFL	BASETYPE
001-0001	ALT	Screening 1	20	20	Y	MIN
001-0001	ALT	Screening 2	25	25	Y	MAX
001-0001	ALT	Week 1	19	20		MIN
001-0001	ALT	Week 1	19	25		MAX
001-0001	ALT	Week 2	21	20		MIN
001-0001	ALT	Week 2	21	25		MAX
001-0001	ALP	Screening 1	25	27		
001-0001	ALP	Screening 2	27	27	Y	
001-0001	ALP	Week 1	26	27		
001-0001	ALP	Week 2	24	27		

- ADaMIG v1.1 indicated for BASETYPE that, if used for any PARAM within a dataset, it should be non-null for all records of that dataset
- BASETYPE is only defined for some of the parameters within a dataset
- Clarified to state that if BASETYPE is used for any PARAM within a dataset, it should be non-null for all records for that PARAM within that dataset

Clarifying Relationship between Primary & Secondary Variables

In ADaM IG v1.2, the text within the CDISC notes for secondary variables was expanded to clarify its relationship to the primary variable. Below is a typical example of this change.

Primary Variable CDISC Notes (v1.1)	Secondary Variable CDISC Notes (v1.1)	Secondary Variable CDISC Notes (v1.2)
Character description of a grouping or pooling of clinical sites for analysis purposes. For example, SITEGR3 is the name of a variable containing site group (pooled site) names, where the grouping has been done according to the third site grouping algorithm, defined in variable metadata; SITEGR3 does not mean the third group of sites	The numeric code for SITEGRy. One-to-one mapping to SITEGRy within a study	The numeric code for SITEGRy. There must be a one-to-one relationship between SITEGRyN and SITEGRy within a study. SITEGRyN cannot be present unless SITEGRy is also present. When SITEGRy and SITEGRyN are present, then on a given record, either both must be populated or both must be null.

Thank You!

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QUESTIONS?



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