Analysis Data Model (ADaM)
Examples in Commonly Used Statistical Analysis Methods

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Notes to Readers

The examples in this document are based on Version 2.1 of the CDISC Analysis Data Model and Version 1.0 of the CDISC Analysis Data Model Implementation Guide.

Revision History

Date	Version	Summary of Changes
December 16, 2011	1.0 Final	Final released version.
September 15, 2011	1.0 Draft	Draft released for public comment.

Note: Please see Appendix B for Representations and Warranties; Limitations of Liability, and Disclaimers.

Contents

1 Introduction

1.1 Purpose

The objective of this document is to provide examples of the Analysis Data Model applied in statistical methods that are commonly used. The Analysis Data Model subject-level analysis dataset (ADSL) and Basic Data Structure (BDS) and the associated metadata are illustrated. Please refer to Version 2.1 of the Analysis Data Model (the ADaM) and Version 1.0 of the Analysis Data Model Implementation Guide (ADaMIG) for required background about the ADaM and the ADaM data structures.

1.2 Common Statistical Analysis Methods

The BDS described in the ADaM and the ADaMIG supports the majority of statistical analyses, it does not support all statistical analyses.

Table 1.2.1 includes a list of statistical analysis methods that are commonly used and the examples provided within the document that could support the analysis methods listed. The analysis methods listed are those referenced in the ClinicalTrials.gov Results Database[1]. In addition to the methods listed below, producing descriptive statistics is another illustrated approach (Example 4).

Table 1.2.1 Common Statistical Analysis Methods

Analysis Method	Example(s) in document that support the analysis
Analysis of Covariance (ANCOVA)	Example 1 (Basic ANCOVA)
Analysis of Variance (ANOVA)	Example 3 (Repeated Measures ANOVA) Example 6 (Multivariate ANOVA)
Chi-squared	Example 2 (Categorical Analysis)
Chi-squared, Corrected	Example 2 (Categorical Analysis)
Cochran-Mantel-Haenszel Mantel Haenszel	Example 2 (Categorical Analysis, the stratification factor would be an additional column in the BDS dataset) Example 8 (Categorical Analysis, using criteria)
Fisher's Exact	Example 2 (Categorical Analysis)
Kruskal-Wallis	Example 1 (Basic ANCOVA)
Log Rank	Refer to *The ADaM Basic Data Structure Applied to Time-to-Event Analyses* (www.cdisc.org/adam)
McNemar	Example 8 (Categorical Analysis, using criteria) – if the values being compared are the baseline and a post-baseline assessment (BASEC and AVALC). If the values being compared are from two different records (e.g., one is not baseline), then a BDS dataset will not be analysis-ready, as a transpose of the data would be required. Refer to Table 2.6.3.2 for an illustration.
Mixed Models Analysis	Example 3 (Repeated Measures ANOVA) Example 7 (Repeated Measures Analysis for a cross-over study)
Regression, Cox	Refer to *The ADaM Basic Data Structure Applied to Time-to-Event Analyses* (www.cdisc.org/adam), specifically the Cox Regression example
Regression, Linear	Example 3 (Repeated Measures ANOVA)
Regression, Logistic	Example 5 (Logistic Regression Analysis)

[1] ClinicalTrials.gov *"Basic Results" Data Element Definitions (DRAFT)*, September 2010, United States National Institutes of Health, viewed 25 October 2010, <http://prsinfo.clinicaltrials.gov/results_definitions.html>.

Table 1.2.1 Common Statistical Analysis Methods

Analysis Method	Example(s) in document that support the analysis
Sign Test	Example 1 (Basic ANCOVA)
t-Test, 1-sided	Example 1 (Basic ANCOVA)
t-Test, 2-sided	Example 1 (Basic ANCOVA)
Wilcoxon (Mann-Whitney)	Example 1 (Basic ANCOVA)

1.3 Points to Consider When Building Analysis Datasets

In developing the examples illustrated in this document, some of the key ADaM concepts and principles applied are:

- **Optimum number of analysis datasets:** As stated in the ADaM, one goal in creating analysis datasets is to have the optimum number of analysis datasets needed to perform the various analyses. A single dataset can support multiple analyses. Examples 1, 2, 3, and 4 illustrate a single analysis dataset used to support multiple statistical analyses. It should also be noted that the same analysis dataset can be used to generate descriptive statistics as illustrated in Example 4.
- **Ordering of variables:** Within this document, no specific ordering of variables within the illustrated datasets is applied. The ADaM states that ideally the ordering of the variables in the analysis dataset follows a logical ordering (not simply alphabetic). Version 2.1 of the ADaM does not provide a specific recommendation for the ordering of the variables. Within this document, the author of each example applied their own logical ordering. Though there is not an across-example consistency of ordering of variables, within an example the ordering of the variables within the illustrated analysis dataset matches the order of the variables as presented in the associated metadata.
- **Identification of source dataset:** When identifying the source dataset for a variable, the immediate predecessor is used, as described in the ADaM. For example, in ADSL the source is identified as DM.AGE in the analysis variable metadata. When AGE is used in other analysis datasets, the source is identified as ADSL.AGE.
- **Parameter value-level metadata:** Throughout this document parameter value-level metadata are included for BDS analysis datasets, as required in variable-level metadata for a BDS analysis dataset (as defined in the ADaM). ADSL analysis variable metadata do not include parameter value-level metadata, as ADSL is a single record per subject structure.
- **Display format metadata element:** It should be noted that the use of display format, as applied to all tables of Analysis Variable Metadata within this document, is intended to display the format that the metadata row is planned to be viewed as for the purpose of a display such as a statistical table and not always as the attributed format contained in the analysis dataset used. A good example of this is contained in Table 2.8.1.2 regarding AVAL. It should be noted that sometimes there is a need to have different metadata within certain variables and the display format does not have to be consistent across these metadata.
- **Analysis-ready:** The analysis dataset should be "analysis-ready," meaning it should contain all of the variables needed for the specific analysis, so that the analysis can be replicated by performing the actual statistical test without first having to manipulate data. In addition to required variables such as subject identifiers and treatment variables, the critical variables included in the analysis dataset will depend on the specific nature of the disease or indication, the analyses planned in the protocol, and the Statistical Analysis Plan (SAP), and may include:
  - baseline values,
  - stratification or grouping variables,
  - selection flags (e.g., population flag),
  - predictor variables (also known as explanatory variables, independent variables, or covariates),

- response variables (also known as dependent variables),
- supportive variables for complex predictors and/or responses,
- supportive variables to facilitate traceability.

Refer to the ADaMIG for descriptions of issues to be considered in designing and constructing analysis datasets and the associated metadata. Examples of a few of these issues include (but are not limited to):

- identification of baseline,
- facilitating subgroup analyses,
- inclusion of transformed analysis values,
- deriving composite/compound parameters,
- identifying imputation of missing values,
- deriving a new variable (column) vs. a new record, and
- inclusion of additional records and/or variables for sensitivity analyses and/or future analyses.

1.4 Conventions Used in this Document

Throughout this document the terms "producer" and "consumer" are used to refer to the originator/sender/owner/sponsor of the data and the user/reviewer/recipient of the data, respectively. These terms are used to simplify the document, and are not intended to imply that these examples only apply to analysis datasets in the context of electronic submissions to regulatory agencies.

There are many decisions to be made by a producer in order to have consistency among the ADaM datasets and associated metadata being developed. Some of the decisions made in developing the examples within this document are highlighted below to provide insight into conventions used in the document, as well as to emphasize some of the decisions to be made by a producer.

- **Parameter identifier:** For simplicity, in many examples in this document only one analysis parameter is illustrated. In the analysis variable metadata provided in the examples, the producer elected to use the value of PARAMCD as the parameter identifier for variables that have metadata dependent on the analysis parameter. For variables expected to be consistent across analysis parameters, the parameter identifier of "*ALL*" is used. Whether to make this distinction within analysis variable metadata for an analysis dataset containing only one analysis parameter is a decision to be made by the producer.
- **Codelists/Controlled Terminology in the metadata:** All of the examples illustrated in this document repeat the codelist metadata from the source dataset or list the valid values for the variable. It should be noted that how repeated codelists are included is a decision to be made by the producer of the data and is impacted by the choice of stylesheet. For example, the producer may elect to have a separate section of the define file be devoted to codelists, with the analysis variable metadata element providing a link to the appropriate codelist (thus avoiding repeating the list for each analysis variable to which it applies). Similarly, if the list of valid values is long, the producer may choose to provide a link to an external codelist, such as a CDISC terminology set.
- **Result identifier:** The "result identifier" in the analysis results metadata identifies the specific analysis result within a display. As illustrated in Table 2.2.1.2 in this document and in the ADaM, the "result identifier" can be left blank, indicating that the results being described are in the analysis display identified, not one specific portion of the display. To emphasize that the element is intentionally left blank, this document uses a convention of noting "<intentionally left blank>." This is not meant to imply a requirement or standard for using this convention.
- **Programming statements can be omitted:** As illustrated in the ADaM, the "programming statements" in the analysis results metadata can be blank, if the information provided in the other metadata elements is sufficient to describe the analysis performed. This is illustrated in Example 1 (Section 2.1) where the programming

statements are provided, and in Example 2 (Section 2.2) where the programming statements element is left blank. To emphasize that the element is intentionally left blank, this document uses a convention of noting "<intentionally left blank>." This is not meant to imply a requirement or standard for using this convention.

- **Selection clause in the programming statements:** Within this document, the selection criteria to be used for the analysis is (in general) not specifically identified in the programming statements for results metadata. This is not meant to imply that this approach should be used in metadata; it is only to simplify the examples in the document.
- **Identification of software:** As stated in the ADaM regarding the programming statements provided in the analysis results metadata, the name and version of the applicable software package should be specified either as part of the metadata or in another document, such as a Reviewer's Guide. Within this document, the information is not provided within the programming statements metadata element.
- **Hyperlinks:** Throughout this document, hyperlinks are denoted by underlined text. It should be noted that multiple hyperlinks are indicated in the examples in this document. The ability to include these links will be driven by the software and/or stylesheet that the producer uses for submissions.
- **Hypothetical source domains:** The purpose of the examples in this document is to demonstrate analysis datasets and metadata for common analysis situations. To avoid clouding the issue with debates about the appropriate Study Data Tabulation Model (SDTM) domains to use as source for the analysis datasets, hypothetical SDTM domains are indicated with "XX" for all non-standard source/derivation algorithms. This is not meant to imply that this approach should be used in metadata; it is only to simplify the examples in the document.

1.5 Caveats and Disclaimers

- **Examples are for illustration only:** Note that the examples in this document are only intended as illustrations and should not be viewed as a statement of the standards themselves. In addition, the examples are intended to illustrate content and not appearance; it is understood that there are many different ways that data can be displayed. This document does not cover display formats.
- **Display of metadata for illustration of content only:** Though the metadata elements have been defined in the ADaM, how the metadata are displayed is a function of the mechanism used to display the content. The presentation formats used in this document are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.
- **Examples not meant to be all inclusive regarding variables:** The examples describe some of the key variables and records that would be included in the dataset. It is not intended to illustrate every possible variable that might be included in the analysis dataset; for example certain variables that are helpful for traceability such as SRCDOM, SRCVAR, and SRCSEQ are not included in the illustrations.
- **Source/Derivation Column:** The algorithms provided in the Source/Derivation column are for illustration purposes only and are not intended to imply universally accepted definitions or derivations of variables. Algorithms are producer defined and dependent on trial and analysis design.
- **No endorsement of vendors or products:** In an effort to provide illustrations of the ADaM concepts, examples are provided that refer to specific programming languages. As with other ADaM documents, references to specific vendor products are examples only and therefore should not be interpreted as an endorsement of these vendors or products.

2 Examples

2.1 Example 1: Basic Analysis of Covariance (ANCOVA)

This example illustrates an analysis dataset that supports a simple analysis of variance including covariates. Included in this illustration are identification of baseline values, change from baseline analysis, and handling of missing data.

The study measured lumbar spine bone mineral density (BMD) at baseline and then every 6 months for 3 years, with the goal of assessing the difference in effect between two treatments – Drug ABC and Placebo. Factors (i.e., machine type and subject's bone mineral density at baseline) that may influence the response are included in the model and the dataset. The response variable is the percent change from baseline in bone mineral density, with an increasing BMD indicating a positive effect. The source datasets (immediate predecessors) for the analysis dataset in this example are assumed to be ADSL and an SDTM domain containing the bone measurements, represented as "XX" in the example. Missing data are imputed using last observation carried forward (LOCF).

2.1.1 Analysis Data Metadata

Table 2.1.1.1 Analysis Dataset Metadata for ANCOVA Example[2]

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADBMD	Lumbar spine bone mineral density analysis data	adbmd.xpt	One record per subject per parameter per analysis visit	STUDYID, USUBJID, PARAMCD, AVISIT	BDS	dsadbmd.sas

In the metadata illustrated in Table 2.1.1.2 and as mentioned in Section 1.4, the producer elected to use the value of PARAMCD as the parameter identifier for variables that have metadata dependent on the analysis parameter. For variables expected to be consistent across analysis parameters, the parameter identifier of "*ALL*" is used. Whether to make this distinction within analysis variable metadata for an analysis dataset containing only one analysis parameter is a decision to be made by the producer.

[2] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement..

Table 2.1.1.2 Analysis Variable Metadata for ANCOVA Example[3]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADBMD	*ALL*	USUBJID	Unique Subject Identifier	text	$20		ADSL.USUBJID
ADBMD	*ALL*	PARAM	Parameter	text	$32	DXA BMD at Lumbar Spine (g/cm^2)	Populated with "DXA BMD at Lumbar Spine (g/cm^2)" for records corresponding to Lumbar Spine Bone Mineral Density (based on XX.XXTEST and XX.XXSTRESU when XX.XXTESTCD="BMDLS")
ADBMD	PARAMCD	PARAMCD	Parameter Code	text	$8	BMDLS	Populated with "BMDLS" for records corresponding to Lumbar Spine Bone Mineral Density (based on XX.XXTESTCD)
ADBMD	*ALL*	AVISIT	Analysis Visit	text	$11	BASELINE, MONTH 6, MONTH 12, MONTH 18, MONTH 24, MONTH 30, MONTH 36,	Refer to Section X.X of the SAP for a detailed description of the windowing and imputation algorithms used to determine the analysis visit based on ADBMD.ADY
ADBMD	*ALL*	AVISITN	Analysis Visit (N)	integer	3.0	2 = BASELINE, 3 = MONTH 6, 4 = MONTH 12, 5 = MONTH 18, 6 = MONTH 24, 7 = MONTH 30, 8 = MONTH 36	Derived based on ADBMD.AVISIT
ADBMD	*ALL*	STUDYID	Study Identifier	text	$12		ADSL.STUDYID
ADBMD	*ALL*	TRTP	Planned Treatment	text	$15	Drug ABC, Placebo	ADSL.TRT01P
ADBMD	*ALL*	SEX	Sex	text	$1	M, F	ADSL.SEX
ADBMD	*ALL*	AGE	Age	integer	3.0		ADSL.AGE

[3] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Table 2.1.1.2 Analysis Variable Metadata for ANCOVA Example[3]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADBMD	*ALL*	RACE	Race	text	$50	BLACK OR AFRICAN AMERICAN, AMERICAN INDIAN OR ALASKA NATIVE, ASIAN, NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER, WHITE	ADSL.RACE
ADBMD	*ALL*	ITTFL	Intent-To-Treat Population Flag	text	$1	Y, N	ADSL.ITTFL
ADBMD	BMDLS	AVAL	Analysis Value	float	8.1		AVAL = XX.XXSTRESN or an imputed value if XX.XXSTRESN is missing, apply the LOCF algorithm, i.e. set AVAL equal to the value for the previous post-baseline time point (AVISIT). If the previous timepoint is baseline, leave AVAL missing
ADBMD	BMDLS	BASE	Baseline Value	float	8.1		BASE=ADBMD.AVAL where ADBMD.ABLFL="Y"
ADBMD	*ALL*	CHG	Change from Baseline	float	8.1		CHG=ADBMD.AVAL - ADBMD.BASE for post-baseline visits
ADBMD	*ALL*	PCHG	Percent Change from Baseline	float	8.2		PCHG=((ADBMD.AVAL - ADBMD.BASE)/ADBMD.BASE)*100 for post-baseline visits
ADBMD	BMDLS	CRIT1	Analysis Criterion 1	text	$50	>3% change from baseline	Populated with ">3% change from baseline" when ADBMD.PARAMCD = "BMDLS" and ADBMD.PCHG>3
ADBMD	BMDLS	CRIT1FL	Criterion 1 Evaluation Result Flag	text	$1	Y	Set to "Y" when ADBMD.CRIT1 is populated
ADBMD	BMDLS	ABLFL	Baseline Record Flag	text	$1	Y	Set to "Y" when the record is the last record prior to first dose of study medication (ADBMD.ADT ≤ ADBMD.TRTSDT)

Table 2.1.1.2 Analysis Variable Metadata for ANCOVA Example[3]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADBMD	BMDLS	DTYPE	Derivation Type	text	$4	LOCF	Populated with "LOCF" if XX.XXSTRESN is missing, to indicate that on that record ADBMD.AVAL is populated using Last Observation Carried Forward method
ADBMD	BMDLS	BMMCHTYP	Machine Type	text	$7	HOLOGIC, LUNAR	XX.XXMETHOD="BMMCHTYP"
ADBMD	*ALL*	TRTSDT	Date of First Exposure to Treatment	integer	yymmdd10.		ADSL.TRTSDT
ADBMD	*ALL*	ADT	Analysis Date	integer	yymmdd10.		Convert date portion of XX.XXDTC from character to a numeric date variable and format using yymmdd10. date format
ADBMD	*ALL*	ADY	Analysis Relative Day	integer	3.0		If ADBMD.TRTSDT less than or equal to ADBMD.ADT then ADY=ADBMD.ADT – ADBMD.TRTSDT+1 Else ADY=ADBMD.ADT - ADBMD.TRTSDT
ADBMD	BMDLS	XXSEQ	Sequence Number	integer	4.0		XX.XXSEQ from the record in the SDTM XX domain containing AVAL. If AVAL is imputed, the sequence number is carried forward along with AVAL.
ADBMD	BMDLS	AWTARGET	Analysis Window Target	integer	4.0		If ADBMD.AVISIT="BASELINE" then ADBMD.AWTARGET=1 Else if ADBMD.AVISIT="MONTH 6" then ADBMD.AWTARGET=183 Else if ADBMD.AVISIT="MONTH 12" then ADBMD.AWTARGET=365 Else if ADBMD.AVISIT="MONTH 18" then ADBMD.AWTARGET=548 Else if ADBMD.AVISIT="MONTH 24" then ADBMD.AWTARGET=730 Else if ADBMD.AVISIT="MONTH 30" then ADBMD.AWTARGET=913 Else if ADBMD.AVISIT="MONTH 36" then ADBMD.AWTARGET=1095
ADBMD	BMDLS	AWTDIFF	Analysis Window Diff from Target	integer	4.0		The absolute value of the difference between ADBMD.ADY and ADBMD.AWTARGET

Table 2.1.1.2 Analysis Variable Metadata for ANCOVA Example[3]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADBMD	BMDLS	ANL01FL	Analysis Record Flag 01	text	$1	Y	Populate with "Y" to identify the record selected to be analyzed for the specific value of AVISIT (already populated based on the analysis window algorithm defined in SAP X.X) within the specified subject when ADBMD.PARAMCD="BMDLS". If there are multiple records for the same subject within the parameter that have the same value of AVISIT, use the record that is closest to ADBMD.AWTARGET. If there are multiple records that are also the same distance from the target, then use the record with the "worst" result (smallest percent change). Sort by unique subject identifier (ADBMD.USUBJID), parameter (ADBMD.PARAMCD), analysis visit (ADBMD.AVISITN), difference from target (ADBMD.AWTDIFF), and value of percent change (ADBMD.PCHG) and set ANL01FL="Y" for the first result

2.1.2 Analysis Dataset

Table 2.1.2.1 is an illustration of the lumbar spine bone mineral density analysis dataset (ADBMD) defined above. The ADBMD dataset illustrated in this example is designed to support multiple analyses, i.e., the ANCOVA, Fisher's Exact, and Repeated Measures analyses in examples 1, 2, and 3, respectively. The example describes some of the key variables and records that would be included in the dataset.

Key points to note in the example are:

CRITy variables: In this example, the presence of the text string in CRIT1 indicates that the specified criterion is satisfied on this record, while a null value indicates that the criterion is not satisfied. CRIT1FL="Y" when CRIT1 is populated, and is null otherwise.

SEQ variable: In this example, the sequence number from the corresponding SDTM domain record is included in the analysis dataset to provide traceability.

ANL01FL: Identifies records that are to be analyzed within each value of AVISIT (e.g., AVISIT="MONTH 24"), applying a selection algorithm if the subject has multiple records with the same AVISIT value.

Rows 5 and 6: Subject 101-001 has two records (Rows 5 and 6) for AVISIT= "MONTH 24". As specified in the SAP and described in the analysis variable metadata, for multiple records at MONTH 24, the record closest to Day 730 is selected and the ANL01FL is populated with "Y". The observations for Rows 5 and 6 occurred on ADY 700 and 740, respectively. Since the observation on row 6 is the closest to Day 730, it is

selected and the ANL01FL is populated. Both records are retained in the dataset for traceability (i.e., to provide the data to be carried forward for imputation) and to allow for additional analyses.

Row 7: The measurement at "MONTH 30" is missing; therefore the record is imputed using LOCF method. Note that the XXSEQ value is also carried forward.

Rows 8-9: Subject 101-001 has two records (Rows 8 and 9) with AVISIT="MONTH 36". Both records are equidistant from the target of Day 1095, i.e. AWTDIFF=2 for both records. The ANL01FL="Y" in Row 8 since this record has the smallest value of PCHG. Both records are retained in the dataset for traceability and to allow for additional analyses.

Rows 1, 10: CRIT1 and CRIT1FL are not populated on these rows because the criterion cannot be evaluated (i.e., PCHG is null on these baseline records).

Rows 8, 11: CRIT1 and CRIT1FL are not populated on these rows because PCHG is not greater than 3.

Rows 14-16: The measurements at MONTHS 24, 30 and 36 are missing; therefore the records are imputed using the LOCF method.

Table 2.1.2.1 Illustration of Analysis Dataset ADBMD

Row	USUBJID	PARAM	PARAMCD	AVISIT	AVISITN	STUDYID	TRTP	SEX	AGE	RACE	ITTFL	AVAL	BASE	CHG	PCHG
1	101-001	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	BASELINE	2	XXX001	Drug ABC	F	39	WHITE	Y	0.992	0.992		
2	101-001	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 6	3	XXX001	Drug ABC	F	39	WHITE	Y	1.025	0.992	0.033	3.33
3	101-001	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 12	4	XXX001	Drug ABC	F	39	WHITE	Y	1.033	0.992	0.041	4.13
4	101-001	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 18	5	XXX001	Drug ABC	F	39	WHITE	Y	1.025	0.992	0.033	3.33
5	101-001	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 24	6	XXX001	Drug ABC	F	39	WHITE	Y	1.060	0.992	0.068	6.85
6	101-001	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 24	6	XXX001	Drug ABC	F	39	WHITE	Y	1.072	0.992	0.080	8.06
7	101-001	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 30	7	XXX001	Drug ABC	F	39	WHITE	Y	1.072	0.992	0.080	8.06
8	101-001	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 36	8	XXX001	Drug ABC	F	39	WHITE	Y	1.021	0.992	0.029	2.92
9	101-001	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 36	8	XXX001	Drug ABC	F	39	WHITE	Y	1.086	0.992	0.094	9.48
10	101-002	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	BASELINE	2	XXX001	Placebo	M	45	ASIAN	Y	0.795	0.795		
11	101-002	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 6	3	XXX001	Placebo	M	45	ASIAN	Y	0.780	0.795	-0.015	-1.89
12	101-002	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 12	4	XXX001	Placebo	M	45	ASIAN	Y	0.834	0.795	0.039	4.91
13	101-002	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 18	5	XXX001	Placebo	M	45	ASIAN	Y	0.838	0.795	0.043	5.41
14	101-002	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 24	6	XXX001	Placebo	M	45	ASIAN	Y	0.838	0.795	0.043	5.41
15	101-002	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 30	7	XXX001	Placebo	M	45	ASIAN	Y	0.838	0.795	0.043	5.41
16	101-002	DXA BMD at Lumbar Spine (g/cm^2)	BMDLS	MONTH 36	8	XXX001	Placebo	M	45	ASIAN	Y	0.838	0.795	0.043	5.41

Table 2.1.2.1 Illustration of Analysis Dataset ADBMD

(Continued)

Row	CRIT1	CRIT1FL	ABLFL	DTYPE	BMMCHTYP	TRTSDT	ADT	ADY	XXSEQ	AWTARGET	AWTDIFF	ANL01FL
1			Y		HOLOGIC	2007-01-02	2007-01-02	1	102	1	0	Y
2	>3% change from baseline	Y			HOLOGIC	2007-01-02	2007-06-13	163	103	183	20	Y
3	>3% change from baseline	Y			HOLOGIC	2007-01-02	2007-12-31	364	104	365	1	Y
4	>3% change from baseline	Y			HOLOGIC	2007-01-02	2008-06-06	522	105	548	26	Y
5	>3% change from baseline	Y			HOLOGIC	2007-01-02	2008-12-01	700	106	730	30	
6	>3% change from baseline	Y			HOLOGIC	2007-01-02	2009-01-10	740	107	730	10	Y
7	>3% change from baseline	Y		LOCF	HOLOGIC	2007-01-02	2009-01-10	740	107	913	173	Y
8					HOLOGIC	2007-01-02	2009-12-29	1093	108	1095	2	Y
9	>3% change from baseline	Y			HOLOGIC	2007-01-02	2010-01-02	1097	109	1095	2	
10			Y		LUNAR	2007-01-15	2007-01-15	1	202	1	0	Y
11					LUNAR	2007-01-15	2007-06-13	150	203	183	33	Y
12	>3% change from baseline	Y			LUNAR	2007-01-15	2008-01-28	379	204	365	14	Y
13	>3% change from baseline	Y			LUNAR	2007-01-15	2008-06-19	522	205	548	26	Y
14	>3% change from baseline	Y		LOCF	LUNAR	2007-01-15	2008-06-19	522	205	730	208	Y
15	>3% change from baseline	Y		LOCF	LUNAR	2007-01-15	2008-06-19	522	205	913	391	Y
16	>3% change from baseline	Y		LOCF	LUNAR	2007-01-15	2008-06-19	522	205	1095	573	Y

2.1.3 Analysis Results

The following data display illustrates an ANCOVA analysis performed using ADBMD as described above.

As described in the protocol and the SAP, the primary efficacy analysis endpoint is the percent change from baseline at Month 24 in the Bone Mineral Density (BMD) at the Lumbar Spine. The analysis is conducted using the Intent-to-Treat (ITT) population, with LOCF imputation for any missing values at Month 24. As the primary efficacy analysis method, an ANCOVA model is used, with planned treatment (as a categorical variable), baseline BMD value, machine type, and baseline BMD value by machine type interaction included as independent variables, and the percent change from baseline as the dependent variable. The adjusted least squares (LS) means and 95% confidence interval are presented.

Table 2.1.3.1 Illustration of Analysis Display Layout for ANCOVA Example[4]

Summary E.1
Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 24
(ITT Population, LOCF Data, ANCOVA Model)

		% Change From Baseline		Treatment Difference (Drug ABC – Placebo)		
	n	LS Mean[a]	95% CI[a]	LS Mean[a]	95% CI[a]	p-value[a]
Drug ABC (N = xxx)	xxx	x.x	(x.x, x.x)			
Placebo (N = xxx)	xxx	x.x	(x.x, x.x)	x.x	(x.x, x.x)	x.xxxx

Page 1 of 1

N = ITT population, n = number of subjects with non-missing percent change from baseline at month 24
CI = Confidence interval
LS = Least squares
[a]Based on ANCOVA model adjusting for planned treatment, baseline BMD value, machine type, and baseline BMD value by machine type interaction.

[4] The style of the display of the results of an analysis will be determined by the producer. The example is intended to illustrate content not appearance.

Table 2.1.3.2 Analysis Results Metadata for ANCOVA Example[5]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.1
DISPLAY NAME	Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 24 (ITT Population, LOCF Data, ANCOVA Model)
RESULT IDENTIFIER	Treatment difference results (LSMean, confidence interval, p-value)
PARAM	DXA BMD at Lumbar Spine (g/cm^2)
PARAMCD	BMDLS
ANALYSIS VARIABLE	PCHG
REASON	Primary efficacy analysis as pre-specified in protocol
DATASET	ADBMD
SELECTION CRITERIA	ITTFL="Y" and PARAM="DXA BMD at Lumbar Spine (g/cm^2)" and AVISIT="MONTH 24" and ANL01FL="Y"
DOCUMENTATION	See SAP Section XX for details. Program: t-bmd-pchg-ancova.sas LS means and 95% CIs are based on ANCOVA model adjusting for planned treatment, baseline BMD value, machine type, and baseline BMD value by machine type interaction.
PROGRAMMING STATEMENTS	PROC MIXED DATA= ADBMD; CLASS TRTP BMMCHTYP; MODEL PCHG = BASE BMMCHTYP BASE*BMMCHTYP TRTP; LSMEANS TRTP / OM PDIFF = CONTROL ("Placebo") CL; RUN;

[5] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

2.2 Example 2: Categorical Analysis (Analysis Dataset From Example 1)

As described in the SAP, a secondary efficacy analysis of the BMD at the Lumbar Spine endpoint is a comparison of the percentage in each treatment group of the number of subjects with non-missing percent change data at Month 36 who had >3% change in BMD from Baseline. Fisher's exact test is used to compare the proportions between the two treatment groups using the ITT population, with no imputation for missing values, i.e., observed case (OC) data.

This categorical analysis example uses the analysis dataset described in Example 1 (i.e., ADBMD, see Section 2.1.1), illustrating how the same analysis dataset can be used for multiple analyses.

2.2.1 Analysis Results

Table 2.2.1.1 Illustration of Analysis Display Layout for Categorical Analysis Example[6]

Summary E.2 **Subjects with >3% Change from Baseline in Lumbar Spine Bone Mineral Density at Month 36** **(ITT Population, OC Data)**		
	Drug ABC (N=xxx)	Placebo (N=xxx)
Subjects completing Month 36	xxx	xxx
Subjects with >3% change from baseline	xxx (xx.x%)	xxx (xx.x%)
P-value [1]		x.xxxx
		Page 1 of 1
N=ITT population OC Data are data as observed (i.e., no imputation for missing values) Subjects with missing BMD data at Month 36 are excluded from the analysis. [1] p-value computed using Fisher's Exact Test.		

In Table 2.2.1.2 the Result Identifier metadata element has intentionally been left blank because the results metadata describe the entire display; there is no need to identify a specific element of the display. As mentioned in Section 1.4, the "result identifier" in the analysis results metadata can be blank, indicating that the results being described are in the analysis display identified, not one specific portion of the display.

In Table 2.2.1.2 the Programming Statements metadata element has also intentionally been left blank, because the metadata producer elected to not include programming statements. (Whether or not to include information in this metadata element is the producer's decision. The example illustrated here is not

[6] The style of the display of the results of an analysis will be determined by the producer. The example is intended to illustrate content not appearance.

intended to imply a standard or requirement for when to leave the element blank.) As mentioned in Section 1.4, the "programming statements" in the analysis results metadata can be blank, if the information provided in the other metadata elements is sufficient to describe the analysis performed.

Table 2.2.1.2 Analysis Results Metadata for Categorical Analysis Example[7]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.2
DISPLAY NAME	Subjects with >3% Change from Baseline in Lumbar Spine Bone Mineral Density at Month 36 (ITT Population, OC Data)
RESULT IDENTIFIER	<intentionally left blank>
PARAM	DXA BMD at Lumbar Spine (g/cm^2)
PARAMCD	BMDLS
ANALYSIS VARIABLE	CRIT1FL
REASON	Pre-specified in SAP
DATASET	ADBMD
SELECTION CRITERIA	ITTFL="Y" and PARAMCD="BMDLS" and AVISIT="MONTH 36" and ANL01FL="Y" and DTYPE=" " and PCHG not missing
DOCUMENTATION	See SAP Section XX for details. Percentage in each treatment group of the number of subjects with non-missing percent change data at Visit 8 (i.e., AVISIT="MONTH 36") who had >3% change in BMD from Baseline. Subjects with missing change from baseline BMD data at Visit 8 are excluded from the analysis. Number of subjects at MONTH 36 with CRIT1FL="Y" divided by the number of subjects at MONTH 36 with non-missing PCHG. Fisher's exact test used for treatment comparison.
PROGRAMMING STATEMENTS	<Intentionally left blank>

[7] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

2.3 Example 3: Repeated Measures Analysis (Analysis Dataset From Example 1)

The analysis described in this example is an ad hoc analysis. The likelihood based repeated measures analysis of BMD change from baseline at Month 24 uses windowed values with no imputation for missing values (i.e., data as observed) from the ITT population.

This repeated measures analysis example uses the analysis dataset described in Example 1 (i.e., ADBMD, see Section 2.1.1), illustrating how the same analysis dataset can be used for multiple analyses.

2.3.1 Analysis Results

Table 2.3.1.1 Illustration of Analysis Display Layout for Repeated Measures Analysis Example[8]

Summary E.3 Lumbar Spine Bone Mineral Density Percent Change From Baseline to Month 24 (ITT Population, OC Data, Repeated Measures Analysis)					
	% Change From Baseline		Treatment Difference (Drug ABC – Placebo)		
	LS Mean[a]	95% CI[a]	LS Mean[a]	95% CI[a]	p-value[a]
Drug ABC (N = xxx)	x.x	(x.x, x.x)			
Placebo (N = xxx)	x.x	(x.x, x.x)	x.x	(x.x, x.x)	x.xxxx
Page 1 of 1					
N = ITT population OC Data = Observed Cases Data (i.e., data as observed with no imputation for missing values) LS = Least squares [a]Based on mixed-effects model repeated measures analysis, adjusting for planned treatment, time and treatment by time interaction, baseline BMD value, and baseline BMD value by time interaction.					

[8] The style of the display of the results of an analysis will be determined by the producer. The example is intended to illustrate content not appearance.

Table 2.3.1.2 Analysis Results Metadata for Repeated Measures Analysis Example[9]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.3
DISPLAY NAME	Lumbar Spine Bone Mineral Density Percent Change From Baseline to Month 24 (ITT Population, OC Data, Repeated Measures Analysis)
RESULT IDENTIFIER	Treatment Difference (LSMean, confidence interval, p-value)
PARAM	DXA BMD at Lumbar Spine (g/cm^2)
PARAMCD	BMDLS
ANALYSIS VARIABLE	PCHG
REASON	ad hoc analysis
DATASET	ADBMD
SELECTION CRITERIA	AVISITN>2 and AVISITN<=6 and ITTFL="Y" and DTYPE = " " and PARAMCD="BMDLS" and ANL01FL="Y"
DOCUMENTATION	Likelihood based repeated measures analysis of BMD percent change from baseline at Month 24, includes LS Means at Week 24, comparison between treatment groups – windowed values with no imputation for missing values (i.e., data as observed) Adjusted means for the percent change from baseline at week 24 and comparisons between treatment groups at Week 24 using a repeated measures model with treatment group (as class variable); time (as class variable); treatment*time interaction; baseline score and baseline*time interaction terms; and an unstructured covariance matrix.
PROGRAMMING STATEMENTS	PROC MIXED DATA=ADBMD; CLASS USUBJID AVISITN TRTPN; MODEL PCHG = TRTPN AVISITN TRTPN*AVISITN BASE BASE*AVISITN / OUTP=PRED DDFM=KR; REPEATED AVISITN / SUBJECT=USUBJID TYPE=UN; LSMEANS TRTPN / DIFF CL; RUN;

[9] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

2.4 Example 4: Descriptive Statistics (Analysis Dataset From Example 1)

Another common analysis technique is to simply describe the data using summary statistics. Examples of descriptive statistics for a continuous endpoint are mean, standard deviation, median, and range. Examples of descriptive statistics for a categorical endpoint are count and percentage. The BDS supports the majority of analyses based on descriptive as well as inferential statistics.

The analysis illustrated here is a summary analysis presenting the mean, standard deviation, median, and range for the Lumbar Spine BMD for each treatment group at each scheduled time point. In addition, a boxplot showing the distribution of the Lumbar Spine BMD at Month 36 is presented. These analyses use the ITT population, with no imputation for missing values at any time point.

This descriptive statistics example uses the analysis dataset described in Example 1 (i.e., ADBMD, see Section 2.1.1), illustrating how the same analysis dataset can be used for multiple analyses, including simple summary statistics and graphical displays. As part of the illustration, analysis results metadata have been included. As stated in the ADaMIG, analysis results metadata are not needed or even advisable for every analysis included in a clinical study report or submission. It is not expected that a descriptive analysis have analysis results metadata associated with it, though there certainly may situations where this would occur (e.g., the descriptive analysis is the primary analysis, an automated system is used to generate results metadata).

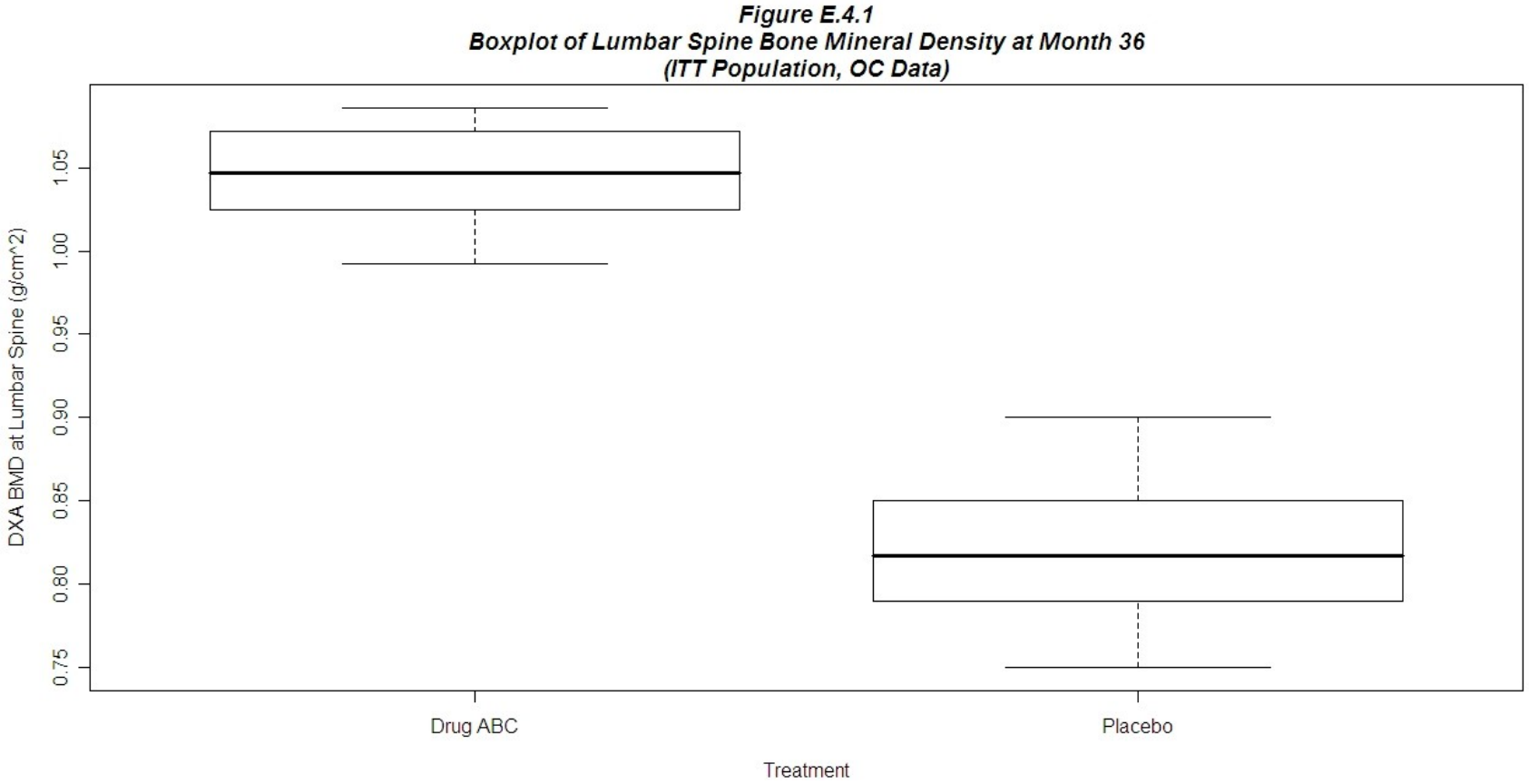
2.4.1 Analysis Results

Table 2.4.1.1 Illustration of Analysis Display Layout for Descriptive Statistics Example[10]

Summary E.4 Summary of Lumbar Spine Bone Mineral Density (g/cm^2) Over Time (ITT Population, OC Data)		
	Drug ABC (N=xxx)	Placebo (N=xxx)
Baseline		
n	xxx	xxx
Mean (SD)	x.xxxx (x.xxxxx)	x.xxxx (x.xxxxx)
Median	x.xxxx	x.xxxx
Min	x.xxx	x.xxx
Max	x.xxx	x.xxx
Month 6		
n	xxx	xxx
Mean (SD)	x.xxxx (x.xxxxx)	x.xxxx (x.xxxxx)
Median	x.xxxx	x.xxxx
Min	x.xxx	x.xxx
Max	x.xxx	x.xxx
etc….		
		Page 1 of 1
N=ITT population OC Data are data as observed (i.e., no imputation for missing values)		

[10] The style of the display of the results of an analysis will be determined by the producer. The example is intended to illustrate content not appearance.

Figure 2.4.1.1 Illustration of Analysis Display Graph for Descriptive Statistics Example[11]



[11] The type and style of graphical displays of analysis data will be determined by the producer. The example is intended to illustrate content not appearance or type.

The purpose of Table 2.4.1.2 and Table 2.4.1.3 is to provide an example of Analysis Results Metadata for analyses based on descriptive statistics. Neither is intended to imply that the provision of Analysis Results Metadata is recommended for all output and displays.

In both Table 2.4.1.2 and Table 2.4.1.3, the Result Identifier metadata element has been intentionally left blank because the results metadata describe the entire display; there is no need to identify a specific element of the display. As mentioned in Section 1.4, the "result identifier" in the analysis results metadata can be blank, indicating that the results being described are in the analysis display identified, not one specific portion of the display. The programming statements provided are based on the R software programming package.

Table 2.4.1.2 Analysis Results Metadata for Descriptive Statistics Tabular Display Example[12]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.4
DISPLAY NAME	Summary of Lumbar Spine Bone Mineral Density (g/cm^2) Over Time (ITT Population, OC Data)
RESULT IDENTIFIER	<intentionally left blank>
PARAM	DXA BMD at Lumbar Spine (g/cm^2)
PARAMCD	BMDLS
ANALYSIS VARIABLE	AVAL
REASON	Pre-specified in SAP
DATASET	ADBMD
SELECTION CRITERIA	ITTFL=="Y" & PARAMCD=="BMDLS" & ANL03FL=="Y"
DOCUMENTATION	See SAP Section XX for details. Summary of Lumbar Spine Bone Mineral Density Measurements in each treatment group at Baseline, Month 6, Month 12, Month 18, Month 24, Month 30, and Month 36.
PROGRAMMING STATEMENTS	aggregate(AVAL,list(TRTP=TRTP,AVISIT=AVISIT),mean) aggregate(AVAL,list(TRTP=TRTP,AVISIT=AVISIT),sd) aggregate(AVAL,list(TRTP=TRTP,AVISIT=AVISIT),median) aggregate(AVAL,list(TRTP=TRTP,AVISIT=AVISIT),min) aggregate(AVAL,list(TRTP=TRTP,AVISIT=AVISIT),max)

[12] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Table 2.4.1.3 Analysis Results Metadata for Descriptive Statistics Graphical Display Example[13]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Figure E.4.1
DISPLAY NAME	Boxplot of Lumbar Spine Bone Mineral Density at Month 36 (ITT Population, OC Data)
RESULT IDENTIFIER	<intentionally left blank>
PARAM	DXA BMD at Lumbar Spine (g/cm^2)
PARAMCD	BMDLS
ANALYSIS VARIABLE	AVAL
REASON	Pre-specified in SAP
DATASET	ADBMD
SELECTION CRITERIA	ITTFL=="Y" & PARAMCD=="BMDLS" & ANL03FL=="Y" & AVISIT=="MONTH 36"
DOCUMENTATION	See SAP Section XX for details. Boxplot of Lumbar Spine Bone Mineral Density Measurements in each treatment group at Month 36.
PROGRAMMING STATEMENTS	boxplot(AVAL~ TRTP,xlab="Treatment",ylab="DXA BMD at Lumbar Spine (g/cm^2)") title(main="Figure E.4.1\nBoxplot of Lumbar Spine Bone Mineral Density at Month 36\n(ITT Population, OC Data)",font.main=4)

[13] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

2.5 Example 5: Logistic Regression Analysis

This example illustrates an analysis dataset (ADPAIN) that supports a logistic regression including covariates. Included in this example is an illustration of the use of the analysis criterion and criterion evaluation result variables CRITy and CRITyFL, and one way they can be used in supporting a categorical analysis.

The study assessed the effect of study drug during a single pain attack. The study measured pain severity (on a scale of 0=no pain to 3=severe pain) at baseline (immediately prior to taking a single dose of randomized study drug) and then every 30 minutes for 2 hours, with the goal of assessing the difference in effect between two treatments – Placebo and Drug XYZ. Factors that might influence the response include age, sex, and the subject's pain level at baseline; therefore they are included as terms in the model and as variables in the analysis dataset. The response variable is whether or not the subject achieved pain relief at 2 hours post-baseline. Pain relief is defined as a reduction in pain from moderate or severe at baseline (i.e., pain severity of at least 2) to mild or no pain (i.e., pain severity of no more than 1) at the specified time, with no use of rescue medication from baseline up to the specified time point. The source datasets (immediate predecessors) for the analysis dataset in this example are assumed to be ADSL and an SDTM domain (represented as "XX" in the example) containing the subject's responses to questions regarding pain severity and rescue medication usage (Yes or No) at each time point. Missing data are imputed using LOCF.

2.5.1 Analysis Data Metadata

Table 2.5.1.1 Analysis Dataset Metadata for Logistic Regression Analysis Example[14]

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADPAIN	Pain severity analysis data	adpain.xpt	One record per subject per parameter per analysis time point	STUDYID, USUBJID, PARAMCD, ATPT	BDS	adpain.sas

Table 2.5.1.2 Analysis Variable Metadata for Logistic Regression Analysis Example[15]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADPAIN	*ALL*	STUDYID	Study Identifier	text	$10		ADSL.STUDYID
ADPAIN	*ALL*	USUBJID	Unique Subject Identifier	text	$20		ADSL.USUBJID

[14] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

[15] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Table 2.5.1.2 Analysis Variable Metadata for Logistic Regression Analysis Example[15]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADPAIN	*ALL*	TRTP	Planned Treatment	text	$10	Drug XYZ, Placebo	ADSL.TRT01P
ADPAIN	*ALL*	ITTFL	Intent-To-Treatment Population Flag	text	$1	Y, N	ADSL.ITTFL
ADPAIN	*ALL*	PARAM	Parameter	text	$32	Pain Severity	Populated with “Pain Severity” (XX.XXTEST) for the records pertaining to this analysis parameter.
ADPAIN	PARAMCD	PARAMCD	Parameter Code	text	$8	SEVERITY	Populated with ”Severity” for records corresponding to Pain Severity (based on XX.XXTESTCD)
ADPAIN	*ALL*	ATPT	Analysis Timepoint	text	$20	BASELINE, 30 MIN, 1 HOUR, 90 MIN, 2 HOUR	XX.XXTPT or the timepoint for the imputed AVAL
ADPAIN	*ALL*	ATPTN	Analysis Timepoint (N)	integer	3.0	1=BASELINE, 2=30 MIN, 3=1 HOUR, 4=90 MIN, 5=2 HOUR	XX.XXTPTNUM or the timepoint number for the imputed AVAL
ADPAIN	*ALL*	ABLFL	Baseline Record Flag	text	$1	Y	“Y” when ADPAIN.ATPT=“BASELINE”
ADPAIN	SEVERITY	AVAL	Analysis Value	integer	1.0	0=No Pain, 1=Mild Pain, 2=Moderate Pain, 3=Severe Pain	XX.XXSTRESN when XX.XXTEST=”Pain Severity” and XX.XXTPT=ATPT or an imputed value if XX.XXSTRESN is missing, set AVAL equal to the value for the previous post-baseline time point. If the previous timepoint is baseline, leave AVAL missing
ADPAIN	SEVERITY	AVALC	Analysis Value (C)	text	$20	No Pain, Mild Pain, Moderate Pain, Severe Pain	XX.XXSTRESC when XX.XXTEST=”Pain Severity” and XX.XXTPT=ATPT or an imputed value if XX.XXSTRESN is missing, set AVALC equal to the value for the previous post-baseline time point. If the previous timepoint is baseline, leave AVALC missing

Table 2.5.1.2 Analysis Variable Metadata for Logistic Regression Analysis Example[15]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADPAIN	SEVERITY	BASE	Baseline Value	integer	1.0	0=No Pain, 1=Mild Pain, 2=Moderate Pain, 3=Severe Pain	AVAL when ADPAIN.ABLFL="Y"
ADPAIN	SEVERITY	BASEC	Baseline Value (C)	text	$20	No Pain, Mild Pain, Moderate Pain, Severe Pain	AVALC when ADPAIN.ABLFL="Y"
ADPAIN	SEVERITY	CRIT1	Analysis Criteria 1	text	$50	Pain Relief at 2 hour	Populated with "Pain Relief at 2 hour" when PARAMCD="SEVERITY" and ATPT="2 HOUR"
ADPAIN	SEVERITY	CRIT1FL	Criterion 1 Evaluation Result Flag	text	$1	Y, N	Null if CRIT1=" " If CRIT1 not null, then set to "Y" or "N": "Y" if ADPAIN.BASE>=2 AND ADPAIN.AVAL<=1 AND ADPAIN.RESCUEFL=" " and ABLFL = " " Else "N"
ADPAIN	*ALL*	AGE	Age	integer	3.0		ADSL.AGE
ADPAIN	*ALL*	SEX	Sex	text	$1	M, F	ADSL.SEX
ADPAIN	SEVERITY	DTYPE	Derivation Type	text	$5	LOCF	Populated with "LOCF" when the value of AVAL is imputed using last observation carried forward:
ADPAIN	SEVERITY	RESCUEFL	Rescue Medication Used Flag	text	$1	Y	"Y" if XX.XXTEST="Rescue Medication Used" and XX.XXTPT=ATPT and XX.XXSTRESC="Y" or if ADPAIN.RESCUEFL = "Y" for previous time point for this subject

2.5.2 Analysis Dataset

Table 2.5.2.1 is an illustration of the pain severity analysis dataset (ADPAIN) defined above. The analysis variable for this example is whether or not the criteria for pain relief have been met (i.e., CRIT1FL). In this example, the approach illustrated for the CRITy and CRITyFL variables is to have the text string in CRIT1 identify the criterion being evaluated, and whether or not the criterion is satisfied is indicated by the value ("Y" or "N") of the CRIT1FL variable. Therefore, CRIT1 is populated for all relevant records within the parameter (i.e., those containing the 2 hour assessments), and valid values for CRIT1FL are "Y" and "N". The ADPAIN example describes some of the key variables and records included in the dataset.

Key points to note in the example are:

Rows 5,10,15: The CRIT1 variables are populated only on these rows because the criterion is not relevant on rows not pertaining to the 2 hour time point, i.e., ATPT="2 HOUR".

Row 5: This subject (Subject 101-001) has no missing values. CRIT1FL is Y on row 5 because BASE≥2 and AVAL≤1 and RESCUEFL are null.

Row 10: Once the RESCUEFL is set to "Y" as for Subject 101-002 (Row 9), all successive rows for the subject will contain RESCUEFL="Y". CRIT1FL is N because RESCUEFL="Y" even though BASE=3 and AVAL=1.

Rows 12-13: The measurements at "90 MIN" and "2 HOUR" are missing for Subject 101-003, therefore the records are imputed using LOCF method (DTYPE="LOCF").

Table 2.5.2.1 Illustration of Analysis Dataset ADPAIN

Row	STUDYID	USUBJID	TRTP	ITTFL	PARAM	PARAMCD	ATPT	ATPTN	ABLFL	AVAL	AVALC	BASE	BASEC	CRIT1	CRIT1FL	AGE	SEX	DTYPE	RESCUEFL
1	AZY389	101-001	Drug XYZ	Y	Pain Severity	SEVERITY	BASELINE	1	Y	3	Severe Pain	3	Severe Pain			34	M		
2	AZY389	101-001	Drug XYZ	Y	Pain Severity	SEVERITY	30 MIN	2		2	Moderate Pain	3	Severe Pain			34	M		
3	AZY389	101-001	Drug XYZ	Y	Pain Severity	SEVERITY	1 HOUR	3		1	Mild Pain	3	Severe Pain			34	M		
4	AZY389	101-001	Drug XYZ	Y	Pain Severity	SEVERITY	90 MIN	4		1	Mild Pain	3	Severe Pain			34	M		
5	AZY389	101-001	Drug XYZ	Y	Pain Severity	SEVERITY	2 HOUR	5		0	No Pain	3	Severe Pain	Pain Relief at 2 hrs	Y	34	M		
6	AZY389	101-002	Placebo	Y	Pain Severity	SEVERITY	BASELINE	1	Y	3	Severe Pain	3	Severe Pain			28	F		
7	AZY389	101-002	Placebo	Y	Pain Severity	SEVERITY	30 MIN	2		3	Severe Pain	3	Severe Pain			28	F		
8	AZY389	101-002	Placebo	Y	Pain Severity	SEVERITY	1 HOUR	3		2	Moderate Pain	3	Severe Pain			28	F		
9	AZY389	101-002	Placebo	Y	Pain Severity	SEVERITY	90 MIN	4		2	Moderate Pain	3	Severe Pain			28	F		Y
10	AZY389	101-002	Placebo	Y	Pain Severity	SEVERITY	2 HOUR	5		1	Mild Pain	3	Severe Pain	Pain Relief at 2 hrs	N	28	F		Y
11	AZY389	101-003	Drug XYZ	Y	Pain Severity	SEVERITY	BASELINE	1	Y	3	Severe Pain	3	Severe Pain			31	F		
12	AZY389	101-003	Drug XYZ	Y	Pain Severity	SEVERITY	30 MIN	2		2	Moderate Pain	3	Severe Pain			31	F		
13	AZY389	101-003	Drug XYZ	Y	Pain Severity	SEVERITY	1 HOUR	3		1	Mild Pain	3	Severe Pain			31	F		
14	AZY389	101-003	Drug XYZ	Y	Pain Severity	SEVERITY	90 MIN	4		1	Mild Pain	3	Severe Pain			31	F	LOCF	
15	AZY389	101-003	Drug XYZ	Y	Pain Severity	SEVERITY	2 HOUR	5		1	Mild Pain	3	Severe Pain	Pain Relief at 2 hrs	Y	31	F	LOCF	

2.5.3 Analysis Results

The following data display illustrates the logistic regression analysis performed using ADPAIN as described above.

As described in the protocol and the SAP, the primary efficacy endpoint is the percentage of subjects with pain relief at 2 hours. A logistic regression analysis is used to compare this percentage between the Drug XYZ and placebo treatment groups. The logistic regression model includes planned treatment, age, sex, and baseline pain severity as independent variables and whether or not the subject achieved pain relief at 2 hours as the response variable. A subject is defined to

have obtained pain relief if their baseline pain is moderate or severe (i.e., pain severity of at least 2) and the pain at the specified time point is mild or none (i.e., pain severity of no more than 1). The odds ratio and 95% confidence interval are presented.

Table 2.5.3.1 Illustration of Analysis Display Layout for Logistic Regression Analysis Example[16]

Summary E.5 **Pain Relief at 2 Hours** **(ITT Population, LOGISTIC Model)**		
	Placebo (N=xxx)	Drug XYZ (N=xxx)
Number (%) with pain relief	xx (xx.x%)	xx (xx.x%)
Odds ratio		x.xx
95% CI of odds ratio		(x.xx,x.xx)
p-value		x.xxxx
		Page 1 of 1
N=ITT population Note: Analysis is based on a logistic regression model adjusting for treatment, age, sex, and baseline pain severity.		

[16] The style of the display of the results of an analysis will be determined by the producer. The example is intended to illustrate content not appearance.

Table 2.5.3.2 Analysis Results Metadata for Logistic Regression Analysis Example[17]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.5
DISPLAY NAME	Pain Relief at 2 Hours (ITT Population, LOGISTIC Model)
RESULT IDENTIFIER	<intentionally left blank>
PARAM	Pain Severity
PARAMCD	SEVERITY
ANALYSIS VARIABLE	CRIT1FL
REASON	Primary efficacy analysis as pre-specified in SAP
DATASET	ADPAIN
SELECTION CRITERIA	ITTFL="Y" and PARAMCD="SEVERITY" and ATPT="2 HOUR"
DOCUMENTATION	Comparing pain relief at 2 hours for Drug XYZ versus placebo. See SAP Section XX for details. Program: t-relief-or-logistic.sas. Odds ratio and 95% CI are based on logistic model adjusting for planned treatment, age, sex, and baseline pain severity
PROGRAMMING STATEMENTS	PROC LOGISTIC DATA= ADPAIN DESCENDING; CLASS TRTP SEX BASE; MODEL CRIT1FL (DESCENDING) = TRTP AGE SEX BASE /EXPB; RUN;

[17] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

2.6 Example 6: Multivariate Analysis of Variance

This example illustrates an analysis dataset (ADMOOD) that contains subscale scores as well as a total score assessing mood. The analysis to be performed will produce estimates of treatment effect for each subscale as well as an assessment of overall treatment effect (i.e., a test of the main effect of study drug on the combined subscales). This example illustrates analysis results metadata for specific items on a summary table.

In the following example, mood is measured using a total mood disturbance score and six subscale scores. The instrument used is the Profile of Mood States (POMS) Assessment form which contains 65 items rated on a 5-point Likert scale where 0=Not at all, 1=a little, 2=moderately, 3=quite a bit, and 4=extremely. The six subscales that make up the factor analysis are as follows: tension-anxiety (9 items with total score ranging from 0 to 36), depression (15 items with total score ranging from 0 to 60), anger-hostility (12 items with total score ranging from 0 to 48), vigor-activity (8 items with total score ranging from 0 to 32), fatigue (7 items with total score ranging from 0 to 28), and confusion-bewilderment (7 items with total score ranging from 0 to 28). The total mood disturbance score ranging from 0 to 200 is calculated by adding up tension-anxiety, depression, anger-hostility, fatigue, and confusion-bewilderment subscale scores and subtracting the vigor subscale score. The analyses performed are based on the subscale and total scores, not on the individual item scores.

Occasionally, there may be a need to perform an analysis that requires multiple dependent variables. (In this context, "variable" refers to a term in a statistical model.) In this type of situation, there is more than one (correlated) dependent variable and these dependent variables cannot simply be combined into one. The researcher might want to test whether there are significant differences between groups on the combined dependent variables. There are many different approaches to doing a multivariate analysis of variance. The ADaM Basic Data Structure (as shown below in Table 2.6.1.2) meets the needs for some of those approaches (e.g., using PROC MIXED in SAS®[18]). Other approaches may require a structure where the multiple dependent variables are all on the same record (row) in the dataset, which is not an ADaM-compliant BDS structure. In this example, the approach taken (not meant to imply a requirement or standard) is to provide the ADaM-compliant BDS analysis dataset, accompanied by metadata describing the simple transposition of the dataset required for a more "horizontal" structure, as illustrated in Table 2.6.3.3. Alternatively, the producer could opt to save the transposed dataset as an ADaM dataset that is not compliant with BDS but fulfills the other requirements of an ADaM dataset. As stated in the ADaMIG, it is incumbent on the user of the ADaM to understand and appreciate when an alternate structure for the analysis dataset is truly needed.

It should be noted that the following example is a simple one, for the purposes of illustration. If the values for the dependent variables are not all found in AVAL, the transposition of the dataset would be more complicated. The source datasets (immediate predecessors) for the analysis dataset in this example are assumed to be ADSL and the SDTM QS (Questionnaires) Findings Domain containing the subject's responses to the mood questionnaire.

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2.6.1 Analysis Data Metadata

Table 2.6.1.1 Analysis Dataset Metadata for Multivariate ANOVA Example[19]

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADMOOD	Mood assessment analysis data	admood.xpt	One record per subject per parameter per analysis visit	STUDYID, USUBJID, PARAMCD, AVISIT	BDS	admood.sas

Table 2.6.1.2 Analysis Variable Metadata for Multivariate ANOVA Example[20]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADMOOD	*ALL*	STUDYID	Study Identifier	text	$6		ADSL.STUDYID
ADMOOD	*ALL*	USUBJID	Unique Subject Identifier	text	$10		ADSL.USUBJID
ADMOOD	*ALL*	TRTP	Planned Treatment	text	$10	Placebo, Drug ZZZ	ADSL.TRT01P
ADMOOD	*ALL*	TRTPN	Planned Treatment (N)	integer	1.0	0 = Placebo, 1 = Drug ZZZ	ADSL.TRT01PN
ADMOOD	*ALL*	ITTFL	Intent-To-Treat Population Flag	text	$1	Y, N	ADSL.ITTFL

[19] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

[20] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Table 2.6.1.2 Analysis Variable Metadata for Multivariate ANOVA Example[20]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADMOOD	*ALL*	PARAM	Parameter	text	$50	Tension/Anxiety Total Score, Depression/Rejection Total Score, Anger/Hostility Total Score, Vigor/Activity Total Score, Fatigue/Inertia Total Score, Confusion/Bewilderment Total Score, Total Score	For records created to contain the total scores populate with the appropriate total score name.
ADMOOD	PARAMCD	PARAMCD	Parameter Code	text	$8	ANXIETY, DPRESS, ANGER, VIGOR, FATIGUE, CONFUS, TOTAL	One-to-one correspondence with ADMOOD.PARAM
ADMOOD	*ALL*	AVISIT	Analysis Visit	text	$25	Baseline, Week 6	QS.VISIT
ADMOOD	*ALL*	AVISITN	Analysis Visit (N)	integer	1.0	2 = Baseline, 4 = Week 6	QS.VISITNUM
ADMOOD	*ALL*	ABLFL	Baseline Record Flag	text	$1	Y	"Y" if record contains the baseline value, i.e., if ADMOOD.AVISITN=2; Otherwise leave blank
ADMOOD	ANXIETY	AVAL	Analysis Value	integer	3.0		Sum of the 9 tension-anxiety items (QS.QSSTRESN) where QS.QSTESTCD has values of ANXIETY1-ANXIETY9 and ADMOOD.USUBJID=QS.USUBJID and ADMOOD.AVISIT=QS.VISIT Set to missing if more than 20% of the assessment items are missing

Table 2.6.1.2 Analysis Variable Metadata for Multivariate ANOVA Example[20]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADMOOD	DPRESS	AVAL	Analysis Value	integer	3.0		Sum of the 15 depression-rejection items (QS.QSSTRESN) where QS.QSTESTCD has values of DPRESS1-DPRESS15 and ADMOOD.USUBJID=QS.USUBJID and ADMOOD.AVISIT=QS.VISIT Set to missing if more than 20% of the assessment items are missing
ADMOOD	ANGER	AVAL	Analysis Value	integer	3.0		Sum of the 12 anger-hostility items (QS.QSSTRESN) where QS.QSTESTCD has values of ANGER1-ANGER12 and ADMOOD.USUBJID=QS.USUBJID and ADMOOD.AVISIT=QS.VISIT Set to missing if more than 20% of the assessment items are missing
ADMOOD	VIGOR	AVAL	Analysis Value	integer	3.0		Sum of the 8 vigor-activity items (QS.QSSTRESN) where QS.QSTESTCD has values of VIGOR1-VIGOR8 and ADMOOD.USUBJID=QS.USUBJID and ADMOOD.AVISIT=QS.VISIT Set to missing if more than 20% of the assessment items are missing
ADMOOD	FATIGUE	AVAL	Analysis Value	integer	3.0		Sum of the 7 fatigue-inertia items (QS.QSSTRESN) where QS.QSTESTCD has values of FATIGUE1-FATIGUE7 and ADMOOD.USUBJID=QS.USUBJID and ADMOOD.AVISIT=QS.VISIT Set to missing if more than 20% of the assessment items are missing
ADMOOD	CONFUS	AVAL	Analysis Value	integer	3.0		Sum of the 7 confusion-bewilderment items (QS.QSSTRESN) where QS.QSTESTCD has values of CONFUS1-CONFUS7 and ADMOOD.USUBJID=QS.USUBJID and ADMOOD.AVISIT=QS.VISIT Set to missing if more than 20% of the assessment items are missing

Table 2.6.1.2 Analysis Variable Metadata for Multivariate ANOVA Example[20]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADMOOD	TOTAL	AVAL	Analysis Value	integer	3.0		Sum of the tension-anxiety (ANXIETY), depression (DPRESS), anger-hostility (ANGER), fatigue (FATIGUE), and confusion-bewilderment (CONFUS) subscales minus the vigor (VIGOR) subscale and ADMOOD.USUBJID=QS.USUBJID and ADMOOD.AVISIT=QS.VISIT Set to missing if more than 20% of the assessment items are missing
ADMOOD	*ALL*	BASE	Baseline Value	integer	3.0		BASE=ADMOOD.AVAL where ADMOOD.ABLFL="Y"
ADMOOD	*ALL*	CHG	Change from Baseline	integer	4.0		CHG=ADMOOD.AVAL-ADMOOD.BASE for post-baseline visits

2.6.2 Analysis Dataset

Table 2.6.2.1 is an illustration of the analysis dataset (ADMOOD) defined above. The ADMOOD example describes some of the key variables and records included in the dataset.

In this simple example, the records in the ADMOOD analysis dataset contain the subscale scores and the total score. The reasons for not including the individual items were 1) as stated in the introduction to this example, the individual item scores are not analyzed as individual items, 2) as stated in the metadata, missing data are handled in the algorithm for computing each subscale score, so there is no individual item imputation to be traced, and 3) it is possible to clearly identify the records in the SDTM domain that are input to the calculations for the subscale scores based on variables in the analysis dataset as defined in the metadata. Given these facts, and the fact that inclusion of the raw item scores would add another 65 records for every visit for each subject, the producer deemed it appropriate to not retain the individual scores in the analysis dataset.

Table 2.6.2.1 Illustration of Analysis Dataset ADMOOD

Row	STUDYID	USUBJID	TRTP	TRTPN	ITTFL	PARAM	PARAMCD	AVISIT	AVISITN	ABLFL	AVAL	BASE	CHG
1	MXX123	101-001	Drug ZZZ	1	Y	Tension/Anxiety Total Score	ANXIETY	Baseline	2	Y	8	8	
2	MXX123	101-001	Drug ZZZ	1	Y	Depression/Rejection Total Score	DPRESS	Baseline	2	Y	3	3	
3	MXX123	101-001	Drug ZZZ	1	Y	Anger/Hostility Total Score	ANGER	Baseline	2	Y	4	4	
4	MXX123	101-001	Drug ZZZ	1	Y	Vigor/Activity Total Score	VIGOR	Baseline	2	Y	8	8	
5	MXX123	101-001	Drug ZZZ	1	Y	Fatigue/Inertia Total Score	FATIGUE	Baseline	2	Y	10	10	
6	MXX123	101-001	Drug ZZZ	1	Y	Confusion/Bewilderment Total Score	CONFUS	Baseline	2	Y	4	4	
7	MXX123	101-001	Drug ZZZ	1	Y	Total Score	TOTAL	Baseline	2	Y	37	37	
8	MXX123	101-001	Drug ZZZ	1	Y	Tension/Anxiety Total Score	ANXIETY	Week 6	4		7	8	-1
9	MXX123	101-001	Drug ZZZ	1	Y	Depression/Rejection Total Score	DPRESS	Week 6	4		5	3	2
10	MXX123	101-001	Drug ZZZ	1	Y	Anger/Hostility Total Score	ANGER	Week 6	4		16	4	12
11	MXX123	101-001	Drug ZZZ	1	Y	Vigor/Activity Total Score	VIGOR	Week 6	4		15	8	7
12	MXX123	101-001	Drug ZZZ	1	Y	Fatigue/Inertia Total Score	FATIGUE	Week 6	4		9	10	-1
13	MXX123	101-001	Drug ZZZ	1	Y	Confusion/Bewilderment Total Score	CONFUS	Week 6	4		3	4	-1
14	MXX123	101-001	Drug ZZZ	1	Y	Total Score	TOTAL	Week 6	4		55	37	18

2.6.3 Analysis Results

In Table 2.6.3.1, the mean change from baseline for each subscale is displayed. The p-value reflects a test for overall treatment effect (i.e., a test of the effect of study drug on the combined subscales). The example illustrates analysis results metadata for specific items on a summary table.

Table 2.6.3.1 Illustration of Analysis Display Layout for Multivariate ANOVA Example[21]

Summary E.6
Multivariate Analysis of Variance Testing the Hypothesis of No Overall Treatment Effect at Week 6 (ITT Population)

Week 6 Change from Baseline Effect Estimate (SE) [1]	Placebo (N=xxx)	Drug ZZZ (N=xxx)
Tension/Anxiety Total Score	x.xx (x.xx)	x.xx (x.xx)
Depression/Rejection Total Score	x.xx (x.xx)	x.xx (x.xx)
Anger/Hostility Total Score	x.xx (x.xx)	x.xx (x.xx)
Vigor/Activity Total Score	x.xx (x.xx)	x.xx (x.xx)
Fatigue/Inertia Total Score	x.xx (x.xx)	x.xx (x.xx)
Confusion/Bewilderment Total Score	x.xx (x.xx)	x.xx (x.xx)
Test for Overall Treatment Effect [2]		
Wilks' Lambda		x.xx
p-value		x.xxxx

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N=ITT Population
[1] Mixed Model Repeated Measures Analysis
[2] Wilks' Lambda multivariate test of treatment effect, with the six mood subscale scores as the dependent variables in the model and treatment the only independent variable.

Table 2.6.3.2 and Table 2.6.3.3 provide analysis results metadata for the estimates of treatment effect on the subscales and for the test for overall treatment effect, respectively. By specifying multiple values in PARAM and PARAMCD, the metadata are indicating that the results are provided for each of these analysis parameters.

It should be noted that the analysis results metadata for the test for overall treatment effect are based on a BDS dataset, but some pre-processing (i.e., transpose of the dataset in this example) is required to facilitate the analysis. Therefore, the dataset ADMOOD is not analysis-ready for the analysis described. This analysis results metadata example is included to illustrate one approach to a situation such as this; it is not meant to imply a standard or requirement.

[21] The style of the display of the results of an analysis will be determined by the producer. The example is intended to illustrate content not appearance.

Table 2.6.3.2 Analysis Results Metadata for Multivariate ANOVA Example – Estimates of Treatment Effect on Subscales[22]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.6
DISPLAY NAME	Multivariate Analysis of Variance Testing the Hypothesis of No Overall Treatment Effect at Week 6 (ITT Population)
RESULT IDENTIFIER	Estimates of Treatment Effect on Subscales
PARAM	Tension/Anxiety Total Score Depression/Rejection Total Score Anger/Hostility Total Score Vigor/Activity Total Score Fatigue/Inertia Total Score Confusion/Bewilderment Total Score
PARAMCD	ANXIETY DPRESS ANGER VIGOR FATIGUE CONFUS
ANALYSIS VARIABLE	CHG
REASON	Secondary efficacy analysis as pre-specified in SAP
DATASET	ADMOOD
SELECTION CRITERIA	ITTFL="Y" and PARAMCD not ="TOTAL" and AVISITN=4
DOCUMENTATION	Multivariate Analysis of Variance of Effect at Week 6 (visit 4). See SAP Section XX for details. Program: t-mood-effect.sas Estimates of Effect are the estimated regression coefficients obtained from PROC MIXED by using the S option on the model statement. The METHOD=ML causes maximum likelihood methods to be used to fit the model. Class variable PARAMCD identifies the response. The REPEATED statement specifies an unstructured covariance matrix among the responses. The interaction of PARAMCD and treatment group is the independent variable.
PROGRAMMING STATEMENTS	PROC MIXED DATA=ADMOOD; CLASS USUBJID PARAMCD TRTPN; MODEL CHG = PARAMCD*TRTPN / NOINT NOTEST S ; REPEATED PARAMCD / SUBJECT=USUBJID TYPE=UN; RUN;

[22] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Table 2.6.3.3 Analysis Results Metadata for Multivariate ANOVA Example – Test for Overall Treatment Effect[23]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.6
DISPLAY NAME	Multivariate Analysis of Variance Testing the Hypothesis of No Overall Treatment Effect at Week 6 (ITT Population)
RESULT IDENTIFIER	Test for Overall Treatment Effect Considering All Subscales
PARAM	Tension/Anxiety Total Score Depression/Rejection Total Score Anger/Hostility Total Score Vigor/Activity Total Score Fatigue/Inertia Total Score Confusion/Bewilderment Total Score
PARAMCD	ANXIETY DPRESS ANGER VIGOR FATIGUE CONFUS
ANALYSIS VARIABLE	AVAL
REASON	Secondary efficacy analysis as pre-specified in SAP
DATASET	ADMOOD with the data transposed so that mood scale scores are all on one row for a specified subject
SELECTION CRITERIA	ITTFL="Y" and PARAMCD not ="TOTAL" and AVISITN=4
DOCUMENTATION	Wilks' Lambda multivariate test of treatment effect. See SAP Section XX for details. Program: t-mood-effect.sas The MANOVA statement in PROC GLM is used to generate the result after first transposing ADMOOD. The six mood subscale scores are the dependent variables in the model, with treatment being the only independent variable.
PROGRAMMING STATEMENTS	PROC TRANSPOSE DATA=ADMOOD OUT=ADMOODHZ; VAR AVAL; ID PARAMCD; BY USUBJID TRTPN; RUN; PROC GLM DATA=ADMOODHZ; CLASS TRTPN; MODEL ANXIETY DPRESS ANGER VIGOR FATIGUE CONFUS = TRTPN / NOUNI; MANOVA H=TRTPN; RUN;

[23] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

2.7 Example 7: Repeated Measures Analysis of a Crossover Study

This example illustrates a randomized, double-blinded, placebo controlled, 4-way crossover design study using a mixed effect model.

The primary criterion for evaluation is the measurement of forced expiratory volume in one second (FEV1) obtained during pulmonary function testing (PFT). FEV1 measurements are collected from 1 hour pre-dose to 23 hours 50 minutes post-dose. The co-primary efficacy endpoints are the FEV1 AUC(0-12) response and AUC(12-24) response after 6 weeks of treatment. FEV1 AUC is defined as the area under the FEV1 curve (AUC) normalized for time. It is calculated from zero time to 12 h [FEV1 AUC(0-12)] and from 12 h to 24 h [FEV1 AUC(12-24)], respectively, using the trapezoidal rule divided by the corresponding duration (i.e., 12 h) to give the results in liters.

This study includes 4 periods with three 14 day wash-out periods. In addition, both study and period baselines are defined to allow for sensitivity analyses. The "study" baseline is defined as the average of two FEV1 measurements (i.e., -1 hour and -10 minute) prior to treatment at Visit 2 and to the administration of the morning dose of randomized treatment. "Period" baselines are defined as the average of the two FEV1 measurements (i.e., -1 hour and -10 minute) at each treatment period (i.e., Visits 2, 5, 8 and 11), prior to administration of the morning dose of randomized treatment. Table 2.7.1 describes the visit schedule, periods, planned study day and calculated relative study day that are used to derive the Study and Period baselines.

Table 2.7.1 Trial Diagram of Visit Schedule and Baseline Derivations

Visit	Period	Baseline Relative to *Study* Start		Baseline Relative to *Period* Start	
		Planned study day for trial period	Calculation of relative study day for trial period	Planned study day for each period	Calculation of relative study day for each period
2	1	1	1	1	1
4	1	43	Visit 4 date - Visit 2 date + 1	43	Visit 4 date - Visit 2 date + 1
14 Day Washout period					
5	2	57	Visit 5 date - Visit 2 date + 1	1	1
7	2	99	Visit 7 date - Visit 2 date + 1	43	Visit 7 date - Visit 5 date + 1
14 Day Washout period					
8	3	113	Visit 8 date - Visit 2 date + 1	1	1
10	3	155	Visit 10 date - Visit 2 date + 1	43	Visit 10 date - Visit 8 date + 1
14 Day Washout period					
11	4	169	Visit 11 date - Visit 2 date + 1	1	1
13	4	211	Visit 13 date - Visit 2 date + 1	43	Visit 13 date - Visit 11 date + 1

2.7.1 Analysis Data Metadata

For this example, three analysis datasets are illustrated: ADSL, ADFEV and ADFEVAUC. The ADSL is the required subject-level analysis dataset and is included here to illustrate how the treatment and period variables are used at the subject level. The ADFEV dataset includes the individual FEV1 responses that are collected during the study and imputed records. The ADFEVAUC dataset includes derived FEV1 AUC response data based on the ADFEV dataset. In this example, a specific illustration of an analysis using ADFEV is not included. However, ADFEV is considered an analysis dataset and could be used for an array of analyses (e.g., change from baseline, percent change from baseline, etc.).

In this example, TRTSDT and TRTEDT are taken from the DM domain while the TRxxSDT, TRxxEDT and corresponding time variables are taken from the SE domain. It is expected in this example that TRTSDT=TR01SDT and TRTEDT=TR04EDT. There is no requirement implied that these variables must be taken from the specified domains. The producer will determine the appropriate source for the variables (e.g., DM, EX, SE, DA) based on the study design and the way the data is collected.

Table 2.7.1.1 Analysis Dataset Metadata for Repeated Measures Analysis of Crossover Example

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADSL	Subject demographic, baseline, and key characteristics	adsl.xpt	One record per subject	STUDYID, USUBJID	ADSL	adsl.sas
ADFEV	Forced expired volume analysis data	adfev.xpt	One record per subject per basetype per period per parameter per analysis time point	STUDYID, USUBJID, BASETYPE, APERIOD, PARAMN, AVISIT, ATPTN	BDS	adfev.sas
ADFEVAUC	Forced expired volume AUC analysis data- for the AUC (0-12 hours) and -the AUC (12-24 hours)	adfevauc.xpt	One record per subject per basetype per period per parameter	STUDYID, USUBJID, BASETYPE, APERIOD, PARAMN	BDS	adfevauc.sas

2.7.2 Analysis Variable Metadata and Analysis Dataset – ADSL

Table 2.7.2.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADSL [24]

Dataset Name	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADSL	STUDYID	Study Identifier	text	$15		DM.STUDYID
ADSL	USUBJID	Unique Subject Identifier	text	$15		DM.USUBJID
ADSL	SITEID	Study Site Identifier	text	$10		DM.SITEID
ADSL	INVNAM	Study Investigator Name	text	$10		DM.INVNAM
ADSL	ARM	Description of Planned Arm	text	$60	DrugA/DrugB/DrugC/Placebo, DrugB/DrugC/Placebo/DrugA, DrugC/Placebo/DrugA/DrugB, Placebo/DrugA/DrugB/DrugC	DM.ARM
ADSL	TRT01P	Planned Treatment for Period 01	text	$60	Drug A, Drug B, Drug C, Placebo	Based on the assigned treatment sequence order. This field will be populated with one of four treatments: "Drug A", "Drug B", "Drug C" or "Placebo", as defined for this subject within this treatment period in SE.ELEMENT
ADSL	TRT02P	Planned Treatment for Period 02	text	$60	Drug A, Drug B, Drug C, Placebo	Based on the assigned treatment sequence order. This field will be populated with one of four treatments: Drug A, Drug B, Drug C or Placebo, as defined for this subject within this treatment period in SE.ELEMENT

[24] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Table 2.7.2.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADSL [24]

Dataset Name	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADSL	TRT03P	Planned Treatment for Period 03	text	$60	Drug A, Drug B, Drug C, Placebo	Based on the assigned treatment sequence order. This field will be populated with one of four treatments: "Drug A", "Drug B", "Drug C" or "Placebo", as defined for this subject within this treatment period in SE.ELEMENT
ADSL	TRT04P	Planned Treatment for Period 04	text	$60	Drug A, Drug B, Drug C, Placebo	Based on the assigned treatment sequence order. This field will be populated with one of four treatments: "Drug A", "Drug B", "Drug C" or "Placebo", as defined for this subject within this treatment period in SE.ELEMENT
ADSL	TRTSEQP	Planned Sequence of Treatments	text	$60	A-B-C-Placebo, B-C-Placebo-A, C-Placebo-A-B, Placebo-A-B-C,	Planned sequence of treatments DM.ARMCD
ADSL	RANDDT	Date of Randomization	integer	YYMMD D10.		Numeric date of the following value: DS.DSDTC where DS.DSTERM="RANDOMIZED"
ADSL	TRTSDT	Date of First Exposure to Treatment	integer	YYMMD D10.		Numeric date of the following value: DM.RFSTDTC
ADSL	TRTSTM	Time of First Exposure to Treatment	integer	TIME5.		Numeric time of the following value: DM.RFSTDTC
ADSL	TRTEDT	Date of Last Exposure to Treatment	integer	YYMMD D10.		Numeric date of the following value: DM.RFENDTC
ADSL	TRTETM	Time of Last Exposure to Treatment	integer	TIME5.		Numeric time of the following value: DM.RFENDTC

Table 2.7.2.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADSL [24]

Dataset Name	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADSL	TR01SDT	Date of First Exposure in Period 01	integer	YYMMD D10.		Numeric date of first exposure to treatment in period 01, from SE.SESTDTC
ADSL	TR01STM	Time of First Exposure in Period 01	integer	TIME5.		Numeric time of first exposure to treatment in period 01, from SE.SESTDTC
ADSL	TR01EDT	Date of Last Exposure in Period 01	integer	YYMMD D10.		Numeric date of last exposure to treatment in period 01, from SE.SEENDTC
ADSL	TR01ETM	Time of Last Exposure in Period 01	integer	TIME5.		Numeric time of last exposure to treatment in period 01, from SE.SEENDTC
ADSL	TR02SDT	Date of First Exposure in Period 02	integer	YYMMD D10.		Numeric date of first exposure to treatment in period 02, from SE.SESTDTC
ADSL	TR02STM	Time of First Exposure in Period 02	integer	TIME5.		Numeric time of first exposure to treatment in period 02, from SE.SESTDTC
ADSL	TR02EDT	Date of Last Exposure in Period 02	integer	YYMMD D 10.		Numeric date of last exposure to treatment in period 02, from SE.SEENDTC
ADSL	TR02ETM	Time of Last Exposure in Period 02	integer	TIME5.		Numeric time of last exposure to treatment in period 02, from SE.SEENDTC
ADSL	TR03SDT	Date of First Exposure in Period 03	integer	YYMMD D10.		Numeric date of first exposure to treatment in period 03, from SE.SESTDTC
ADSL	TR03STM	Time of First Exposure in Period 03	integer	TIME5.		Numeric time of first exposure to treatment in period 03, from SE.SESTDTC
ADSL	TR03EDT	Date of Last Exposure in Period 03	integer	YYMMD D10.		Numeric date of last exposure to treatment in period 03, from SE.SEENDTC

Table 2.7.2.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADSL [24]

Dataset Name	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADSL	TR03ETM	Time of Last Exposure in Period 03	integer	TIME5.		Numeric time of last exposure to treatment in period 03, from SE.SEENDTC
ADSL	TR04SDT	Date of First Exposure in Period 04	integer	YYMMD D10.		Numeric date of first exposure to treatment in period 04, from SE.SESTDTC
ADSL	TR04STM	Time of First Exposure in Period 04	integer	TIME5.		Numeric time of first exposure to treatment in period 04, from SE.SESTDTC
ADSL	TR04EDT	Date of Last Exposure in Period 04	integer	YYMMD D10.		Numeric date of last exposure to treatment in period 04, from SE.SEENDTC
ADSL	TR04ETM	Time of Last Exposure in Period 04	integer	TIME5.		Numeric time of last exposure to treatment in period 04, from SE.SEENDTC
ADSL	MHDUR	Duration of COPD [years]	float	8.1		MH.MHDUR at MH.MHTERM=<Trial Diagnosis>
ADSL	SMOKDC	Smoking History	text	$20	Currently Smokes, Ex-smoker	Currently Smokes if SU.SUTRT="CIGARETTES" and SU.SUENDTC=" " Ex-Smoker if SU.SUTRT="CIGARETTES" and SU.SUENDTC is not " " and numeric version of SU.SUENDTC is prior to DM.RFSTDTC
ADSL	SMYMDC	When Stopped Smoking	text	8		Date portion of SU.SUENDTC where SU.SUTRT="CIGARETTES"
ADSL	SMPKY	Smoking History - Pack Years	float	4.1		SU.SUDOSE where SU.SUTRT="CIGARETTES"
ADSL	ALCCDC	Alcohol History	text	$20	Drink – no interf., Non-drinker	"Drink – no interf." if SU.SUTRT="ALCOHOL" and SU.SUENRTPT="ONGOING" "Non-Drinker" if SU.SUTRT="ALCOHOL" and SU.SUOCCUR ="N"

Table 2.7.2.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADSL [24]

Dataset Name	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADSL	HEIGHTBL	Height at Baseline (cm)	integer	8		The last available of VS.VSSTRESN for VS.VSTESTCD="HEIGHT" before or on the first dose date (ADSL.TRTSDT)
ADSL	WEIGHTBL	Weight at Baseline (kg)	float	8		The last available of VS.VSSTRESN for VS.VSTESTCD="WEIGHT" before or on the first dose date (ADSL.TRTSDT)
ADSL	AGE	Age	integer	8		DM.AGE
ADSL	AGEU	Age Units	text	$4	Years	DM.AGEU
ADSL	SEXN	Sex (N)	integer	1	1= Male, 2= Female	Numeric value of DM.SEX
ADSL	SEX	Sex	text	$1	M, F	DM.SEX
ADSL	RACE	Race	text	$40	AMERICAN INDIAN OR ALASKA NATIVE, ASIAN, BLACK OR AFRICAN AMERICAN, NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER, WHITE	DM.RACE
ADSL	COUNTRY	Country	text	$10	USA	DM.COUNTRY
ADSL	SAFFL	Safety Population Flag	text	$2	N, Y	All treated subjects will be included in the safety set.
ADSL	FASFL	Full Analysis Set Population Flag	text	$2	N, Y	All subjects with baseline data and any evaluable post-dosing data for the first co-primary endpoint will be included in the full analysis set.

Rows 1-4: Include treatment variables for each period on subject level.

Include key baseline variables (e.g., SEX, RACE, SMOKDC (Smoking history), SMPKY (Smoking history - pack years)) for chronic obstructive pulmonary disease (COPD).

Table 2.7.2.2 Illustration of Analysis Dataset ADSL

Row	STUDYID	USUBJID	SITEID	INVNAM	ARM	TRT01P	TRT02P	TRT03P	TRT04P	TRTSEQP	RANDDT	TRTSDT	TRTSTM
1	501	501-001	XYZ001	Smith	DrugA/DrugB/DrugC/Placebo	Drug A	Drug B	Drug C	Placebo	A-B-C-Placebo	2009-09-03	2009-09-03	7:45
2	501	501-002	XYZ002	Jones	DrugB/DrugC/Placebo/DrugA	Drug B	Drug C	Placebo	Drug A	B-C-Placebo-A	2009-09-02	2009-09-02	8:00
3	501	501-003	XYZ004	Adam	DrugC/Placebo/DrugA/DrugB	Drug C	Placebo	Drug A	Drug B	C-Placebo-A-B	2009-09-09	2009-09-09	8:26
4	501	501-004	XYZ006	Wills	Placebo/DrugA/DrugB/DrugC	Placebo	Drug A	Drug B	Drug C	Placebo-A-B-C	2009-09-02	2009-09-02	8:35

Row	TRTEDT	TRTETM	TR01SDT	TR01STM	TR01EDT	TR01ETM	TR02SDT	TR02STM	TR02EDT	TR02ETM	TR03SDT	TR03STM	TR03EDT	TR03ETM	TR04SDT
1	2010-04-02	7:56	2009-09-03	7:45	2009-10-16	7:49	2009-10-29	7:50	2009-12-11	7:49	2009-12-24	7:50	2010-02-05	7:49	2010-02-18
2	2010-04-01	8:39	2009-09-02	8:00	2009-10-15	8:04	2009-10-28	8:05	2009-12-10	7:59	2009-12-23	8:00	2010-02-04	7:59	2010-02-17
3	2010-04-08	8:56	2009-09-09	8:26	2009-10-22	8:19	2009-11-04	8:20	2009-12-17	8:09	2009-12-30	8:10	2010-02-11	8:09	2010-02-24
4	2010-04-01	8:35	2009-09-02	8:35	2009-10-15	8:25	2009-10-28	8:26	2009-12-10	8:04	2009-12-23	8:05	2010-02-04	8:34	2010-02-17

Row	TR04STM	TR04EDT	TR04ETM	MHDUR	SMOKDC	SMYMDC	SMPKY	ALCCDC	HEIGHTBL	WEIGHTBL	AGE	AGEU	SEXN	SEX	RACE	SAFFL	FASFL
1	7:40	2010-04-02	7:55	1.8	Currently Smokes		32	Drink – no interf.	157	59.0	47	Years	1	M	WHITE	Y	Y
2	8:00	2010-04-01	8:12	2.0	Ex-smoker	1995	30	Non-drinker	170	192.8	50	Years	2	F	ASIAN	Y	Y
3	8:10	2010-04-08	8:22	3.0	Currently Smokes		51	Drink – no interf.	178	72.6	69	Years	1	M	WHITE	Y	Y
4	8:35	2010-04-01	8:11	8.0	Ex-smoker	2005	44	Non-drinker	180	33.9	57	Years	1	M	WHITE	Y	Y

2.7.3 Analysis Variable Metadata and Analysis Dataset – BDS Datasets

For this trial, the producer could create one analysis dataset that includes the FEV1 measurements, imputed FEV1 measurements for missing data and derived FEV1 AUC measurements. Alternatively, the producer could create two analysis datasets. The first analysis dataset includes the FEV1 measurements and the imputed FEV1 measurements for missing data. The second analysis dataset includes the derived FEV1 AUC measurements. The latter approach is illustrated below. The following examples describe the content of the ADFEV and ADFEVAUC analysis datasets.

Table 2.7.3.1 is an illustration of the metadata for the ADFEV analysis dataset. Extra variables may be included so that additional analyses could be performed.

Table 2.7.3.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEV [25]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEV	*ALL*	STUDYID	Study Identifier	text	$15		ADSL.STUDYID

[25] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Table 2.7.3.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEV [25]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEV	*ALL*	USUBJID	Unique Subject Identifier	text	$20		ADSL.USUBJID
ADFEV	*ALL*	SITEID	Study Site Identifier	text	$10		ADSL.SITEID
ADFEV	*ALL*	BASETYPE	Baseline Type	text	$40	Study, Period 1, Period 2, Period 3, Period 4	BASETYPE is “Study” for records using the study baseline (i.e., the baseline record at treatment period 1) BASETYPE is the appropriate period for records using the period baselines for each treatment period
ADFEV	*ALL*	PARAM	Parameter	text	$60	Forced expired volume in 1 second [L]	Populated with ”Forced expired volume in 1 second [L]” (based on XX.XXTEST) for the records pertaining to this analysis parameter.
ADFEV	PARAMCD	PARAMCD	Parameter Code	text	$8	FEV1	Populated with ”FEV1” for records corresponding to FEV1 (based on XX.XXTESTCD)
ADFEV	FEV1	PARAMN	Parameter (N)	integer	8	1=FEV1	Map ADFEV.PARAM to PARAMN - Numeric version of the PARAM
ADFEV	*ALL*	AVISIT	Analysis Visit	text	$11	Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14	XX.VISIT or the analysis visit for the imputed AVAL

Table 2.7.3.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEV [25]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEV	*ALL*	ATPT	Analysis Timepoint	text	$40	1 hour pre-dose, 30 minutes pre-dose, 10 minutes pre-dose, Pre-dose average, 30 minutes post-dose, 1 hour post-dose, 2 hours post-dose, 3 hours post-dose, 4 hours post-dose, 6 hours post-dose, 8 hours post-dose, 10 hours post-dose, 11 hours 50 minutes post-dose, 12 hours 30 minutes post-dose, 13 hours post-dose, 14 hours post-dose, 22 hours post-dose, 23 hours post-dose, 23 hours 50 minutes post-dose	XX.XXTPT or the timepoint for the imputed AVAL

Table 2.7.3.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEV [25]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEV	*ALL*	ATPTN	Analysis Timepoint(N)	integer	TIME8.	-1:00:00, -0:30:00, -0:10:00, 0:00:00, 0:30:00, 1:00:00, 2:00:00, 3:00:00, 4:00:00, 6:00:00, 8:00:00, 10:00:00, 11:50:00, 12:30:00, 13:00:00, 14:00:00, 22:00:00, 23:00:00, 23:50:00	XX.XXTPTNUM or the timepoint number for the imputed AVAL
ADFEV	*ALL*	ATM	Analysis Time	integer	TIME8.		Numeric time portion of XX.XXDTC
ADFEV	*ALL*	TRTP	Planned Treatment	text	$15	Drug A, Drug B, Drug C, Placebo	If ADFEV.APERIODC="Period 1" then TRTP= ADSL.TRT01P If ADFEV.APERIODC="Period 2" then TRTP= ADSL.TRT02P If ADFEV.APERIODC="Period 3" then TRTP= ADSL.TRT03P If ADFEV.APERIODC="Period 4" then TRTP= ADSL.TRT04P
ADFEV	*ALL*	APERIOD	Period	integer	8	1= Period 1, 2= Period 2, 3= Period 3, 4= Period 4	Numeric version of ADFEV.APERIODC
ADFEV	*ALL*	APERIODC	Period (C)	text	$40	Period 1, Period 2, Period 3, Period 4	"Period 1" if VISIT is 2 to 4, "Period 2" if VISIT is 5 to 7, "Period 3" if VISIT is 8 to 10, "Period 4" if VISIT is 11 to 13

Table 2.7.3.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEV [25]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEV	*ALL*	TRTSEQP	Planned Sequence of Treatments	text	$60	A-B-C-Placebo, B-C-Placebo-A, C-Placebo-A-B, Placebo-A-B-C	ADSL.TRTSEQP
ADFEV	FEV1	AVAL	Analysis Value	float	Best12.		FEV1 measurements collected from 1 hour pre-dose to 23 hours 50 minutes post-dose; numeric version of XX.XXSTRESN or an imputed value Imputation methods: Create a new record to contain the average of the two pre-dose values. (“AVERAGE”) For subjects taking a short-acting beta agonist (SABA) or short-acting anticholinergic (SAMA) as rescue medication, any observations on and for eight hours after the time of the rescue medication will be set to missing and imputed by the least favorable observation at that visit prior to the time of rescue medication administration (“WOCFWV”: Worst observation carried forward within visit) If there are non-missing data before and after the missing data, the missing data will be imputed using linear interpolation taking time of the measurement into account (“INTERPOL”: Linear interpolation) If there are no observed data after the missing data and it is the first visit of a period the missing data will be imputed using last observation carried forward. (“LOCF”: Last observation carried forward)
ADFEV	*ALL*	BASE	Baseline Value	float	Best12.		BASE=ADFEV.AVAL where ADFEV.ABLFL=“Y”

Table 2.7.3.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEV [25]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEV	FEV1	ABLFL	Baseline Record Flag	text	$1	Y	If ADFEV.BASETYPE="Study" & ADFEV.DTYPE="AVERAGE" & ADFEV.APERIOD=1 then ABLFL="Y" If the first 6 characters of ADFEV.BASETYPE="Period" & ADFEV.DTYPE="AVERAGE" & ADFEV.APERIOD in (1,2,3,4) then ABLFL="Y"
ADFEV	*ALL*	CHG	Change from Baseline	float	Best12.		CHG=ADFEV.AVAL-ADFEV.BASE
ADFEV	*ALL*	PCHG	Percent Change from Baseline	float	Best12.		PCHG=((ADFEV.AVAL-ADFEV.BASE)/ADFEV.BASE)*100
ADFEV	FEV1	DTYPE	Derivation Type	text	$40	AVERAGE, WOCFWV, INTERPOL, LOCF	Populated with imputation method used when the value of AVAL is imputed
ADFEV	*ALL*	TRTSDT	Date of First Exposure to Treatment	integer	yymmdd10.		ADSL.TRTSDT
ADFEV	*ALL*	ADT	Analysis Date	integer	yymmdd10.		Numeric date of the following value: XX.XXDTC
ADFEV	*ALL*	ADY	Analysis Relative Day	integer	3.0		If ADFEV.BASETYPE="Study" then If ADFEV.TRTSDT less than or equal to ADFEV.ADT then ADY= ADFEV.ADT - ADFEV.TRTSDT+1 else ADY= ADFEV.ADT - ADFEV.TRTSDT For x=1 to 4: If ADFEV.BASETYPE="Period x" and ADFEV.APERIOD=x then do; if ADFEV.TR0xSDT less than or equal to ADFEV.ADT then ADY= ADFEV.ADT - ADFEV.TR0xSDT +1 else ADY= ADFEV.ADT - ADFEV.TR0xSDT

Table 2.7.3.1 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEV [25]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEV	*ALL*	PLANADY	Planned Analysis Relative Day	integer	3.0		If ADFEV.BASETYPE="Study" then PLANADY=SV.VISITDY If the first 6 characters of ADFEV.BASETYPE="Period" then do; If SV.VISITDY in (2, 5, 8) then PLANADY=1 else; If SV.VISITDY in (4, 7, 10) then PLANADY=43; end;
ADFEV	*ALL*	FASFL	Full Analysis Set Population Flag	text	$1	N, Y	ADSL.FASFL
ADFEV	*ALL*	ANL01FL	Analysis Record Flag 01	text	$1	Y	ANL01FL will be set to missing for the following: 1.) pre-dose measurements used to derive baseline. 2.) cases where rescue medication is given during the serial PFT measurements at a visit and subsequent PFT values are included in the source PFT data 3.) cases where a subject has an exacerbation during a washout period which is still ongoing at the start of the next treatment period and there are PFT data 4.) cases where there are PFT data for a period during which no study drug is given 5.) cases where there are PFT data for a visit after drug stop date for the same period

For this trial, FEV1 measurements are obtained at 1 hour and 10 minutes pre-dose at visits 2, 5, 8 and 11. The FEV1 measurements at visit 2 are used to calculate the "Study Baseline" values and the FEV1 measurements at visits 5, 8 and 11 are used to calculate the "Period Baseline" values. At visits 4, 7, 10 and 13, after approximately 43 days of treatment, FEV1 measurements are collected at 30 minutes pre-dose to 23 hours 50 minutes post-dose. Table 2.7.3.2 is an illustration of the ADFEV analysis dataset. The ADFEV example describes some of the key variables and records included in the dataset.

Rows 1-53: BASETYPE is set to "Study". Though not illustrated here, the subject would also have records with BASETYPE set to "Period 1", "Period 2", "Period 3", or "Period 4" to allow the calculation of CHG and PCHG using the appropriate baseline value. Study and Period baselines are defined to allow for sensitivity analyses. Because each period has a different baseline, BASETYPE must be different for each period.

Row 3: The FEV1 baseline measurement as identified by the variable ABLFL=Y. Also, DTYPE = AVERAGE which indicates that this record is derived. According to the SAP the baseline value is defined as the average of two pre-dose values (Rows 1 and 2).

Rows 1, 2, 20, 21: FEV1 measurements are obtained at 1 hour and 10 minutes pre-dose at visits 2, 5, 8 and 11; therefore ANL01FL= NULL.

Rows 4, 36: FEV1 measurements are collected at 30 minutes pre-dose at visits 4,7, 10 and 13; therefore ANL01FL=NULL.

Row 18: FEV1 measurement is imputed using linear interpolation within subject and visit. If there are non-missing data before and after the missing data, the missing data is to be imputed using linear interpolation taking time of the measurement into account.

Rows 50-51: Subject took a short-acting beta agonist (SABA) or short-acting anticholinergic (SAMA) as rescue medication (Row 50). FEV1 measurements on and for eight hours after the time of the rescue medication are to be set to missing and imputed by the least favorable observation at that visit (WOCFWV) prior to the time of rescue medication administration (Row 51).

Rows 52-53: FEV1 measurement collected within the 8 hours of taking rescue medication (Row 52). FEV1 measurement is imputed by WOCFWV method (Row 53).

Table 2.7.3.2 Illustration of Analysis Dataset ADFEV[26]

Row	USUBJID	BASETYPE	PARAM	PARAMCD	AVISIT	ATPTN	TRTP	APERIODC	TRTSEQP	AVAL	BASE	ABLFL	DTYPE	ANL01FL
	FEV1 measurements are obtained at 1 hour and 10 minutes pre-dose at visits 2, 5, 8 and 11. These measurements are used to derive the Study and Period baseline records.													
1	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 2	-1:00:00	Drug A	Period 1	A-B-C-Placebo	1.67				
2	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 2	-0:10:00	Drug A	Period 1	A-B-C-Placebo	1.83				
3	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 2	0:00:00	Drug A	Period 1	A-B-C-Placebo	1.75		Y	AVERAGE	Y
	FEV1 measurements are collected at 30 minutes pre-dose to 23 hours 50 minutes post-dose at visits 4, 7, 10 and 13. To preserve space, only a few records are included in the example.													
4	501-001	Study	Forced expired volume	FEV1	Visit 4	-0:30:00	Drug	Period 1	A-B-C-	1.70	1.75			

[26] The illustration does not include all the variables from the ADFEV dataset.

Table 2.7.3.2 Illustration of Analysis Dataset ADFEV[26]

Row	USUBJID	BASETYPE	PARAM	PARAMCD	AVISIT	ATPTN	TRTP	APERIODC	TRTSEQP	AVAL	BASE	ABLFL	DTYPE	ANL01FL
			in 1 second [L]				A		Placebo					
5	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 4	0:30:00	Drug A	Period 1	A-B-C-Placebo	1.81	1.75			Y
6	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 4	0:1:00	Drug A	Period 1	A-B-C-Placebo	1.90	1.75			Y
	FEV1 measurements are also collected at 2, 3, 4, 6, 8, 10, 11:50, 12:30, 13, 14, hours post-dose. To preserve space, these records are not included in the example.													
17	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 4	22:00:00	Drug A	Period 1	A-B-C-Placebo	1.73	1.75			Y
18	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 4	23:00:00	Drug A	Period 1	A-B-C-Placebo	1.86	1.75		INTERPOL	Y
19	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 4	23:50:00	Drug A	Period 1	A-B-C-Placebo	1.91	1.75			Y
	FEV1 measurements are obtained at 1 hour and 10 minutes pre-dose at visits 2, 5, 8 and 11. FEV1 measurements are also collected at 2, 3, 4, 5, 6, 8, 10, 11:50, 12:30, 13, 14, 22, 23, 23 and 23:50 minutes post-dose. To preserve space, these records are not included in the example.													
20	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 5	-1:00:00	Drug B	Period 2	A-B-C-Placebo	1.54	1.75			
21	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 5	-0:10:00	Drug B	Period 2	A-B-C-Placebo	1.60	1.75			
22	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 5	1:00:00	Drug B	Period 2	A-B-C-Placebo	1.77	1.75			Y
	FEV1 measurements are collected at 30 minutes pre-dose to 23 hours 50 minutes post-dose at visits 4, 7, 10 and 13.													
36	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 7	-0:30:00	Drug B	Period 2	A-B-C-Placebo	1.65	1.75			
37	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 7	0:30:00	Drug B	Period 2	A-B-C-Placebo	1.84	1.75			Y
	FEV1 measurements are also collected at 1, 2, 3, 4, 6, 8, 10, 11:50, 12:30, 13 and 14 hours post-dose. To preserve space, these records are not included in the example.													
49	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 7	22:00:00	Drug B	Period 2	A-B-C-Placebo	1.59	1.75			Y
50	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 7	23:00:00	Drug B	Period 2	A-B-C-Placebo	1.83	1.75			
51	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 7	23:00:00	Drug B	Period 2	A-B-C-Placebo	1.59	1.75		WOCFWV	Y
52	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 7	23:50:00	Drug B	Period 2	A-B-C-Placebo	1.81	1.75			
53	501-001	Study	Forced expired volume in 1 second [L]	FEV1	Visit 7	23:50:00	Drug B	Period 2	A-B-C-Placebo	1.59	1.75		WOCFWV	Y
	The ADFEV dataset would also include the following: • A set of FEV1 measurements for Periods 3 and 4.													

Table 2.7.3.2 Illustration of Analysis Dataset ADFEV[26]

Row	USUBJID	BASETYPE	PARAM	PARAMCD	AVISIT	ATPTN	TRTP	APERIODC	TRTSEQP	AVAL	BASE	ABLFL	DTYPE	ANL01FL
	• Sets of FEV1 measurements where BASETYPE = "Period 1", "Period 2", "Period 3", "Period 4".													

This trial includes two efficacy endpoints. The efficacy endpoints are the FEV1 AUC(0-12) response and AUC(12-24) response after 6 weeks of treatment. The FEV1 AUC(0-12) and AUC(12-24) responses are derived using the FEV1 measurements, which are found in the ADFEV dataset. The ADFEVAUC dataset includes the derived FEV1 AUC response endpoints, key variables to perform the analysis along with baseline variables (e.g., SEX, RACE, SMOKDC, SMPKY) for chronic obstructive pulmonary disease (COPD) that can be used for additional analyses.

Table 2.7.3.3 is an illustration of the metadata for the ADFEVAUC analysis dataset.

Table 2.7.3.3 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEVAUC [27]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEVAUC	*ALL*	STUDYID	Study Identifier	text	$15		ADFEV.STUDYID
ADFEVAUC	*ALL*	USUBJID	Unique Subject Identifier	text	$20		ADFEV.USUBJID
ADFEVAUC	*ALL*	SITEID	Study Site Identifier	text	$10		ADFEV.SITEID
ADFEVAUC	*ALL*	BASETYPE	Baseline Type	text	$40	Study, Period 1, Period 2, Period 3, Period 4	ADFEV.BASETYPE
ADFEVAUC	FEVAUC12	PARAM	Parameter	text	$60	FEV1 AUC (0-12) [L]	"FEV1 AUC (0-12) [L]" for records created to contain the FEV AUC(0-12) hour values
ADFEVAUC	FEVAUC24	PARAM	Parameter	text	$60	FEV1 AUC (12-24) [L]	"FEV1 AUC (12-24) [L]" for records created to contain the FEV AUC(12-24) hour values

[27] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Table 2.7.3.3 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEVAUC [27]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEVAUC	PARAMCD	PARAMCD	Parameter Code	text	$8	FEVAUC12, FEVAUC24	Populate with the appropriate text, depending on time period covered, for records created to contain the FEV AUCvalues ("FEVAUC12" for the 0-12 hour calculated value and "FEVAUC24" for the 12-24 hour calculated value)
ADFEVAUC	*ALL*	PARAMN	Parameter (N)	integer	8	23= FEV1 AUC (0-12) [L], 24= FEV1 AUC (12-24) [L]	Map ADFEVAUC.PARAM to PARAMN - Numeric version of the PARAM
ADFEVAUC	*ALL*	ATPT	Analysis Timepoint	text	$40	0-12h, 12-24h	If ADFEVAUC.PARAMCD="FEVAUC12" then APTPT = "0-12h" If ADFEVAUC.PARAMCD="FEVAUC24" then APTPT = "12-24h"
ADFEVAUC	FEVAUC12	AVAL	Analysis Value	float	8.3		Using records where ADFEV.USUBJID, ADFEV.BASETYPE, and ADFEV.APERIOD match those for this record and where ADFEV.PARAMCD = "FEV": If ADFEV.VISIT in (4, 7, 10, 13), then AVAL is the FEV1 AUC (0-12) [L] calculated from zero to 12 hours using the trapezoidal rule divided by the corresponding duration (i.e., 12 h) to give the results in liters.
ADFEVAUC	FEVAUC24	AVAL	Analysis Value	float	8.3		Using records where ADFEV.USUBJID, ADFEV.BASETYPE, and ADFEV.APERIOD match those for this record and where ADFEV.PARAMCD = "FEV": If ADFEV.VISIT in (4, 7, 10, 13), then AVAL is the FEV1 AUC (12-24) [L] calculated from 12 to 24 hours using the trapezoidal rule divided by the corresponding duration (i.e., 12 h) to give the results in liters.
ADFEVAUC	*ALL*	BASE	Baseline Value	float	8.2		ADFEVAUC.AVAL from the record where ADFEVAUC.ABLFL="Y", and where ADFEVAUC.USUBJID, ADFEVAUC.BASETYPE, and ADFEVAUC.APERIOD match those for this record.

Table 2.7.3.3 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEVAUC [27]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEVAUC	*ALL*	CHG	Change from Baseline	float	8.3		CHG=ADFEVAUC.AVAL-ADFEVAUC.BASE, using the values from this record
ADFEVAUC	*ALL*	PCHG	Percent Change from Baseline	float	8.2		PCHG=((ADFEVAUC.AVAL-ADFEVAUC.BASE)/ADFEVAUC.BASE)*100, using the values from this record
ADFEVAUC	*ALL*	APERIOD	Period	integer	8	1= Period 1, 2= Period 2, 3= Period 3, 4= Period 4	Numeric version of ADFEVAUC.APERIODC
ADFEVAUC	*ALL*	APERIODC	Period (C)	text	$40	Period 1, Period 2, Period 3, Period 4	ADFEV.APERIODC
ADFEVAUC	*ALL*	TRTP	Planned Treatment	text	$15	Drug A, Drug B, Drug C, Placebo	ADFEV.TRTP
ADFEVAUC	*ALL*	TRTSEQP	Planned Sequence of Treatments	text	$60	A-B-C-Placebo, B-C-Placebo-A, C-Placebo-A-B, Placebo-A-B-C	ADFEV.TRTSEQP
ADFEVAUC	*ALL*	TRTSDT	Date of First Exposure to Treatment	integer	yymmdd10.		ADFEV.TRTSDT
ADFEVAUC	*ALL*	ADY	Analysis Relative Day	integer	3.0		ADFEV.ADY from the record where ADFEV.USUBJID, ADFEV.BASETYPE, and ADFEV.APERIOD match those for this record
ADFEVAUC	*ALL*	FASFL	Full Analysis Set Population Flag	text	$1	N, Y	ADFEV.FASFL
ADFEVAUC	*ALL*	SEX	Sex	text	$1	M, F	ADSL.SEX

Table 2.7.3.3 Analysis Variable Metadata for Repeated Measures Analysis of Crossover Example - ADFEVAUC [27]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADFEVAUC	*ALL*	RACE	Race	text	$50	BLACK OR AFRICAN AMERICAN, AMERICAN INDIAN OR ALASKA NATIVE, ASIAN, NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER, WHITE	ADSL.RACE
ADFEVAUC	*ALL*	SMOKDC	Smoking History	text	$20	Currently Smokes, Ex-smoker	ADSL.SMOKDC
ADFEVAUC	*ALL*	SMPKY	Smoking History - Pack Years	float	4.1		ADSL.SMPKY

Table 2.7.3.4 is an illustration of the ADFEVAUC analysis dataset. The ADFEVAUC example describes some of the key variables and records that would be included in the dataset.

Rows 1-8: FEV1 AUC(0-12) measurements are derived using the FEV1 measurements, which are found in the ADFEV dataset. FEV1 AUC is defined as the area under the FEV1 curve (AUC) normalized for time. It is calculated from zero time to 12 h [FEV1 AUC (0-12)] and from 12 h to 24 h [FEV1 AUC (12-24)], respectively, using the trapezoidal rule divided by the corresponding duration (i.e., 12 h) to give the results in liters. The division by the length of the dosing interval for calculation of AUC is done for ease of interpretation (i.e., FEV measured in 1 sec with the units being liters). The raw AUC is used rather than the logs since the distribution of the FEV1 data does not include extreme values.

BASE = The baseline measurements from the ADFEV analysis dataset.

Rows 1-4: BASETYPE= Study. The FEV1 measurements at visit 2 are used to calculate the Study Baseline values.

Rows 5-8: BASETYPE is set to the appropriate Period value. The FEV1 measurements at visits 5, 8 and 11 are used to calculate the Period Baseline values.

Table 2.7.3.4 Illustration of Analysis Dataset ADFEVAUC[28]

Row	USUBJID	SITEID	BASETYPE	PARAM	PARAMCD	AVAL	BASE	CHG	APERIODC	TRTP	TRTSEQP
1	501-001	XYZ001	Study	FEV1 AUC (0-12) [L]	FEVAUC12	1.855	1.75	0.105	Period 1	Drug A	A-B-C- Placebo
2	501-001	XYZ001	Study	FEV1 AUC (0-12) [L]	FEVAUC12	1.820	1.75	0.070	Period 2	Drug B	A-B-C- Placebo
3	501-001	XYZ001	Study	FEV1 AUC (0-12) [L]	FEVAUC12	1.664	1.75	-0.085	Period 3	Drug C	A-B-C- Placebo
4	501-001	XYZ001	Study	FEV1 AUC (0-12) [L]	FEVAUC12	1.796	1.75	0.046	Period 4	Placebo	A-B-C- Placebo
5	501-001	XYZ001	Period 1	FEV1 AUC (0-12) [L]	FEVAUC12	1.855	1.75	0.105	Period 1	Drug A	A-B-C- Placebo
6	501-001	XYZ001	Period 2	FEV1 AUC (0-12) [L]	FEVAUC12	1.820	1.59	0.230	Period 2	Drug B	A-B-C- Placebo
7	501-001	XYZ001	Period 3	FEV1 AUC (0-12) [L]	FEVAUC12	1.664	1.38	0.284	Period 3	Drug C	A-B-C- Placebo
8	501-001	XYZ001	Period 4	FEV1 AUC (0-12) [L]	FEVAUC12	1.796	1.44	0.356	Period 4	Placebo	A-B-C- Placebo
	The ADFEVAUC dataset would also include the following: • A set of FEV1 AUC(12-24) measurements (i.e., PARAMCD=FEVAUC24) where BASETYPE = "Study" for Periods 1-4 • A set of FEV1 AUC(12-24) measurements (i.e., PARAMCD=FEVAUC24) where BASETYPE = "Period1", "Period 2", "Period 3", "Period 4".										

2.7.4 Analysis Results

The analysis results metadata below describe the analysis of the co-primary endpoints. PARAM and PARAMCD reflect this by specifying the two analysis parameters.

[28] [28] The illustration does not include all the variables in ADFEV.

Table 2.7.4.1 Illustration of Analysis Display Layout for Repeated Measures Analysis of Crossover Example[29]

Summary E.7

FEV1 AUC(0-12) and AUC(12-24) Adjusted Mean (SE) Responses and Comparisons to Placebo After 6 weeks Treatment
(FAS Population, Repeated Measures Analysis)

Time			Treatment	Difference		
Interval	Treatment	N	Mean (SE)	Mean (SE)	p-value	95% C.I.
0-12 hr	Placebo	xxx	x.xxx (x.xxx)			
	Drug A	xxx	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxxx	(x.xxx,x.xxx)
	Drug B	xxx	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxxx	(x.xxx,x.xxx)
	Drug C	xxx	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxxx	(x.xxx,x.xxx)
12-24 hr	Placebo	xxx	x.xxx (x.xxx)			
	Drug A	xxx	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxxx	(x.xxx,x.xxx)
	Drug B	xxx	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxxx	(x.xxx,x.xxx)
	Drug C	xxx	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxxx	(x.xxx,x.xxx)

N= FAS (full analysis set) population
Based on a mixed effects repeated measures model with terms for site, subject within site, treatment and period
Response is defined as change from baseline; Common Baseline Mean (SE) = x.xxx (x.xxx)

[29] The style of the display of the results of an analysis will be determined by the producer. The example is intended to illustrate content not appearance.

Table 2.7.4.2 Analysis Results Metadata for Repeated Measures Analysis of Crossover Example[30]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.7
DISPLAY NAME	FEV1 AUC(0-12) and AUC(12-24) Adjusted Mean (SE) Responses and Comparisons to Placebo After 6 weeks Treatment (FAS Population, Imputed Data, Repeated Measures Analysis)
RESULT IDENTIFIER	<intentionally left blank>
PARAM	FEV1 AUC (0-12) [L] and FEV1 AUC (12-24) [L]
PARAMCD	FEVAUC12 and FEVAUC24
ANALYSIS VARIABLE	CHG
REASON	Planned analysis per the protocol
DATASET	ADFEVAUC
SELECTION CRITERIA	PARAMCD in (“FEVAUC12”, “FEVAUC24”) and BASETYPE= “Study” and FASFL= “Y”
DOCUMENTATION	Response is defined as the change from study baseline. The statistical model for the primary endpoints is a mixed effect model with terms for siteid, subject within site, treatment and period. In the mixed effect model, a compound symmetry structure covariance matrix will be used to model within subject covariance.
PROGRAMMING STATEMENTS	PROC MIXED DATA= ADFEVAUC METHOD=REML ORDER=INTERNAL; BY PARAMCD; CLASS TRTP SITEID USUBJID APERIOD; MODEL CHG=TRTP SITEID APERIOD/SOLUTION DDFM=KR; REPEATED APERIOD/SUBJECT=USUBJID(SITEID) TYPE=CS; LSMEANS TRTP/PDIFF CL; ODS OUTPUT LSMEANS=WORK.LSMEANS1; ODS OUTPUT DIFFS=WORK.DIFFS1; RUN;

[30] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

2.8 Example 8: Categorical Analysis of Subjects Meeting Hy's Law Criteria

This example illustrates an analysis dataset (ADLBHY) that supports an analysis of laboratory data based on Hy's Law criteria, i.e., an analysis of certain liver function parameters used collectively to ascertain the extent of drug induced liver injury. Included in this illustration are the creation of new rows to contain the information as to whether or not the subject met the specified criteria for that visit, the use of PARAMTYP to clearly identify these derived records, and the use of the CRITy and SHIFTy variables. This example also illustrates that the display format for a variable is another attribute that can vary within analysis parameter, as seen in the display format metadata element for AVAL.

There are, of course, other ways to design an analysis dataset to support this analysis. For example, the CRITy variables and the additional rows could simply be incorporated into ADLB, rather than creating a second analysis dataset. The producer elected to create two analysis datasets (ADLB and ADLBHY) to facilitate traceability and the navigation and manipulation of the physical dataset. The producer considered and rejected adding the information as to the meeting of the Hy's Law criteria as flags in the ADLB dataset (instead of as rows). This approach is not used because multiple parameters are used to determine the value of the flag, therefore it is a function of more than one parameter and should be added as a new parameter (refer to Rule 5 in the ADaMIG). This example illustrates one way of designing the analysis dataset; it is not meant to imply a standard or requirement that this is the only viable approach.

Various analysis approaches might be used, including (but not limited to) simple statistical summaries of the data, shift tables, and Cochran-Mantel-Haenszel (CMH) tests. The analysis approach used in this example is for illustration purposes only; it is not meant to imply a standard or requirement.

Subjects received either Drug XYZ or Placebo and had laboratory assessments performed at each visit. Subjects are then assessed at each time point as to whether or not they met Hy's Law criteria (based on lab values from the same blood sample, i.e., not across visits). The SAP specified that shifts from baseline (met criteria, did not meet criteria) are to be provided. CMH tests, stratifying by status at baseline, are to be performed to compare the two treatment groups. Two variations of a modified Hy's Law criteria are to be analyzed. The first considered subjects with transaminase (alanine transaminase [ALT] or aspartate transaminase [AST]) elevations of greater than 1.5 times upper limit of normal (ULN) as meeting the criteria. The second further narrowed the assessment of abnormality to require total bilirubin elevations to be greater than 1.5 times ULN in addition to transaminase elevations of greater than 1.5 times ULN.

The source datasets (immediate predecessors) for the analysis dataset in this example are assumed to be ADSL and ADLB. The variable used to hold the ULN is ANRHIN. In the ADaMIG, the corresponding character variable (ANRHI) is defined. In this situation the producer determined that the numeric version of the variable is more useful for comparison purposes.

There are many variations of Hy's Law that can be applied; there are additional lab parameters that might be included, as well as varying definitions of the criteria used (e.g., cutoffs of 3 times ULN). One way that these ad hoc analyses can be supported is to have all the lab parameters of interest on one row so that a consumer can more easily explore how they are related. The current ADaM basic data structure does not support this approach. The illustrated analysis dataset is not designed to be analysis-ready for these ad hoc analyses. One approach to facilitating these ad hoc analyses is to provide the programming statements for transposing the BDS dataset, similar to the approach used in Example 6 (see Section 2.6.3).

2.8.1 Analysis Data Metadata

Table 2.8.1.1 Analysis Dataset Metadata for Categorical Analysis of Subjects Meeting Hy's Law Criteria Example [31]

Dataset Name	Dataset Description	Dataset Location	Dataset Structure	Key Variables of Dataset	Class of Dataset	Documentation
ADLBHY	Hy's Law analysis data, including lab data used to assess Hy's Law criteria	adlbhy.xpt	One record per subject per parameter per analysis visit	STUDYID, USUBJID, PARAMCD, AVISIT	BDS	adlbhy.sas

Table 2.8.1.2 Analysis Variable Metadata for Categorical Analysis of Subjects Meeting Hy's Law Criteria Example [32]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADLBHY	*ALL*	STUDYID	Study Identifier	text	$10		ADSL.STUDYID
ADLBHY	*ALL*	USUBJID	Unique Subject Identifier	text	$10		ADSL.USUBJID
ADLBHY	*ALL*	SAFFL	Safety Population Flag	text	$1	Y, N	ADSL.SAFFL
ADLBHY	*ALL*	TRTP	Planned Treatment	text	$10	Drug XYZ, Placebo	ADSL.TRT01P
ADLBHY	*ALL*	TRTPN	Planned Treatment Number	integer	1.0	1=Drug XYZ, 0=Placebo	ADSL.TRT01PN
ADLBHY	*ALL*	AVISIT	Analysis Visit	text	$40	BASELINE, WEEK 2, WEEK 4	ADLB.AVISIT
ADLBHY	*ALL*	AVISITN	Analysis Visit (N)	integer	1.0	1=BASELINE, 2=WEEK 2, 3=WEEK 4	ADLB.AVISITN

[31] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

[32] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Table 2.8.1.2 Analysis Variable Metadata for Categorical Analysis of Subjects Meeting Hy's Law Criteria Example [32]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADLBHY	*DEFAULT*	PARAM	Parameter	text	$100	Total Bilirubin (umol/L), ALT(U/L), AST(U/L)	For records with a corresponding record in ADLB, populate with the value of ADLB.PARAM
ADLBHY	HYS1FL	PARAM	Parameter	text	$100	Elevated Transminase	For records created to contain the Hy's Law Elevated Transminase criteria result, populate with "Elevated Transminase"
ADLBHY	HYS2FL	PARAM	Parameter	text	$100	Elevated Transminase and Elevated Bilirubin	For records created to contain the Hy's Law Elevated Transminase and Elevated Bilirubin criteria result, populate with "Elevated Transminase and Elevated Bilirubin"
ADLBHY	PARAMCD	PARAMCD	Parameter Code	text	$8	BIL, ALT, AST, HYS1FL, HYS2FL	One-to-one correspondence with PARAM For records with a corresponding record in ADLB, ADLBHY.PARAMCD=ADLB.PARAMCD If PARAM="Elevated Transminase", ADLBHY.PARAMCD="HYS1FL" If PARAM="Elevated Transminase and Elevated Bilirubin", ADLBHY.PARAMCD="HYS2FL"
ADLBHY	*ALL*	PARAMTYP	Parameter Type	text	$7	DERIVED	Populated with "DERIVED" for records created to contain the Elevated Transminase or the Elevated Transminase and Elevated Bilirubin, blank otherwise
ADLBHY	*DEFAULT*	AVAL	Analysis Value	float	7.3		ADLB.AVAL
ADLBHY	HYS1FL	AVAL	Analysis Value	float	1.0	1, 0	If AVALC="Y" on the record then AVAL=1, If AVALC="N" on the record then AVAL=0.
ADLBHY	HYS2FL	AVAL	Analysis Value	float	1.0	1, 0	If AVALC="Y" on the record then AVAL=1, If AVALC="N" on the record then AVAL=0.
ADLBHY	*DEFAULT*	AVALC	Analysis Value (C)	text	$7		ADLB.AVALC
ADLBHY	HYS1FL	AVALC	Analysis Value (C)	text	$7	Y, N	Considering the ADLBHY records for which ADLBHY.USUBJID and ADLBHY.AVISIT match those for this record, set AVALC to "Y" if at least one of the records with ADLBHY.PARAMCD in ("ALT","AST") have CRIT1FL="Y", set AVALC to "N" otherwise

Table 2.8.1.2 Analysis Variable Metadata for Categorical Analysis of Subjects Meeting Hy's Law Criteria Example [32]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADLBHY	HYS2FL	AVALC	Analysis Value (C)	text	$7	Y, N	Considering the ADLBHY records for which ADLBHY.USUBJID and ADLBHY.AVISIT match those for this record, set AVALC to "Y" if at least one of the records with ADLBHY.PARAMCD in ("ALT","AST") have CRIT1FL="Y" and if the record with ADLBHY.PARAMCD="BIL" has CRIT1FL="Y", set AVALC to "N" otherwise
ADLBHY	*DEFAULT*	BASE	Baseline Value	float	7.3		ADLB.BASE
ADLBHY	HYS1FL	BASE	Baseline Value	float	1, 0	1, 0	ADLBHY.BASEC from record where ADLBHY.USUBJID and ADLBHY.AVISIT match those for this record and ADLBHY.ABLFL="Y".
ADLBHY	HYS2FL	BASE	Baseline Value	float	1.0	1, 0	ADLBHY.BASEC from record where ADLBHY.USUBJID and ADLBHY.AVISIT match those for this record and ADLBHY.ABLFL="Y".
ADLBHY	*ALL*	BASEC	Baseline Value(C)	text	$7		ADLBHY.AVALC from record where ADLBHY.USUBJID and ADLBHY.AVISIT match those for this record and ADLBHY.ABLFL="Y"
ADLBHY	*DEFAULT*	ANRHIN	Analysis Normal Range Upper Limit (N)	float	7.3		ADLB.ANRHIN
ADLBHY	HYS1FL	ANRHIN	Analysis Normal Range Upper Limit (N)	float			Not populated for records with PARAMCD="HYS1FL"
ADLBHY	HYS2FL	ANRHIN	Analysis Normal Range Upper Limit (N)	float			Not populated for records with PARAMCD="HYS2FL"

Table 2.8.1.2 Analysis Variable Metadata for Categorical Analysis of Subjects Meeting Hy's Law Criteria Example [32]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADLBHY	*ALL*	ABLFL	Baseline Record Flag	text	$1	Y	"Y" if record contains the baseline value, i.e., if ADLBHY.AVISITN=1; blank otherwise
ADLBHY	*DEFAULT*	CRIT1	Analysis Criterion 1	text	$100		Blank if ADLBHY.PARAMTYP="DERIVED"
ADLBHY	BIL	CRIT1	Analysis Criterion 1	text	$100	BIL(AVAL)>1.5*ULN	"BIL(AVAL)>1.5*ULN" when ADLBHY.PARAMCD="BIL"
ADLBHY	ALT	CRIT1	Analysis Criterion 1	text	$100	ALT(AVAL)>1.5*ULN	"ALT(AVAL)>1.5*ULN" when ADLBHY.PARAMCD="ALT"
ADLBHY	AST	CRIT1	Analysis Criterion 1	text	$100	AST(AVAL)>1.5*ULN	"AST(AVAL)>1.5*ULN" when ADLBHY.PARAMCD="AST"
ADLBHY	*DEFAULT*	CRIT1FL	Criterion 1 Evaluation Result Flag	text	$1		Blank if ADLBHY.PARAMTYP="DERIVED"
ADLBHY	BIL	CRIT1FL	Criterion 1 Evaluation Result Flag	text	$1	Y, N	"Y" if ADLBHY.AVAL>1.5*ADLBHY.ANRHIN, "N" otherwise
ADLBHY	ALT	CRIT1FL	Criterion 1 Evaluation Result Flag	text	$1	Y, N	"Y" if ADLBHY.AVAL>1.5*ADLBHY.ANRHIN, "N" otherwise
ADLBHY	AST	CRIT1FL	Criterion 1 Evaluation Result Flag	text	$1	Y, N	"Y" if ADLBHY.AVAL>1.5*ADLBHY.ANRHIN, "N" otherwise
ADLBHY	*ALL*	CRIT1FN	Criterion 1 Evaluation Result Flag (N)	integer	1.0	1=Y, 0=N	From ADLBHY.CRIT1FL
ADLBHY	*DEFAULT*	SHIFT1	Shift 1	text	$20		Blank if ADLBHY.PARAMTYP="DERIVED" or if ADLBHY.ABLFL="Y"

Table 2.8.1.2 Analysis Variable Metadata for Categorical Analysis of Subjects Meeting Hy's Law Criteria Example [32]

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADLBHY	HYS1FL	SHIFT1	Shift 1	text	$20	Normal to Normal, Normal to Met Criteria, Met Criteria to Normal, Met Criteria to Met Criteria	Using values on this record: "Normal to Normal" if ADLBHY.BASEC="N" and ADLBHY.AVALC="N", "Normal to Met Criteria" if ADLBHY.BASEC="N" and ADLBHY.AVALC="Y", "Met Criteria to Normal" if ADLBHY.BASEC="Y" and ADLBHY.AVALC="N", "Met Criteria to Met Criteria" if ADLBHY.BASEC="Y" and ADLBHY.AVALC="Y"
ADLBHY	HYS2FL	SHIFT1	Shift 1	text	$20	Normal to Normal, Normal to Met Criteria, Met Criteria to Normal, Met Criteria to Met Criteria	Using values on this record: "Normal to Normal" if ADLBHY.BASEC="N" and ADLBHY.AVALC="N", "Normal to Met Criteria" if ADLBHY.BASEC="N" and ADLBHY.AVALC="Y", "Met Criteria to Normal" if ADLBHY.BASEC="Y" and ADLBHY.AVALC="N", "Met Criteria to Met Criteria" if ADLBHY.BASEC="Y" and ADLBHY.AVALC="Y"
ADLBHY	*ALL*	SHIFT1N	Shift 1 (N)	integer		1=Normal to Normal, 2=Normal to Met Criteria, 3=Met Criteria to Normal, 4=Met Criteria to Met Criteria	From ADLBHY.SHIFT1

2.8.2 Analysis Dataset

Table 2.8.2.1 illustrates the analysis dataset (ADLBHY) defined above. The ADLBHY example describes some of the key variables and records included in the dataset. In this example, the approach illustrated for the CRITy and CRITyFL variables is to have the text string in CRIT1 identify the criterion being evaluated, and whether or not the criterion is satisfied is indicated by the value ("Y" or "N") of the CRIT1FL variable. This approach facilitates the traceability of the derivation of the Hy's Law analysis values.

The SHIFT1 variable is used to facilitate the shift table required in the analysis. For the purposes of this example, the producer chose to use PARAMTYP to indicated the parameters derived from other parameters.

Key points of interest in the example:

Rows 1-3, 6-8, 11-13: The values of ALT, AST, and BIL for the illustrated subject (Subject 101-001) at the specified visits. The values are in AVAL (AVALC contains a character version of AVAL). CRIT1FL identifies whether the specified criteria are met for that analysis visit ("Y" if AVAL/ANRHIN>1.5, "N" if no). The SHIFT1 and SHIFT1N variables are not populated.

Rows 4, 5: On Row 4,AVALC = "N" because the CRIT1FL values on rows 2 and 3 are both "N". Subject **101-**001 did not meet the first Hy's Law Criteria illustrated for AVISIT="BASELINE". AVALC on Row 5 is also "N" because neither AST nor ALT > 1.5xULN. SHIFT1 is not populated because these are baseline rows.

Row 9: AVALC = "Y" because the CRIT1FL value on row 7 is "Y". The subject met the first Hy's Law Criteria illustrated for AVISIT="WEEK 2". SHIFT1="Normal to Met Criteria" indicates that the subject did not meet the criteria at baseline, but did at Week 2.

Row 10: AVALC = "N" because the CRIT1FL value on row 6 is "N". The subject did not meet the additional requirement for bilirubin for AVISIT="WEEK 2". SHIFT1="Normal to Normal" indicates that the subject did not meet the criteria at baseline or at Week 2.

Row 14: AVALC = "Y" because the CRIT1FL value on row 12 is "Y". The subject met the first Hy's Law Criteria illustrated for AVISIT="WEEK 4". SHIFT1="Normal to Met Criteria" indicates that the subject did not meet the criteria at baseline, but did at Week 4.

Row 15: AVALC = "Y" because the CRIT1FL values on rows 11 and 12 are both "Y". The subject met the second Hy's Law Criteria illustrated for AVISIT="WEEK 4". SHIFT1="Normal to Met Criteria" indicates that the subject did not meet the criteria at baseline, but did at Week 4.

Table 2.8.2.1 Illustration of Analysis Dataset ADLBHY

Row	STUDYID	USUBJID	SAFFL	TRTP	TRTPN	AVISIT	AVISITN	PARAM	PARAMCD	PARAMTYP	AVAL	AVALC
1	AZY389	101-001	Y	Drug XYZ	1	BASELINE	1	Total Bilirubin (umol/L)	BIL		32	32
2	AZY389	101-001	Y	Drug XYZ	1	BASELINE	1	ALT(U/L)	ALT		30	30
3	AZY389	101-001	Y	Drug XYZ	1	BASELINE	1	AST(U/L)	AST		31	31
4	AZY389	101-001	Y	Drug XYZ	1	BASELINE	1	Elevated Transminase	HYS1FL	DERIVED	0	N
5	AZY389	101-001	Y	Drug XYZ	1	BASELINE	1	Elevated Transminase and Elevated Bilirubin	HYS2FL	DERIVED	0	N
6	AZY389	101-001	Y	Drug XYZ	1	WEEK 2	2	Total Bilirubin (umol/L)	BIL		24	24
7	AZY389	101-001	Y	Drug XYZ	1	WEEK 2	2	ALT(U/L)	ALT		54	54
8	AZY389	101-001	Y	Drug XYZ	1	WEEK 2	2	AST (U/L)	AST		45	45
9	AZY389	101-001	Y	Drug XYZ	1	WEEK 2	2	Elevated Transminase	HYS1FL	DERIVED	1	Y
10	AZY389	101-001	Y	Drug XYZ	1	WEEK 2	2	Elevated Transminase and Elevated Bilirubin	HYS2FL	DERIVED	0	N
11	AZY389	101-001	Y	Drug XYZ	1	WEEK 4	3	Total Bilirubin (umol/L)	BIL		33	33
12	AZY389	101-001	Y	Drug XYZ	1	WEEK 4	3	ALT (U/L)	ALT		52	52
13	AZY389	101-001	Y	Drug XYZ	1	WEEK 4	3	AST (U/L)	AST		47	47
14	AZY389	101-001	Y	Drug XYZ	1	WEEK 4	3	Elevated Transminase	HYS1FL	DERIVED	1	Y
15	AZY389	101-001	Y	Drug XYZ	1	WEEK 4	3	Elevated Transminase and Elevated Bilirubin	HYS2FL	DERIVED	1	Y

Row	BASE	BASEC	ANRHIN	ABLFL	CRIT1	CRIT1FL	CRIT1FN	SHIFT1	SHIFT1N
1	32	32	21	Y	BIL(AVAL)>1.5*ULN	Y	1		
2	30	30	34	Y	ALT(AVAL)>1.5*ULN	N	0		
3	31	31	34	Y	AST(AVAL)>1.5*ULN	N	0		
4	0	N		Y					
5	0	N		Y					
6	32	32	21		BIL(AVAL)>1.5*ULN	N	0		
7	30	30	34		ALT(AVAL)>1.5*ULN	Y	1		
8	31	31	34		AST(AVAL)>1.5*ULN	N	0		
9	1	N						Normal to Met Criteria	2
10	0	N						Normal to Normal	1
11	32	32	21		BIL(AVAL)>1.5*ULN	Y	1		
12	30	30	34		ALT(AVAL)>1.5*ULN	Y	1		
13	31	31	34		AST(AVAL)>1.5*ULN	N	0		
14	0	N						Normal to Met Criteria	2
15	0	N						Normal to Met Criteria	2

2.8.3 Analysis Results

The following data display illustrates the Shift table and CMH analysis performed using ADLBHY as described above. The shift table summarizes whether or not a subject's status changed from baseline during the treatment period for changes based on threshold ranges and changes based on Hy's Law and Modified Hy's Law. Comparisons between Placebo and Treatment are illustrated by CMH test at each visit.

Table 2.8.3.1 Illustration of Analysis Display Layout for Categorical Analysis of Subjects Meeting Hy's Law Criteria Example[33]

Summary E.8
Shifts of Hy's Law Values During Treatment
(Safety Population)

			Placebo (N=xxx)		Drug XYZ (N=xxx)		
Modified Hy's Law Criteria	Visit	Shift [1]	Normal at Baseline	Met Criteria at Baseline	Normal at Baseline	Met Criteria at Baseline	p-value [2]
Elevated Transminase [3]	Week 2	n	xxx	xxx	xxx	xxx	x.xxx
		Normal	xxx (x.x%)	xxx (x.x%)	xxx (x.x%)	xxx (x.x%)	
		Met Criteria	xxx (x.x%)	xxx (x.x%)	xxx (x.x%)	xxx (x.x%)	
Elevated Transminase and Elevated Bilirubin [4]		n	xxx	xxx	xxx	xxx	x.xxx
		Normal	xxx (x.x%)	xxx (x.x%)	xxx (x.x%)	xxx (x.x%)	
		Met Criteria	xxx (x.x%)	xxx (x.x%)	xxx (x.x%)	xxx (x.x%)	
	Etc.						

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N=Safety Population
Only subjects with baseline results are included in the summary.
[1] A change will be considered shifting from normal at baseline to met criteria or from met criteria at baseline to normal at each visit during the treatment.
[2] CMH test for general association.
[3] Transaminase 1.5 x ULN (i.e., ALT or AST)
[4] Transaminase 1.5 x ULN (i.e., ALT or AST) and Total Bili 1.5 x ULN

[33] The style of the display of the results of an analysis will be determined by the producer. The example is intended to illustrate content not appearance.

Table 2.8.3.2 Analysis Results Metadata for Categorical Analysis of Subjects Meeting Hy's Law Criteria Example [34]

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.8
DISPLAY NAME	Shifts of Hy's Law Values During Treatment (Safety Population)
RESULT IDENTIFIER	CMH Test for general association
PARAM	Elevated Transminase, Elevated Transminase and Elevated Bilirubin
PARAMCD	HYS1FL, HYS2FL
ANALYSIS VARIABLE	SHIFT1N
REASON	Secondary safety analysis as pre-specified in SAP
DATASET	ADLBHY
SELECTION CRITERIA	SAFFL="Y" and PARAMCD in ("HYS1FL","HYS2FL")
DOCUMENTATION	Shift table summarizing whether or not a subject's status changed from baseline during the treatment period for changes based on threshold ranges and changes based on Hy's Law. Comparisons between Placebo and Treatment are illustrated by Cochran-Mantel-Haenszel (CMH) test.
PROGRAMMING STATEMENTS	PROC FREQ DATA=ADLBHY; TABLES SHIFT1N*TRTPN / LIST MISSING CMH; BY AVISITN PARAMCD; OUT = RSLTS OUTPCT MISSPRINT; OUTPUT OUT=CMHRSLT CMH; RUN;

[34] The presentation formats used in this document for metadata are for the purposes of illustration of content only, and are not intended to imply any type of display standard or requirement.

Appendices

Appendix A: Abbreviations and Acronyms

The following is a list of abbreviations and acronyms used multiple times in this document. Not included here are explanations of the various SDTM domains (e.g., QS, DM). Also not included is a description of the variables referenced:

ADaM	CDISC Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guide
ADSL	ADaM Subject-Level Analysis Dataset
ALT	Alanine Transminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Transminase
AUC	Area Under the Curve
BDS	ADaM Basic Data Structure
BMD	Bone Mineral Density
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
DXA	Bone density scanning, also called dual-energy x-ray absorptiometry
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in One Second
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LS	Least Squares
MANOVA	Multivariate Analysis of Variance
OC	Observed Cast
PFT	Pulmonary Function Testing
POMS	Profile of Mood States
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SE	Standard Error
ULN	Upper Limit of Normal

Appendix B: Representations And Warranties; Limitations of Liability, And Disclaimers

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