Analysis Data Model

Prepared by the CDISC Analysis Dataset Model Team (ADaM)

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Notes to Readers

This is Version 2.1 of the Analysis Data Model Document, posted for comment by the CDISC Analysis Data Model team (ADaM). Modifications to this document have been made to correspond to the development of the Analysis Data Model Implementation Guide (ADaMIG).

Revision History

Date	Version	Description
2/15/2006	v 2.0	Reformatted from General Considerations v1.0, incorporating Subject-level model, emphasizing requirements and naming and content rules and guidelines.
5/31/2006	V2.0	Incorporate comments from public review
8/11/2006	V2.0	Final document
12/18/2007	V2.1	First maintenance update. Refer to Appendix 8.6 for a list of modifications made.

Note: Please see Appendix 8.7 for Representations and Warranties; Limitations of Liability, and Disclaimers.

Contents

1 Introduction / Purpose

This document describes the Analysis Data Model (ADaM), which specifies the general data structure, metadata, and content typically found in analysis datasets and accompanying documentation. This document is based on material prepared by the ADaM Team of the Clinical Data Interchange Standards Consortium (CDISC). The descriptions in this document build on the nomenclature of the SDTM V3.x standard, adding attributes and variables required as appropriate for statistical analyses. (Note that "SDTM V3.x" refers to SDTM Version 3.1 and all subsequent versions.)

Clinical trials are unique and the design of analysis datasets will be driven by the scientific and medical objectives of the study. However, a key underlying principle must be that the structure and content of the analysis datasets be designed to provide clear, unambiguous communication of the science and statistics of the trial. The purpose of ADaM is to provide a framework that enables reviewers to have a clear understanding of the analysis datasets and analysis results provided in a submission.

The availability of standardized analysis datasets and metadata provides many benefits to regulatory reviewers. The primary benefit of ADaM is in the clear communication of the science and statistics of the clinical trial. In addition, standardized analysis dataset structures allow the development of standard software tools that will facilitate the access, manipulation, and viewing of the analysis datasets. Reviewers can be trained in the principles of standardized datasets, and thus be able to work with the data more effectively with less preparation time.

It cannot be emphasized enough that early and effective cross-communication between regulatory reviewers and sponsor is requisite for mutual success and to achieve the full benefits of analysis datasets.

This document outlines key principles to follow in designing analysis datasets and related metadata. The four types of metadata associated with analysis datasets (analysis dataset metadata, analysis variable metadata, value level metadata, and analysis results metadata) are described and examples provided. Finally, the requirement for a subject-level analysis dataset (ADSL) will be presented. ADSL and its related dataset documentation are always required even if no other analysis datasets are submitted.

This document provides the core of the ADaM concepts and standards. A detailed ADaM Implementation Guide (ADaMIG) will be published separately to assist in applying these core concepts. The basic ADaM structure will be described in the ADaMIG, along with such practical considerations as naming conventions, variables required for inclusion in analysis datasets, and solutions to various issues that will arise when designing analysis datasets. Though the basic ADaM structure will facilitate most statistical analyses, a submission will generally include a set of other special purpose analysis datasets of specific standardized structures to represent additional important information. Examples include ADSL, ADAE (adverse event analysis dataset), and time to event analysis datasets. Documents addressing these special

purpose analysis datasets or illustrating the use of the basic ADaM structure for statistical analyses will be developed as companion documents to the ADaMIG.

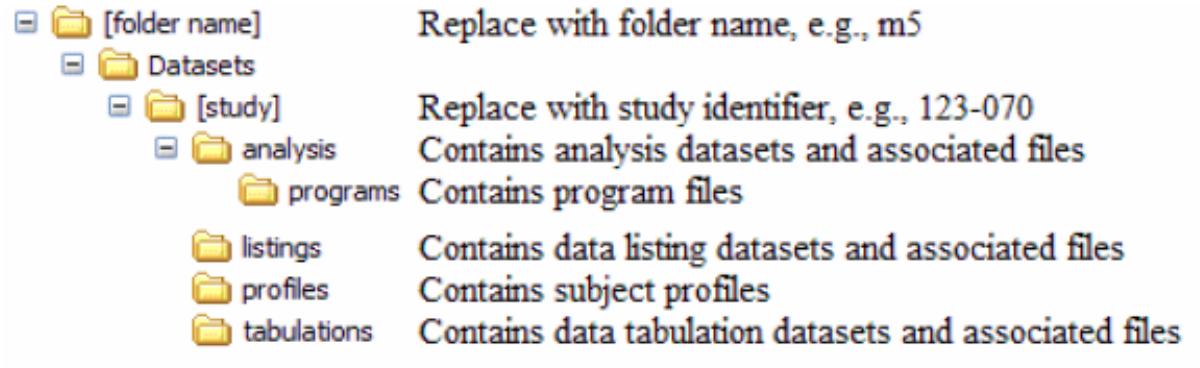
In an effort to provide illustration of ADaM concepts, examples will be provided that make reference to specific programming languages. Throughout ADaM documents, references to specific vendor products are examples only and should not be interpreted as an endorsement.

2 Background / Motivation

The marketing approval process for regulated human and animal health products often includes the submission of data from clinical trials. In the United States, data are a required element of a submission to the FDA as expressed in the Code of Federal Regulations (CFR). The FDA established the regulatory basis for wholly electronic submission of data in 1997 with the publication of regulations on the use of electronic records in place of paper records (21 CFR Part 11). In 1999, the FDA standardized the file format (SAS Version 5 Transport Files) for electronically submitting non-clinical and clinical data collected in clinical trials with the first of a series of guidance documents that described the submission of clinical data and data definition (i.e., metadata) files for those clinical data in PDF format (Define.PDF). As of 2005, metadata could be submitted via the XML metadata (Define.XML) in place of the Define.PDF, as described in the FDA document regarding study data specifications. ("Study Data Specifications," refer to Appendix 8.1 for URL.) More information about Define.XML can be found on the CDISC website. (Refer to Appendix 8.1 for URL.)

In parallel with the development of new clinical data submission guidance, the FDA has adopted the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) standards for regulatory submissions and has issued a guidance on the electronic Common Technical Document (eCTD) as its framework for electronic communications regarding pharmaceutical product applications. ("FDA Guidance," refer to Appendix 8.1 for URL.)

According to public presentations made by FDA representatives and FDA guidance documents on the eCTD, submitted data can be classified into four types: 1) Data tabulations, 2) Data listings, 3) Analysis datasets, and 4) Subject profiles. These data are referred to in 21 CFR 11 as Case Report Tabulations (CRTs) and in ICH E3 as Individual Patient Data Listings (E3 16.4). The specification for organizing datasets and their associated files in folders is summarized in the following figure, from the "Study Data Specifications." (Refer to Appendix 8.1 for URL.)



Historically, listings and subject profiles have been submitted as documents, not datasets. Data tabulations and analysis datasets are typically submitted as datasets and are defined as:

- **Study Data Tabulations (SDTM)** – datasets containing data collected during the study and organized by clinical domain. These datasets are described in the CDISC Study Data Tabulation Model Implementation Guide (Version 3.x). ("SDTMIG," refer to Appendix 8.1 for URL.)
- **Analysis Datasets** – datasets used for statistical analysis and reporting by the sponsor. These datasets are submitted in addition to the study tabulation datasets (SDTM) and are described within this document.

For the purposes of simplifying this document, analysis datasets will be discussed within the context of electronic submissions to the FDA. However, the analysis data model is applicable to a wide range of drug development activities in addition to regulatory submissions. It provides a standard for transferring datasets between sponsors and CROs, development partners and independent data monitoring committees. As adoption of the model becomes more universal, in–licensing, out–licensing and mergers will be facilitated by providing a common model for analysis data and documentation across sponsors. The same principles and standards will apply, regardless of the purpose of the analysis datasets.

3 Overview of Analysis Data Models

3.1 Key Principles

The overall principle in designing Analysis Datasets and related metadata is that there must be clear and unambiguous communication of the content, source and quality of the datasets supporting the statistical analyses performed in a clinical study. Inherent in this is a need for a

level of traceability to allow an understanding of the relationship of analysis values to the study tabulation data.

Sponsors should strive to submit analysis datasets that can be analyzed with little or no additional programming or complex data manipulations. Such datasets are said to be "Analysis-ready" or "One Statistical Procedure Away" from the statistical results. This approach eliminates or greatly reduces the amount of programming required by the statistical reviewers. Appendix 8.3 gives an example of applying this principle in SAS, but the concepts apply to all statistical packages.

Analysis Datasets should be useable by currently available tools, but should provide machine-readable metadata to facilitate future standard analysis tool development. Metadata and other documentation should provide clear, concise communication of the analytic results of a clinical trial from the sponsor to the regulatory reviewers, including statistical methods, transformations, assumptions, derivations and imputations performed. The metadata, programs and other documentation serve to codify the analyses described in the Statistical Analysis Plan (SAP) as well as other analyses performed, and are discussed in detail in Sections 5 and 6.

Key Principles for Analysis Datasets

Analysis datasets should:

- facilitate clear and unambiguous communication and provide a level of traceability
- be useable by currently available tools
- be linked to machine-readable metadata
- be analysis-ready

3.2 Analysis Data Flow Diagram in Research Process

The typical general flow of data from its source through the analysis results is shown in Figure 1.

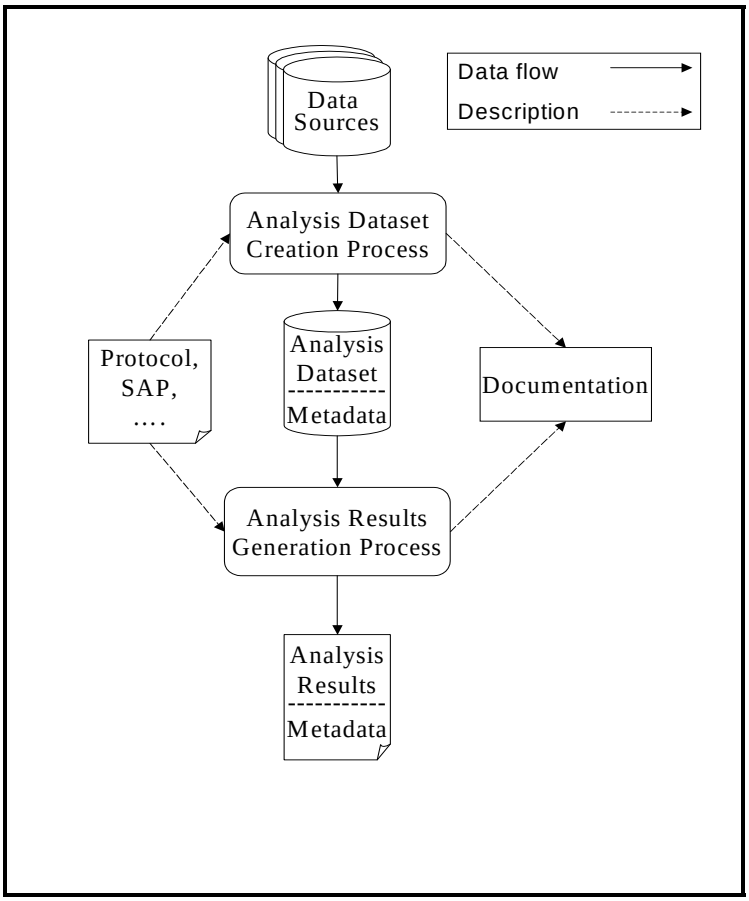


Figure 1: Analysis Data Flow

A variety of sources are possible for analysis datasets. One source, and the source of data used for ADaM examples, is the SDTM datasets submitted as part of a regulatory submission and/or other ADaM datasets, such as the Subject Level Analysis Dataset (ADSL). In all cases, the data sources should be clearly described in the metadata and the analysis dataset creation documentation. (Refer to Section 5.4)

To facilitate clear communication, a distinction is made between the processes of Analysis Dataset Creation and Analysis Results Generation. These two processes have distinct purposes and should each be clearly described and documented.

- **Analysis Dataset Creation** – The processing and programming steps used to create the Analysis Datasets. The analysis dataset along with variable and value level metadata are defined in this step. Additional documentation may include programs or code fragments and links to the Protocol or Statistical Analysis Plan.
- **Analysis Results Generation** – The programming steps used to generate an analysis result, using submitted data as input. The analysis results metadata are defined in this step. Additional documentation may include analysis results programs or code fragments and links to the Statistical Analysis Plan or statistical appendix of the final report. The output is the results presentation and display objects (e.g., tables, data for graphics, test statistics, p-values, etc.).

These processes, datasets, results, metadata and documentation are discussed in detail in the following sections of this document.

3.3 Metadata Components

The analysis datasets and related metadata will facilitate the review of the clinical trial data and the analyses performed. There are four types of metadata described in this document. These include:

- Analysis dataset metadata provides certain key pieces of information describing each analysis dataset, including documentation and/or analysis dataset creation programs. (Refer to Section 5.1)
- Analysis variable metadata describes the variables within the analysis datasets, including links to relevant documentation providing additional details about the source and creation of the analysis variables, e.g. detailed descriptions of algorithms involved and/or references to analysis dataset creation programs. (Refer to Section 5.4)
- Analysis variable value-level metadata describes the measurements or analysis endpoints at the variable value level. Typically, the data structure is "vertical" where a variable contains multiple measurements or analysis endpoints. (Refer to Section 5.5)
- Analysis results metadata provides certain key pieces of information describing each important display, including which analysis dataset was used and links to relevant documentation providing details about the analyses performed, e.g. a specific section of the statistical analysis plan and/or analysis generation programs. (Refer to Section 6)

Analysis results metadata provides a link between an analysis result and the analysis dataset used to calculate the result. The other types of metadata relate solely to the analysis dataset, with the analysis dataset metadata describing the analysis dataset as a whole and the analysis variable metadata and value-level metadata describing the variables and observations within the dataset.

4 Analysis Datasets

4.1 Practical Considerations

An analysis dataset will gather from various sources (e.g., study tabulation datasets) all of the variables required for performing the statistical analysis it is designed to support. For example, data may be required from the disposition, demographics, subject characteristics, vital signs, questionnaires, and exposure domains. By gathering the data into an analysis dataset, including any derived variables, further complicated data manipulation will not be required prior to the analysis. An example of a composite endpoint requiring complex algorithms and source variables from multiple datasets is shown in Appendix 8.5.

In creating analysis datasets, one goal should be to have the optimum number of analysis datasets needed to accomplish the various analyses, with the minimum requirement being a subject-level analysis dataset. Analysis datasets should be designed to allow analysis and review with little or no programming or data processing. Redundancy between analysis datasets will often be necessary so that the datasets are analysis-ready (e.g., age in the adverse event analysis data set as well as an efficacy dataset). In addition, redundancy between analysis datasets and SDTM domain datasets is acceptable. An analysis dataset can be designed so that it can be used for multiple analyses. To aid in the review and use of analysis variables, there may be variables included that are not actually used in any of the submitted analyses, but are still of interest to the sponsor or reviewer (e.g., an identification flag for subjects who had an event of clinical interest). Analysis datasets will be provided to support the analyses in a report or submission.

Analysis datasets will be named using the convention "ADxxxxxx." The subject-level analysis dataset will be named "ADSL" as described in Section 7. For all other analysis datasets the xxxxxx portion of the name will be sponsor-defined, using a common naming convention across a given submission or multiple submissions for a product. Naming conventions for variables created (not to be confused with any standard variables required by SDTM) within the analysis should follow the standardized variable names defined in the ADaM Implementation Guide. Otherwise the analysis variable names will be sponsor-defined, and should also follow a common naming convention across a given submission or multiple submissions for a product. This should allow for optimum clarity for any reviewer.

Analysis datasets must:

- include a subject-level analysis dataset named "ADSL" (Refer to Section 7)
- consist of the optimum number of analysis datasets needed to allow analysis and review with little or no additional programming or data processing
- maintain SDTM variable attributes if the identical variable name also exists in an SDTM dataset
- be named using the convention "ADxxxxxx"
- follow naming conventions for datasets and variables that are sponsor-defined and applied consistently across a given submission or multiple submissions for a product

Although this document discusses some of the statistical and programming issues that arise in the creation of an analysis dataset, it is by no means a complete list. Trial design, statistical methods, sponsor SOPs and "real world" issues that arise during the conduct of the trial may complicate definitions and derivations.

The following comments identify some statistical and programming issues to be considered in creating analysis datasets, but should not be interpreted as the only issues for a specific trial. To facilitate review and comprehension of the analysis datasets and analysis results, these issues may be important to represent in either Analysis Dataset or Analysis Results documentation or metadata.

- How are missing values handled in the analysis dataset? If a missing value is replaced by an imputed value (such as the last observation or the mean of existing values), what

indication of that will be included in the analysis dataset? This imputation should be clearly documented and represented in the analysis dataset.

- The visit window is often computed using the decision rules from the SAP. On rare occasions (hopefully), this may also require human intervention for cases not anticipated in the SAP. It is possible that the visit window will need to be computed in an interim dataset before endpoints can be computed. In most cases, this interim dataset would not be submitted. All decisions and processing steps of the visit windowing process should be fully documented.
- If the analysis results in p-values or other comparative statistics, data should be included in the analysis dataset that will allow the statistic to be produced with minimal additional computation. The documentation accompanying the analysis dataset should specify clearly how the statistic was produced, including any multiple comparison procedures that might have been used. For example, if the analysis is a Cochran-Mantel-Haenszel comparison between treatment groups of the proportion of subjects who responded to treatment, controlling for age group, the age group of the subject as well as whether or not the subject responded to treatment will be included in the analysis dataset.
- If multiple records are eligible for analysis, the record actually analyzed should be clearly identified. For example, if the maximum on-treatment value is to be summarized, that record should be flagged. Or if the value closest to the protocol-defined scheduled visit is to be analyzed, that record should be flagged.
- Variables that are changed or derived (e.g., logarithmic transformation, percent change from baseline) from the original data should be clearly identified. The algorithm used for the change or derivation, including the names of the variables containing the source or original data, and the reason for the change or derivation should be documented within the metadata.
- When a statistical analysis is based on a derived variable that is obtained from multiple records, such as a derived value that is calculated as the average across several records, or when a statistical analysis uses just a subset of records, such as using just those visits that adhere to a visit windowing rule, the decision must be made whether to retain all of the original records in the analysis dataset. As a general rule, if the derivations or decisions can adequately be described in the metadata, then only records used for analysis need to be included in the analysis dataset. If the metadata does not provide an adequate description, then all the original records should be retained.

Sponsors should consult the ADaM Implementation Guide for examples of how to address these situations using the basic ADaM structure.

5 Analysis Dataset Documentation

Analysis dataset documentation provides the link between the general description of the analysis (as found in the Protocol Data Analysis Section, SAP or the reported analysis methods) and the source data. The source(s) of the Analysis Dataset should be clearly documented, allowing the reviewer to trace back data items to the study tabulation data. (Given that the ADaM standard has been developed as part of the larger family of CDISC standards, it is assumed that there is a relationship that can be described by metadata between the analysis datasets and the study tabulation data.) The analysis dataset metadata and analysis variable metadata form an important part of this documentation. Depending on the complexity of the algorithms involved, the trial design, and the content and structure of the analysis dataset, written documentation and analysis file generation programs may also be submitted as part of the analysis dataset documentation.

5.1 Analysis Dataset Metadata

The Analysis Dataset Metadata conforms to the CDISC Submission Metadata Model. ("Metadata," refer to Appendix 8.1 for URLs.) The datasets should have descriptive names, should indicate "analysis" or "statistics" in both the dataset label and description. The dataset should specify the PURPOSE in the dataset metadata that provides information about why the analysis dataset was created and/or how it is to be used. The dataset names should always use "AD" as prefix. Analysis dataset metadata should include the following data fields: dataset name, description, purpose, structure, key variables, documentation, and dataset location. Refer to Section 7 for an example of analysis dataset metadata.

5.2 Analysis Dataset Creation Documentation

Written documentation may include descriptions of the source datasets and dependencies, processing steps, and scientific decisions pertaining to creation of the dataset. This documentation should clearly distinguish those derivations and decision rules that were specified a priori from those changes and decisions that were data-driven. Key issues for consideration in analysis dataset creation documentation include (but are not limited to):

- Derived variables or records
- Added observations (e.g., for time-point analysis or imputed data capture)
- Visit windows
- Omitted observations
- Multiple observations
- Imputed data

- Missing data
- Dropouts
- Data item-specific derivations, i.e. changes to a data value for a specific observation.

5.3 Analysis Dataset Creation Programs

Statistical software programs may also be included as part of the analysis dataset documentation. These programs may be classified into three levels of increasing functionality and complexity:

- As pseudo-code embedded in written documentation of the creation of the dataset
- As code fragments that a reviewer could include in a program
- As stand alone, fully-functioning programs that replicate the creation of the dataset in another programming environment.

It should be noted that FDA requirements on submission of programs and how they will be used in the review of a submission are currently (i.e., at the time of the writing of this document) under development. In the interim, the alternatives listed above might be appropriate documentation of analysis datasets transferred between sponsors and other parties, independent of FDA guidance.

5.4 Analysis Variable Metadata

The analysis variable metadata describes each variable in the analysis dataset. The Source column provides details about where the variable came from in the source data or how the variable was derived (i.e., computational method). This column should be used to identify the immediate predecessor data file and can contain hyperlinked text which will refer to the reviewer to additional information. This column differs from the ORIGIN attribute since Origin identifies the location of the first occurrence of the variable. The following data fields can be used to describe analysis variables: variable name, variable label, source / computational method, variable type, length / format, and codelist / controlled terms. Refer to Section 7 and Appendix 8.5 for illustrations of analysis variable metadata.

5.5 Analysis Variable Value-Level Metadata

When datasets are normalized in structure, one variable can contain multiple types of information. In SDTM, for example, the variable --TEST, contains a unique description for every type of test included in that Findings domain. Similarly, in an analysis dataset the variable PARAM contains a unique description for every analysis parameter included in that dataset. Consequently, there could be multiple records per subject for a single visit or time point, with the analysis parameter identifiers stored in the Parameter Code/Description variables, and the analysis parameter values stored in analysis result variables. Since the unique Parameter Code/Description could have different attributes there would be a need to provide value-level metadata for this information. By referencing the value-level metadata, the user of the dataset can determine the unique values found in the dataset and should be able to understand the value specific-attributes and derivation algorithms for each value. Value-level metadata should include

the following attributes for each of the variable values: description, source / computational method, length / format, and codelist / controlled terms.

Value-level metadata is described as part of the proposed DEFINE.XML standard. ("Define.XML," refer to Appendix 8.1 for URL.) Refer to Section 8.5 for an illustration of value-level metadata.

6 Analysis Results Metadata

Analysis results metadata describes the major attributes of each important analysis result in a report. (Analysis results metadata may not be necessary for every analysis included in a report or submission, but only for the key analyses. The determination of which analyses are key analyses will be agreed between the sponsor and the recipient of the data.) Analysis results may include statistical statements in the report such as treatment effect and p-values, tables or figures. Analysis results metadata will provide critical information concerning an analysis in a standard format in a predictable location. This will allow reviewers to link from a statistical result to metadata describing the analysis, the reason for performing the analysis, and the datasets and programs used to generate the analysis. Note that analysis results metadata is not part of an analysis dataset, but one of the attributes of analysis metadata describes the analysis datasets used in the analysis. The following attributes can be used to describe each key analysis.

- **ANALYSIS NAME –** A unique identifier for the specific analysis. The column may include a table number or other sponsor-specific reference, such as the title of the display.
- **DESCRIPTION –** A text description of the contents of the display. This will normally contain more information than the title of the display.
- **REASON –** The high-level reason for performing this analysis. It will indicate when the analysis was planned and the purpose of the analysis within the body of evidence. Examples of analysis reason are 'Pre-specified in Protocol,' 'Pre-specified in SAP,' 'Data Driven,' 'Requested by FDA.' Using consistent terminology in this field will allow ease in searching and identifying analyses.
- **DATASET –** the name of the dataset(s) used in the analysis. In most cases, this will be a single dataset. If multiple datasets are used, they should all be listed here. The column may also include specific selection criteria for analysis subset and / or numerator so that the reviewer can easily identify the appropriate records from the analysis dataset (e.g., "where ITTFL=Y").
- **DOCUMENTATION –** contains the information about how the analysis was performed. This information could be a text description, or a link to another document such as the protocol or statistical analysis plan, or a link to an analysis generation program (i.e., a

statistical software program used to generate the analysis result). The analysis method could be documented in the protocol or the statistical analysis plan, or somewhere on the display itself. What the documentation column contains will depend on the level of detail required to describe the analysis itself, whether or not the sponsor will be providing a corresponding analysis generation program, and sponsor-specific requirements and standards.

Additional information that the sponsor may consider important for inclusion in the analysis results metadata include the type of analysis (e.g., patient-level summary, event-level summary, line listing) and a list of the variables in the analysis dataset that are used in the analysis.

Refer to Appendix 8.4 for an example of analysis results metadata.

7 Subject-Level Analysis Dataset

A subject-level analysis dataset and its related dataset documentation are always required even if no other analysis datasets are submitted. The dataset will have one record per subject and will be named "ADSL." ADSL can be used for multiple types of analyses, including descriptive, categorical, and modeling, depending on what variables are included in it. However, this does not mean that ADSL should be forced to support all analyses in order to minimize the number of analysis datasets. Additional analysis datasets may be advantageous since they could include only the variables that are needed to support a specific set of analyses. ADSL can be used as a basis for other analysis datasets, but this does not mean that all ADSL variables need to be included in these other datasets – the inclusion of many variables into one or more analysis datasets for the sole reason that their dataset structures are similar may impede clear and concise communication with the reviewer. As noted in Section 4.1, a goal should be to have the optimum number of analysis datasets needed to accomplish the various analyses, with the minimum requirement being ADSL.

Table 1 provides an example of analysis dataset metadata for ADSL.

Table 1 Example of Analysis Dataset Metadata for ADSL

Dataset	Dataset Description	Location	Structure	Purpose	Key Variables	Documentation
ADSL	Contains key information for subject disposition, demographic, and baseline characteristics.	*pathname*/adsl.xpt	One record per subject	Used for analysis of disposition, demographics	USUBJID	SAP, DS_ADSL.SAS

The critical variables included in ADSL will depend on the specific nature of the disease and on the protocol, but will usually include (refer to ICH E3 [see Appendix 8.1 for URL] for a more detailed listing and to the ADaMIG for further description including required variables):

- Demographic variables (age, sex, race, other relevant factors)
- Disease factors (including baseline values for critical clinical measurements carried out during the study or identified as important indicators of prognosis or response to therapy)
- Treatment code/group
- Other factors that might affect response to therapy
- Other possibly relevant variables (e.g., smoking, alcohol intake, menstrual status for women)

ADSL will also contain all of the variables that are important for describing the study population. These variables will describe the subjects or events in a clinical trial prior to treatment, or group the subjects or events in some way for analysis purposes. There may be variables included that are not actually used in any of the submitted analyses, but are still of interest to the sponsor or the reviewer. As mentioned before, note that the data assembled into ADSL can also be used as a source for other analysis datasets for grouping subjects or events.

In summary, the critical variables in ADSL will include those that are either descriptive, known to affect the subject's response to drug (in terms of either efficacy or safety), used as strata for randomization, or identify the subject or event as belonging to specific subgroups (e.g. population flags). For example, subjects may be randomized after being stratified by age group because it is believed that younger subjects respond differently to the study drug. In this situation, a subject's age category would be considered a critical variable for a study and included in ADSL.

Table 2 provides an illustration of analysis variable metadata for a few of the variables that might be found in ADSL. This illustration is not meant to list all of the required ADSL variables, or all of the other variables that might be considered for ADSL.

Table 2 Illustration of Analysis Variable Metadata (only selected variables are displayed)

ADSL - Subject-level analysis dataset					
Variable Name	**Variable Label**	**Type**	**Length / Format**	**Codelist / Controlled Terms**	**Source / Computational Method**
STUDYID	Study Identifier	Char	10		DM.STUDYID
USUBJID	Unique Subject Identifier	Char	20		DM.USUBJID
SITEID	Study Site Identifier	Char	6		DM.SITEID
AGE	Age	Num	3		DM.AGE
SEX	Sex	Char	1	M, F, U	DM.SEX
ARM	Description of Planned Arm	Char	200		DM.ARM
TRT1P	Planned Treatment for Period 1	Char	9	Placebo XXX112233	Derived from DM.ARM

TRT1A	Actual Treatment for Period 1	Char	9	Placebo XXX112233	Derived from EX.TRT
TRTSTDT	Start Date of Treatment	Num	Date9		Numeric date derived from EX.EXSTDTC
DSREAS	Reason for discontinuation	Char	3	AE=Adverse Event PV=Protocol Violation LTF=Lost to Follow-Up OTH=Other	Derived from DS.DSDECOD where DS.DSCAT = DISPOSITION EVENT and DS.DSDECOD not equal COMPLETED, OTH if DS.DSDECOD is other non-missing value, missing if DS.DSDECOD=COMPLETED

ICH Guidance (Ref: ICH E3 Guidance for Industry: Structure and Content of Clinical Study Reports, Section 11.2 6) recommends that "in addition to tables and graphs giving group data for baseline variables, relevant individual patient demographic and baseline data… for all individual patients randomized (broken down by treatment and by center or multi-center studies) should be presented in by-patient tabular listings." Often a reviewer and sponsor will agree that submission of subject-level data will meet this requirement. If that is the case, ADSL will have to include those variables needed to meet this regulatory requirement.

Screen failure data, if submitted, should not be included in ADSL. This will avoid unnecessarily complicating the use of ADSL as a basis for other analysis datasets, as a source for calculations of denominators for many analyses, and as a source for review of randomized subjects. If there is a need to provide a screen failure analysis, it is recommended that a subject-level dataset specific to screen failures be included. This dataset will be named ADSLSF and will contain one record per screen failure. The dataset will have the same columns as ADSL, leaving empty the columns not relevant to screen failures. This matching structure will facilitate combining the two subject-level datasets for an analysis, if needed.

8 Appendices

8.1 Links referenced in document

CDISC Define.xml Team. "Case Report Tabulation Data Definition Specification (define.xml)." <http://www.cdisc.org/standards/index.html>

CDISC Submission Data Standards (SDS) Group. "CDISC Study Data Tabulation Model Implementation Guide: Human Clinical Trials" (SDTMIG). <http://www.cdisc.org/standards/index.html>

CDISC SDS Metadata Team. "Metadata Submission Guidelines, Appendix to the Study Data Tabulation Model Implementation Guide." <http://www.cdisc.org/standards/index.html>

CDISC Submission Data Standards (SDS) Group. "Study Data Tabulation Model." (SDTM) <http://www.cdisc.org/standards/index.html>

Christiansen, D and Kubick, W. "CDISC Submission Metadata Model, Version 2.0.", November 2001 <http://www.cdisc.org/pdf/SubmissionMetadataModelV2.pdf>

FDA Center for Drug Evaluation and Research. "Study Data Specifications, Version 1.4." <http://www.fda.gov/cder/regulatory/ersr/Studydata.pdf>

FDA. "Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications." <http://www.fda.gov/cder/guidance/7087rev.pdf>

ICH Expert Working Group. "ICH Harmonised Tripartite Guideline: Structure And Content of Clinical Study Reports - E3." <http://www.ich.org/LOB/media/MEDIA479.pdf>

8.2 Definitions

ADaM Basic Structure – The data structure described in the ADaMIG that will be used for the majority of analyses, regardless of the therapeutic area or type of analysis. The ADaM structure is a normalized design that can be loosely described as one record per subject per analysis parameter per analysis timepoint.

ADaM Implementation Guide (ADaMIG) – A document that includes the detailed basic ADaM structure, standard variable names, and examples for analysis datasets.

Analysis Datasets – Datasets used for statistical analysis and reporting by the sponsor; submitted in addition to the study tabulation datasets.

Analysis Dataset Creation Program – Statistical software program used to create the analysis dataset.

Analysis Dataset Documentation - A document that may include descriptions of the source datasets, processing steps, and scientific decisions pertaining to creation of the dataset. Analysis dataset creation programs may also be included.

Analysis Dataset Metadata – Provides information describing each analysis dataset

Analysis Generation Programs – Statistical software programs used to generate an analysis, provide an "audit trail" (e.g., step-by-step process of how a result was obtained) for important results.

Analysis Results Documentation – Written documentation will include descriptions of planned and ad hoc analyses. The documentation may consist of the protocol, the statistical analysis plan, the statistical methods section of the study report, and analysis generation programs.

Analysis Results Metadata – Describes the major attributes of each important analysis result in a report

Analysis Variable Metadata – Describes the variables within the analysis dataset

Analysis Variable Value-Level Metadata – Describes the various possibilities included in variables in the analysis dataset that contain more than one type of measure

CDISC – Clinical Data Interchange Standards Consortium

Study Tabulation Datasets - Datasets in which each record is a single observation for a subject. ("Study Data Specifications," refer to Appendix 8.1 for URL.)

Submission Data Domain Standards – Released by the CDISC SDS Team, Version 3.x consists of two documents: the Study Data Tabulation Model (SDTM), which represents the underlying conceptual model behind the SDS standards, and the SDTM Implementation Guide (SDTMIG), which includes the detailed domain descriptions, assumptions, and examples. Note that "SDTM V3.x" refers to SDTM Version 3.1 and all subsequent versions. (Refer to Appendix 8.1 for URL.)

SDTM - Study Data Tabulation Model – Document which represents the underlying conceptual model behind the SDS standards. It defines a standard structure for study data tabulations that are to be submitted as part of a product application to a regulatory authority. ("SDS documents," refer to Appendix 8.1 for URL.)

SDTM Implementation Guide (**SDTMIG) -** Document which includes the detailed domain descriptions, assumptions, and examples for human clinical trials. ("SDTMIG," refer to Appendix 8.1 for URL.)

8.3 Illustration of Analysis-Ready

To illustrate the concept of "analysis-ready," consider the demographic table shown below. For this example, the comparability of the treatment groups for certain subject characteristics is computed and displayed. ("ICH E3," Section 11.2, refer to Appendix 8.1 for URL.) Analysis-ready does not mean that this formatted table can be generated in a single statistical procedure. Rather it means that each statistic in the table can be replicated by running a standard statistical procedure (SAS PROC, S-PLUS function…) using the appropriate analysis dataset as input. This means that reviewers can replicate and explore these results with little or no data manipulation, allowing reviewers to concentrate on the results, not on programming.

528 **Table DEM1 – Demographics by Treatment Assignment for all randomized patients**

		Placebo	Drug A	P-value*
NUMBER OF SUBJECTS RANDOMIZED		nn	nn	
Number of subjects eligible per protocol		nn (xx%)	nn (xx%)	
Age (yrs) Mean(SD)		xx (xx.x)	xx (xx.x)	0.xxx
Sex N(%)	Female	nn (xx%)	nn (xx%)	
	Male	nn (xx%)	nn (xx%)	
Race N(%)	White	nn (xx%)	nn (xx%)	0.xxx
	Black	nn (xx%)	nn (xx%)	
	……	nn (xx%)	nn (xx%)	
Baseline Weight (kg) Mean(SD)		xxx (xx.x)	xxx (xx.x)	0.xxx
Baseline Height (cm) Mean(SD)		xxx (xx.x)	xxx (xx.x)	0.xxx

*Continuous variables will be analyzed using t-test. Categorical variables will be compared using chi-square.

529 **NOTE: This is an illustrative example of analysis-ready datasets. It is not a**
530 **recommendation to perform hypothesis tests for baseline characteristics.**

531 For example, the following SAS code will replicate results of Table DEM1 using an analysis
532 dataset containing the appropriate variables.

```
533       PROC tabulate data=r.ADSL f=4.0;
534       class pprotfl trt1p;
535       table all pprotfl, trt1p*(n pctn<all pprotfl>);
536       run;

537       PROC freq data=r.ADSL;
538       table race*trt1p/chisq nopercent norow;
539       run;

540       PROC ttest data=r.ADSL ci=none;
541       class trt1p;
542       var age weightbl heightbl;
543       run;
```

544 The following annotated SAS procedure output results relate the SAS output with the
545 corresponding elements of Table DEM1.

A1234567 - Demographics by Treatment Assignment

The TTEST Procedure

Statistics

Variable	TRT1P	N	Lower CL Mean	Mean	Upper CL Mean	Std Dev	Std Err	Minimum	Maximum
Age	PLACEBO	15	56.368	62.8	69.232	11.614	2.9987	43	78
Age	DRUG A	13	57.915	62.769	67.623	8.0328	2.2279	52	81
Age	Diff (1-2)		-7.852	0.0308	7.9132	10.12	3.8347		
WEIGHTBL	PLACEBO	15	73.553	77.567	81.58	7.2478	1.8714	63.5	91
WEIGHTBL	DRUG A	13	74.105	78.885					
WEIGHTBL	Diff (1-2)		-7.207	-1.318					
HEIGHTBL	PLACEBO	15	171.57	176.2					
HEIGHTBL	DRUG A	13	167.83	173.15					
HEIGHTBL	Diff (1-2)		-3.629	3.0462					

T-Tests

Variable	Method	Variances	DF	t Value	Pr > |t|
Age	Pooled	Equal	26	0.01	0.9937
Age	Satterthwaite	Unequal	24.9	0.01	0.9935
WEIGHTBL	Pooled	Equal	26	-0.46	0.6493
WEIGHTBL	Satterthwaite	Unequal	24.6	-0.46	0.6516
HEIGHTBL	Pooled	Equal	26	0.94	0.3569
HEIGHTBL	Satterthwaite	Unequal	25	0.93	0.3591

Age (yrs) Mean (SD)	xx (xx.x)	xx (xx.x)	0.xxx

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A1234567 - Demographics by Treatment Assignment

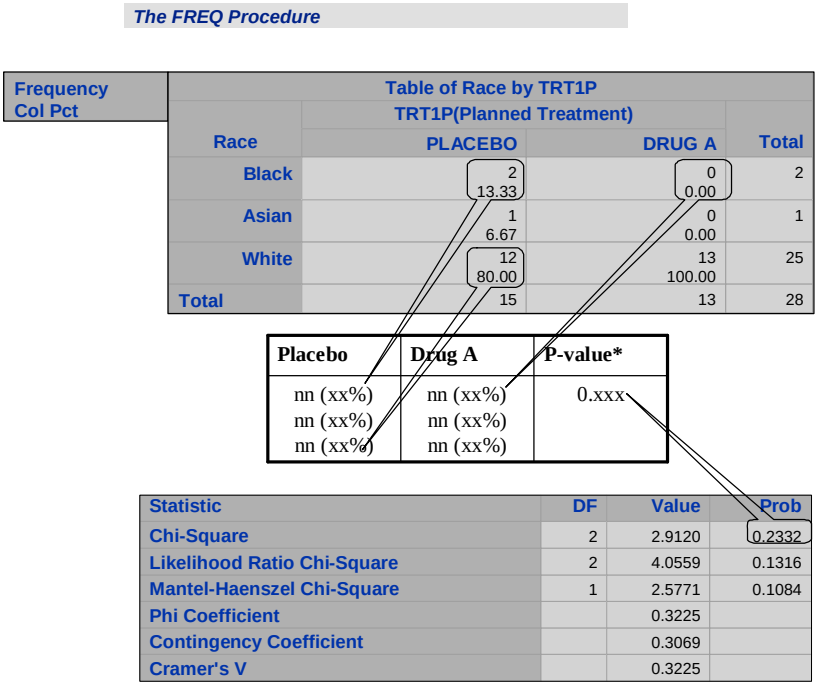
PROC Tabulate

	Planned Treatment			
	PLACEBO		DRUG A	
	N	PctN	N	PctN
All	15	100	13	100
Per Protocol Flag				
N	2	13	1	8
Y	13	87	12	92

	Placebo	Drug A
Number of subjects randomized	nn	nn
Number of subjects eligible per protocol	nn (xx%)	nn (xx%)

547

548



It is often the case that analysis-ready datasets can also be used for subset analyses without additional programming. For example, the following SAS code can be used to generate a table similar to Table DEM1 for only those subjects meeting the “per protocol” criteria.

```
PROC freq data=r.ADSL(where=(pprotfl eq 'Y'));
table race*trt1p/chisq nopercent norow;
run;

PROC ttest data=r.ADSL(where=(pprotfl eq 'Y')) ci=none;
class trt1p;
var age weightbl heightbl;
run;
```

8.4 Analysis Results Metadata Example

Table 3 provides an example of analysis results metadata. The analysis described is the Population Summary included in the analysis package. In this example, the data displays are identified by number and display title. The items underlined in the example could be hyperlinks to the data display in the clinical study report, to the analysis dataset metadata elsewhere in the Define file, and to specific pages of the Statistical Analysis Plan (SAP)

566 **Table 3 Analysis Results Metadata Example**

Analysis	Table 14-1.01 - Summary of Populations
Description	Summary of number of subjects in each analysis population
Reason	pre-specified in SAP
Dataset	Subject level analysis dataset containing demographics and baseline characteristics (ADSL)
Documentation	SAP Section 9.1, The number of subjects in each analysis population (Safety, ITT, and Per Protocol), following the flow of subjects by specifying the number of subjects excluded from each population by reason for exclusion. The summary will be by treatment group.

567 ## 8.5 Composite Endpoint Example

568 This example, based on the International Headache Society Guidelines, describes a composite
569 endpoint that requires data from an efficacy dataset (headache severity at different time points),
570 as well as from adverse experiences and concomitant medications datasets. The endpoint is
571 "Sustained migraine pain and symptom free." It illustrates how an apparently simple binary
572 outcome variable (outcome of the treatment of a single headache episode) has complex
573 underpinnings and draws from data elements from different source datasets.

574 The endpoint (sustained migraine pain and symptom free) is defined as:

575 • Headache severity of either Moderate or Severe at Baseline AND

576 • Headache severity of No Pain by 2 hours post dose (i.e., after initial dose of test
577 medication) AND

578 • No headache recurrence within 48 hours post dose AND

579 • No rescue medications for analgesia or anti-emetic from time of initial dose through 48
580 hours post dose AND

581 • No associated symptoms (nausea, vomiting, photophobia, phonophobia) from 2 through
582 48 hours post dose.

583 For this example, the following definitions and specifications apply:

584 Headache severity

585 Headache severity is subjectively rated by patients at pre-specified time points (baseline,
586 0.5, 1, 1.5, 2, 3, and 4 hours post dose) on a scale from Grade 0 (no pain) to 3 (severe
587 pain).

588 Associated Symptoms

589 The patient will record whether the following associated symptoms were present or
590 absent at regular time points (baseline, 2, and 4 hours post dose): photophobia,
591 phonophobia, nausea, vomiting.

592 In addition, patients are instructed to list any of the above symptoms as an "Adverse
593 Symptom" on the diary card if it: (1) shows an unusual increase in intensity after they
594 have taken their test medication or, (2) otherwise shows an important change in character
595 after they have taken their test medication, as compared with their usual migraine
596 symptoms. All such symptoms will be recorded by the investigator as adverse

experiences. Therefore, to fully assess the absence of associated symptoms the adverse event dataset must also be scanned.

Headache Recurrence

Headache recurrence is defined as the return of headache to Grade 2 or 3 (moderate or severe) within 48 hours post dose in patients who report pain relief (mild or no pain) at 2 hours post dose. Patients will be instructed to record the maximum headache severity between 2 and 24 hours post-initial dose and between 24 and 48 hours post-initial dose.

Rescue Medications

The patient will record any additional analgesics/anti-emetics taken after any test dose, documenting date, clock time (AM/PM), name of drug (e.g., codeine), the number of tablets/capsules, and the dose per tablet/capsule. Rescue medication is also defined as taking any additional doses of test medication within 48 hours post dose. The use of rescue medications is determined using the concomitant medication and exposure datasets.

To determine whether or not a patient meets the criteria for sustained migraine pain and symptom free, the answers to each of the five criteria must be determined. In the illustration below, it is assumed that the answers to all of the questions inherent in the criteria are retained in the analysis dataset. This assumption is for illustration purposes only and is not intended to imply this is a requirement for an analysis dataset. The analysis variable metadata for the analysis parameter is illustrated in Table 4. (Not all of the analysis dataset variables are included in this illustration.) The basic ADaM structure for analysis datasets will necessitate including value-level metadata to fully describe the components of the analysis dataset. The analysis variable value-level metadata in Table 5 describes the source / computational method, length / format, and codelist / controlled terminology for the analysis variables storing the results (i.e., AVAL/AVALC in this example) for each of the questions, identified by the Parameter Code/Description (i.e., PARAM/PARAMCD). Rather than attempt to describe specific SDTM domains and variables for this example, a simple text description is provided for the source / computational method. In "real" metadata, this metadata element should actually point to the specific domain and variable, and should include how to identify which record in the domain is the source of the data. (e.g., when QSCAT=xxx for this USUBJID).

Table 4 Illustration of Analysis Variable Metadata for Analysis Parameter (only selected variables are displayed)

Variable Name	Variable Label	Type	Length / Format	Codelist / Controlled Terms	Source / Computational Method
PARAM	Parameter Description	Char	75	*[1]	

[1] The presence of an asterisk (*) in the 'Controlled Terms or Format' column indicates that a discrete set of values (controlled terminology) exists or is expected for this variable. This set of values may be sponsor defined in cases where standard vocabularies have not yet been identified.

Variable Name	Variable Label	Type	Length / Format	Codelist / Controlled Terms	Source / Computational Method
PARAMCD	Parameter Code	Char	8	HASPNFR HASEV_BL HASEV_2 HARECUR HARESCUE HASYMPD HASYMPAE	
PARAMN	Parameter Number	Num	2	1=HASPNFR 2=HASEV_BL 3=HASEV_2 4=HARECUR 5=HARESCUE 6=HASYMPD 7=HASYMPAE	Derived from PARAMCD
AVAL	Analysis Value	Num	1		see value-level metadata
AVALC	Character Analysis Value	Char	1		see value-level metadata

629

630 **Table 5 Illustration of analysis variable value-level metadata**

				Value Specific		
Source dataset	**PARAMCD Value**	**PARAM Value**	**Result Variable**	**Length / Format**	**Codelist / Controlled Terms**	**Source / Computational Method**
ADxxx	HASPNFR	Sustained migraine pain and symptom free from 2-48 hours post-dose	AVALC	1	N=No Y=Yes Blank=Missing	International Headache Society Guidelines, For this subject and attack, Y" if Headache severity of either Moderate or Severe at Baseline (HASEV_BL=2 or 3) AND Headache severity of No Pain by 2 hours (HASEV_2=0) AND No headache recurrence within 48 hours (HARECUR=N) AND No rescue medications for analgesia or antiemetic from time of initial dose through 48 hours post baseline (HARESCUE=N) AND No associated symptoms (nausea, vomiting, photophobia, phonophobia) from 2 through 48 hours (HASYMP_D=N and HASYMPAE=N).
ADxxx	HASEV_BL	Headache severity at baseline	AVAL	1	0=No pain 1=Mild pain 2=Moderate pain 3=Severe pain	Diary card data, baseline headache severity for this subject.
ADxxx	HASEV_2	Headache severity at 2 hours post-dose	AVAL	1	0=No pain 1=Mild pain 2=Moderate pain 3=Severe pain	Diary card data, 2-hour post-dose headache severity for this subject.
ADxxx	HARECUR	Headache Recurrence within 48 hours post-dose	AVALC	1	N=No headache recurrence Y=Headache did recur Blank=Missing	Diary card data, max headache severity between 2 and 24 hours post-initial dose and between 24 and 48 hours post-initial dose = 0 (no pain).

				Value Specific		
Source dataset	**PARAMCD Value**	**PARAM Value**	**Result Variable**	**Length / Format**	**Codelist / Controlled Terms**	**Source / Computational Method**
ADxxx	HARESCUE	Rescue medications taken from initial dose through 48 hours post-dose	AVALC	1	N=No rescue medication taken Y=Rescue medication taken Blank=Missing	No analgesics or anti-emetics taken from time of initial dose through 48 hours post-dose (CM domain). In addition, no additional doses of study medication taken from time of initial dose through 48 hours post-dose (EX domain).
ADxxx	HASYMPD	Associated symptoms as indicated on diary card from 2-48 hours post-dose	AVALC	1	N=No associated symptoms present Y=Associated symptoms are present Blank=Missing	Diary card data, no photophobia, phonophobia, nausea or vomiting at 2 or 4 hours post dose.
ADxxx	HASYMPAE	Associated symptoms as indicated in AE datasets from 2-48 hours post-dose	AVALC	1	N=No associated symptoms present Y=Associated symptoms are present Blank=Missing	No photophobia, phonophobia, nausea or vomiting noted as AE from 2-48 hours post-dose. (AE domain)

This example illustrates that the source / computational method could be quite lengthy and complicated. For complex derived variables the Source field could provide a link to external documentation that explains the various sources of data and the algorithms involved in creating the variable.

8.6 Revision History

Changes from Analysis Data Model v2.0 to v2.1

Version 2.1 represents the second formal release of the Analysis Data Model. The original version was released as the Analysis Data Model V2.0 in August 2006.

Version 2.1 includes the following changes:

- The removal of the analysis dataset variables and ADSL examples. This information is now located in the ADaM Implementation Guide. Simplified examples of metadata incorporated in the document.
- Corrections made to the introduction to add value-level metadata, remove satellite documents, add an introduction to the ADaM IG and the ADaM basic structure and other minor editorial changes.
- Removed ‘draft’ from the guidance on eCTD.

- Changed all references of SDTM v3.1.1 to 3.x.
- Modified the first key principle of analysis datasets to include a level of traceability, and added a sentence about traceability.
- Added the input source used for ADaM examples is SDTM.
- Added value-level metadata to Section 3.3.
- Removed that if a variable exists in SDTM that can be used for analysis without any change, then this variable should be included in the analysis dataset "as is", with all SDTM attributes retained.
- Removed that SDTM naming fragments should be used where feasible.
- Corrected that analysis datasets will be provided to support the analysis in a report and not just key analyses.
- Corrected and shortened the programming and statistical issues to be considered when creating analysis datasets. Also referred to the ADaM Implementation Guide for examples how to address these issues.
- Added data fields that should be included in analysis dataset and variable metadata.
- Added more details on value-level metadata including attributes.
- Removed appendix 8.2 (Suggested Terminology to be used in "Reason" within Analysis Results Metadata) and included some of the reasons in Section 6.
- Added ADaM Basic Structure and ADaM Implementation Guide to the definitions.
- Replaced Section 8.4 illustration of value-level metadata with illustration of analysis results metadata.
- Modified composite endpoint example (Section 8.5) to contain example of analysis variable metadata and analysis variable value-level metadata.
- Added additional links to Section 8.1 and changed formatting of references and citations of references.
- Modified formatting of document.
- Modified to make ADSL a requirement, even if no other analysis datasets submitted.
- Added requirement that screen failure data, if submitted, be included in ADSLSF and not in ADSL.

8.7 Representations and Warranties; Limitations of Liability, and Disclaimers

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