CDISC & JMP Clinical Workshop
April 2023

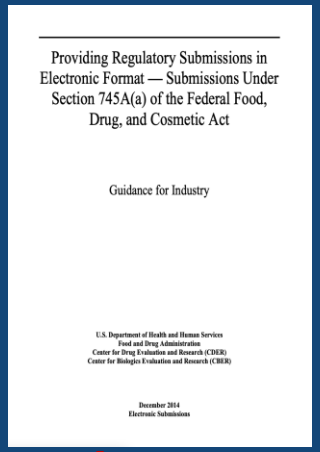
Rhonda Facile
VP, Partnerships and Development

Agenda

- Welcome, CDISC Overview, Regulatory Environment - Rhonda
- CDISC SDTM overview and practical implementation examples - Christine
- Analysis Results Metadata and practical implementation examples - Richard
- JMP Clinical background and usages in regulatory agencies - Wenjun
- Q & A
- Break
- JMP Clinical Demo – Geoffrey
  - Import, functions, reports, templates, AE reporting strategies Q & A
- Adjourn

CDISC Standards and Global Regulation

https://www.fda.gov/media/88120/download



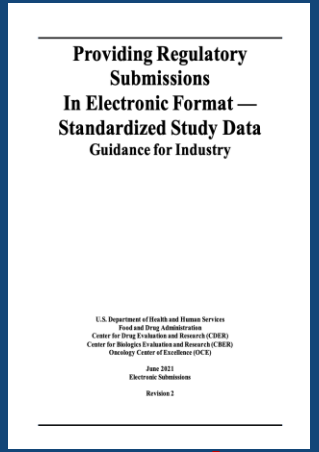
Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2014
Electronic Submissions

https://www.fda.gov/media/82716/download



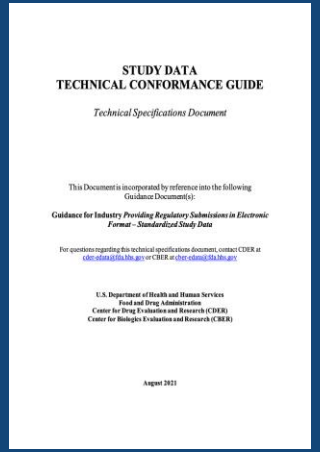
Providing Regulatory Submissions In Electronic Format — Standardized Study Data

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

June 2021
Electronic Submissions
Revision 2

https://www.fda.gov/media/147233/download



STUDY DATA TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov or CBER at cber-edata@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2021

https://www.pmda.go.jp/english/review-services/reviews/0002.html

BINDING DOCUMENTS

- CDISC standards are required for submission to FDA and Japan PMDA
- CDISC standards are the only standards recognized for submissions by China NMPA
- CDISC standards can be used for patient-level data submission to EU EMA

Data Standards Catalogs

CDISC Standards	US FDA	Japan PMDA	China
Controlled Terminology	✓		
SEND	✓		
SDTM	✓	✓	Recommended
ADaM	✓	✓	Recommended
Define-XML	✓	✓	
Analysis Results Metadata (ARM)		✓	

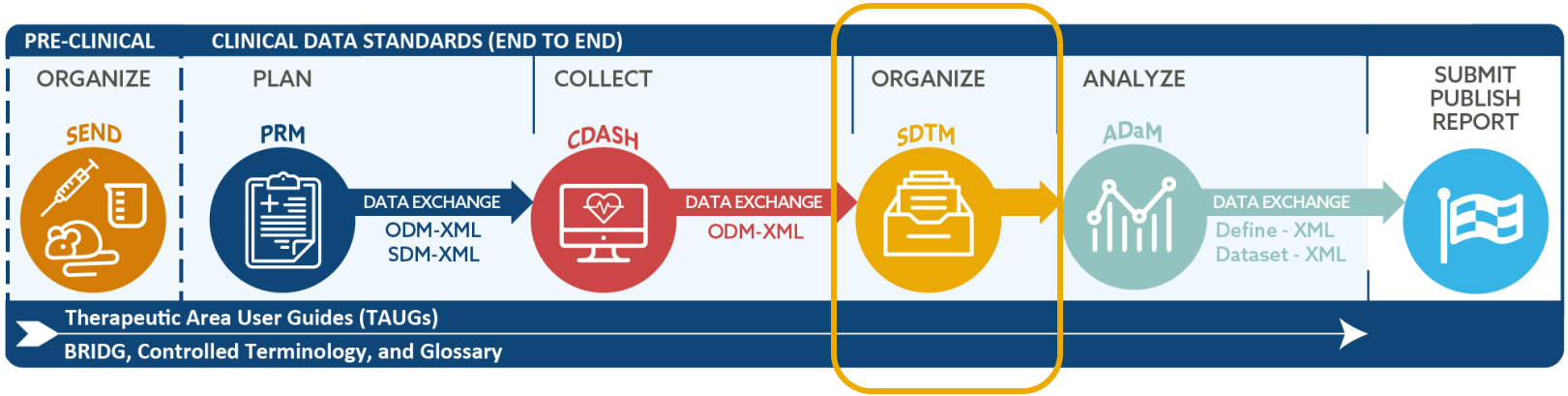
CDISC SDTM and Implementation Examples

Bess LeRoy

Head of Standards Projects

About SDTM

The Study Data Tabulation Model (SDTM) is part of the CDISC suite of standards.



The SDTM supports the research process by providing a standard way to organize and format data that are collected and generated during a study.

About SDTM

The SDTM is:

- A CDISC foundational standard that establishes a standard way to tabulate data across studies.
  - *Tabulation* refers to the organization of data in tables.
- Designed to represent:
  - Collected data regardless of the method of collection
    - e.g., Data collected via Case Report Forms (CRFs), data from vendors
  - Prespecified data such as data defined in a protocol
  - Selected derivations to support data use
    - Such as submission and review

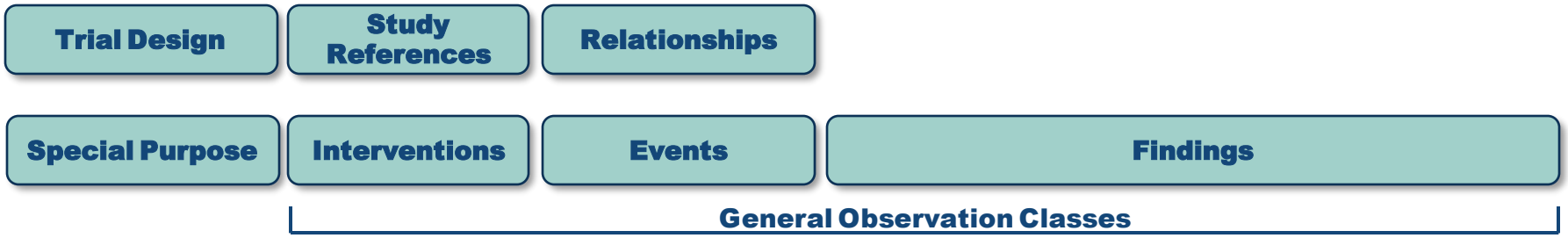
Data represented per the SDTM are “as collected” without imputation rules or other rules that may be needed for analysis applied.

About SDTM

The SDTM defines the building blocks to organize data using standard variables with standard data types and other standard metadata

Most data collected or generated as part of a study will be represented using SDTM General Observation Classes and Special Purpose Domains

Data can also be represented using SDTM Trial Design Model, Study References, and Relationship Datasets



About SDTM

The SDTM defines the building blocks to organize data using standard variables with standard data types and other standard metadata

3.2 Special-purpose Domains

In addition to the 3 general observation classes, a submission will generally include a set of other special-purpose datasets of specific standardized structures to represent additional important information. A Demographics special-purpose domain is included with human and animal studies (see Section 3.2.1, Demographics). Other special-purpose domains may be included.

3.2.1 Demographics

Each study must include 1 standardized set of observations in a specific structure; this is the Demographics domain described here. Demographics is the parent domain for all other observations for subjects and should be identified with the domain code of "DM". The DM domain describes the essential characteristics of the study subjects, and is used by reviewers for selecting subsets of subjects for analysis. The DM domain, as with other datasets, includes identifiers, a topic variable, timing variables, and qualifiers. See the respective implementation guides for further guidance regarding use of additional identifier and timing variables.

Subject Demographics Domain Variables

#	Variable Name	Variable Label	Type	Format	Role	Variable(s) Qualified	Usage Restrictions	Variable C-code	Definition	Notes	Examples
1	STUDYID	Study Identifier	Char		Identifier			C83082	A sequence of characters used by the sponsor to uniquely identify the study.		
2	DOMAIN	Domain Abbreviation	Char		Identifier			C49558	An abbreviation for a collection of observations, with a topic-specific commonality.	2-character abbreviation, which must be "DM".	

Implementing the SDTM

SDTM is a foundational model from which we build different implementations.

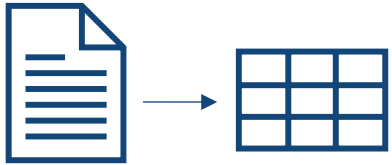
CDISC Implementation Guides provide instructions to implement standard variables with standard data types and other standard metadata in the SDTM.

The SDTM is implemented for drug submissions per the:

Study Data Tabulation Model
Implementation Guide: Human Clinical Trials

Implementing the SDTM

Standard variables with standard data types and other standard metadata in the SDTM are implemented as domains per Implementation Guides



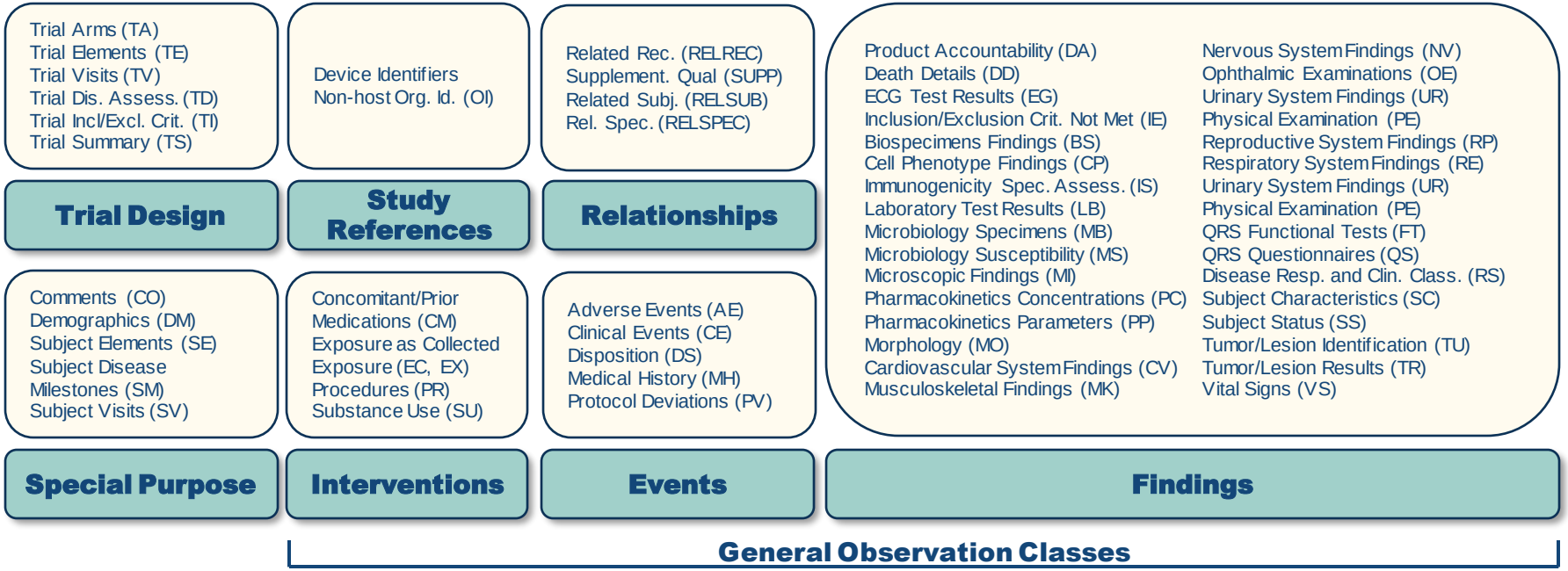
Domains are:

- Logical groupings of related data
- Generally aligned with implementation of a single dataset file to represent data in scope for a domain
  - In some cases, a dataset implemented for a domain may be split into physically separate dataset files to support submission when needed and as allowable by the regulatory authority.

The SDTM and Implementation

The SDTM and SDTMIG Human Clinical Trials

* Not all domains are shown



Implementing the SDTM

All implemented datasets are structured as flat files with:

- Rows representing collected observations
- With data points for observations represented in columns, i.e., variables

DM – Examples

Example 1

dm.xpt

Row	STUDYID	DOMAIN	USUBJID	SUBJID	RFSTDTC	RFENDTC	RFXSTDTC	RFXENDTC	RFICDTC	RFPENDTC	SITEID	INVNAM	BRTHDTC	AGE	AGEU	SEX	RACE	ETHNIC	ARMCD	ARM	ACTARMCD	ACTARM	ARMNRS	ACTARMUD	COUNTRY
1	ABC123	DM	ABC12301001	01001	2006-01-12	2006-03-10	2006-01-12	2006-03-10	2006-01-03	2006-04-01	01	JOHNSON, M	1948-12-13	57	YEARS	M	WHITE	HISPANIC OR LATINO	A	Drug A	A	Drug A			USA
2	ABC123	DM	ABC12301002	01002	2006-01-15	2006-02-28	2006-01-15	2006-02-28	2006-01-04	2006-03-26	01	JOHNSON, M	1955-03-22	50	YEARS	M	WHITE	NOT HISPANIC OR LATINO	P	Placebo	P	Placebo			USA
3	ABC123	DM	ABC12301003	01003	2006-01-16	2006-03-19	2006-01-16	2006-03-19	2006-01-02	2006-03-19	01	JOHNSON, M	1938-01-19	68	YEARS	F	BLACK OR AFRICAN AMERICAN	NOT HISPANIC OR LATINO	P	Placebo	P	Placebo			USA
4	ABC123	DM	ABC12301004	01004					2006-01-07	2006-01-08	01	JOHNSON, M	1941-07-02			M	ASIAN	NOT HISPANIC OR LATINO					SCREEN FAILURE		USA
5	ABC123	DM	ABC12302001	02001	2006-02-02	2006-03-31	2006-02-02	2006-03-31	2006-01-15	2006-04-12	02	GONZALEZ, E	1950-06-23	55	YEARS	F	AMERICAN INDIAN OR ALASKA NATIVE	NOT HISPANIC OR LATINO	P	Placebo	P	Placebo			USA
6	ABC123	DM	ABC12302002	02002	2006-02-03	2006-04-05	2006-02-03	2006-04-05	2006-01-10	2006-04-25	02	GONZALEZ, E	1956-05-05	49	YEARS	F	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDERS	NOT HISPANIC OR LATINO	A	Drug A	A	Drug A			USA

The Goal

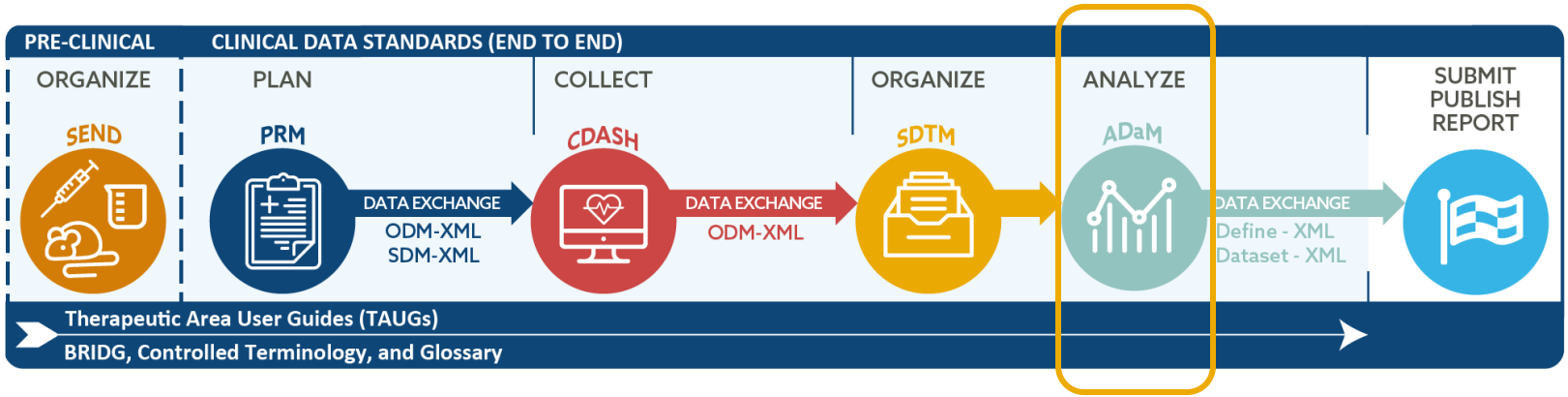
When the SDTM is implemented, data collected and generated for the same topic look the same from study to study, and from sponsor to sponsor.

This standardization enables:

- Familiarization with standard datasets such that implementers and reviewers can find the data they need
- Data storage/warehousing
- Analysis and reporting activities, including:
  - Further standardization downstream to support analysis and reporting
  - Use of automated tools, such as JMP, to support analysis and reporting

A bit about ADaM

The Analysis Data Model (ADaM) is also part of the CDISC suite of standards.



The ADaM supports the research process by defining standards for the creation and submission of analysis datasets and results, such datasets:

- Are generally based on SDTM datasets
- Support use of automated tools, such as JMP, to support analysis and reporting

Implementation Examples

There are many SDTM practical implementation examples to review.

For this workshop, we will focus on implementation of domains generally used to evaluate safety.

- Demographics (DM)
- Exposure (EX)
- Adverse Events (AE)
- Laboratory Test Results (LB)
- Disposition (DS)

Demographics (DM)

5.2 Demographics (DM)

DM – Description/Overview

A special-purpose domain that includes a set of essential standard variables that describe each subject in a clinical study. It is the parent domain for all other observations for human clinical subjects.

DM – Specification

dm.xpt, Demographics — Special Purpose. One record per subject, Tabulation.

DM – Examples

Example 1

dm.xpt

Row	STUDYID	DOMAIN	USUBJID	SUBJID	RFSTDTC	RFENDTC	RFXSTDTC	RFXENDTC	RFICDTC	RFPENDTC	SITEID	INVNAM	BRTHDTC	AGE	AGEU	SEX	RACE	ETHNIC	ARMCD	ARM	ACTARMCD	ACTARM	ARMNRS	ACTARMUD	COUNTRY
1	ABC123	DM	ABC12301001	01001	2006-01-12	2006-03-10	2006-01-12	2006-03-10	2006-01-03	2006-04-01	01	JOHNSON, M	1948-12-13	57	YEARS	M	WHITE	HISPANIC OR LATINO	A	Drug A	A	Drug A			USA
2	ABC123	DM	ABC12301002	01002	2006-01-15	2006-02-28	2006-01-15	2006-02-28	2006-01-04	2006-03-26	01	JOHNSON, M	1955-03-22	50	YEARS	M	WHITE	NOT HISPANIC OR LATINO	P	Placebo	P	Placebo			USA
3	ABC123	DM	ABC12301003	01003	2006-01-16	2006-03-19	2006-01-16	2006-03-19	2006-01-02	2006-03-19	01	JOHNSON, M	1938-01-19	68	YEARS	F	BLACK OR AFRICAN AMERICAN	NOT HISPANIC OR LATINO	P	Placebo	P	Placebo			USA
4	ABC123	DM	ABC12301004	01004					2006-01-07	2006-01-08	01	JOHNSON, M	1941-07-02			M	ASIAN	NOT HISPANIC OR LATINO					SCREEN FAILURE		USA
5	ABC123	DM	ABC12302001	02001	2006-02-02	2006-03-31	2006-02-02	2006-03-31	2006-01-15	2006-04-12	02	GONZALEZ, E	1950-06-23	55	YEARS	F	AMERICAN INDIAN OR ALASKA NATIVE	NOT HISPANIC OR LATINO	P	Placebo	P	Placebo			USA
6	ABC123	DM	ABC12302002	02002	2006-02-03	2006-04-05	2006-02-03	2006-04-05	2006-01-10	2006-04-25	02	GONZALEZ, E	1956-05-05	49	YEARS	F	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDERS	NOT HISPANIC OR LATINO	A	Drug A	A	Drug A			USA

Exposure (EX)

6.1.3.1 Exposure (EX)

EX – Description/Overview

An interventions domain that contains the details of a subject's exposure to protocol-specified study treatment. Study treatment may be any intervention that is prospectively defined as a test material within a study, and is typically but not always supplied to the subject.

EX – Specification

ex.xpt, Exposure — Interventions. One record per protocol-specified study treatment, constant-dosing interval, per subject, Tabulation.

The EX dataset shows the unmasked administrations. Two tablets from bottle A became 1000 mg of drug X extended release for subject ABC1001, but 500 mg of drug Z for subject ABC2001. Note that there is no record in the EX dataset for non-occurrence of study treatment. The non-occurrence of study drug for subject ABC2001 is reflected in the gap in time between the 2 EX records.

ex.xpt

Row	STUDYID	DOMAIN	USUBJID	EXSEQ	EXLNKID	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXDOSFRQ	EXROUTE	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
1	ABC	EX	ABC1001	1	A2-20110114	DRUG X	1000	mg	TABLET, EXTENDED RELEASE	QD	ORAL	TREATMENT	2011-01-14	2011-01-28	1	15
2	ABC	EX	ABC2001	1	A2-20110114	DRUG Z	500	mg	TABLET	QD	ORAL	TREATMENT	2011-01-14	2011-01-23	1	10
3	ABC	EX	ABC2001	2	A2-20110125	DRUG Z	500	mg	TABLET	QD	ORAL	TREATMENT	2011-01-25	2011-01-28	12	15

Adverse Events (AE)

6.2.1 Adverse Events (AE)

AE – Description/Overview

An events domain that contains data describing untoward medical occurrences in a patient or subjects that are administered a pharmaceutical product and which may not necessarily have a causal relationship with the treatment.

AE – Specification

ae.xpt, Adverse Events — Events. One record per adverse event per subject, Tabulation.

In this example, a CRF module included at several visits asked whether nausea, vomiting, or diarrhea occurred. The responses to the probing questions "Yes", "No", or "Not Done" were represented in the Findings About (FA) domain (see Section 6.4, Findings About Events or Interventions). If "Yes", the investigator was instructed to complete the AE CRF. In the AE dataset, data on AEs solicited via prespecification on the CRF have an AEPRESP value of "Y". For AEs solicited by a general question, AEPRESP is null. RELREC may be used to relate AE records and FA records.

Rows 1-2: Show that nausea and vomiting were prespecified on a CRF, as indicated by AEPRESP = "Y". The subject did not experience diarrhea, so no record for that term exists in the AE dataset.

Row 3: Shows an example of an AE (headache) that was not prespecified on a CRF, as indicated by a null value for AEPRESP.

ae.xpt

Row	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AEDECOD	AEPRESP	AEBODSYS	AESEV	AESER	AEACN	AEREL	AEOUT	EPOCH	AESTDTC	AEENDTC	AESTDY	AEENDY
1	ABC123	AE	123101	1	NAUSEA	Nausea	Y	Gastrointestinal disorders	SEVERE	N	DOSE REDUCED	RELATED	RECOVERED/RESOLVED	TREATMENT	2005-10-12	2005-10-13	2	3
2	ABC123	AE	123101	2	VOMITING	Vomiting	Y	Gastrointestinal disorders	MODERATE	N	DOSE REDUCED	RELATED	RECOVERED/RESOLVED	TREATMENT	2005-10-13T13:00	2005-10-13T19:00	3	3
3	ABC123	AE	123101	3	HEADACHE	Headache		Nervous system disorders	MILD	N	DOSE NOT CHANGED	POSSIBLY RELATED	RECOVERED/RESOLVED	TREATMENT	2005-10-21	2005-10-21	11	11

Laboratory Test Results (LB)

6.3.5.6 Laboratory Test Results (LB)

LB – Description/Overview

A findings domain that contains laboratory test data such as hematology, clinical chemistry and urinalysis.

LB – Specification

lb.xpt, Laboratory Test Results — Findings. One record per lab test per time point per visit per subject, Tabulation.

Row	STUDYID	DOMAIN	USUBJID	LBSEQ	LBGRPID	LBTESTCD	LBTEST	LBTSTCND	LBCAT	LBSCAT	LBORRES	LBORRESU
1	ABC	LB	ABC-001-001	1		ALB	Albumin		CHEMISTRY		30	g/L
2	ABC	LB	ABC-001-001	2	A	ALP	Alkaline Phosphatase		CHEMISTRY		398	IU/L
3	ABC	LB	ABC-001-001	3	A	ALP	Alkaline Phosphatase		CHEMISTRY		350	IU/L
4	ABC	LB	ABC-001-001	4	A	ALP	Alkaline Phosphatase		CHEMISTRY			
5	ABC	LB	ABC-001-001	5	A	ALP	Alkaline Phosphatase		CHEMISTRY			
6	ABC	LB	ABC-001-001	6		CRP	C Reactive Protein		CHEMISTRY		2.5	mg/L
7	ABC	LB	ABC-001-001	7		CRYOGLBN	Cryoglobulin	1D COLD INCUBATION	CHEMISTRY		ABSENT	
8	ABC	LB	ABC-001-001	8		PSA	Prostate Specific Antigen		CHEMISTRY		3.3	ug/L
9	ABC	LB	ABC-001-001	9		PROT	Protein		CHEMISTRY		200	g/L

Disposition

6.2.4 Disposition (DS)

DS – Description/Overview

An events domain that contains information encompassing and representing data related to subject disposition.

DS – Specification

ds.xpt, Disposition — Events. One record per disposition status or protocol milestone per subject, Tabulation.

ds.xpt

Row	STUDYID	DOMAIN	USUBJID	DSSEQ	DSTERM	DSDECOD	DSCAT	DSSCAT	EPOCH	DSDTC	DSSTDTC
1	ABC123	DS	123101	1	INFORMED CONSENT OBTAINED	INFORMED CONSENT OBTAINED	PROTOCOL MILESTONE		SCREENING	2003-09-21	2003-09-21
2	ABC123	DS	123101	2	RANDOMIZED	RANDOMIZED	PROTOCOL MILESTONE		SCREENING	2003-09-30	2003-09-30
3	ABC123	DS	123101	3	COMPLETED	COMPLETED	DISPOSITION EVENT	STUDY PARTICIPATION	SCREENING	2003-09-30	2003-09-29
4	ABC123	DS	123101	4	COMPLETED	COMPLETED	DISPOSITION EVENT	STUDY PARTICIPATION	TREATMENT	2003-10-31	2003-10-31
5	ABC123	DS	123101	5	COMPLETED	COMPLETED	DISPOSITION EVENT	STUDY PARTICIPATION	FOLLOW-UP	2003-11-15	2003-11-15
6	ABC123	DS	123102	1	INFORMED CONSENT OBTAINED	INFORMED CONSENT OBTAINED	PROTOCOL MILESTONE		SCREENING	2003-11-21	2003-11-21
7	ABC123	DS	123102	2	SUBJECT DENIED MRI PROCEDURE	PROTOCOL VIOLATION	DISPOSITION EVENT	STUDY PARTICIPATION	SCREENING	2003-11-22	2003-11-20

JMP Clinical Background and Usage at Regulatory Agencies

Dr. Wenjun Bao

Thank You!