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CDISC Transport Standards - A Glance

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ABSTRACT

CDISC has published various standards over a period of years as part of transport standards to enable exchange of data conformant with CDISC foundation standards and their therapeutic area extensions. Such transport standards have gained immense usage across clinical trial life cycle, enabling regulatory to review them quickly and facilitate exchange of information across. This presentation would touch upon such standards such as,

- Clinical Trial Registry XML (CTR-XML)
- ODM-XML
- SDM-XML
- Define-XML
- Dataset-XML
- RDF
- LAB

giving details pertaining to the content it carries, structure, value it serves as a transport standard, regulatory implications, and roadmap of using such transport standards in clinical trial life cycle.

INTRODUCTION

Clinical research is essential for advancing medicine and improving patient quality of life. The expansive scope of clinical research combined with the pervasiveness of technology has given rise to increasing volumes of data, and strategies are needed to process and exchange it effectively. As clinical trials continue to grow in complexity, systematic mechanisms to collect, process, analyze, and integrate data across systems and organizational boundaries have become increasingly important. Clinical research can no longer be considered an isolated venture and is increasingly conducted in network structures where seamless data exchange is critical to operational efficiency and effectiveness. Clinical data standards improve the efficiency and quality of clinical research and more broadly of healthcare delivery in general.

Within the realm of healthcare informatics there exists a broad array of data standards that meet a variety of needs. The Clinical Data Interchange Standards Consortium (CDISC) creates data standards for clinical research that complement, and in a growing number of cases, interact with a variety of healthcare standards.

The FDA has stated that, “improving the efficiency and effectiveness of medical product development is a national priority”. Regulatory electronic submissions have grown more complex with the average submission now a staggering 3.4 million pages, an increase of 1,423% since 2005. With this scale, inefficiencies in the clinical research data lifecycle add considerable time and expense to new medical product development. Increasing efficiency requires that the networked organizations participating in clinical development exchange data seamlessly. The 2014 CDISC business case claims that using CDISC standards from the beginning of the process can save approximately $180 million per submission.

The very question of improving efficiency & effectiveness led to development and adoption of transport standards widely by Pharmaceutical companies and Software Vendors. Highlights of why new set of transport standards were discussed early on in November 2012 is listed below:

- The SAS XPORT transport format should be replaced by a more modern data exchange standard for electronic regulatory submissions to FDA based on current prevailing XML technology.
- The choice of transport standards for study data should capitalize on existing knowledge and investment within the global bio-pharmaceutical industry.
- The choice of transport standards should ensure that commonly used data structures, specifically domain datasets and analysis files and their associated metadata, can be accurately exchanged, utilized and reproduced.

CDISC has two basic type of standards, one that holds the content, data, metadata and terminology and the other which is called transport standard to move the data using XML technology. ODM XML is one of the key Transport

Standards in moving data within clinical data capture process which comprises of Protocol Representation, Trial Design and CRF design. Then, evolution of transport standards has been defined for trial registry update namely CTR-XML which are required as per regulatory requirements and later came the submission of information using DEFINE XML again to regulatory.

CLINICAL TRIAL REGISTRY XML (CTR-XML)

CTR-XML lets technology vendors implement tools that support a "write once, use many times" solution based on a single XML file that holds the information needed to generate submissions for multiple clinical trials for clinical trial registry submissions primarily to the World Health Organization (WHO), European Medicines Agency (EMA) EudraCT Registry and United States ClinicalTrials.gov.

A clinical trials registry is an official platform and catalog for registering a clinical trial. Clinical trials are conducted to allow safety and efficacy data to be collected for health interventions (e.g., drugs, diagnostics, devices, therapy protocols).

A clinical trials register is the formal record of an internationally agreed minimum amount of information about a clinical trial. This record is usually stored in and managed using a database. A clinical trials registry is the entity that houses the register, and is responsible for ensuring the completeness and accuracy of the information it contains, and that the registered information is used to inform health care decision making. A clinical trials registry is more than its database.

At its core, the CTR standard is inspired by the International Committee of Medical Journal Editors (ICMJE), and is based upon the 20-item WHO Trial Registration Data Set as well as EudraCT specific extensions. The CTR standard maximizes the re-use of existing CDISC transport standards by extending the Operational Data Model (ODM-XML) and including Study/Trial Design Model (SDM-XML) content. This makes the standard a more general solution that any trial registry could potentially use as the means to populate their registry with structured content from a clinical trial sponsor's system.

The standard, known as the Clinical Trial Registry (CTR) XML, is inspired by the International Committee of Medical Journal Editors (ICMJE), and is based upon the 20-item WHO Trial Registration Data Set as well as EudraCT specific extensions. CTR-XML will help companies harmonize messages to international registries, and technology vendors will be able to support a "write once, use many times" tool based on a single XML file, CDISC said. The standard is based upon the common elements mapped between the registries, which are based upon the 20-item WHO Trial Registration Data Set.

STRUCTURE OF THE CTR-XML

CTR-XML uses elements and attributes from four namespaces. The following principles were applied in deciding which namespaces to use for each piece of information to be submitted:

- CTR information elements that are part of the ODM are used as is.
- CTR information elements that are part of SDM-XML are used as is. In a few cases where a SDM-XML element is conceptually the same as a CTR element but is missing a sub-component, the SDM-XML element has been extended.
- CTR information elements that are not part of the ODM or SDM-XML, but are defined in the EudraCT XML schemas, are used without extensions.
- CTR information elements that are not part of the ODM, SDM-XML or the EudraCT XML schemas are defined as part of the CTR-XML extension.

VALIDATION OF A CTR-XML DOCUMENT

A valid CTR-XML document must:

- Properly reference versions of the CDISC standards.
- Be well formed and conform to the CTR-XML schemas.
- Meet all the requirements documented in the specification document of CTR-XML.

The ctr1-0-0.xsd XML schema should be used to validate CTR-XML documents.

OPERATIONAL DATA MODEL (ODM)-XML

ODM-XML is a vendor-neutral, platform-independent format for exchanging and archiving clinical and translational research data, along with their associated metadata, administrative data, reference data, and audit information. ODM-XML facilitates the regulatory-compliant acquisition, archival and exchange of metadata and data. It has become the language of choice for representing case report form content in many electronic data capture (EDC) tools.

Efficient communication of a clinical study protocol and case report forms during all stages of a human clinical study is important for many stakeholders. An electronic and structured study representation format that can be used

throughout the whole study life-span can improve such communication and potentially lower total study costs. The most relevant standard for representing clinical study data, applicable to unregulated as well as regulated studies, is the Operational Data Model (ODM) in development since 1999 by the Clinical Data Interchange Standards Consortium (CDISC). ODM's initial objective was exchange of case report forms data but it is increasingly utilized in other contexts.

ODM was not originally developed based on an existing clinical research or healthcare data model, but instead was designed using a bottom-up approach to meet the established data interchange, archival, and audit trail requirements. The initial focus was on a general, vendor neutral structure and syntax; industry level data models and semantics were given little consideration.

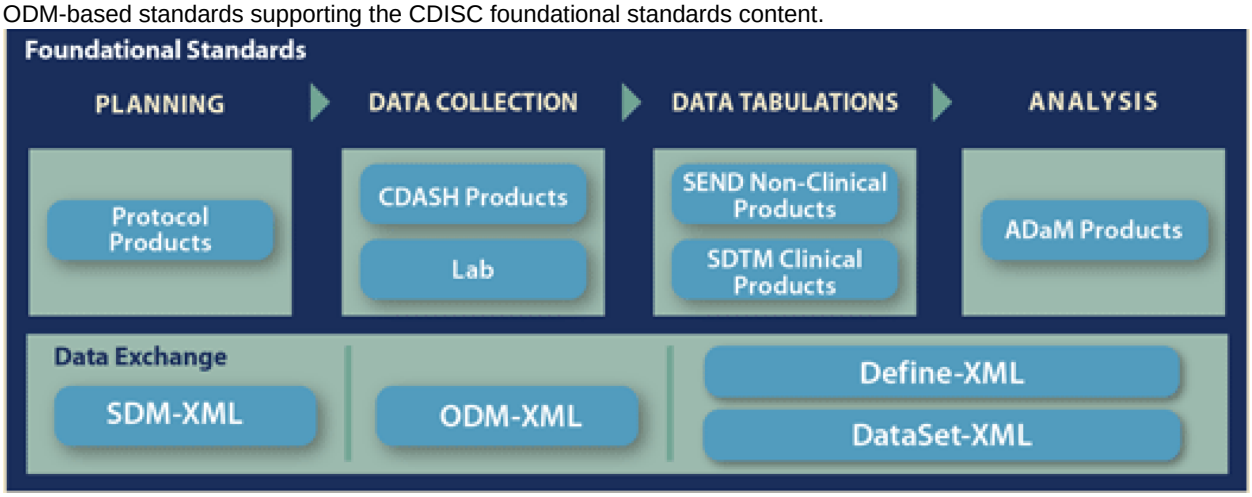
The ODM standard plays a key role in clinical research informatics, including areas such as data exchange, archival, U.S. Food and Drug Administration (FDA) submission, and interoperability with healthcare data. Within the highly data-centric domain of clinical research, the XML-based ODM is the standard exchange format for case report form (CRF) data and metadata.

The first production version of ODM was published in October 2000 and was demonstrated in two connections on events in 2001.The current ODM version, v1.3.2, was published in December of 2013. ODM, now based on XML schema, remains under active development by the CDISC XML Technologies Team, and while the original ODM requirements remain highly relevant, use of the standard has extended well beyond the original design.

ODM-XML v1.3.2 is the most current version of the standard. Many CDISC standards have been developed by extending ODM-XML including: Define-XML, SDM-XML, Dataset-XML, CTR-XML and CT-XML. ODM-XML provides a common base structure for these standard extensions easing the learning curve and implementation complexity.

Figure below highlights the CDISC foundational standards covered by ODM, and standardized extensions such as Clinical Data Acquisition Standards Harmonization (CDASH) that describes the basic data collection fields for domains, the Study Data Tabulation Model (SDTM) that describes a standard structure for study data tabulations, and the Analysis Data Model (ADaM) that describes metadata models and examples for analysis datasets.

ODM-based standards supporting the CDISC foundational standards content.



The EDC and EHR Infrastructure phase of the lifecycle focuses on setting up the EDC data collection system and the EHR integration infrastructure to support future clinical research studies. This phase occurs once, and the infrastructure may be reused across multiple studies. After the EDC and EHR integration infrastructure has been setup, each of the remaining phases is executed for each clinical research study executed. The planning phase covers creating a study protocol and representing it in a machine-readable format, formulating a study design, submitting a study to clinical trial registries (such as ClinicalTrials.gov), setting up a study within an EDC or other clinical data management system (CDMS), creating CRFs, defining a study schedule of events, and importing CRFs from form libraries. The Data Collection phase of the lifecycle focuses on the data collection and interchange that occurs during study execution and represents an original ODM use case. The Data Tabulations and Analysis phase in

the lifecycle combines the third and fourth phases shown in above Figure and focuses on the generation of datasets in support of standardized tabulations, analysis datasets, reporting and regulatory submissions. Study Archival is the final phase of the data lifecycle and focuses on archiving the study data and metadata such that it complies with the federal regulations. It represents another original ODM use case.

CDISC's Operational Data Model (ODM) is the most versatile standard of CDISC's suite. It is primarily an XML-based transport format defined via an XML Schema. Additionally, ODM has a powerful underlying data model that represents,

- all metadata for specifying a clinical study including events, forms and item definitions,
- all clinical facts about subjects that were acquired during the study plus audit log entries,
- administrative information like user accounts and electronic signatures,
- reference data that help to interpret the clinical data,
- support for versioning, and
- is extensible by custom vendor extensions.

The CDISC Operational Data Model (ODM), which has been in production use for more than ten years, is an ideal choice as a new study data exchange standard for the following reasons:

- ODM can streamline the clinical development process by supporting metadata-driven data transport end-to-end across the entire clinical research lifecycle, with traceability from protocol through analysis.
- ODM is fully compliant with regulatory guidance and 21 CFR Part 11, including audit trail and electronic signatures.
- ODM is already widely understood and used extensively for global clinical research, and can be deployed for submissions without significant added financial burden on industry.
- ODM is fully compatible with current metadata submission standards, and is the basis for the CDISC define.xml standard already accepted by FDA.
- ODM accurately represents and easily reproduces tabular dataset structures, including those structured according to the CDISC Study Design Model, CDASH, SDTM, SEND and ADaM standards that are already widely used in industry and at the FDA.
- ODM is supported by NCI EVS as an exchange format for CDISC controlled terminology.
- ODM is already supported by major technology providers of clinical data information systems used for regulated clinical research.
- ODM has been successfully used in conjunction with HL7 CDA formatted data from Electronic Healthcare Record systems to support research under an HHS sponsored interoperability specification.
- ODM can represent more complex relationships between data events recorded per the research protocol.
- ODM can be easily and rapidly extended through the CDISC standards development process to address emerging new requirements as they arise.

FILE CONFORMITY

An XML file conforms to the ODM 1.3.2 standard only if it satisfies all the criteria detailed in this standard. These criteria include both syntactic constraints and semantic ones. The syntactic constraints are,

- The ODM file must be a well-formed XML file
- The ODM file must conform to the XML Namespace standard
- The ODM file must contain only elements and attributes defined in the ODM standard schema or in a valid vendor extension schema, and must satisfy the rules about element nesting and the formats of attribute values and element bodies.
- The ODM file must contain a prolog and a single (top-level) ODM element.
- The ODM file must use the ODM 1.3 namespace, which is http://www.cdisc.org/ns/odm/v1.3
- The ODMVersion attribute on the top level ODM element must be set to "1.3.2"

Example of prolog and top level ODM element:

```
<?xml version="1.0" encoding="UTF-8"?>
<ODM xmlns="http://www.cdisc.org/ns/odm/v1.3"
    xmlns:ds="http://www.w3.org/2000/09/xmldsig#"
    xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"

    xsi:schemaLocation="http://www.cdisc.org/ns/odm/v1.3 ODM1-3-2.xsd"

    ODMVersion="1.3.2"
    FileOID="000-00-0000"
    FileType="Transactional"
    Description="Sample ItemData Extension"

    AsOfDateTime="2013-02-04T07:57:00"
    CreationDateTime="2013-02-06T10:30:00">
```

SYSTEM CONFORMITY

The value of the ODM standard, like any information standard, is enhanced when systems can be developed with the assumption that ODM files have a high level of conformity. However, the ODM also provides value in that it provides both a standard and a technology for the interchange of clinical data where none has existed in the past. The conformity statements below represent an attempt at balancing the need for quality control with respect to the standard with the need for flexibility when encouraging adoption and innovation:

A computing system that processes information in ODM format can claim conformance to this standard only if it obeys the following rules.

- Generated ODM files must satisfy all the correctness rules in this standard, both syntactic and semantic.
- A receiving system must be able to read any ODM file that satisfies all the correctness rules in this standard, both syntactic and semantic.
- ODM files must validate against the ODM schema for the ODM version indicated in the ODM root element.
- Information included in generated ODM files must be accurate according to the rules of this standard as defined in this specification.
- A receiving system must interpret information read from an ODM file accurately according to the rules of this standard as defined in this specification.
- Generated ODM files need not include information that is not normally handled or stored by the generating system.
- A receiving system may selectively ignore information read from an ODM file if that information is not normally handled or stored by the receiving system.
- A receiving system may constrain the range of data values, keys, names, and so on, that it is capable of handling or storing.
- Systems that receive ODM clinical data files but do not normally support one or more of the datatypes specified in section 2.14, should accept clinical data of the unsupported types as text.
- All system limitations (rules 6 through 9) must be documented.
- If conformity is dependent on certain modes or settings, this must also be documented.

ENTITIES AND ELEMENTS

The ODM model assumes that a study's clinical data will consist of several kinds of entities. These include subjects, study events, forms, item groups, items, and annotations.

Entities and Elements	Description
item	An item is an individual clinical data item, such as a single systolic blood pressure reading. Items are collected together into item groups
item group	An item group is a closely related set of items that are generally analyzed together. (Item groups are sometimes referred to as "records" and are associated with "panels" or "tables".) Item groups are aggregated into forms.

Entities and Elements	Description
form	A form is analogous to a page in a paper CRF book or electronic CRF screen. A form generally collects a set of logically and temporally related information. A series of forms is collected as part of a study event.
study event	A study event is a reusable package of forms usually corresponding to a study data-collection event.
subject	A subject is a patient participating in the study.
annotation	An annotation is a comment applied to a subject, study event, form, item group, or item. Annotations can also be applied to pairs of entities.
StudyEventDef	A StudyEventDef describes a particular type of study event (mostly by listing the types of forms it can contain).
FormDef	A FormDef describes a particular type of form.
ItemGroupDef	An ItemGroupDef describes a particular type of item group.
ItemDef	An ItemDef describes a particular type of item.

The clinical data of a study will typically have many actual study events corresponding to each StudyEventDef, many actual forms corresponding to each FormDef, and so on.

An ODM file (like any XML file) consists of a tree of elements. The clinical data elements in an ODM file represent either the state of a clinical entity or a change to the state of that entity. These elements include the SubjectData, StudyEventData, FormData, ItemGroupData, ItemData, and Annotation elements.

Each such element contains key attributes that identify the data entity that it provides information for. Frequently, many data elements will correspond to a single data entity. This can occur when a series of updates are being applied to a single entity, or when an audit trail is being represented.

Similarly, there are XML elements corresponding to metadata entities.

STUDY/TRIAL DESIGN MODEL-XML

Study/Trial Design Model in XML (SDM-XML) is an extension of ODM-XML and allows organizations to provide rigorous, machine-readable, interchangeable descriptions of the designs of their clinical studies, including treatment plans, eligibility and times and events. SDM-XML defines three key sub-modules – Structure, Workflow, and Timing – permitting various levels of detail in any representation of a clinical study's design.

The clinical research study protocol is the plan that describes the study's objectives, methodology, statistical considerations, and the organization of the study. This plan includes the design of the study, which includes the arm descriptions, the schedule of activities, the eligibility criteria and summary information. Several CDISC standards represent aspects of the study design, but do not specify the study design completely. For instance, the Operational Data Model (ODM) represents the metadata for the data collected in the study, but does not describe the planned timing of the study events. The Study Data Tabulation Model (SDTM) includes trial design datasets, but only pertains to the visits, which are only part of the activity schedule.

As for the Protocol Representation Model (PRM), it is a conceptual model that includes the study design, but has no specification details. The CDISC Study Design Model (SDM) has been developed to specify the study design. It extends the core ODM and consists of the following sub-components that model the design of the study, not its execution. The SDM is modelled in XML.

- Structure: epochs, arms, cells, segments, activities
- Workflow: decision points, branches
- Timing: when activities should happen

STRUCTURAL ELEMENTS

Structural elements are comprised of the "building blocks" of a study design: objects such as Epochs, Cells, Arms and Segments, as well as Activities. These are the objects that can act as nodes in a study design workflow, or as objects between which timing constraints may be applied.

Example:

Structure Overview

	Screening epoch	Treatment epoch	Follow-up epoch
Placebo arm	Screening Cell	Treatment Cell (Blinded)	Follow-up Cell (Blinded)
Low dose arm			
High dose arm			

Epochs

Name	Description	Entry Criteria	Exit Criteria
Screening epoch	Screening Epoch		
Treatment epoch	Treatment Epoch	• Entry criterion for treatment epoch *(Entry condition for treatment epoch)* • The inclusion/exclusion criteria for the study are applied here.	• Exit criterion for treatment epoch *(Exit condition for treatment epoch)*
Follow-up epoch	Follow-up Epoch		

Arms

Name	Description
Placebo arm	Placebo arm: a placebo is being administered
Low dose arm	Low-dose arm: 50 cm2 TTS Formulation E, 54 mg xanomeline
High dose arm	High-dose arm: 75 cm2 TTS Formulation E, 81 mg xanomeline

Cells

Name	Description	Blinded/Unblinded	Epoch	Arm(s)	Segment(s)	Entry Criteria	Exit Criteria
Screening Cell		Unblinded	Screening epoch	• Placebo arm • Low dose arm • High dose arm	• Screening segment		
Treatment Cell		Blinded	Treatment epoch	• Placebo arm • Low dose arm • High dose arm	• Treatment segment		
Follow-up Cell		Blinded	Follow-up epoch	• Placebo arm • Low dose arm • High dose arm	• Follow-up segment		

WORKFLOW

Study workflows are defined using a set of constructs that make it possible for a study designer to specify possible study participant paths through a study.

Workflow is specified in a section of XML distinct from that of the structural elements. However, workflow objects commonly reference objects defined in the Structure section of the document. This separation of concerns allows the potential for different workflow representations to be applied to the same set of structural elements.

Example:

Workflow Transitions

Name	Description	Source Activity	Target Activity	Condition	Transition Name	Transition Description	Timing Constraint
Trial start transition		trial start activity	informed consent activity	Default	(default) transition to informed consent		
Transition from informed consent activity		informed consent activity	patient number assignment activity	Informed Consent condition	conditional transition from informed consent to patient number assigned		• Transition timing constraint 1 name
			trial finish activity	Default	default transition from informed consent to study finish		
transition to activity taking demographics, education and habits		patient number assignment activity	Demographics, Education and Habits data collection activity	Default	default transition to transition to activity taking demographics, education and habits		
Transition to mini-mental state test activity		Demographics, Education and Habits data collection activity	Mini-mental state activity	Default	Default transition to mini-mental state test activity		
transition to Hachinski test		Mini-mental state activity	Hachinski test Activity	Condition that subject has MMSE score of 10 to 23	conditional transition to Hachinski test		
			trial finish activity	Default	Transition to Trial Finish as MMS leads to exclusion		
Transition between Hachinski test and Medical History		Hachinski test Activity	medical history activity	Condition Hachinski Ischemic Scale score of <= 4	Conditional Transition between Hachinski test and Medical History		
			trial finish activity	Default	Defaut transition to Trial Finish due to Hachinski score exclusion		
Transitions from Medical History Activity		medical history activity	vital signs activity	Default	Transition to Vital Signs Activity		
Trial finish due to high fever		assess high fever activity	trial finish activity	Default	Trial finish due to high fever		• at high fever, go to trial finish within 1 day

Triggers

Name	Description	Structural Element	Structural Element Type	Target Activity	Condition	Transition Name	Transition Description	Timing Constraint
Fever trigger		Treatment epoch	Epoch	assess high fever activity	Condition that subject has high fever (>38.5C / 101.3F)	conditional transition when subject has high fever		
				assess fever activity	Default	default transition from when subject has fever		• Transition timing constraint 2
Headache trigger		Treatment epoch	Epoch	Assess headache	Default	Default transition upon headache		

TIMING

Timing constraints, like structural definitions and workflow definitions, are declared in their own sub-section of an SDM-XML document, within an element named Timing. Timing constraints may apply either to activities or to workflow transitions. Note, however, that this relationship is one-way – elements declared in the structural or workflow areas of the document never reference timing elements.

Example:

Workflow Transition Timing Constraints

Name	Description	Transition	Type	Target	Granularity	PreWindow	PostWindow	Base Subsequent Schedule On
Transition timing constraint 1 name	english description	conditional transition from informed consent to patient number assigned	StartToStart	PT24H				Planned
Transition timing constraint 2	Upon fever, react within one hour	default transition from when subject has fever	FinishToStart	PT1H				Planned
at high fever, go to trial finish within 1 day		Trial finish due to high fever	StartToStart	P1D				Planned

Absolute Timing Constraints

Name	Description	Target	Granularity	PreWindow	PostWindow
Absolute timing constraint on informed consent activity		2009-09-20T11:07:23-05:00			

Relative Timing Constraints

Name	Description	Predecessor Activity	Successor Activity	Type	Target	Granularity	PreWindow	PostWindow	Base Subsequent Schedule On
relative timing constraint between activity informed consent and activity patient number assignment		informed consent activity	patient number assignment activity	FinishToStart	P7D				Planned
Timing constraint between ambulatory ECG placement and removal	All patients will undergo a 24-hour Ambulatory ECG at Visit 2 (prior to the initiation of study medication). Although every effort will be made to obtain the entire 24-hour ambulatory ECG recording, this may not always be feasible because of patient behavior or technical difficulties. The minimal recording period for an ambulatory ECG to be considered interpretable will be 8 hours, of which at least 3 hours must be sleep.	ambulatory ECG placement activity	ambulatory ECG removal activity	StartToStart	PT24H		PT16H		Planned
Timing constraint for treatment visit 1 (visit 4)	For the first 8 weeks of treatment, patients will be assessed at clinic visits every 2 weeks.	patient randomization activity	Start of treatment visit 1 (visit 4)	StartToStart	P14D				Planned

DEFINE-XML

Define-XML transmits metadata that describes any tabular dataset structure. When used with the CDISC content standards, it provides the metadata for human and animal model datasets using the SDTM and/or SEND standards and analysis datasets using ADaM. Define-XML is required by the United States Food and Drug Administration (FDA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for every study in each electronic submission to inform the regulators which datasets, variables, controlled terms, and other specified metadata were used.

FDA CDER and CBER have indicated support for v1.0 and v2.0 of Define-XML in the FDA Data Standards Catalog. The FDA has also announced the end of support for Define-XML v1.0 for studies that start 12 months after March 15, 2017.

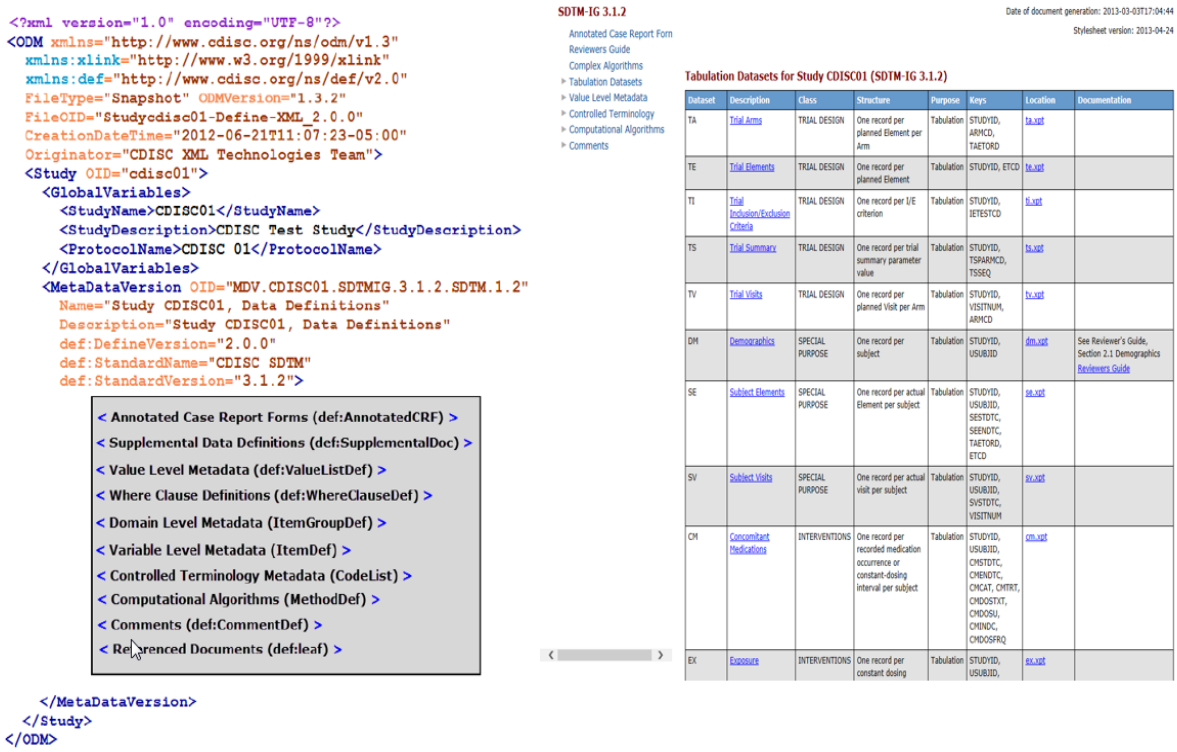
Define-XML v2.0 represents a significant update to Define-XML v1.0 in response to implementation experience with v1.0, the evolution of the SDTM, SEND and ADaM standards and best practices by SDTM and ADaM metadata experts. Key enhancements include:

- Support for CDISC Controlled Terminology
- Flexible definition of Value Level Metadata
- Enhanced documentation of data origin or source
- Improved support for ADaM metadata
- Improved handling of comments.

Define-XML v2.0 is the most current version of this standard and its use is recommended.

DEFINE-XML DOCUMENT STRUCTURE

The below shows the XML that would comprise the minimal structure of any ODM 1.3.2 document that contains a Define-XML document. It illustrates a valid Define-XML document header and the gray box illustrates the set of elements that comprise this standard in the order in which they should appear in a valid Define-XML file.



The key metadata components to support submissions are:

- Dataset definitions
- Dataset variable definitions
- Controlled Terminology definitions
- Value list definitions
- Links to supporting documents
- Computational method definitions
- Comments definitions

DATASET-XML

Dataset-XML supports the exchange of dataset data based on Define-XML metadata. Dataset-XML complements Define-XML and provides an alternative to the SAS V5 Transport format for the exchange of study datasets for CDISC's Foundational standards. Dataset-XML is a truly non-proprietary, global standard, removing many SAS V5 Transport file restrictions (the current file format required by the FDA and PMDA), such as 8-character variable names and 200-character text fields.

CDISC developed Dataset-XML v1.0 as a drop-in replacement for SAS V5 XPORT to enable testing using existing processes. New Dataset-XML features were intentionally not implemented to simplify the comparison. Now that Dataset-XML v1.0 has been shown to work as a SAS V5 XPORT replacement, the CDISC XML Technologies Team will add additional features in the next versions, including improved relationships and traceability.

Dataset-XML supports exchanging tabular data in clinical research applications using ODM-based XML technologies, enabling communication of study results and regulatory submissions. Dataset-XML is a truly non-proprietary, global standard, removing many SAS V5 Transport file restrictions, such as 8-character variable names and 200-character text fields.

Dataset-XML can represent any tabular dataset including SDTM, ADaM, SEND, or non-standard legacy datasets. Noteworthy items relating to Dataset-XML v1.0 include:

- Alternative to SAS Version 5 Transport (XPORT) format for datasets
- ODM-based model for representation of SEND, SDTM, ADaM or legacy datasets
- Capable of supporting CDISC regulatory data submissions
- Based on Define-XML v2 or v1 metadata, easy to reference

- Dataset-XML supports all language encodings supported by XML

In November 2013, the Food and Drug Administration (FDA) issued a Federal Register (FR) Notice of a Pilot Project called “Transport Format for the Submission of Regulatory Study Data.” The purpose of the pilot was to conduct an initial analysis of CDISC’s DS-XML as an alternative solution to the challenges of SAS XPORT V5 transport. Additional testing will be needed to evaluate cost versus effectiveness as an alternate transport format. FDA envisions conducting several pilots to evaluate new transport formats before a decision is made to support a new format. The initial pilot ended with challenges encoding and file sizes.

DATASET-XML DOCUMENT STRUCTURE

The below show the basic structure of any ODM v1.3.2 document that contains Dataset-XML content.

Dataset-XML document structure using the ClinicalData element

```
<?xml version="1.0" encoding="UTF-8"?>
<ODM
  xmlns="http://www.cdisc.org/ns/odm/v1.3"
  xmlns:xlink="http://www.w3.org/1999/xlink"
  xmlns:data="http://www.cdisc.org/ns/Dataset-XML/v1.0"
  FileType="Snapshot"
  ODMVersion="1.3.2"
  data:DatasetXMLVersion="1.0"
  FileOID="www.cdisc.org.Studycdisc01-Define-XML_2.0.0(IG.CM)"
  PriorFileOID="www.cdisc.org.Studycdisc01-Define-XML_2.0.0"
  Originator="CDISC Dataset-XML Team"
  CreationDateTime="2014-03-20T21:45:33">
  <ClinicalData
    StudyOID="cdisc01"
    MetaDataVersionOID="MDV.CDISC01.SDTMIG.3.1.2.SDTM.1.2">
    <!-- Dataset (CM) -->
    <ItemGroupData ItemGroupOID="IG.CM" data:ItemGroupDataSeq="1">
      <ItemData ItemOID="IT.STUDYID" Value="CDISC01"/>
      <ItemData ItemOID="IT.CM.DOMAIN" Value="CM"/>
      <ItemData ItemOID="IT.USUBJID" Value="CDISC01.100008"/>
      <ItemData ItemOID="IT.CM.CMSEQ" Value="1"/>
      <ItemData ItemOID="IT.CM.CMTRT" Value="PROCARDIA XL"/>
      …
    </ItemGroupData>
    …
  </ClinicalData>
</ODM>
```

Dataset-XML document structure using ReferenceData

```
<?xml version="1.0" encoding="UTF-8"?>
<ODM
  xmlns="http://www.cdisc.org/ns/odm/v1.3"
  xmlns:xlink="http://www.w3.org/1999/xlink"
  xmlns:data="http://www.cdisc.org/ns/Dataset-XML/v1.0"
  FileType="Snapshot"
  ODMVersion="1.3.2"
  data:DatasetXMLVersion="1.0"
  FileOID="www.cdisc.org.Studycdisc01-Define-XML_2.0.0(IG.TA)"
  PriorFileOID="www.cdisc.org.Studycdisc01-Define-XML_2.0.0"
  Originator="CDISC Dataset-XML Team"
  CreationDateTime="2014-03-20T21:45:33" >
  <ReferenceData
    StudyOID="cdisc01"
    MetaDataVersionOID="MDV.CDISC01.SDTMIG.3.1.2.SDTM.1.2">
    <!-- Dataset (TA) -->
    <ItemGroupData ItemGroupOID="IG.TA" data:ItemGroupDataSeq="1">
      <ItemData ItemOID="IT.STUDYID" Value="CDISC01"/>
      <ItemData ItemOID="IT.TA.DOMAIN" Value="TA"/>
      <ItemData ItemOID="IT.TA.ARMCD" Value="PLACEBO"/>
      <ItemData ItemOID="IT.TA.ARM" Value="Placebo"/>
      <ItemData ItemOID="IT.TA.TAETORD" Value="1"/>
      <ItemData ItemOID="IT.TA.ETCD" Value="SCREEN"/>
      <ItemData ItemOID="IT.TA.ELEMENT" Value="Screening"/>
      <ItemData ItemOID="IT.TA.EPOCH" Value="SCREEN"/>
    </ItemGroupData>
      …
  </ReferenceData>
</ODM>
```

DATASET-XML AND DEFINE-XML

Dataset-XML defines a standard format for transporting tabular dataset data in XML. The metadata for a dataset contained within an Dataset-XML document must be specified using the Define-XML standard. The Define-XML must be contained within the same folder as the dataset document files. Each Dataset-XML file contains data for a single dataset but a single define.xml file describes all the datasets included in the folder. The Dataset-XML file containing the data may be linked to the define.xml file containing the metadata by the PriorFileOID attribute on the root ODM node.

BENEFITS OF DATASET-XML

- Open, non-proprietary standard without the field width or data set and variable naming restrictions of SAS V5 Transport files
- Supports representation of data relationships, metadata versions and audit trails
- Harmonized with BRIDG, CDISC Controlled Terminology
- Data elements include references to metadata in Define-XML
- Straightforward implementation starting from SDTM data in SAS
- Supports FDA goal of encouraging open source reviewer tool development
- Facilitates Validation since both data and metadata share underlying technology
- Enables re-thinking some of the length restrictions in standards

RESOURCE DESCRIPTION FRAMEWORK (RDF)

CDISC Standards in RDF provides a representation of the CDISC Foundational standards in a model based on the Resource Description Framework (RDF). RDF provides executable, machine-readable CDISC standards from CDISC SHARE. This file format is a “linked data” view of the standards as an ontology.

The Resource Description Framework (RDF) provides a universal, mathematically precise, and computable language that can express a wide range of information. RDF can express information about meta-models, models, and data in the same universal language. Once expressed in RDF, information can be represented, accessed, computed, integrated, and exchanged without the need for any translations. This representation in RDF avoids information mismatches that often happen when systems interface with each other. RDF provides a consistent language and

modeling framework, identical at design and run-time. As a W3C Recommendation, it can fulfill the role of a standard language to express and exchange standards.

Version 1.0 of the CDISC Standards in RDF, prepared by the PhUSE CS Semantic Technology Working Group, consists of two documents:

- CDISC Standards in RDF Reference Guide v1 Final - provides a reference to the representation of the existing foundational CDISC standards in a model based on the Resource Description Framework (RDF).
- CDISC Standards in RDF User Guide v1 Final – describes how to access and use the RDF files and provides background on their creation.

The Semantic Web provides a common framework that allows data to be shared and reused across application, enterprise, and community boundaries. It is a collaborative effort led by W3C with participation from many researchers and industrial partners. RDF, which is one of the fundamental building blocks of the Semantic Web, gives a formal definition for that interchange.

RDF- the Resource Description Framework is a standard model for data interchange on the Web. RDF has features that facilitate data merging even if the underlying schemas differ, and it specifically supports the evolution of schemas over time without requiring all the data consumers to be changed.

The fundamental model of RDF is independent of XML. RDF is a model describing qualified (or named) relationships between two (Web) resources, or between a Web resource and a literal. At that fundamental level, the only commonality between RDF and the XML World is the usage of the XML Schema datatypes to characterize literals in RDF.

The key elements of the RDF meta-model are based on the ISO 11179 standard for Metadata Registries (MDR), a standard that also provides the background model for the CDISC metadata registry called SHARE.

RDF SCHEMAS FOR CDISC FOUNDATIONAL STANDARDS

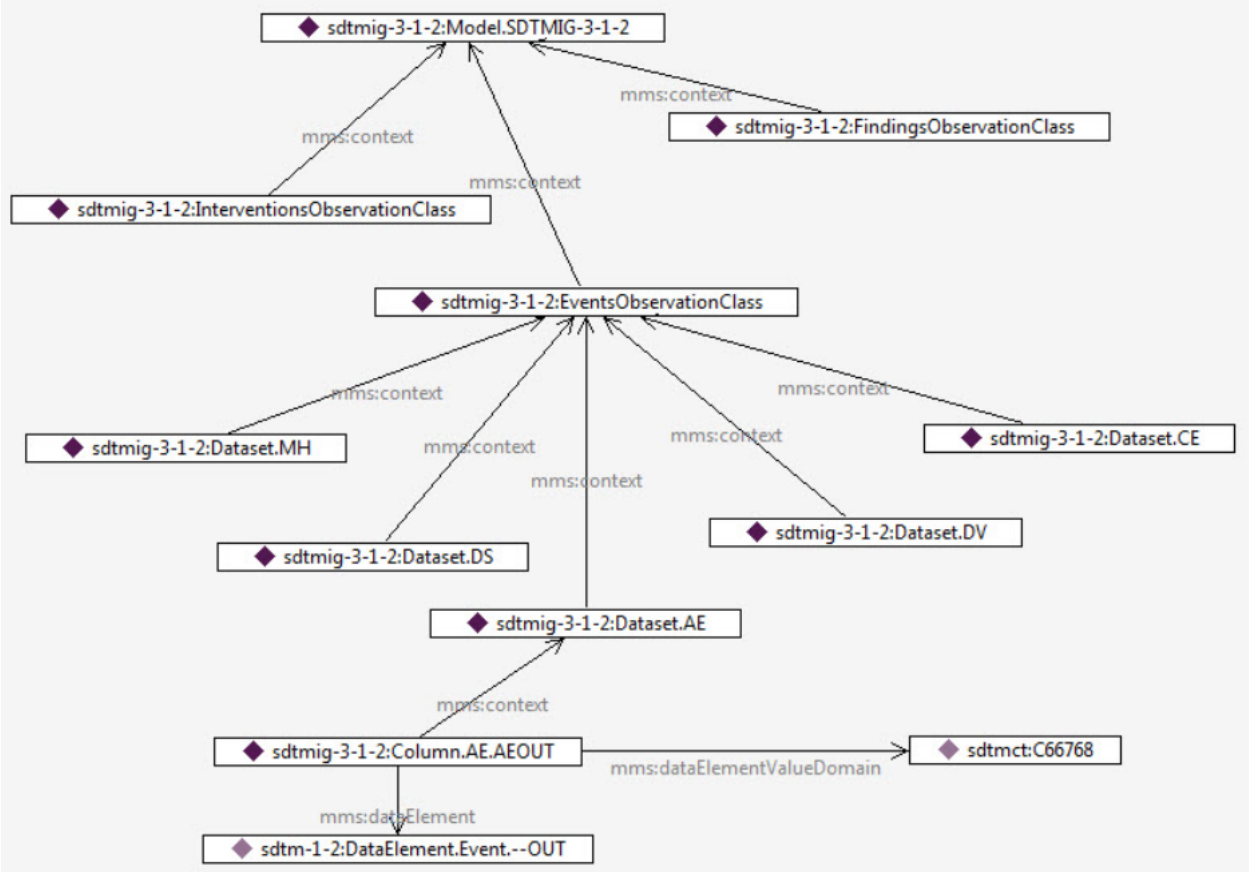
Three RDF schemas have been defined and layered that enable the description of the CDISC foundational standards for CDASH, SDTM, SEND, and ADaM, together with their controlled terminologies.

- The meta-model schema (namespace prefix mms) is a generic RDF schema with elements from ISO 11179 that allows the specification of data oriented models in a unified way.
- The CT schema (namespace prefix cts) defines additional predicates used by the NCI EVS to publish the CDISC controlled terminology in RDF.
- The CDISC schema (namespace prefix cdiscs) introduces additional classes and predicates to capture CDISC specific model information.

These schemas have been layered, i.e. the CDISC Schema imports the CT Schema, which in its turn imports the Meta-Model Schema. It is therefore sufficient to use the CDISC Schema to have all the schema elements available when defining a new CDISC model. The following sections give detailed descriptions for each of these schemas.

EXAMPLE RDF GRAPH FOR SDTM IG 3.1.2

Representing subjects and objects of triples as nodes, and predicates of triples as directed edges between nodes, one can see that the information expressed by a set of triples is in fact a directed graph, which expresses the intrinsic data model of an RDF data set.

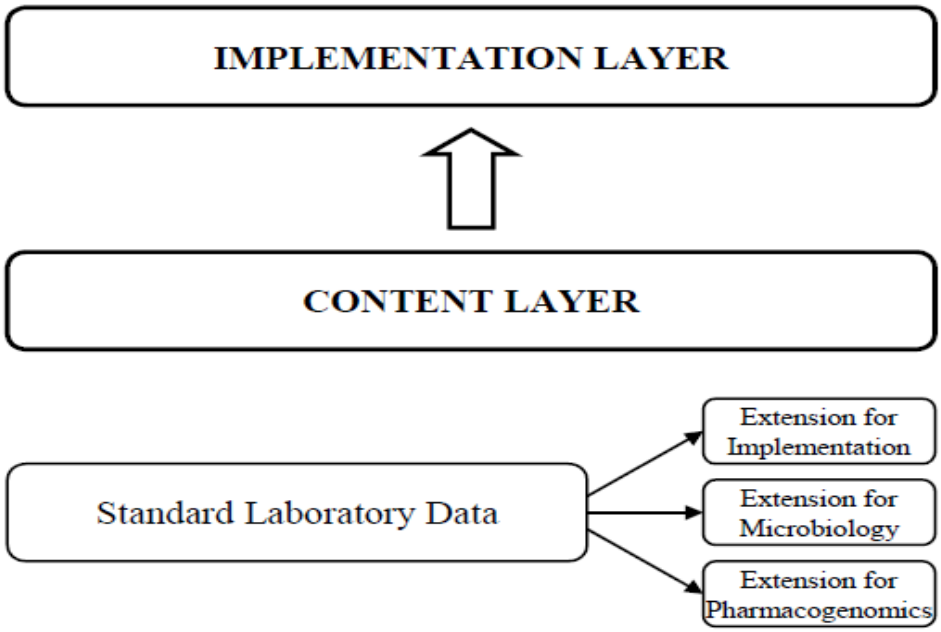


LABORATORY DATA MODEL (LAB)

LAB provides a standard model for the acquisition and exchange of laboratory data, primarily between labs and sponsors or CROs. The LAB standard was specifically designed for the interchange of lab data acquired in clinical trials.

Standard models for the interchange of laboratory data do exist already but they are very seldom used within the biopharmaceutical industry. Examples of such standards are ACDM, ASTM, HL7 and X12. The main reason standards such as these have not been more accepted by the industry is that they have limited applicability to clinical trial data and hence have limited use to central laboratories, CROs or biopharmaceutical companies

The design of the model is thus as follows:



The first layer would be the content layer and above that would be an implementation layer, the idea being that the content would not change but the implementation could. The advantage of this approach is that it offers flexibility but retains control: it doesn't make the use of the model dependent upon any one implementation and if different implementations are used the content remains the same so the standard still applies.

CONCLUSION

CDISC Transport Standards enable the exchange of data conformant with CDISC Foundational Standards and their Therapeutic Area extensions. Each of the standards described above plays its roles in transportation of data during the entire phase of clinical trials from Study Design and all the way to regulatory submission. These standards are used as references for transportation of trial data from trial sites, central laboratories, and regulatory filings.

REFERENCES

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3. The BRIDG Project: A Technical Report - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2274793/
4. Translational Research and Patient Safety in Europe - D5.4 Specification for functional eCRF and DSS - http://www.i-hd.eu/i-HD/assets/File/TRANSFoRm/D5_4%20Specification%20for%20functional%20eCRF%20and%20DSS_TRANSFoRm.pdf

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