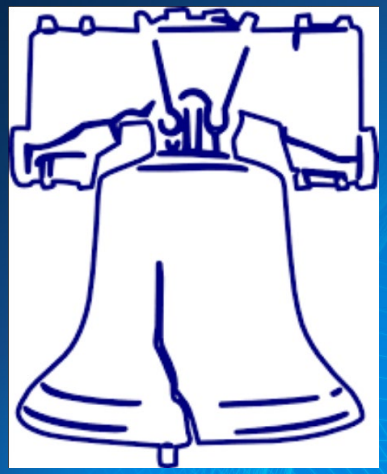

PhilaSUG
Fall 2018 meeting
October 30th

The Present and Future of Define-XML

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CDISC Data Exchange Standards Team

Agenda

- Define-XML
- Analysis Results Metadata for Define-XML
- Preview of Define-XML 2.1

Define-XML

Define-XML What is it?

- CDISC XML Technology standard that provides machine readable **metadata** for any tabular dataset structure.
- Primary use case: describe datasets for the purpose of submissions to regulatory authorities
- Required by **FDA** (USA) and **PMDA** (Japan) for all CDISC submissions.
- Reviewers need **metadata** that describes the content of each submission.

SDTM-IG 3.1.2

- Annotated Case Report
- Reviewers Guide
- Complex Algorithms
- ► Tabulation Datasets
- ► Value Level Metadata
- ► Controlled Terminology
- ► Computational Algorithm
- ► Comments

Date of document generation: 2013-03-03T17:04:44

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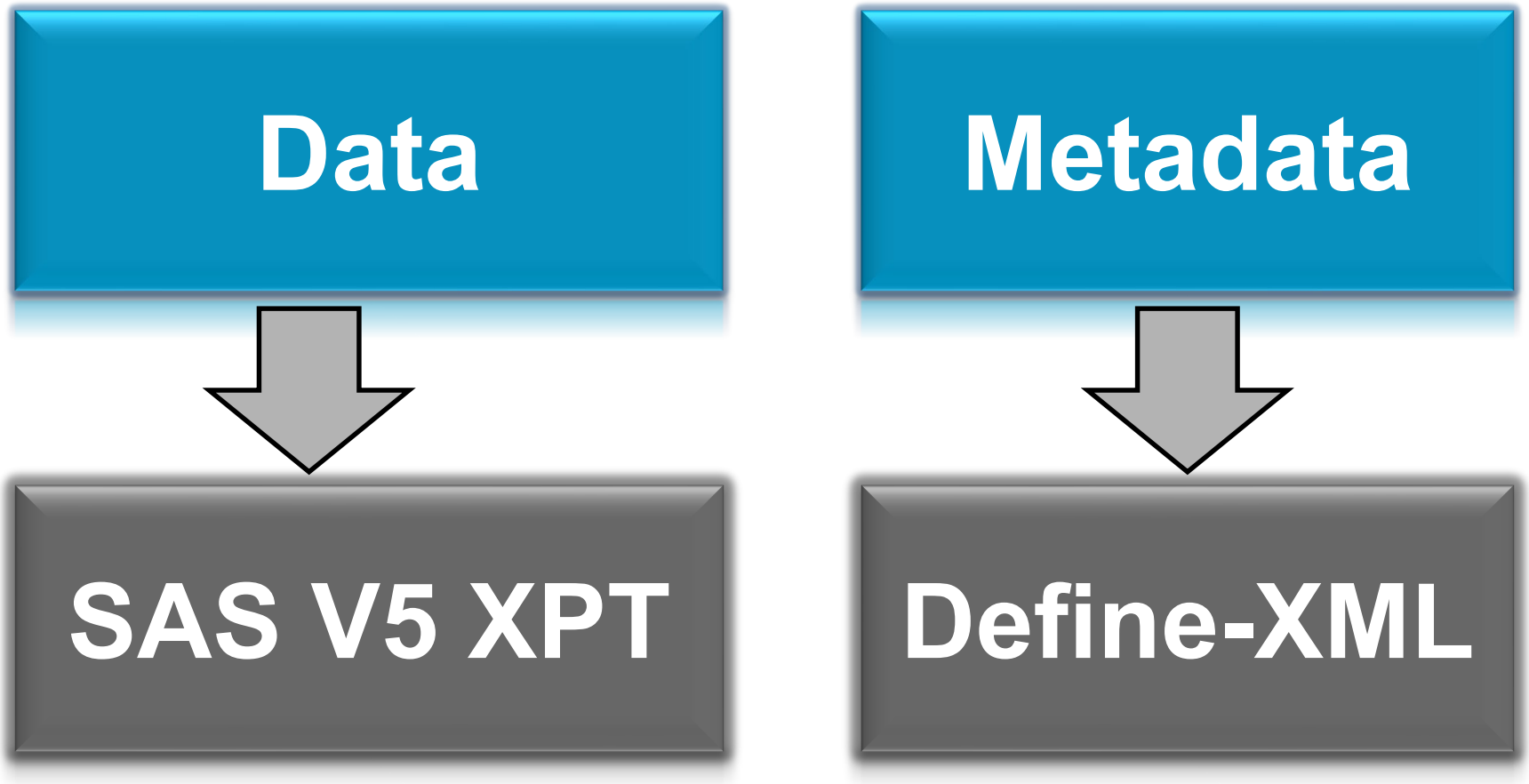
Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
TA	Trial Arms	TRIAL DESIGN	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD	ta.xpt	
TE	Trial Elements	TRIAL DESIGN	One record per planned Element	Tabulation	STUDYID, ETCD	te.xpt	
TI	Trial Inclusion/Exclusion Criteria	TRIAL DESIGN	One record per I/E criterion	Tabulation	STUDYID, IETESTCD	ti.xpt	
TS	Trial Summary	TRIAL DESIGN	One record per	Tabulation	STUDYID	ts.xpt	

CDISC Standards in Submissions Today



Define-XML History

March 2005

- **Define-XML v1.0** (Case Report Tabulation Data Definition Specification v1.0)
- FDA has announced the **end of support** for Define-XML v1.0 for studies that start 12 months after March 15, 2017

March 2013

- **Define-XML v2.0**
- Accepted by FDA since August 2013

January 2015

- **Analysis Results Metadata** v1.0 extension for **Define-XML v2.0**
- Not yet requested by FDA; requested by PMDA

2018

- **Define-XML v2.1** - Public Review round 2 ended on September 4th 2018. Still in development.

Define-XML What is it ?

```
<?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:def="http://www.cdisc.org/ns/def/v2.0"
   FileType="Snapshot" ODMVersion="1.3.2"
   FileOID="BestPharmaceuticals.com/Study5894/1"
   CreationDateTime="2018-04-15T16:30:23-05:00"
   Originator="Best Pharmaceuticals">
   <Study OID="BestPharmaceuticals.com/Study5894">
     <GlobalVariables>
       <StudyName>Study 5894</StudyName>
       <StudyDescription>Study 5894</StudyDescription>
       <ProtocolName>BestPharmaceuticals 5894</ProtocolName>
     </GlobalVariables>
     <MetaDataVersion OID="MDV.BP5894.SDTMIG.3.2.SDTM.1.4"
       Name="Study 5894, Data Definitions"
       Description="Study 5894, Data Definitions"
       def:DefineVersion="2.0.0"
       def:StandardName="SDTM-IG"
       def: StandardVersion="3.2">

       < Annotated Case Report Forms (def:AnnotatedCRF) >
       < Supplemental data Definitions (def:SupplementalDoc) >
       < Value Level Metadata (def:ValueListDef) >
       < Where Clause Definitions (def:WhereClauseDef) >
       < Dataset Level Metadata (ItemGroupDef) >
       < Variable level Metadata (ItemDef) >
       < Controlled Terminology Metadata (CodeList) >
       < Computational Algorithms (MethodDef) >
       < Comments (def:CommentDef) >
       < Referenced Documents (def:leaf) >

     </MetaDataVersion>
   </Study>
 </ODM>
```

Define-XML is the name of the standard

define.xml is the name of a file

Define-XML What is it ?

- Provides machine readable metadata about:
  - **Study**
    - Name, Description, Protocol name
  - **Datasets**
    - Name, Label, Domain, Structure, Class, Purpose, Keys, Comments, Dataset Location, ...
  - **Variables**
    - Name, Label, Data Type, Length, Significant Digits, Display Format, Controlled Terms, Origin, Derivations, Comments...
  - **Controlled Terminology / Dictionaries**
  - **Derivations** (algorithms, computations, methods)
  - **Supporting Documents** (aCRF, Supplemental Data Definitions, Reviewer Guides, ...)
  - (Parameter) **Value Level Metadata**

Define-XML in Detail

Study Metadata

Define-XML Study Metadata

```
<?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:def="http://www.cdisc.org/ns/def/v2.0"
   FileType="Snapshot" ODMVersion="1.3.2"
   FileOID="BestPharmaceuticals.com/Study5894/1"
   CreationDateTime="2018-04-15T16:30:23-05:00"
   Originator="Best Pharmaceuticals">
   <Study OID="BestPharmaceuticals.com/Study5894">
     <GlobalVariables>
       <StudyName>Study 5894</StudyName>
       <StudyDescription>Study 5894</StudyDescription>
       <ProtocolName>BestPharmaceuticals 5894</ProtocolName>
     </GlobalVariables>
```

- **FileOIDs** should be universally unique if at all possible. One way to ensure this is to prefix every FileOID with an Internet domain name owned by the creator of the ODM file or database (followed by a /). For example, FileOID="BestPharmaceuticals.com/Study5894/1" might be a good way to denote the first file in a series for study 5894 from Best Pharmaceuticals
- Similarly, **StudyOIDs** should be universally unique if at all possible

Define-XML Study Metadata

- Only 3 elements (but a lot more in SDTM Trial Summary domain, and in ODM CTR-XML).

```
<Study OID="BestPharmaceuticals.com/Study5894">
  <GlobalVariables>
    <StudyName>Study 5894</StudyName>
    <StudyDescription>Study 5894</StudyDescription>
    <ProtocolName>BestPharmaceuticals 5894</ProtocolName>
  </GlobalVariables>
  <MetaDataVersion OID="MDV.BP5894.SDTMIG.3.2.SDTM.1.4"
    Name="Study 5894, Data Definitions"
    Description="Study 5894, Data Definitions"
    def:DefineVersion="2.0.0"
    def:StandardName="SDTM-IG"
    def: StandardVersion="3.2">
```

Define-XML Study Metadata

- **StudyName** is a short name for the study.
  The sponsor's internal name assigned to the study. In case there is no internal name can be the same as ProtocolName.
- **StudyDescription** is a longer description of the study, for example, the full study title from the protocol.
- **ProtocolName** is the official identifier of the study as specified in the protocol. It is the Protocol Number assigned to the study by a regulatory agency.

Define-XML Study Metadata

```
<MetaDataVersion OID="MDV.BP5894.SDTMIG.3.2.SDTM.1.4"
  Name="Study 5894, Data Definitions"
  Description="Study 5894, Data Definitions"
  def:DefineVersion="2.0.0"
  def:StandardName="SDTM-IG"
  def: StandardVersion="3.2">
```

- **MetaDataVersion/@Description** attribute can contain additional information about the submitted metadata. It can contain a name and version of a terminology standard used, a reason for an update, additional standards (e.g., SDTMIG-AP) used for specific domains and etc. It is expected that this kind of information will be provided in the reviewer's guide, that is why this attribute is optional and sponsor can decide not to provide it.
- Will be more structured in Define-XML v2.1

Define-XML Study Metadata

```
<MetaDataVersion OID="MDV.BP5894.SDTMIG.3.2.SDTM.1.4"
  Name="Study 5894, Data Definitions"
  Description="Study 5894, Data Definitions"
  def:DefineVersion="2.0.0"
  def:StandardName="SDTM-IG"
  def: StandardVersion="3.2">
```

- **MetaDataVersion/@def:StandardName** allowed values:
  - **ADaM-IG**
  - **SDTM-IG**
  - **SEND-IG**

Case sensitive !

Define-XML in Detail

Dataset Metadata

Define-XML Dataset Metadata

- Tabulation and Analysis datasets have to be described with metadata:
  - **Name**
  - **Label** – Text description
  - **Domain**
  - **Structure**
  - **Class** information (FINDINGS, EVENTS, INTERVENTIONS, ...)
  - **Purpose** (Tabulation or Analysis)
  - **Repeating** - More than one record per subject or only one record per subject
  - Does the dataset contain **reference data**?
  - **SAS dataset name**
  - **Location** – Where is the dataset file located?
  - **Documentation** – Comment, optionally including a document reference (Annotated CRF, Reviewer's Guide)

Define-XML Dataset Metadata

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
TA	Trial Arms	TRIAL DESIGN	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD	ta.xpt	
TE	Trial Elements	TRIAL DESIGN	One record per planned Element	Tabulation	STUDYID, ETCD	te.xpt	
TI	Trial Inclusion/Exclusion Criteria	TRIAL DESIGN	One record per I/E criterion	Tabulation	STUDYID, IETESTCD	ti.xpt	
TS	Trial Summary	TRIAL DESIGN	One record per trial summary parameter value	Tabulation	STUDYID, TSPARMCD, TSSEQ	ts.xpt	
TV	Trial Visits	TRIAL DESIGN	One record per planned Visit per Arm	Tabulation	STUDYID, VISITNUM, ARMCD	tv.xpt	
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide

Analysis Datasets for Study CDISC-Sample (ADaM-IG 1.0)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
ADSL	Subject-Level Analysis	SUBJECT LEVEL ANALYSIS DATASET	one record per subject	Analysis	USUBJID	adsl.xpt	Screen Failures are excluded since they are not needed for this study analysis
ADQSADAS	ADAS-Cog Analysis	BASIC DATA STRUCTURE	One record per subject per parameter per analysis visit per analysis date	Analysis	USUBJID, PARAMCD, AVISIT, ADT	adqsadas.xpt	See referenced dataset creation program and Analysis Data Reviewer's Guide, Section 2.1 adqsadas.sas Analysis Data Reviewer's Guide

Define-XML Dataset Metadata

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide

```
<!-- Dataset Definition (DM) -->
<ItemGroupDef OID="IG.DM"
  Domain="DM" Name="DM" Repeating="No" IsReferenceData="No" SASDatasetName="DM"
  Purpose="Tabulation" def:Structure="One record per subject" def:Class="SPECIAL PURPOSE"
  def:CommentOID="COM.DOMAIN.DM" def:ArchiveLocationID="LF.DM">
  <Description>
    <TranslatedText xml:lang="en">Demographics</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.STUDYID" OrderNumber="1" Mandatory="Yes" KeySequence="1"/>
  <ItemRef ItemOID="IT.DM.DOMAIN" OrderNumber="2" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.USUBJID" OrderNumber="3" Mandatory="Yes" KeySequence="2" MethodOID="MT.USUBJID"/>
  <ItemRef ItemOID="IT.DM.SUBJID" OrderNumber="4" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.RFSTDTC" OrderNumber="5" Mandatory="No" MethodOID="MT.RFSTDTC"/>
  <ItemRef ItemOID="IT.DM.RFENDTC" OrderNumber="6" Mandatory="No" MethodOID="MT.RFENDTC"/>

   ...

  <ItemRef ItemOID="IT.DM.ARM" OrderNumber="15" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.COUNTRY" OrderNumber="16" Mandatory="Yes"/>
  <def:leaf ID="LF.DM" xlink:href="dm.xpt">
    <def:title>dm.xpt</def:title>
  </def:leaf>
</ItemGroupDef>
```

Define-XML Dataset Metadata - Domain

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
SUPPDM	Supplemental Qualifiers for DM (Demographics)	RELATIONSHIP	One record per IDVAR, IDVARVAL, and QNAM value per subject	Tabulation	STUDYID, RDOMAIN, USUBJID, IDVAR, IDVARVAL, QNAM	suppdm.xpt	

```
<ItemGroupDef OID="IG.SUPPDM" Name="SUPPDM" Repeating="Yes" IsReferenceData="No"
  SASDatasetName="SUPPDM" Domain="DM" Purpose="Tabulation" def:Class="RELATIONSHIP"
  def:Structure="One record per IDVAR, IDVARVAL, and QNAM value per subject"
  def:ArchiveLocationID="LF.SUPPDM">
  <Description>
   <TranslatedText xml:lang="en">Supplemental Qualifiers for DM</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.SUPPDM.STUDYID" Mandatory="Yes" OrderNumber="1" KeySequence="1"/>
  <ItemRef ItemOID="IT.SUPPDM.RDOMAIN" Mandatory="Yes" OrderNumber="2" KeySequence="2" MethodOID="MT.SUPPDM.RDOMAIN"/>
   ...
  <ItemRef ItemOID="IT.SUPPDM.QORIG" Mandatory="Yes" OrderNumber="9"/>
  <ItemRef ItemOID="IT.SUPPDM.QEVAL" Mandatory="No" OrderNumber="10"/>
  <Alias Context="DomainDescription" Name="Demographics"/>
  <def:leaf ID="LF.SUPPDM" xlink:href="../transport/cdisc-sdtm-3.1.2/suppdm.xpt">
    <def:title>suppdm.xpt</def:title>
  </def:leaf>
</ItemGroupDef>
```

Define-XML Dataset Metadata - Class

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide

- Class is controlled by CDISC/NCI Controlled Terminology GNRLOBSC

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value
C103329		No	General Observation Class	GNRLOBSC
C103375	C103329		General Observation Class	ADAM OTHER
C103371	C103329		General Observation Class	BASIC DATA STRUCTURE
C103372	C103329		General Observation Class	EVENTS
C103373	C103329		General Observation Class	FINDINGS
C135396	C103329		General Observation Class	FINDINGS ABOUT
C132357	C103329		General Observation Class	INTEGRATED BASIC DATA STRUCTURE
C132358	C103329		General Observation Class	INTEGRATED OCCURRENCE DATA STRUCTURE
C132359	C103329		General Observation Class	INTEGRATED SUBJECT LEVEL
C103374	C103329		General Observation Class	INTERVENTIONS
C123454	C103329		General Observation Class	OCCURRENCE DATA STRUCTURE
C103376	C103329		General Observation Class	RELATIONSHIP
C103377	C103329		General Observation Class	SPECIAL PURPOSE
C147271	C103329		General Observation Class	STUDY REFERENCE
C103378	C103329		General Observation Class	SUBJECT LEVEL ANALYSIS DATASET
C103379	C103329		General Observation Class	TRIAL DESIGN

Define-XML Dataset Metadata - Keys

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide

```
<!-- Dataset Definition (DM) -->
<ItemGroupDef OID="IG.DM"
  Domain="DM" Name="DM" Repeating="No" IsReferenceData="No" SASDatasetName="DM"
  Purpose="Tabulation" def:Structure="One record per subject" def:Class="SPECIAL PURPOSE"
  def:CommentOID="COM.DOMAIN.DM" def:ArchiveLocationID="LF.DM">
  <Description>
    <TranslatedText xml:lang="en">Demographics</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.STUDYID" OrderNumber="1" Mandatory="Yes" KeySequence="1"/>
  <ItemRef ItemOID="IT.DM.DOMAIN" OrderNumber="2" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.USUBJID" OrderNumber="3" Mandatory="Yes" KeySequence="2" MethodOID="MT.USUBJID"/>
  <ItemRef ItemOID="IT.DM.SUBJID" OrderNumber="4" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.RFSTDTC" OrderNumber="5" Mandatory="No" MethodOID="MT.RFSTDTC"/>
  <ItemRef ItemOID="IT.DM.RFENDTC" OrderNumber="6" Mandatory="No" MethodOID="MT.RFENDTC"/>

   ...

  <ItemRef ItemOID="IT.DM.ARM" OrderNumber="15" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.COUNTRY" OrderNumber="16" Mandatory="Yes"/>
  <def:leaf ID="LF.DM" xlink:href="dm.xpt">
    <def:title>dm.xpt</def:title>
  </def:leaf>
</ItemGroupDef>
```

Define-XML Dataset Metadata - Location

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide

```
<!-- Dataset Definition (DM) -->
<ItemGroupDef OID="IG.DM"
  Domain="DM" Name="DM" Repeating="No" IsReferenceData="No" SASDatasetName="DM"
  Purpose="Tabulation" def:Structure="One record per subject" def:Class="SPECIAL PURPOSE"
  def:CommentOID="COM.DOMAIN.DM" def:ArchiveLocationID="LF.DM">
  <Description>
    <TranslatedText xml:lang="en">Demographics</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.STUDYID" OrderNumber="1" Mandatory="Yes" KeySequence="1"/>
  <ItemRef ItemOID="IT.DM.DOMAIN" OrderNumber="2" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.USUBJID" OrderNumber="3" Mandatory="Yes" KeySequence="2" MethodOID="MT.USUBJID"/>
  <ItemRef ItemOID="IT.DM.SUBJID" OrderNumber="4" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.RFSTDTC" OrderNumber="5" Mandatory="No" MethodOID="MT.RFSTDTC"/>
  <ItemRef ItemOID="IT.DM.RFENDTC" OrderNumber="6" Mandatory="No" MethodOID="MT.RFENDTC"/>

   ...

  <ItemRef ItemOID="IT.DM.ARM" OrderNumber="15" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.COUNTRY" OrderNumber="16" Mandatory="Yes"/>
  <def:leaf ID="LF.DM" xlink:href="dm.xpt">
    <def:title>dm.xpt</def:title>
  </def:leaf>
</ItemGroupDef>
```

Define-XML Dataset Metadata - Comments

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide

```
<!-- Dataset Definition (DM) -->
<ItemGroupDef OID="IG.DM"
  Domain="DM" Name="DM" Repeating="No" IsReferenceData="No" SASDatasetName="DM"
  Purpose="Tabulation" def:Structure="One record per subject" def:Class="SPECIAL PURPOSE"
  def:CommentOID="COM.DOMAIN.DM" def:ArchiveLocationID="LF.DM">
  <Description>
    <TranslatedText xml:lang="en">Demographics</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.STUDYID" OrderNumber="1" Mandatory="Yes" KeySequence="1"/>
  <ItemRef ItemOID="IT.DM.DOMAIN" OrderNumber="2" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.USUBJID" OrderNumber="3" Mandatory="Yes" KeySequence="2" MethodOID="MT.USUBJID"/>
  <ItemRef ItemOID="IT.DM.SUBJID" OrderNumber="4" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.RFSTDTC" OrderNumber="5" Mandatory="No" MethodOID="MT.RFSTDTC"/>
  <ItemRef ItemOID="IT.DM.RFENDTC" OrderNumber="6" Mandatory="No" MethodOID="MT.RFENDTC"/>

   ...

  <ItemRef ItemOID="IT.DM.ARM" OrderNumber="15" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.COUNTRY" OrderNumber="16" Mandatory="Yes"/>
  <def:leaf ID="LF.DM" xlink:href="dm.xpt">
    <def:title>dm.xpt</def:title>
  </def:leaf>
</ItemGroupDef>
```

Define-XML Dataset Metadata - Comments

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide

```
<!-- Comment Definition: Long Comment, included in a PDF file -->
<def:CommentDef OID="COM.DOMAIN.DM">
  <Description>
    <TranslatedText xml:lang="en">See Reviewer's Guide, Section 2.1 Demographics</TranslatedText>
  </Description>
  <def:DocumentRef leafID="LF.ReviewersGuide">
    <def:PDFPageRef PageRefs="section2.1" Type="NamedDestination"/>
  </def:DocumentRef>
</def:CommentDef>
```

```
<def:leaf ID="LF.ReviewersGuide" xlink:href="reviewersguide.pdf">
  <def:title>Reviewers Guide</def:title>
</def:leaf>
```

Define-XML in Detail

Variable Metadata

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	DM	Identifier	Two-character abbreviation for the domain.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product. This must be a unique number, and could be a compound identifier formed by concatenating STUDYID-SITEID-SUBJID.	Req
SUBJID	Subject Identifier for the Study	Char		Topic	Subject identifier, which must be unique within the study. Often the ID of the subject as recorded on a CRF.	Req
RFSTDTC	Subject Reference Start Date/Time	Char	ISO 8601	Record Qualifier	Reference Start Date/time for the subject in ISO 8601 character format. Usually equivalent to date/time when subject was first exposed to study treatment. Required for all randomized subjects; will be null for all subjects who did not meet the milestone the date requires, such as screen failures or unassigned subjects.	Exp
RFENDTC	Subject Reference End Date/Time	Char	ISO 8601	Record Qualifier	Reference End Date/time for the subject in ISO 8601 character format. Usually equivalent to the date/time when subject was determined to have ended the trial, and often equivalent to date/time of last exposure to study treatment. Required for all randomized subjects; null for screen failures or unassigned subjects.	Exp
RFXSTDTC	Date/Time of First Study Treatment	Char	ISO 8601	Record Qualifier	First date of exposure to any protocol-specified treatment or therapy, equal to the earliest value of EXSTDTC.	Exp
RFXENDTC	Date/Time of Last Study Treatment	Char	ISO 8601	Record Qualifier	Last date of exposure to any protocol-specified treatment or therapy, equal to the latest value of EXENDTC (or the latest value of EXSTDTC if EXENDTC was not collected or is missing).	Exp

Define-XML Variable Metadata

- **Name** - up to 8 characters following CDISC standards
- **Label** - Text description, up to 40 characters
- **DataType** - text, integer, float, date, time, datetime, partialDate, partialTime, partialDatetime, incompleteDatetime, durationDatetime
- **Length**, **SignificantDigits**, **DisplayFormat**
- **SASFieldName**
- **Role** - Optional, how the variable is used
- **CodeList** Reference to Controlled Terminology (NCI or sponsor defined) or Dictionary (MedDRA, ...)
- **Origin** - source or origin of the data: CRF, Derived, Assigned, Protocol, eDT, Predecessor)
- **Derivation (Method)** –The algorithm used to compute data values
- **Comment** - other information about the dataset or variable that may be useful for the data reviewer. More lengthy comments may be in an accompanying Reviewer Guide.

Define-XML SDTM Variable Metadata

Demographics (DM) [Location: dm.xpt]

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
STUDYID	Study Identifier	1	text	7		Protocol	
DOMAIN	Domain Abbreviation		text	2	["DM" = "Demographics"] <Domain Abbreviation (DM)>	Assigned	
USUBJID	Unique Subject Identifier	2	text	14		Derived	Concatenation of STUDYID and SUBJID
SUBJID	Subject Identifier for the Study		text	6		CRF Page 3	
RFSTDTC	Subject Reference Start Date/Time		date		ISO8601	Derived	RFSTDTC = first date/time of study drug, for safety subject. Null for screen failures.
RFENDTC	Subject Reference End Date/Time		date		ISO8601	Derived	RFENDTC = termination date, for safety subjects. Null for screen failures.
SITEID	Study Site Identifier		text	3		CRF Page 3	
BRTHDTC	Date/Time of Birth		date		ISO8601	CRF Page 6	
AGE	Age		integer	2		Derived	Age at Screening Date (Screening Date - Birth date). For the complete algorithm see the referenced external document. Complex Algorithms
AGEU	Age Units		text	5		Assigned	Defaulted to YEARS
SEX	Sex		text	1	["F" = "Female", "M" = "Male", "U" = "Unknown"] <Sex>	CRF Page 6	

Define-XML ADaM Variable Metadata

Subject-Level Analysis (ADSL) [Location: adsl.xpt]

Variable	Label	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment
STUDYID	Study Identifier	text	12		Predecessor: DM.STUDYID
USUBJID	Unique Subject Identifier	text	11		Predecessor: DM.USUBJID
SUBJID	Subject Identifier for the Study	text	4		Predecessor: DM.SUBJID
SITEID	Study Site Identifier	text	3		Predecessor: DM.SITEID
SITEGR1	Pooled Site Group 1	text	3		Derived: refer to SAP, Section 7.1 - if not pooled then SITEGR1=SITEID. If pooled, SITEGR1 will be 900
ARM	Description of Planned Arm	text	20	["Placebo", "Xanomeline Low Dose", "Xanomeline High Dose"] <ARM>	Predecessor: DM.ARM
TRT01P	Planned Treatment for Period 01	text	20	["Placebo", "Xanomeline Low Dose", "Xanomeline High Dose"] <ARM>	Predecessor: DM.ARM
TRT01PN	Planned Treatment for Period 01 (N)	integer	8	["0" = "Placebo", "54" = "Xanomeline Low Dose", "81" = "Xanomeline High Dose"] <ARMN>	Assigned: Numeric code for TRT01P which corresponds to the randomized dose

Define-XML Variable Metadata

```
<!-- Dataset Definition (DM) -->
<ItemGroupDef OID="IG.DM"
  Domain="DM" Name="DM" Repeating="No" IsReferenceData="No" SASDatasetName="DM"
  Purpose="Tabulation" def:Structure="One record per subject" def:Class="SPECIAL PURPOSE"
  def:CommentOID="COM.DOMAIN.DM" def:ArchiveLocationID="LF.DM">
  <Description>
    <TranslatedText xml:lang="en">Demographics</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.STUDYID" OrderNumber="1" Mandatory="Yes" KeySequence="1"/>
  <ItemRef ItemOID="IT.DM.DOMAIN" OrderNumber="2" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.USUBJID" OrderNumber="3" Mandatory="Yes" KeySequence="2" MethodOID="MT.USUBJID"/>
  <ItemRef ItemOID="IT.DM.SUBJID" OrderNumber="4" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.RFSTDTC" OrderNumber="5" Mandatory="No" MethodOID="MT.RFSTDTC"/>
  <ItemRef ItemOID="IT.DM.RFENDTC" OrderNumber="6" Mandatory="No" MethodOID="MT.RFENDTC"/>

   ...

  <ItemRef ItemOID="IT.DM.ARM" OrderNumber="15" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.COUNTRY" OrderNumber="16" Mandatory="Yes"/>
  <def:leaf ID="LF.DM" xlink:href="dm.xpt">
    <def:title>dm.xpt</def:title>
  </def:leaf>
</ItemGroupDef>



<ItemDef OID="IT.STUDYID" Name="STUDYID" DataType="text" Length="7" SASFieldName="STUDYID">
  <Description>
    <TranslatedText xml:lang="en">Study Identifier</TranslatedText>
  </Description>
  <def:Origin Type="Protocol"/>
</ItemDef>
```

Define-XML SDTM Variable Metadata – ItemGroupDef/ItemRef

Demographics (DM) [Location: dm.xpt]

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
STUDYID							
DOMAIN							
USUBJID							
SUBJID							
RFSTDTC							
RFENDTC							
SITEID							
BRTHDTC							
AGE							
AGEU							
SEX							

```
<ItemGroupDef OID="IG.DM" Domain="DM" Name="DM" Repeating="No"
  IsReferenceData="No" SASDatasetName="DM" Purpose="Tabulation"
  def:Structure="One record per subject" def:Class="SPECIAL PURPOSE"
  def:CommentOID="COM.DOMAIN.DM" def:ArchiveLocationID="LF.DM">
  <Description>
    <TranslatedText xml:lang="en">Demographics</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.STUDYID" OrderNumber="1" Mandatory="Yes" KeySequence="1"/>
  <ItemRef ItemOID="IT.DM.DOMAIN" OrderNumber="2" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.USUBJID" OrderNumber="3" Mandatory="Yes" KeySequence="2" Meth
  <ItemRef ItemOID="IT.DM.SUBJID" OrderNumber="4" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.RFSTDTC" OrderNumber="5" Mandatory="No" MethodOID="MT.RFST
  <ItemRef ItemOID="IT.DM.RFENDTC" OrderNumber="6" Mandatory="No" MethodOID="MT.RFEN
  <ItemRef ItemOID="IT.DM.SITEID" OrderNumber="7" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.BRTHDTC" OrderNumber="8" Mandatory="No"/>
  <ItemRef ItemOID="IT.DM.AGE" OrderNumber="9" Mandatory="Yes" MethodOID="MT.AGE"/>
  <ItemRef ItemOID="IT.DM.AGEU" OrderNumber="10" Mandatory="No"/>
  <ItemRef ItemOID="IT.DM.SEX" OrderNumber="11" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.RACE" OrderNumber="12" Mandatory="No"/>
  <ItemRef ItemOID="IT.DM.ETHNIC" OrderNumber="13" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.ARMCD" OrderNumber="14" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.ARM" OrderNumber="15" Mandatory="Yes"/>
  <ItemRef ItemOID="IT.DM.COUNTRY" OrderNumber="16" Mandatory="Yes"/>
  <def:leaf ID="LF.DM" xlink:href="dm.xpt">
    <def:title>dm.xpt</def:title>
  </def:leaf>
</ItemGroupDef>
```

Define-XML SDTM Variable Metadata – ItemGroupDef/ItemRef

Demographics (DM) [Location: dm.xpt]

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
STUDYID	Study Identifier	1	text	7		Protocol	
DOMAIN	Domain Abbreviation		text	2	["DM" = "Demographics"] <Domain Abbreviation (DM)>	Assigned	
USUBJID							
SUBJID							
RFSTDTC							
RFENDTC							
SITEID							
BRTHDTC							
AGE							
AGEU							
SEX							

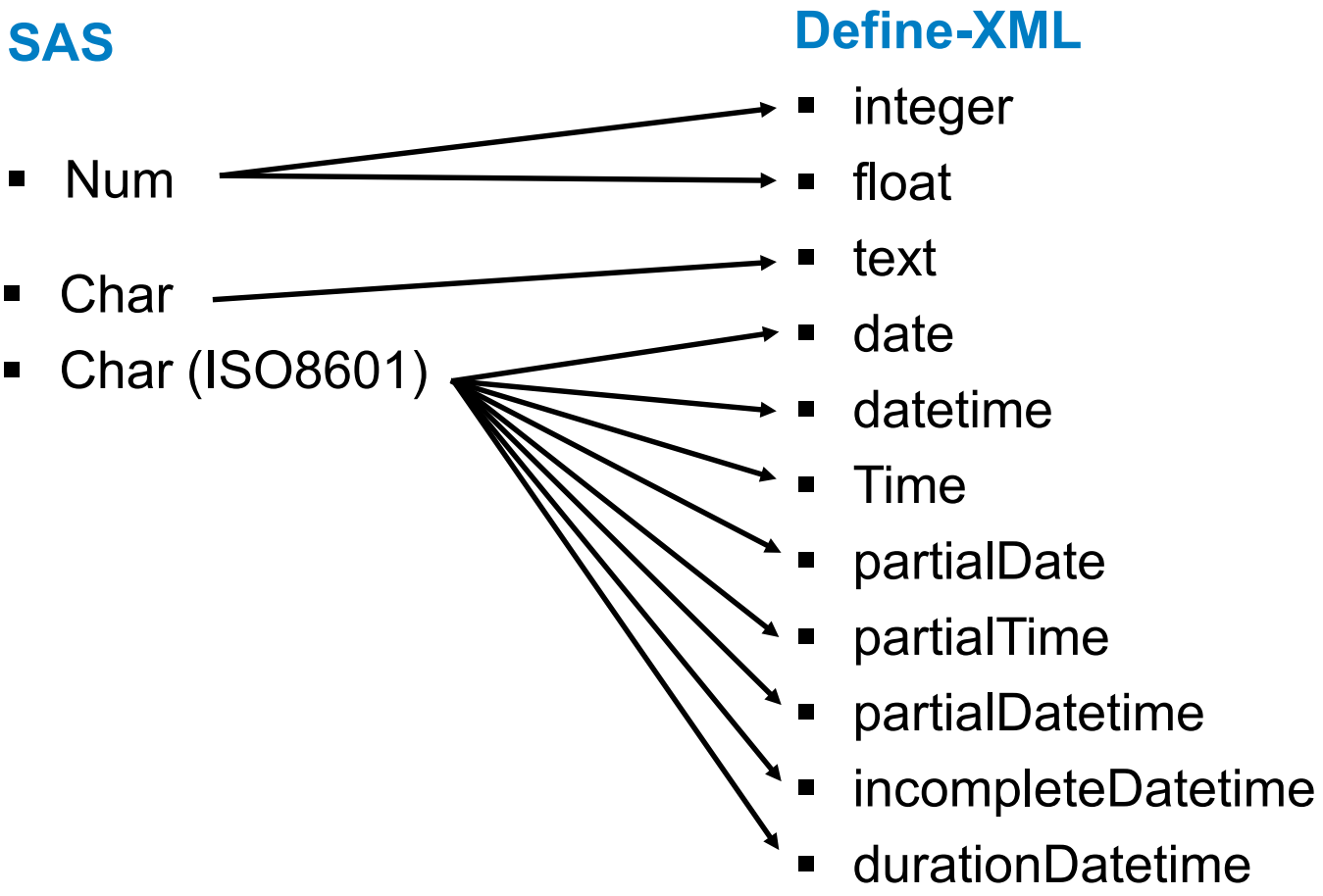
```
<ItemGroupDef OID="IG.DM" Domain="DM" Name="DM" Repeating="No"
  IsReferenceData="No" SASDatasetName="DM" Purpose="Tabulation"
  def:Structure="One record per subject" def:Class="SPECIAL PURPOSE"
  def:CommentOID="COM.DOMAIN.DM" def:ArchiveLocationID="LF.DM">
  <Description>
    <TranslatedText xml:lang="en">Demographics</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.STUDYID" OrderNumber="1" Mandatory="Yes" KeySequence="1"/>
  <ItemRef ItemOID="IT.DM.DOMAIN" OrderNumber="2" Mandatory="Yes"/>

</ItemGroupDef>

<ItemDef OID="IT.DM.DOMAIN" Name="DOMAIN" DataType="text" Length="2" SASFieldName="DOMAIN">
  <Description>
    <TranslatedText xml:lang="en">Domain Abbreviation</TranslatedText>
  </Description>
  <CodeListRef CodeListOID="CL.DM.DOMAIN"/>
  <def:Origin Type="Assigned"/>
</ItemDef>
```

Variable Metadata – Data Types

SDTM, ADaM SEND data type conversions to XML data types in Define-XML



Define-XML Variable Metadata – ISO8601 Data Types

Define-XML Data Type	Example	Example
date	YYYY-MM-DD	2016-05-07
datetime	YYYY-MM-DD**T**HH:MM:SS	2016-05-07T15:05:44
time	HH:MM:SS	15:05:44
partialDate	YYYY[-MM[-DD]]	2016-05
partialTime	HH[:MM[:SS]]	15:05
partialDatetime	YYYY[-MM[-DD]]THH[:MM[:SS]]	2016-05-07T15:05
incompleteDatetime	[YYYY|-]-[MM|-]-[DD|-]T [HH|-]:[MM|-]:[SS|-]	2016---07 2016---07T-:15
durationDatetime	PnYnMnDTnHnMnS or PnW (there are more representations)	P14DT7H57M P2W

- The date and time data types represent the **planned** specificity of the collected data, and not an interpretation of the actual collected values.
- am/pm is not allowed in the specification for the hour
- ISO 8601 allows decimals in the representation of seconds

Variable Metadata - Data Types and Length

- ItemDef **Length** attribute is required when DataType is **text**, **integer** or **float**
  - **text**: Maximum allowable length
  - **integer**: The largest allowable integer width
  - **float**: The largest allowable whole number width plus the maximum number of decimal digits
    (example: xxx.xx Length=5)

- For **integer** and **float** it is different from the SAS definition, which number of bytes for storage
- ItemDef **SignificantDigits** attribute is required for float variables
- It is invalid to use the **Length** attribute with other data types.

Define-XML Variable Metadata – def:Origin - SDTM

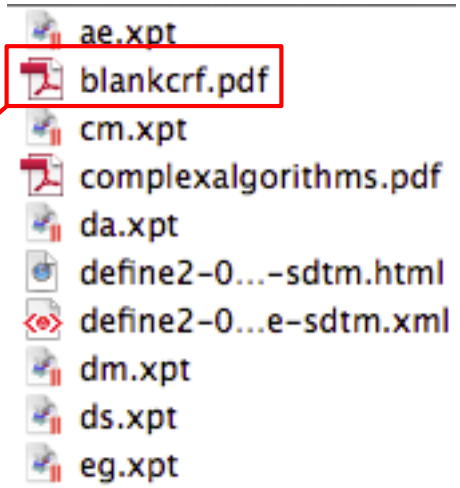
Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
STUDYID	Study Identifier	1	text	7		Protocol	
DOMAIN	Domain Abbreviation		text	2	["AE" = "Adverse Events"] <Domain Abbreviation (AE)>	Assigned	
USUBJID	Unique Subject Identifier	2	text	14		Derived	Concatenation of STUDYID and SUBJID
AESEQ	Sequence Number		integer	1		Derived	Sequential number identifying records within each USUBJID in the domain.
AESPID	Sponsor-Defined Identifier		text	4		CRF Page 21	
AETERM	Reported Term for the Adverse Event		text	25		CRF Page 21	
AEMODIFY	Modified Reported Term		text	9		Assigned	
AEDECOD	Dictionary-Derived Term	3	text	18	Adverse Event Dictionary	Assigned	
AEBODSYS	Body System or Organ Class		text	52	Adverse Event Dictionary	Assigned	
AESEV	Severity/Intensity		text	8	["MILD" = "Grade 1", "MODERATE" = "Grade 2", "SEVERE" = "Grade 3"] <Severity/Intensity Scale for Adverse Events>	CRF Page 21	

Define-XML Variable Metadata – def:Origin - SDTM

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
AEACN	Action Taken with Study Treatment		text	30	["DOSE NOT CHANGED", "DOSE REDUCED", "DRUG INTERRUPTED", "DRUG WITHDRAWN"] <Action Taken with Study Treatment>	CRF Page 21	

```
<ItemDef OID="IT.AE.AEACN" Name="AEACN" DataType="text" Length="30" SASFieldName="AEACN">
  <Description>
    <TranslatedText xml:lang="en">Action Taken with Study Treatment</TranslatedText>
  </Description>
  <CodeListRef CodeListOID="CL.ACN"/>
  <def:Origin Type="CRF">
    <def:DocumentRef leafID="LF.blankcrf">
      <def:PDFPageRef PageRefs="21" Type="PhysicalRef"/>
    </def:DocumentRef>
  </def:Origin>
</ItemDef>

 <def:leaf ID="LF.blankcrf" xlink:href="blankcrf.pdf">
   <def:title>Annotated Case Report Form</def:title>
 </def:leaf>
```




```
<td>CRF Page <a href="blankcrf.pdf#page=21">21</a>
</td>
```

Define-XML Variable Metadata – Origin *

Allowable Values	Definition	SDTM	ADaM
CRF	Collected on CRF. Variable has a reference to an annotated CRF.	☑	
Derived	Data value calculated from other data values by an algorithm or reproducible rule, defined by the sponsor.	☑	☑
Assigned	Data values set independent of subject related data values (e.g. Domain).	☑	☑
Protocol	Data values defined in the study protocol.	☑	
eDT	Data received via electronic data transfer. Refers to data collected via data streams, such as laboratory, ECG, or IVRS.	☑	
Predecessor	Data value is a direct copy of a variable in another dataset.	☑	☑

- We forgot SEND! (COLLECTED, DERIVED, OTHER, NOT AVAILABLE).
  Check the Define-XML v2 Errata (https://wiki.cdisc.org/display/PUB/Define-XML+2.0+Errata).

Define-XML Variable Metadata – def:Origin - ADaM

Variable	Label	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment
AVISIT	Analysis Visit	text	16	["Baseline", "Week 8", "Week 16", "Week 24"] <AVISIT>	Derived: Derived based on windowing algorithm described in SAP, Section 8.2
AVISITN	Analysis Visit (N)	integer	8	["0" = "Baseline", "8" = "Week 8", "16" = "Week 16", "24" = "Week 24"] <AVISITN>	Assigned: Numeric code for AVISIT
VISIT	Visit Name	text	19	VISIT	Predecessor: QS.VISIT
VISITNUM	Visit Number	float	8	VISITNUM	Predecessor: QS.VISITNUM
ADY	Analysis Relative Day	integer	8		Derived: ADY = ADT - TRTSDT + 1, if ADT>=TRTSDT. ADY = ADT - TRTSDT, if ADT<TRTSDT.
ADT	Analysis Date	integer	8		Derived: SAS date from QS.QSDTC

```
<ItemDef OID="IT.ADQSADAS.VISIT" Name="VISIT" SASFieldName="VISIT" DataType="text" Length="19">
  <Description>
    <TranslatedText xml:lang="en">Visit Name</TranslatedText>
  </Description>
  <CodeListRef CodeListOID="CL.VISIT"/>
  <def:Origin Type="Predecessor">
    <Description>
      <TranslatedText xml:lang="en">QS.VISIT</TranslatedText>
    </Description>
  </def:Origin>
</ItemDef>
```

A convention,
not machine readable!

Define-XML Variable Metadata – def:Origin - ADaM

Variable	Label	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment
AVISIT	Analysis Visit	text	16	["Baseline", "Week 8", "Week 16", "Week 24"] <AVISIT>	Derived: Derived based on windowing algorithm described in SAP, Section 8.2

```
<ItemGroupDef OID="IG.ADQSADAS" Name="ADQSADAS" SASDatasetName="ADQSADAS" Repeating="Yes"
  IsReferenceData="No" Purpose="Analysis"
  def:Structure="One record per subject per parameter per analysis visit per analysis date" def:Class="BASIC DATA STRUCTURE"
  def:CommentOID="COM.ADQSADAS" def:ArchiveLocationID="LF.ADQSADAS">
  <Description>
    <TranslatedText xml:lang="en">ADAS-Cog Analysis</TranslatedText>
  </Description>
  ...
  <ItemRef ItemOID="IT.ADQSADAS.AVISIT" OrderNumber="18" Mandatory="No" KeySequence="3" MethodOID="MT.ADQSADAS.AVISIT"/>
  ...
</ItemGroupDef>


<ItemDef OID="IT.ADQSADAS.AVISIT" Name="AVISIT" SASFieldName="AVISIT" DataType="text" Length="16">
  <Description>
    <TranslatedText xml:lang="en">Analysis Visit</TranslatedText>
  </Description>
  <CodeListRef CodeListOID="CL.AVISIT"/>
  <def:Origin Type="Derived"/>
</ItemDef>


<MethodDef OID="MT.ADQSADAS.AVISIT" Name="CM.ADQSADAS.AVISIT" Type="Computation">
  <Description>
    <TranslatedText xml:lang="en">Derived based on windowing algorithm described in SAP, Section 8.2</TranslatedText>
  </Description>
</MethodDef>
```

A MethodDef can also have a DocumentRef.

DEFINE-XML IN DETAIL

CONTROLLED TERMINOLOGY METADATA

Define-XML Controlled Terminology Metadata

- Enumerations
- Codelists
- Dictionary References

Define-XML Controlled Terminology Metadata

Causality [CL.AEREL]

Enumeration

Permitted Value (Code)
NOT RELATED
POSSIBLY RELATED
RELATED

Planned Arm Code [CL.ARMCD]

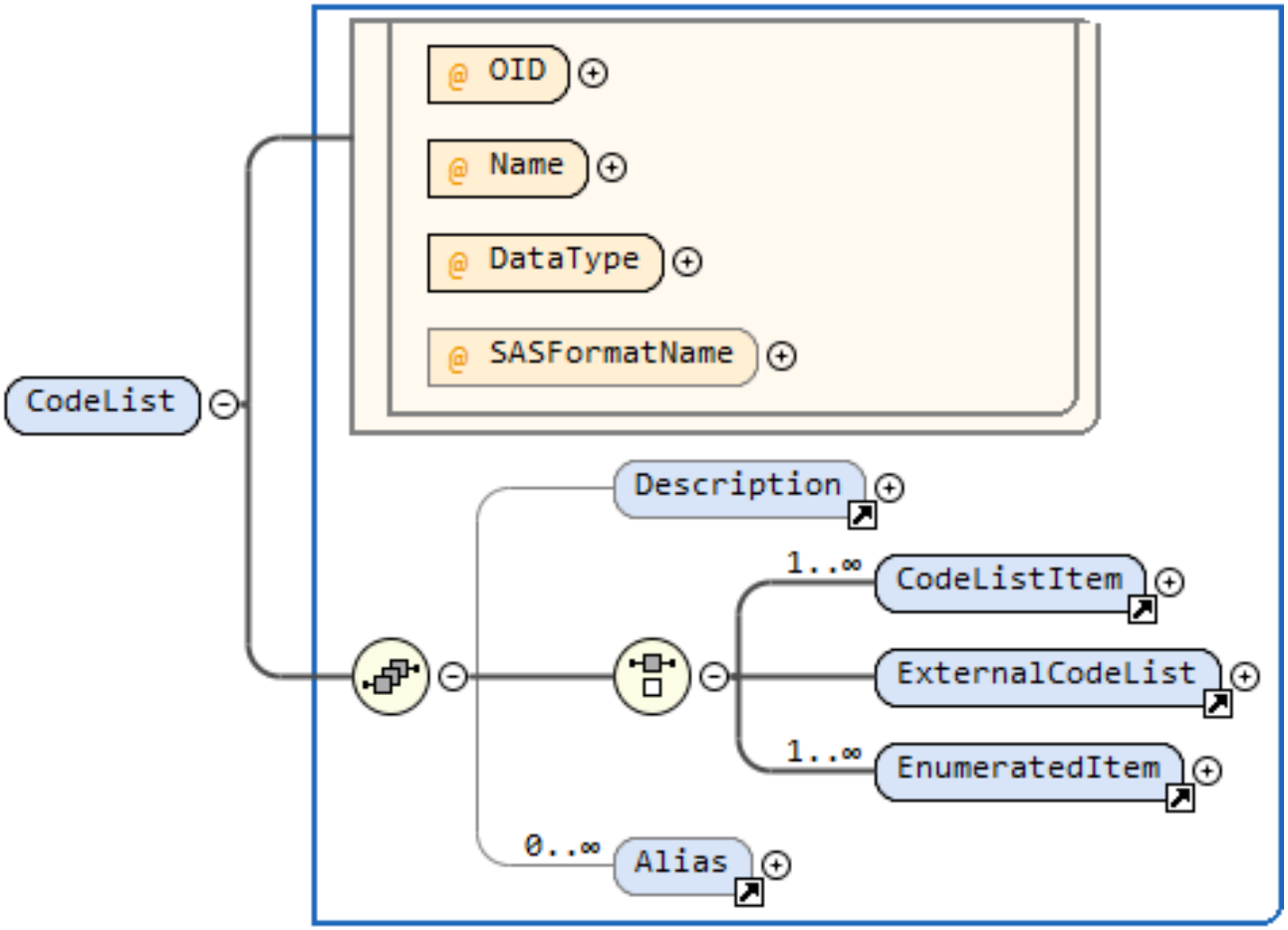
CodeList

Permitted Value (Code)	Display Value (Decode)
WONDER10	Miracle Drug 10 mg
WONDER20	Miracle Drug 20 mg
PLACEBO	Placebo
SCRNFAIL	Screen Failure

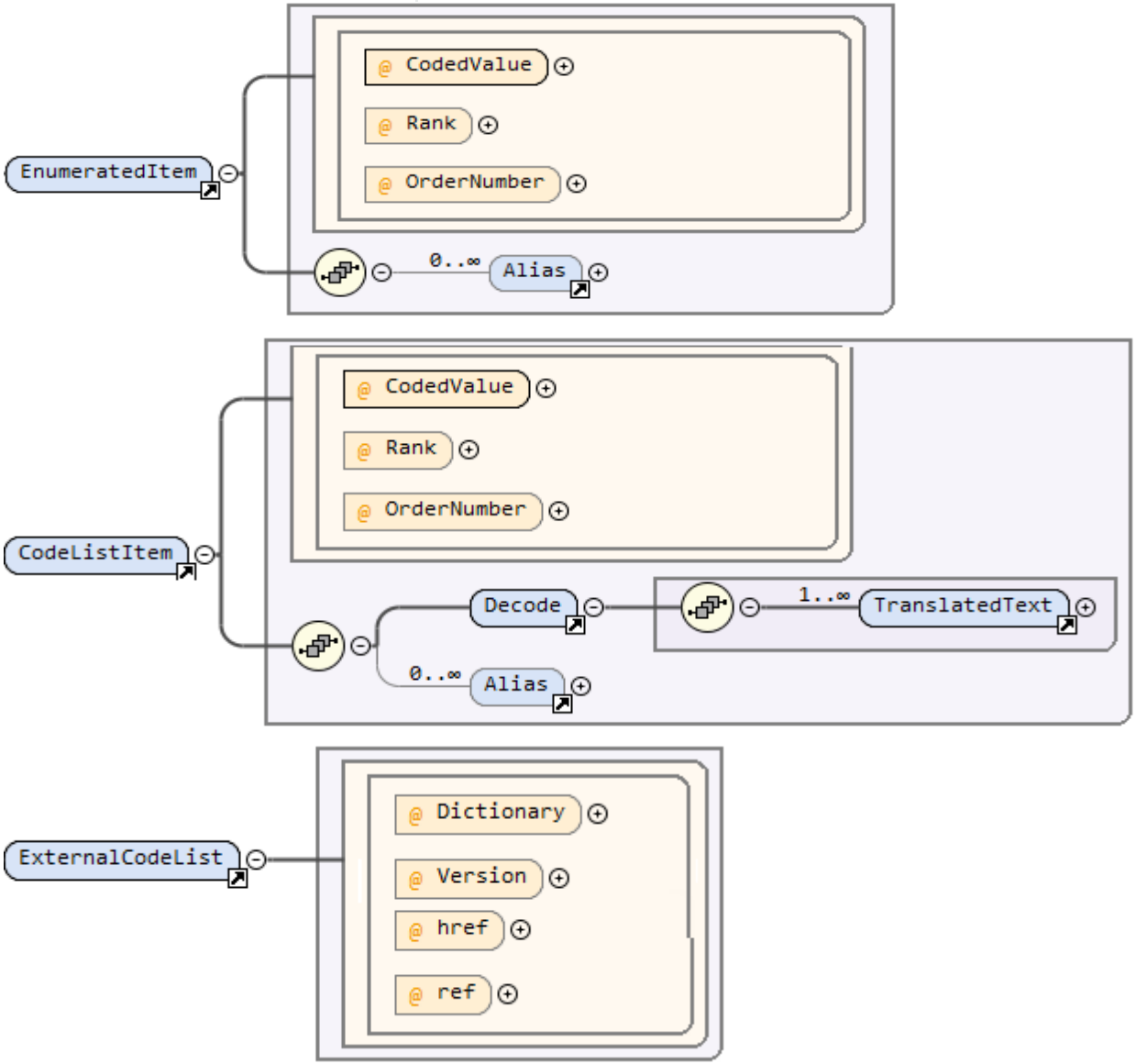
External Dictionaries

Reference Name	External Dictionary	Dictionary Version
Adverse Event Dictionary (CL.AEDICT_F)	MEDDRA	8.0
Drug Dictionary (CL.DRUGDICT_F)	WHODRUG	200204
ISO3166 (CL.ISO3166)	ISO3166	

Define-XML Controlled Terminology Metadata



Define-XML Controlled Terminology Metadata



Controlled Terminology Metadata - Enumeration example

Causality [CL.AEREL]

Permitted Value (Code)
NOT RELATED
POSSIBLY RELATED
RELATED

```
<CodeList OID="CL.AEREL" Name="Causality" DataType="text">
  <EnumeratedItem CodedValue="NOT RELATED"/>
  <EnumeratedItem CodedValue="POSSIBLY RELATED"/>
  <EnumeratedItem CodedValue="RELATED"/>
</CodeList>
```

Define-XML

Controlled Terminology Metadata - CodeList example

Planned Arm Code [CL.ARMCD]

Permitted Value (Code)	Display Value (Decode)
WONDER10	Miracle Drug 10 mg
WONDER20	Miracle Drug 20 mg
PLACEBO	Placebo
SCRNFAIL	Screen Failure

```
<CodeList OID="CL.ARMCD" Name="Planned Arm Code" DataType="text" SASFormatName="$ARMCD">
  <CodeListItem CodedValue="PLACEBO" OrderNumber="3">
    <Decode>
      <TranslatedText xml:lang="en">Placebo</TranslatedText>
    </Decode>
  </CodeListItem>
  <CodeListItem CodedValue="SCRNFAIL" OrderNumber="4">
    <Decode>
      <TranslatedText xml:lang="en">Screen Failure</TranslatedText>
    </Decode>
  </CodeListItem>
  <CodeListItem CodedValue="WONDER10" OrderNumber="1">
    <Decode>
      <TranslatedText xml:lang="en">Miracle Drug 10 mg</TranslatedText>
    </Decode>
  </CodeListItem>
  <CodeListItem CodedValue="WONDER20" OrderNumber="2">
    <Decode>
      <TranslatedText xml:lang="en">Miracle Drug 20 mg</TranslatedText>
    </Decode>
  </CodeListItem>
</CodeList>
```

OrderNumber indicates display order.

Rank indicates ranking significance (small, medium, large)

Define-XML

Controlled Terminology Metadata - Dictionary Reference example

External Dictionaries

Reference Name	External Dictionary	Dictionary Version
Adverse Event Dictionary (CL.AEDICT)	MedDRA	8.0

```
<CodeList OID="CL.AEDICT" Name="Adverse Event Dictionary" DataType="text">
  <ExternalCodeList Dictionary="MedDRA" Version="8.0" href="http://www.meddra.org/"/>
</CodeList>
```

Define-XML Controlled Terminology Metadata

- CDISC Controlled Terminology (CT) is defined for many SDTM and SEND variables, and for a few ADaM variables
  - Maintained in the US National Cancer Institute (NCI) Enterprise Vocabulary System
- Where there is a CDISC defined Controlled Vocabulary, cross-references to the relevant NCI codes should be provided in CodeLists using the ODM Alias element.
  - Context attribute must be nci:ExtCodeID
- Some CDISC CTs are Extensible meaning sponsor may add new terms
  - New terms should only be added if they are distinct in meaning from the existing terms.

Define-XML Controlled Terminology Metadata

Severity/Intensity Scale for Adverse Events [CL.AESEV, *C66769*]

Permitted Value (Code)	Display Value (Decode)
MILD [*C41338*]	Grade 1
MODERATE [*C41339*]	Grade 2
SEVERE [*C41340*]	Grade 3

```
<CodeList OID="CL.AESEV" Name="Severity/Intensity Scale for Adverse Events"
  DataType="text" SASFormatName="$AESEV">
  <CodeListItem CodedValue="MILD" Rank="1">
    <Decode>
      <TranslatedText xml:lang="en">Grade 1</TranslatedText>
    </Decode>
    <Alias Name="C41338" Context="nci:ExtCodeID"/>
  </CodeListItem>
  <CodeListItem CodedValue="MODERATE" Rank="2">
    <Decode>
      <TranslatedText xml:lang="en">Grade 2</TranslatedText>
    </Decode>
    <Alias Name="C41339" Context="nci:ExtCodeID"/>
  </CodeListItem>
  <CodeListItem CodedValue="SEVERE" Rank="3">
    <Decode>
      <TranslatedText xml:lang="en">Grade 3</TranslatedText>
    </Decode>
    <Alias Name="C41340" Context="nci:ExtCodeID"/>
  </CodeListItem>
  <Alias Name="C66769" Context="nci:ExtCodeID"/>
</CodeList>
```

Use Alias elements for CDISC Controlled Terminology C-Codes

Define-XML Controlled Terminology Metadata

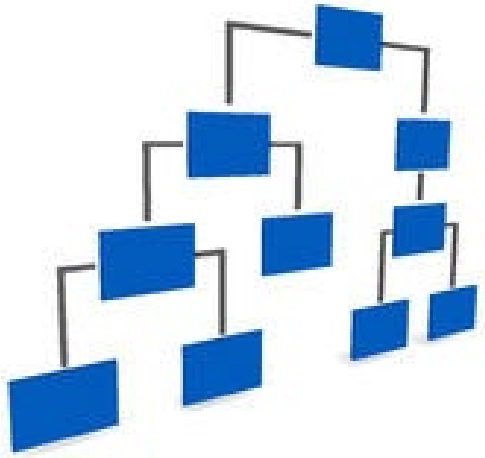
Unit (CM) [CL.CMUNIT, *C71620*]

Permitted Value (Code)
CAPSULE [*C48480*]
IU [*C48579*]
TABLET [*C48542*]
VIAL [*C48551*]
g [*C48155*]
mL [*C28254*]
mL/hr [*]

```
<CodeList OID="CL.CMUNIT" Name="Unit (CM)" DataType="text">
  <EnumeratedItem CodedValue="CAPSULE" OrderNumber="1">
    <Alias Name="C48480" Context="nci:ExtCodeID"/>
  </EnumeratedItem>
  <EnumeratedItem CodedValue="IU" OrderNumber="2">
    <Alias Name="C48579" Context="nci:ExtCodeID"/>
  </EnumeratedItem>
  <EnumeratedItem CodedValue="mL/hr" OrderNumber="7" def:ExtendedValue="Yes"/>
  <EnumeratedItem CodedValue="mL/kg" OrderNumber="8">
    <Alias Name="C67411" Context="nci:ExtCodeID"/>
  </EnumeratedItem>
```

DEFINE-XML IN DETAIL

VALUE LEVEL METADATA



Define-XML Value Level Metadata

- (Parameter) Value Level Metadata defines **metadata** for a **variable** under a specific **condition**
- Needed in the highly normalized data structure of SDTM, SEND and ADaM (generally one record per subject per test code or parameter per visit or observation)
- Examples:
  - **VSORRES**, **VSSTRESN** or **VSTRESU** based on the value of **VSTESTCD**
  - SuppQuals: **QVAL** bases on the value of **QNAM**
  - **LBORRES** based on the value of **LBCAT**, **LBSPEC**, **LBMETHOD**, **LBTESTCD**
  - **AVAL**, **BASE**, **CHG** based on the value of **PARAMCD**

Define-XML Value Level Metadata

- When metadata for a variable varies in a meaningful way that depends on values of other dataset variables, value level metadata (VLM) should be provided.
- Can be provided for any dataset variable
- Condition can be based on values of multiple variables with more complicated conditions (not just EQUAL)
- Examples:
  - VSTESTCD **EQ** "SYSBP" and VSPOS **EQ** "STANDING“
  - PARAMCD **IN** ("ACITM01", "ACITM02", ... , "ACITM14")
  - PARAMCD **NE** "ACTTOT“
- Available: LT, LE, GT, GE, EQ, NE, IN, NOTIN
- Unambiguous interpretation by a computer

Define-XML SDTM Value Level Metadata

Value Level Metadata - SC [SCORRES]

Variable	Where	Type	Length / Display Format	Controlled Terms or Format	Origin	Derivation/Comment
SCORRES	SCTESTCD EQ EDLEVEL (Education Level)	text	24		CRF Page 6	
SCORRES	SCTESTCD EQ MARISTAT (Marital Status)	text	17	Marital Status	CRF Page 6	
SCORRES	SCTESTCD EQ SUBJINIT (Subject Initials)	text	3		CRF Page 3	

Value Level Metadata - LB [LBORRES]

Variable	Where	Type	Length / Display Format	Controlled Terms or Format	Origin	Derivation/Comment
LBORRES	LBTESTCD EQ BILI (Bilirubin) AND LBCAT EQ CHEMISTRY AND LBSPEC EQ BLOOD	float	3		eDT	
LBORRES	LBTESTCD EQ BUN (Blood Urea Nitrogen) AND LBCAT EQ CHEMISTRY AND LBSPEC EQ BLOOD	float	4		eDT	

Define-XML ADaM (Parameter) Value Level Metadata

Parameter Value List - ADQSADAS [AVAL]

Variable	Where	Type	Length / Display Format	Controlled Terms or Format	Origin	Derivation/Comment
AVAL	PARAMCD IN ("ACITM01" (Word Recall Task) , "ACITM02" (Naming Objects And Fingers (Refer To 5 C) , "ACITM14" (Recall Of Test Instructions))	integer	8		Derived	QS.QSSTRESN where QSTESTCD=PARAMCD
AVAL	PARAMCD EQ ACTOT (Adas-Cog(11) Subscore)	integer	8		Derived	Sum of ADAS scores for items 1, 2, 4, 5, 6, 7, 8, 11, 12, 13, and 14, see Analysis Data Reviewers Guide (Page 3) for details on adjusting for missing values. Analysis Data Reviewer's Guide (analysis-data-reviewers-guide.pdf)

Define-XML Value Level Metadata

```
<ItemDef OID="IT.ADQSADAS.AVAL" Name="AVAL" SASFieldName="AVAL"
         DataType="integer" Length="8">
    <Description>
      <TranslatedText xml:lang="en">Analysis Value</TranslatedText>
    </Description>
    <def:ValueListRef ValueListOID="VL.ADQSADAS.AVAL"/>
 </ItemDef>


<def:ValueListDef OID="VL.ADQSADAS.AVAL">
   <ItemRef ItemOID="IT.ADQSADAS.QSSEQ.ACITM01-ACITM14" Mandatory="No">
      <def:WhereClauseRef WhereClauseOID="WC.ADQSADAS.QSSEQ.ACITM01-ACITM14"/>
   </ItemRef>
   <ItemRef ItemOID="IT.ADQSADAS.QSSEQ.ACTOT" Mandatory="No">
      <def:WhereClauseRef WhereClauseOID="WC.ADQSADAS.QSSEQ.ACTOT"/>
    </ItemRef>
</def:ValueListDef>
```

Define-XML Value Level Metadata

```
<def:ValueListDef OID="VL.ADQSADAS.AVAL">
  <ItemRef ItemOID="IT.ADQSADAS.AVAL.ACITM01-ACITM14" Mandatory="No"
    MethodOID="MT.ADQSADAS.AVAL.ACITM01-ACITM14">
    <def:WhereClauseRef WhereClauseOID="WC.ADQSADAS.AVAL.ACITM01-ACITM14"/>
  </ItemRef>
  <ItemRef ItemOID="IT.ADQSADAS.AVAL.ACTOT" Mandatory="No"
    MethodOID="MT.ADQSADAS.AVAL.ACTOT">
    <def:WhereClauseRef WhereClauseOID="WC.ADQSADAS.AVAL.ACTOT"/>
  </ItemRef>
</def:ValueListDef>


<def:WhereClauseDef OID="WC.ADQSADAS.AVAL.ACITM01-ACITM14">
  <RangeCheck Comparator="IN" SoftHard="Soft" def:ItemOID="IT.ADQSADAS.PARAMCD">
    <CheckValue>ACITM01</CheckValue>
...
    <CheckValue>ACITM14</CheckValue>
  </RangeCheck>
</def:WhereClauseDef>

<def:WhereClauseDef OID="WC.ADQSADAS.AVAL.ACTOT">
  <RangeCheck Comparator="EQ" SoftHard="Soft" def:ItemOID="IT.ADQSADAS.PARAMCD">
    <CheckValue>ACTOT</CheckValue>
  </RangeCheck>
</def:WhereClauseDef>
```

Define-XML Value Level Metadata

```
<def:ValueListDef OID="VL.ADQSADAS.AVAL">
  <ItemRef ItemOID="IT.ADQSADAS.AVAL.ACITM01-ACITM14" Mandatory="No"
    MethodOID="MT.ADQSADAS.AVAL.ACITM01-ACITM14">
    <def:WhereClauseRef WhereClauseOID="WC.ADQSADAS.AVAL.ACITM01-ACITM14"/>
  </ItemRef>
  <ItemRef ItemOID="IT.ADQSADAS.AVAL.ACTOT" Mandatory="No"
    MethodOID="MT.ADQSADAS.AVAL.ACTOT">
    <def:WhereClauseRef WhereClauseOID="WC.ADQSADAS.AVAL.ACTOT"/>
  </ItemRef>
</def:ValueListDef>
```

```
<ItemDef OID="IT.ADQSADAS.AVAL.ACITM01-ACITM14" Name="AVAL" SASFieldName="AVAL"
  DataType="integer" Length="8">
  <Description>
    <TranslatedText xml:lang="en">Analysis Value</TranslatedText>
  </Description>
  <def:Origin Type="Derived"/>
</ItemDef>
```

```
<MethodDef OID="MT.ADQSADAS.AVAL.ACITM01-ACITM14" Name="CM.ADQSADAS.AVAL.ACITM01-ACITM14"
  Type="Computation">
  <Description>
    <TranslatedText xml:lang="en">QS.QSSTRESN where QSTESTCD=PARAMCD</TranslatedText>
  </Description>
</MethodDef>
```

Define-XML Variable Metadata - Methods

- Algorithms (Methods) must be provided if any variables or values are defined as derived
- To enhance traceability users are encouraged to provide descriptions that include accurate and consistent references to source variables and derivations.
- Targeted at non-programmers, so written in **plain English**, not in syntax.
- For cases where the algorithm description is longer than a few lines, needs more than text, or formatting is needed, a reference can be made to a page or section in a supplemental document containing the additional details.

Define-XML Variable Metadata - Methods

Demographics (DM) [Location: dm.xpt]

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
AGE	Age		integer	2		Derived	Age at Screening Date (Screening Date - Birth date). For the complete algorithm see the referenced external document. Complex Algorithms

```
<ItemGroupDef OID="IG.DM" Domain="DM" Name="DM" Repeating="No"
  IsReferenceData="No" SASDatasetName="DM" Purpose="Tabulation"
  def:Structure="One record per subject" def:Class="SPECIAL PURPOSE"
  def:CommentOID="COM.DOMAIN.DM" def:ArchiveLocationID="LF.DM">
  <Description>
    <TranslatedText xml:lang="en">Demographics</TranslatedText>
  </Description>

  <ItemRef ItemOID="IT.DM.AGE" OrderNumber="9" Mandatory="Yes" MethodOID="MT.AGE"/>

</ItemGroupDef>

<MethodDef OID="MT.AGE" Name="Algorithm to derive AGE" Type="Computation">
  <Description>
    <TranslatedText xml:lang="en">Age at Screening Date (Screening Date - Birth date).
For the complete algorithm see the referenced external document.</TranslatedText>
  </Description>
  <def:DocumentRef leafID="LF.ComplexAlgorithms">
    <def:PDFPageRef PageRefs="DM" Type="NamedDestination"/>
  </def:DocumentRef>
</MethodDef>

<def:leaf ID="LF.ComplexAlgorithms" xlink:href="complexalgorithms.pdf">
  <def:title>Complex Algorithms</def:title>
</def:leaf>
```

Define-XML Comments

- ✔ Comments may be added to dataset, variable and value level metadata.
- ✖ Comments should not be used to store information about computational algorithms/derivations or origin (even though the stylesheet might display them together).

Adverse Events Analysis Dataset (ADAE) [Location: adae.xpt]

Variable	Label	Key	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment

Define-XML Comments

Demographics (DM) [Location: dm.xpt]

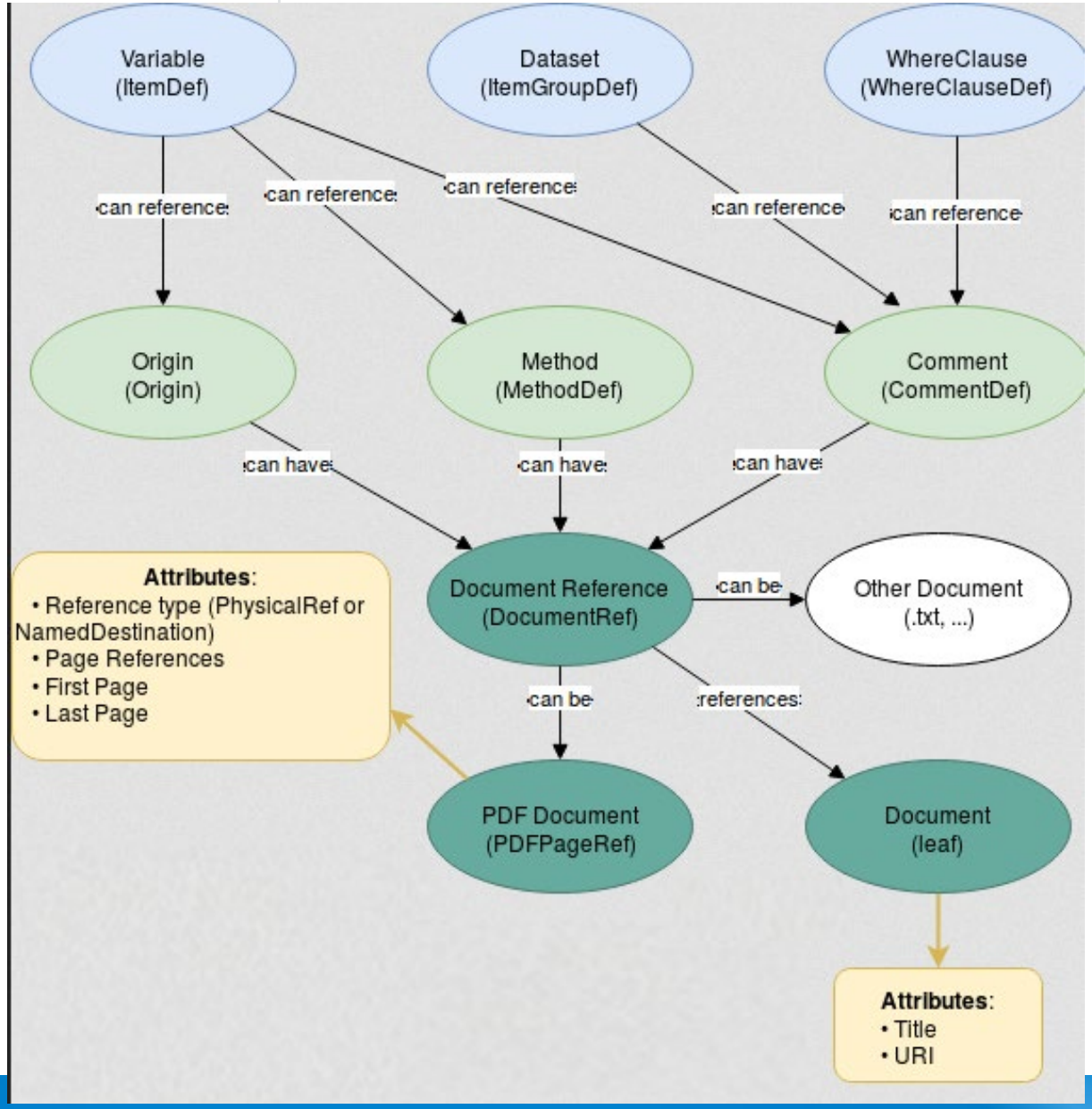
Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
ARMCD	Planned Arm Code		text	8	["PLACEBO" = "Placebo", "SCRNFAIL" = "Screen Failure", "WONDER10" = "Miracle Drug 10 mg", "WONDER20" = "Miracle Drug 20 mg"] <Planned Arm Code>	Assigned	Assigned based on Randomization Number. See Note 2.1 Reviewers Guide

```
<ItemDef OID="IT.DM.ARMCD" Name="ARMCD" DataType="text" Length="8" SASFieldName="ARMCD"
  def:CommentOID="COM.ARMCD">
  <Description>
    <TranslatedText xml:lang="en">Planned Arm Code</TranslatedText>
  </Description>
  <CodeListRef CodeListOID="CL.ARMCD"/>
  <def:Origin Type="Assigned"/>
</ItemDef>

<def:CommentDef OID="COM.ARMCD">
  <Description>
    <TranslatedText xml:lang="en">Assigned based on Randomization Number. See Note 2.1</TranslatedText>
  </Description>
  <def:DocumentRef leafID="LF.ReviewersGuide"/>
</def:CommentDef>

<def:leaf ID="LF.ReviewersGuide" xlink:href="reviewersguide.pdf">
  <def:title>Reviewers Guide</def:title>
</def:leaf>
```

Define-XML Document References



Define-XML Document References

```
<def:Origin Type="CRF">
  <def:DocumentRef leafID="LF.blankcrf">
    <def:PDFPageRef PageRefs="9 22" Type="PhysicalRef"/>
  </def:DocumentRef>
</def:Origin>

<def:CommentDef OID="COM.DOMAIN.DM">
  <Description>
    <TranslatedText xml:lang="en">See Reviewer's Guide, Section 2.1 Demographics</TranslatedText>
  </Description>
  <def:DocumentRef leafID="LF.ReviewersGuide">
    <def:PDFPageRef PageRefs="section2.1" Type="NamedDestination"/>
  </def:DocumentRef>
</def:CommentDef>

<def:leaf ID="LF.ReviewersGuide" xlink:href="reviewersguide.pdf">
  <def:title>Reviewers Guide</def:title>
</def:leaf>
```

Displaying Define-XML

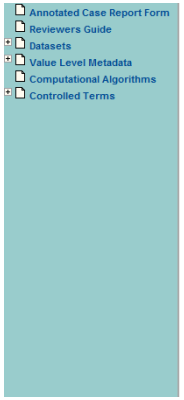
Define-XML

- The Define-XML specification Does **not** describe how this metadata should be displayed

Display is not part of the standard

Datasets for Study study1

Dataset	Description	Structure	Purpose	Keys	Location
AE	Adverse Events	Events - One record per adverse event per subject	Tabulation	STUDYID USUBJID AEDECOD AESTDTC	Adverse Events SAS transport file
CE	Clinical Events	Events - One record per event per subject	Tabulation	STUDYID USUBJID CETERM CESTDTC	Clinical Events SAS transport file
CM	Concomitant Medications	Interventions - One record per recorded medication occurrence or constant-dosing interval per subject	Tabulation	STUDYID USUBJID CMTRT CMSTDTC	Concomitant Medications SAS transport file
CO	Comments	Special Purpose Domains - One record per comment per subject	Tabulation	STUDYID USUBJID COSEQ	Comments SAS transport file
DA	Drug Accountability	Findings - One record per drug accountability finding per subject	Tabulation	STUDYID USUBJID DATESTCD DADTC	Drug Accountability SAS transport file
DM	Demographics	Special Purpose Domains - One record per subject	Tabulation	STUDYID USUBJID	Demographics SAS transport file
DS	Disposition	Events - One record per disposition status or protocol milestone per subject	Tabulation	STUDYID USUBJID DSDECOD DSSTDTC	Disposition SAS transport file



Datasets for Study CDISC01

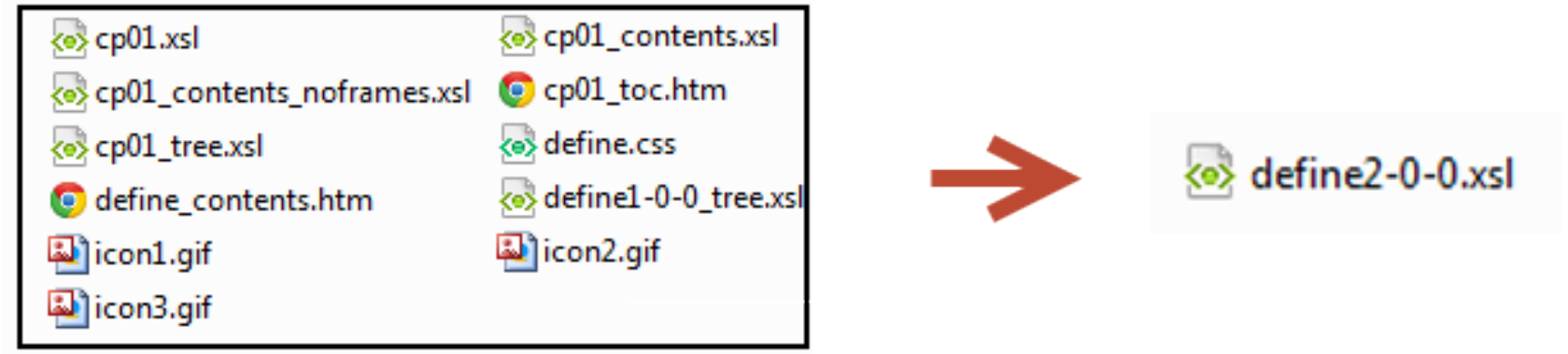
Dataset	Description	Class	Structure	Purpose	Keys
TA	Trial Arms	Trial Design	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD
TE	Trial Elements	Trial Design	One record per planned Element	Tabulation	STUDYID, ETCD
TI	Trial Inclusion/Exclusion Criteria	Trial Design	One record per I/E criterion	Tabulation	STUDYID, IETESTCD
TS	Trial Summary	Trial Design	One record per trial summary parameter value	Tabulation	STUDYID, TSPARMC TSSEQ
TV	Trial Visits	Trial Design	One record per planned Visit per Arm	Tabulation	STUDYID, VISITNUM ARMCD
DM	Demographics	Special	One record per	Tabulation	STUDYID, USUBJID

SDTM Datasets for Study CDISCPILOT01

Dataset	Description	Class	Structure	Purpose
TA	Trial Arms	Trial Design	One record per planned Element per Arm	Tabulation
TE	Trial Elements	Trial Design	One record per planned Element	Tabulation
TI	Trial Inclusion/ Exclusion Criteria	Trial Design	One record per I/E criterion	Tabulation
TS	Trial Summary	Trial Design	One record per trial summary parameter value	Tabulation
TV	Trial Visits	Trial Design	One record per planned Visit per Arm	Tabulation
DM	Demographics	Special Purpose	One record per subject	Tabulation
SE	Subject Elements	Special Purpose	One record per actual Element per subject	Tabulation
SV	Subject Visits	Special Purpose	One record per actual visit per subject	Tabulation
CM	Concomitant Medications	Interventions	One record per recorded medication occurrence or constant-dosing interval per subject	Tabulation
EX	Exposure	Interventions	One record per constant dosing	Tabulation

Define-XML | Display

- The Define-XML standard does not dictate how a stylesheet should display a define.xml file.
- An example stylesheet is provided, however this can be altered to satisfy alternate visualization needs.
- The example stylesheet is only one file



Define-XML Display

- The example CDISC stylesheet conforms to web standards and follows accessibility guidelines
- Reviewed by FDA in 2013
- It should behave much better than older stylesheets
- Uses JavaScript, but degrades gracefully when JavaScript is disabled
- Printing looks quite acceptable
- It might make sense to also submit the HTML rendition; since not every browser allows rendition of the stylesheet

Define-XML Display

SDTM-IG 3.1.2

- Annotated Case Report For
- Reviewers Guide
- Complex Algorithms
- ▶ Tabulation Datasets
- ▶ Value Level Metadata
- ▶ Controlled Terminology
- ▶ Computational Algorithms
- ▶ Comments

Date of document generation: 2013-03-03T17:04:44

Stylesheet version: 2013-04-24

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
TA	Trial Arms	TRIAL DESIGN	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD	ta.xpt	
TE	Trial Elements	TRIAL DESIGN	One record per planned Element	Tabulation	STUDYID, ETCD	te.xpt	
TI	Trial Inclusion/Exclusion Criteria	TRIAL DESIGN	One record per I/E criterion	Tabulation	STUDYID, IETESTCD	ti.xpt	
TS	Trial Summary	TRIAL DESIGN	One record per trial summary parameter value	Tabulation	STUDYID, TSPARMCD, TSSEQ	ts.xpt	
TV	Trial Visits	TRIAL DESIGN	One record per planned Visit per Arm	Tabulation	STUDYID, VISITNUM, ARMCD	tv.xpt	
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide
SE	Subject Elements	SPECIAL PURPOSE	One record per actual Element per subject	Tabulation	STUDYID, USUBJID, SESTDTC, SEENDTC, TAETORD, ETCD	se.xpt	
SV	Subject Visits	SPECIAL PURPOSE	One record per actual visit per subject	Tabulation	STUDYID, USUBJID, SVSTDTC,	sv.xpt	

CDISC Wiki: XSL Stylesheet Library

http://wiki.cdisc.org/display/PUB/Stylesheet+Library

Stylesheet Library

Created by Joe Ben Clark, last modified by Sam Hume on Mar 16, 2017

Introduction

This page represents style sheets produced by the CDISC community. As the style sheets included with the CDISC XML Technologies standards are updated, these new versions will be made available here for download and use. Other style sheets for use with the standards may also be included here to provide alternative views of standards content to meet the needs of different use cases. A style sheet represents a particular view of XML content. The CDISC XML standards do not dictate how a style sheet should display XML content.

All style sheets are provided as is and without warranties (see the CDISC Representations and Warranties, Limitations of Liability, and Disclaimers). Issues found in any of the style sheets may be reported using JIRA (for example Define-XML style sheet issues can be reported at http://jira.cdisc.org/browse/DEF).

Style Sheets

Style Sheet File	Standard	Provided By	Publication Date	Status	Description
Define-XML v2.0 style sheet	Define-XML v2.0	XML Technologies Team (@Lex Jansen)	2013-04-24	Published	• The original style sheet included in the Define-XML v2.0 standard. Included in the .zip file with the standard specification and schema.
ODM1-3-1-simple-overview001.xslt	ODM	@Vojtech Huser	2014-12-10		• Simple view of an ODM file • Example file: 05_Raloxifene_Study-SurgicalFindingsForm.ODM.xml
Define-XML v2.0 style sheet	Define-XML v2.0	XML Technologies Team (@Lex Jansen)	2015-01-16	Published	• The style sheet published with version 1.0 of the Analysis Results Metadata Specification for Define-XML v2.0 • This is an improved version of the 2013-04-24 Define-XML v2.0 style sheet. • It is not required to have Analysis Results Metadata to be able to use this improved style sheet with Define-XML v2.0 • Changes are listed in the beginning of the style sheet
http://figshare.com/articles/Protocol_Knowledge_Representation/1096216	CT.gov XML -> (ODM+SDM)	@Vojtech Huser	2014-12-10		transform CT.gov XML into ODM+SDM

Define-XML

Display – New stylesheet being developed at PhUSE

CDISC01

- Annotated Case Report Form
- ▸ Supplemental Documents
- ▸ Datasets
- ▸ Controlled Terminology
- ▸ Derivations

Expand all VLM

Collapse all VLM

Date/Time of Define-XML document generation: 2013-03-03T17:04:44
Define-XML version: 2.0.0
Stylesheet version: 2018-03-01 - DRAFT v0.991

Standard	SDTM-IG 3.1.2
Study Name	CDISC01
Study Description	CDISC Test Study
Protocol Name	CDISC01
Metadata Name	Study CDISC01, Data Definitions
Metadata Description	Study CDISC01, Data Definitions

Datasets

Dataset	Description	Class	Structure	Purpose	Keys	Documentation	Location
TA	Trial Arms	TRIAL DESIGN	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD		ta.xpt
TE	Trial Elements	TRIAL DESIGN	One record per planned Element	Tabulation	STUDYID, ETCD		te.xpt
TI	Trial Inclusion/Exclusion Criteria	TRIAL DESIGN	One record per I/E criterion	Tabulation	STUDYID, IETESTCD		ti.xpt
TS	Trial Summary	TRIAL DESIGN	One record per trial summary parameter value	Tabulation	STUDYID, TSPARMCD, TSSEQ		ts.xpt
TV	Trial Visits	TRIAL DESIGN	One record per planned Visit per Arm	Tabulation	STUDYID, VISITNUM, ARMCD		tv.xpt
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide [section2.1]	dm.xpt

Define-XML

Display – New stylesheet being developed at PhUSE

DM (Demographics) - SPECIAL PURPOSE [Location: dm.xpt]

Related Supplemental Qualifiers Dataset: SUPPDM (Supplemental Qualifiers for DM)

Variable	Label / Description	Type	Length or Display Format	Controlled Terms or ISO Format	Origin / Source / Derivation / Comment
STUDYID	Study Identifier	text	7		Protocol
DOMAIN	Domain Abbreviation	text	2	Domain Abbreviation (DM) • "DM" = "Demographics"	Assigned
USUBJID	Unique Subject Identifier	text	14		Derived Concatenation of STUDYID and SUBJID Formal Expression
SUBJID	Subject Identifier for the Study	text	6		CRF Annotated Case Report Form [3]
RFSTDTC	Subject Reference Start Date/Time	date		ISO 8601	Derived RFSTDTC = first date/time of study drug, for safety subject. Null for screen failures.
SEX	Sex	text	1	Sex • "F" = "Female" • "M" = "Male" • "U" = "Unknown"	CRF Annotated Case Report Form [6]
RACE	Race	text	40	Race [7 Terms]	CRF Annotated Case Report Form [6]
ETHNIC	Ethnicity	text	22	Ethnic Group • "HISPANIC OR LATINO" • "NOT HISPANIC OR LATINO"	CRF Annotated Case Report Form [6]

Define-XML

Display – New stylesheet being developed at PhUSE

VS (Vital Signs) - FINDINGS [Location: vs.xpt]

Related Supplemental Qualifiers Dataset: SUPPVS (Supplemental Qualifiers for VS)						
Variable	**Where Condition**	**Label / Description**	**Type**	**Length or Display Format**	**Controlled Terms or ISO Format**	**Origin / Source / Derivation / Comment**
STUDYID		Study Identifier	text	7		Protocol
DOMAIN		Domain Abbreviation	text	2	Domain Abbreviation (VS) • "VS" = "Vital Signs"	Assigned
USUBJID		Unique Subject Identifier	text	14		Derived Concatenation of STUDYID and SUBJID Formal Expression
VSSEQ		Sequence Number	integer	2		Derived Sequential number identifying records within each USUBJID in the domain.
VSTESTCD		Vital Signs Test Short Name	text	20	Vital Signs Test Code [6 Terms]	Assigned
VSTEST		Vital Signs Test Name	text	24	Vital Signs Test Name [6 Terms]	CRF Annotated Case Report Form [11]
VSPOS		Vital Signs Position of Subject	text	7		CRF Annotated Case Report Form [11]
VSORRES VLM		Result or Finding in Original Units	text	30		CRF Annotated Case Report Form [11]

Define-XML

Display – New stylesheet being developed at PhUSE

VS (Vital Signs) - FINDINGS [Location: vs.xpt]

Related Supplemental Qualifiers Dataset: SUPPVS (Supplemental Qualifiers for VS)						
Variable	**Where Condition**	**Label / Description**	**Type**	**Length or Display Format**	**Controlled Terms or ISO Format**	**Origin / Source / Derivation / Comment**
STUDYID		Study Identifier	text	7		Protocol
DOMAIN		Domain Abbreviation	text	2	Domain Abbreviation (VS)	Assigned
VSORRES VLM		Result or Finding in Original Units	text	30		CRF Annotated Case Report Form [11]
	VSTESTCD = "DIABP" (Diastolic Blood Pressure)	Diastolic Blood Pressure (Orig U)	integer	2		CRF Annotated Case Report Form [11]
	VSTESTCD = "FRMSIZE" (Body Frame Size)	Body Frame Size (Orig U)	text	6	Size • "LARGE" • "MEDIUM" • "SMALL"	CRF Annotated Case Report Form [11]
	VSTESTCD = "HEIGHT" (Height)	Height (Orig U)	float	5.1		CRF Annotated Case Report Form [11]
	VSTESTCD = "PULSE" (Pulse	Pulse Rate (Orig U)	integer	2		CRF

Analysis Results Metadata for Define-XML

Why Analysis Results Metadata ?

- **Traceability** is a fundamental principle in ADaM:
  - It enables the reader to understand the data flow from **collection** to **SDTM** and **ADaM** to **Analysis Results**
- Analysis Results Metadata provides **traceability** from **results** in a statistical display to the **data** in the analysis datasets
- Analysis Results Metadata includes:
  - Identification of critical analysis displays and particular results
  - Details on analysis performed (reason, underlying analysis dataset(s), selection criteria, documentation, programming statements)
- Facilitates documentation and reproduction of the analysis results
- Not needed - or even advisable - for every analysis in a submission

ADaM Results Metadata v1 for Define-XML v2

PMDA – New Study Data Technical Conformance Guide (April 27, 2015) *

- In order for the review of clinical study data to progress smoothly, it is important that the relationship between the analysis results shown in the application documents and the analysis datasets is easily understandable. Therefore, the definition documents of the ADaM datasets should preferably include Analysis Results Metadata ...
- For the format of the Analysis Results Metadata, the applicant should refer to the Analysis Results Metadata Specification for Define-XML by CDISC to the extent possible, but if it is difficult to include it into the definition document, it is possible to submit it as a separated file in PDF format.

* Advanced Review with Electronic Data Promotion Group
(http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html)
PMDA Technical conformance guide (in Japanese) http://www.pmda.go.jp/files/000204728.pdf
Provisional Translation (as of July 2015) http://www.pmda.go.jp/files/000206449.pdf

ADaM Results Metadata v1 for Define-XML v2

ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]

Protocol: CDISCPILOT01 *Page 1 of 1*
Population: Efficacy

Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF

Analysis Variable(s)

CHG (Change from Baseline)

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Baseline			
n	79	81	74
Mean (SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.74)
[illegible] (Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;57)
	79	81	74
[illegible] (SD)	26.7 (13.79)	26.4 (13.18)	22.8 (12.48)
Median (Range)	24.0 (5;62)	25.0 (6;62)	20.0 (3;62)
Change from Baseline			
n	79	81	74
Mean (SD)	2.5 (5.80)	2.0 (5.55)	1.5 (4.26)
Median (Range)	2.0 (-11;16)	2.0 (-11;17)	1.0 (-7;13)
p-value(Dose Response) [1][2]			0.245
p-value(Xan - Placebo) [1][3]		0.569	0.233
Diff of LS Means (SE)		-0.5 (0.82)	-1.0 (0.84)
95% CI		(-2.1;1.1)	(-2.7;0.7)
p-value(Xan High - Xan Low) [1][3]			0.520
Diff of LS Means (SE)			-0.5 (0.84)
95% CI			(-2.2;1.1)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rtf_eff1.sas *21:05 Monday, June 26, 2006*

ADaM Results Metadata v1 for Define-XML v2

Analysis Results Metadata (Summary) for Study CDISC-Sample

Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population) Dose response analysis for ADAS-Cog changes from baseline Pairwise comparisons to placebo for ADAS-Cog changes from baseline
Table 14-5.02 Incidence of Treatment Emergent Serious Adverse Events by Treatment Group Incidence of Treatment Emergent Serious Adverse Events by Treatment Group

Table 14-3.01

Display	Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
Analysis Result	**Dose response analysis for ADAS-Cog changes from baseline**
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]
Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose). SAP Section 10.1.1

Programming Statements	[SAS version 9.2]
	`proc glm data = ADQSADAS;`
	`  where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT";`
	`  class SITEGR1;`
	`  model CHG = TRTPN SITEGR1;`
	`run;`
	at14-3-01.sas

Analysis Result	**Pairwise comparisons to placebo for ADAS-Cog changes from baseline**
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)

ADaM Results Metadata v1 for Define-XML v2

Analysis Results Metadata (Detail) for Study CDISC Sample

Table 14-3.01

Display	Table 14-3.01 Primary Endpoint Analysis: ADAS Cog - Summary at Week 24 - LOCF (Efficacy Population)
Analysis Result	Dose response analysis for ADAS Cog changes from baseline
Analysis Parameter(s)	ParamCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADQSADAS ParamCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"
Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose). SAP Section 10.1.1
Programming Statements	[SAS version 9.2] proc glm data = ADQSADAS; where EFFFL="Y" and ANL01FL="Y" and AVISIT="Week 24" and PARAMCD="ACTOT"; class model run;
Analysis Result	Parameter

10.1. Primary Efficacy Endpoints

10.1.1. ADAS-COG (11)

The primary analysis of the ADAS-Cog (11) at Week 24 will use the efficacy population with LOCF imputation for any missing values at Week 24. A secondary analysis will be performed for the Week 24 endpoint using the completers subset using observed data. For each of these analyses, an ANCOVA model will be used with the baseline score, site and treatment included as independent variables. Treatment will be included as a continuous variable, and results for a test of dose response will be produced. Interaction

ADaM Results Metadata v1 for Define-XML v2

- For Define-XML v2 **only**
- Utilizes various Define-XML v2 constructs
  - WhereClause
  - Document reference support
  - Comment support

- It is recommended to move to Define-XML v2
- FDA has announced that support for CRT-DDS 1.0 (Define-XML 1.0) is ending in March 2018

ADaM Results Metadata v1 for Define-XML v2

```
ODM
  Study
    GlobalVariables
    MetaDataVersion
      def:SupplementalDoc
      def:ValueListDef
      def:WhereClauseDef
      ItemGroupDef
      ItemDef
      CodeList
      MethodDef
      def:CommentDef
      def:leaf
      arm:AnalysisResultDisplays
```

ADaM Results Metadata v1 for Define-XML v2

- Updated Define-XML v2 XSL Stylesheet
- Works for ADaM, SDTM, SEND (with or without Results Metadata)
  - Bug fixes
  - Many improvements for linking to external PDF documents with physical page references or named destinations

  - Check the CDISC stylesheet library wiki page: https://wiki.cdisc.org/display/PUB/Stylesheet+Library

ADaM Results Metadata v1 for Define-XML v2

Table 5.3.1 Analysis Results Metadata Fields

Analysis Results Metadata Field	Description
DISPLAY IDENTIFIER	A unique identifier for the specific analysis display (such as a table or figure number)
DISPLAY NAME	Title of display, including additional information if needed to describe and identify the display (e.g., analysis population)
RESULT IDENTIFIER	Identifies the specific analysis result within a display. For example, if there are multiple p-values on a display and the analysis results metadata specifically refers to one of them, this field identifies the p-value of interest. When combined with the display identifier provides a unique identification of a specific analysis result.
PARAM	The analysis parameter in the BDS analysis dataset that is the focus of the analysis result. Does not apply if the result is not based on a BDS analysis dataset.
PARAMCD	Corresponds to PARAM in the BDS analysis dataset. Does not apply if the result is not based on a BDS analysis dataset.
ANALYSIS VARIABLE	The analysis variable being analyzed
REASON	The rationale for performing this analysis. It indicates when the analysis was planned (e.g., "Pre-specified in Protocol," "Pre-specified in SAP," "Data Driven," "Requested by Regulatory Agency") and the purpose of the analysis within the body of evidence (e.g., "Primary Efficacy," "Key Secondary Efficacy," "Safety"). The terminology used is sponsor defined. An example of a reason is "Primary Efficacy Analysis as Pre-specified in Protocol."
DATASET	The name of the dataset used to generate the analysis result. In most cases, this is a single dataset. However, if multiple datasets are used, they are all listed here.
SELECTION CRITERIA	Specific and sufficient selection criteria for analysis subset and / or numerator – a complete list of the variables and their values used to identify the records selected for the analysis. Though the syntax is not ADaM-specified, the expectation is that the information could easily be included in a WHERE clause or something equivalent to ensure selecting the exact set of records appropriate for an analysis. This information is required if the analysis does not include every record in the analysis dataset.
DOCUMENTATION	Textual description of the analysis performed. This information could be a text description, pseudo code, 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 contents of the documentation metadata element contains depends on the level of detail required to describe the analysis itself, whether or not the sponsor is providing a corresponding analysis generation program, and sponsor-specific requirements and standards. This documentation metadata element will remain free form, meaning it will not become subject to a rigid structure or controlled terminology.
PROGRAMMING STATEMENTS	The software programming code used to perform the specific analysis. This includes, for example, the model statement (using the specific variable names) and all technical specifications needed for reproducing the analysis (e.g., covariance structure). The name and version of the applicable software package should be specified either as part of this metadata element or in another document, such as a Reviewer's Guide (see Appendix B for more information about a Reviewer's Guide).

- Display Identifier
- Display name
- Result Identifier
- Parameter (Code/Decode)
- Analysis Variable
- Reason
- Dataset
- Selection Criteria
- Documentation
- Programming Statements

* Version 2.1 of the Analysis Data Model (ADaM) Document, December 17, 2009

ADaM Results Metadata v1 for Define-XML v2

Analysis Results Metadata Field	Description
DISPLAY IDENTIFIER	A unique identifier for the specific analysis display (such as a table or figure number)
DISPLAY NAME	Title of display, including additional information if needed to describe and identify the display (e.g., analysis population)
RESULT IDENTIFIER	Identifies the specific analysis result within a display. For example, if there are multiple p-values on a display and the analysis results metadata specifically refers to one of them, this field identifies the p-value of interest. When combined with the display identifier provides a unique identification of a specific analysis result.

```
<arm:AnalysisResultDisplays>
  <arm:ResultDisplay OID="RD.Table_14-3.01" Name="Table 14-3.01">
    <Description>
      <TranslatedText xml:lang="en">Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Pop
    </Description>
    <def:DocumentRef leafID="LF.Table-14-3.01">
      <def:PDFPageRef PageRefs="2" Type="PhysicalRef"/>
    </def:DocumentRef>
    <arm:AnalysisResult
      OID="AR.Table_14-3.01.R.1" ParameterOID="IT.ADQSADAS.PARAMCD"
      AnalysisReason="SPECIFIED IN SAP" AnalysisPurpose="PRIMARY OUTCOME MEASURE">
      <Description>
        <TranslatedText xml:lang="en">Dose response analysis for ADAS-Cog changes from baseline</TranslatedText>
      </Description>
```

ADaM Results Metadata v1 for Define-XML v2

Analysis Results Metadata Field	Description
DISPLAY IDENTIFIER	A unique identifier for the specific analysis display (such as a table or figure number)
DISPLAY NAME	Title of display, including additional information if needed to describe and identify the display (e.g., analysis population)
RESULT IDENTIFIER	Identifies the specific analysis result within a display. For example, if there are multiple p-values on a display and the analysis results metadata specifically refers to one of them, this field identifies the p-value of interest. When combined with the display identifier provides a unique identification of a specific analysis result.

Analysis Results Metadata (Summary) for Study CDISC-Sample

Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population) Dose response analysis for ADAS-Cog changes from baseline Pairwise comparisons to placebo for ADAS-Cog changes from baseline
Table 14-5.02 Incidence of Treatment Emergent Serious Adverse Events by Treatment Group Incidence of Treatment Emergent Serious Adverse Events by Treatment Group

Analysis Results Metadata (Detail) for Study CDISC-Sample

Table 14-3.01

Display	Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
Analysis Result	Dose response analysis for ADAS-Cog changes from baseline

ADaM Results Metadata v1 for Define-XML v2

PARAM	The analysis parameter in the BDS analysis dataset that is the focus of the analysis result. Does not apply if the result is not based on a BDS analysis dataset.
PARAMCD	Corresponds to PARAM in the BDS analysis dataset. Does not apply if the result is not based on a BDS analysis dataset.
ANALYSIS VARIABLE	The analysis variable being analyzed
REASON	The rationale for performing this analysis. It indicates when the analysis was planned (e.g., "Pre-specified in Protocol," "Pre-specified in SAP," "Data Driven," "Requested by Regulatory Agency") and the purpose of the analysis within the body of evidence (e.g., "Primary Efficacy," "Key Secondary Efficacy," "Safety"). The terminology used is sponsor defined. An example of a reason is "Primary Efficacy Analysis as Pre-specified in Protocol."

```
<arm:AnalysisResult
  OID="AR.Table_14-3.01.R.1"
  ParameterOID="IT.ADQSADAS.PARAMCD"
  AnalysisReason="SPECIFIED IN SAP"
  AnalysisPurpose="PRIMARY OUTCOME MEASURE">
  <Description>
    <TranslatedText xml:lang="en">Dose response analysis for ADAS-Cog changes from baseline</TranslatedText>
  </Description>
  <arm:AnalysisDatasets>
    <arm:AnalysisDataset ItemGroupOID="IG.ADQSADAS" >
      <def:WhereClauseRef WhereClauseOID="WC.Table_14-3.01.R.1.ADQSADAS" />
      <arm:AnalysisVariable ItemOID="IT.ADQSADAS.CHG"/>
    </arm:AnalysisDataset>
  </arm:AnalysisDatasets>
```

ADaM Results Metadata v1 for Define-XML v2

PARAM	The analysis parameter in the BDS analysis dataset that is the focus of the analysis result. Does not apply if the result is not based on a BDS analysis dataset.
PARAMCD	Corresponds to PARAM in the BDS analysis dataset. Does not apply if the result is not based on a BDS analysis dataset.
ANALYSIS VARIABLE	The analysis variable being analyzed
REASON	The rationale for performing this analysis. It indicates when the analysis was planned (e.g., "Pre-specified in Protocol," "Pre-specified in SAP," "Data Driven," "Requested by Regulatory Agency") and the purpose of the analysis within the body of evidence (e.g., "Primary Efficacy," "Key Secondary Efficacy," "Safety"). The terminology used is sponsor defined. An example of a reason is "Primary Efficacy Analysis as Pre-specified in Protocol."

Analysis Result	Dose response analysis for ADAS-Cog changes from baseline
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]

ADaM Results Metadata v1 for Define-XML v2

PARAM	The analysis parameter in the BDS analysis dataset that is the focus of the analysis result. Does not apply if the result is not based on a BDS analysis dataset.
PARAMCD	Corresponds to PARAM in the BDS analysis dataset. Does not apply if the result is not based on a BDS analysis dataset.
ANALYSIS VARIABLE	The analysis variable being analyzed
REASON	The rationale for performing this analysis. It indicates when the analysis was planned (e.g., "Pre-specified in Protocol," "Pre-specified in SAP," "Data Driven," "Requested by Regulatory Agency") and the purpose of the analysis within the body of evidence (e.g., "Primary Efficacy," "Key Secondary Efficacy," "Safety"). The terminology used is sponsor defined. An example of a reason is "Primary Efficacy Analysis as Pre-specified in Protocol."

1	Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)
2	C117745		Yes	Analysis Purpose	ANLPURP	Analysis Purpose
3	C98724	C117745		Analysis Purpose	EXPLORATORY OUTCOME MEASURE	Exploratory Outcome Measure
4	C98772	C117745		Analysis Purpose	PRIMARY OUTCOME MEASURE	Primary Outcome Measure
5	C98781	C117745		Analysis Purpose	SECONDARY OUTCOME MEASURE	Secondary Outcome Measure
6	C117744		Yes	Analysis Reason	ANLREAS	Analysis Reason
7	C117750	C117744		Analysis Reason	DATA DRIVEN	
8	C117751	C117744		Analysis Reason	REQUESTED BY REGULATORY AGENCY	
9	C117752	C117744		Analysis Reason	SPECIFIED IN PROTOCOL	

ADaM Results Metadata v1 for Define-XML v2

DATASET	The name of the dataset used to generate the analysis result. In most cases, this is a single dataset. However, if multiple datasets are used, they are all listed here.
SELECTION CRITERIA	Specific and sufficient selection criteria for analysis subset and / or numerator – a complete list of the variables and their values used to identify the records selected for the analysis. Though the syntax is not ADaM-specified, the expectation is that the information could easily be included in a `WHERE` clause or something equivalent to ensure selecting the exact set of records appropriate for an analysis. This information is required if the analysis does not include every record in the analysis dataset.

```
<arm:AnalysisDatasets def:CommentOID="COM.JOIN-ADSL-ADAE">
  <arm:AnalysisDataset ItemGroupOID="IG.ADAE">
    <def:WhereClauseRef WhereClauseOID="WC.Table_14-5.02.R.1.ADAE" />
    <arm:AnalysisVariable ItemOID="IT.ADAE.AEBODSYS"/>
    <arm:AnalysisVariable ItemOID="IT.ADAE.AEDECOD"/>
  </arm:AnalysisDataset>
  <arm:AnalysisDataset ItemGroupOID="IG.ADSL">
    <def:WhereClauseRef WhereClauseOID="WC.Table_14-5.02.R.1.ADSL"/>
  </arm:AnalysisDataset>
</arm:AnalysisDatasets>
```

```
<def:CommentDef OID="COM.JOIN-ADSL-ADAE">
  <Description>
    <TranslatedText xml:lang="en">Get denominators for percentages from ADSL and counts and numerato
  </Description>
</def:CommentDef>
```

ADaM Results Metadata v1 for Define-XML v2

DATASET	The name of the dataset used to generate the analysis result. In most cases, this is a single dataset. However, if multiple datasets are used, they are all listed here.
SELECTION CRITERIA	Specific and sufficient selection criteria for analysis subset and / or numerator – a complete list of the variables and their values used to identify the records selected for the analysis. Though the syntax is not ADaM-specified, the expectation is that the information could easily be included in a `WHERE` clause or something equivalent to ensure selecting the exact set of records appropriate for an analysis. This information is required if the analysis does not include every record in the analysis dataset.

Data References (incl. Selection Criteria)	ADAE [TRTEMFL = "Y" and AESER = "Y"] ADSL [SAFFL = "Y"] Get denominators for percentages from ADSL and counts and numerators from ADAE. Join ADAE with ADSL based on the unique subject identifier (USUBJID) keeping only records in ADAE for the numerator.

ADaM Results Metadata v1 for Define-XML v2

DOCUMENTATION	Textual description of the analysis performed. This information could be a text description, pseudo code, 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 contents of the documentation metadata element contains depends on the level of detail required to describe the analysis itself, whether or not the sponsor is providing a corresponding analysis generation program, and sponsor-specific requirements and standards. This documentation metadata element will remain free form, meaning it will not become subject to a rigid structure or controlled terminology.
PROGRAMMING STATEMENTS	The software programming code used to perform the specific analysis. This includes, for example, the model statement (using the specific variable names) and all technical specifications needed for reproducing the analysis (e.g., covariance structure). The name and version of the applicable software package should be specified either as part of this metadata element or in another document, such as a Reviewer's Guide (see Appendix B for more information about a Reviewer's Guide).

```
<arm:Documentation>
  <Description>
  <TranslatedText xml:lang="en">Linear model analysis of CHG for dose response; using randomized do
  </TranslatedText>
  </Description>
  <def:DocumentRef  leafID="LF.SAP-SEC-10.1.1">
    <def:PDFPageRef PageRefs="4" Type="PhysicalRef"/>
  </def:DocumentRef>
</arm:Documentation>
<arm:ProgrammingCode Context="SAS version 9.2">
<arm:Code>
proc glm data = ADQSADAS;
  where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT";
  class SITEGR1;
  model CHG = TRTPN SITEGR1;
run;
</arm:Code>
</arm:ProgrammingCode>
```

ADaM Results Metadata v1 for Define-XML v2

DOCUMENTATION	Textual description of the analysis performed. This information could be a text description, pseudo code, 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 contents of the documentation metadata element contains depends on the level of detail required to describe the analysis itself, whether or not the sponsor is providing a corresponding analysis generation program, and sponsor-specific requirements and standards. This documentation metadata element will remain free form, meaning it will not become subject to a rigid structure or controlled terminology.
PROGRAMMING STATEMENTS	The software programming code used to perform the specific analysis. This includes, for example, the model statement (using the specific variable names) and all technical specifications needed for reproducing the analysis (e.g., covariance structure). The name and version of the applicable software package should be specified either as part of this metadata element or in another document, such as a Reviewer's Guide (see Appendix B for more information about a Reviewer's Guide).

```
<arm:Documentation>
  <Description>
    <TranslatedText xml:lang="en">Unique count of subjects that experienced an Adverse Event by Pr
    </TranslatedText>
  </Description>
  <def:DocumentRef  leafID="LF.SAP-SEC-11.2">
    <def:PDFPageRef PageRefs="5" Type="PhysicalRef"/>
  </def:DocumentRef>
</arm:Documentation>
<arm:ProgrammingCode Context="SAS version 9.2">
  <def:DocumentRef leafID="LF.at14-5-02.sas" />
</arm:ProgrammingCode>
```

ADaM Results Metadata v1 for Define-XML v2

DOCUMENTATION	Textual description of the analysis performed. This information could be a text description, pseudo code, 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 contents of the documentation metadata element contains depends on the level of detail required to describe the analysis itself, whether or not the sponsor is providing a corresponding analysis generation program, and sponsor-specific requirements and standards. This documentation metadata element will remain free form, meaning it will not become subject to a rigid structure or controlled terminology.
PROGRAMMING STATEMENTS	The software programming code used to perform the specific analysis. This includes, for example, the model statement (using the specific variable names) and all technical specifications needed for reproducing the analysis (e.g., covariance structure). The name and version of the applicable software package should be specified either as part of this metadata element or in another document, such as a Reviewer's Guide (see Appendix B for more information about a Reviewer's Guide).

Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose). SAP Section 10.1.1

Programming Statements	[SAS version 9.2]
	`proc glm data = ADQSADAS;`
	`  where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT";`
	`  class SITEGR1;`
	`  model CHG = TRTPN SITEGR1;`
	`run;`

ADaM Results Metadata v1 for Define-XML v2

DOCUMENTATION	Textual description of the analysis performed. This information could be a text description, pseudo code, 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 contents of the documentation metadata element contains depends on the level of detail required to describe the analysis itself, whether or not the sponsor is providing a corresponding analysis generation program, and sponsor-specific requirements and standards. This documentation metadata element will remain free form, meaning it will not become subject to a rigid structure or controlled terminology.
PROGRAMMING STATEMENTS	The software programming code used to perform the specific analysis. This includes, for example, the model statement (using the specific variable names) and all technical specifications needed for reproducing the analysis (e.g., covariance structure). The name and version of the applicable software package should be specified either as part of this metadata element or in another document, such as a Reviewer's Guide (see Appendix B for more information about a Reviewer's Guide).

Documentation	Unique count of subjects that experienced an Adverse Event by Preferred Term, System Organ Class, and Treatment Group and percentages based on the number of subjects in the safety population within each treatment group. The total number of times an event occurred was recorded by Preferred Term, System Organ Class, and Treatment Group. Fisher's exact test was used for treatment comparison of event rates. SAP Section 11.2
Programming Statements	[SAS version 9.2] at14-5-02.sas

Preview of Define-XML v2.1

Define-XML 2.1 Key new features

- Versioning of Standards and Controlled Terminology
  - Clearly identifying standards
  - Identifying non-standard domains
  - Identifying non-standard variables
  - Identifying sponsor defined controlled terminology
- Enhanced Origin/Source information
- Dataset Class expanded with SubClass
- Added HasNoData attribute for SDTM datasets and variables
- Use of Alias for longer SAS names
- XML Schema enumerations
- Various enhancements (Context, additional Descriptions and Comments, DocumentRef/@Title)

Define-XML 2.1

Versioning of Standards and Controlled Terminology

- **Define-XML v2.0** identifies only one version of a standard, for example SDTM-IG 3.1.2
- **Define-XML v2.0** does not identify which version of CDISC/NCI Controlled Terminology is used

```
<MetaDataVersion OID="MDV.CDISC01"
  Name="Study CDISC01, Data Definitions"
  Description="Study CDISC01, Data Definitions"
  def:DefineVersion="2.0.0"
  def:StandardName="SDTM-IG"
  def:StandardVersion="3.1.2">
```

Define-XML 2.1

Versioning of Standards and Controlled Terminology

- **Define-XML v2.1** introduces capability for identifying the content standards and the controlled terminology package used by metadata definitions within a Define-XML file.
- Content standards are represented using the **Standards** element within the *MetaDataVersion* element.
- For Define-XML documents used for submissions, the Standards Element is Required
- Datasets must reference a standard or be identified as a Non-Standard/Custom dataset.
- Only really a change for SDTM/SEND since ADaM already defines an ADaM Other Class.

Define-XML 2.1

Versioning of Standards and Controlled Terminology

```
<MetaDataVersion OID="MDV.CDISC01"
  Name="Study CDISC01, Data Definitions"
  Description="Study CDISC01, Data Definitions"
  def:DefineVersion="2.0.0"
  def:StandardName="SDTM-IG"
  def:StandardVersion="3.1.2">
```

Version 2.0

```
<MetaDataVersion OID="MDV.CDISC01"
  Name="Study CDISC01, Data Definitions"
  Description="Study CDISC01, Data Definitions"
  def:DefineVersion="2.1.0">

  <def:Standards>
    <def:Standard OID="STD.IG.SDTM312"
      Name="SDTMIG" Type="IG"
      Version="3.1.2" Status="Final" />
    <def:Standard OID="STD.CT.SDTM201406"
      Name="CDISC/NCI" Type="CT" PublishingSet="SDTM"
      Version="2014-06-19" Status="Final" />
  </def:Standards>
```

Version 2.1

Define-XML 2.1

Versioning of Standards and Controlled Terminology

```
<def:Standards>
  <def:Standard OID="STD.SDTMIG-3.2" Name="SDTMIG" Type="IG" Version="3.2"
    Status="Final" def:CommentOID="COM.STD2"/>
  <def:Standard OID="SDTM-MD-MDES 1.0"  Name="SDTMIG-MD" Type="IG" Version="1.0"
    Status="Final" def:CommentOID="COM.STD.MD"/>
  <def:Standard OID="STD.CT-2016-12-16" Name="CDISC/NCI" Type="CT" PublishingSet="SDTM"
    Version="2016-12-16" Status="Final" def:CommentOID="COM.CT1"/>
</def:Standards>
```

Standards for Study CDISC Sample

Standard	Type	Status	Documentation
SDTMIG 3.2	IG	Final	The CDISC01 study was originally modeled on SDTM 3.1.2 but was updated when SDTM 3.2 was published.
SDTMIG-MD 1.0	IG	Final	Two domains from the SDTM Medical Devices Standard are included in this submission.
CDISC/NCI SDTM 2016-12-16	CT	Final	This CT version corresponds to the newest CT available in production at the time of preparing this example, just to illustrate best practices: 1) keeping the data and metadata as per the most current CT, if at all possible, 2) using only one CT version, if not allowed or agreed otherwise with the receiver of the data and metadata package. Reviewers should be aware that this is only an example and no attempt has been made to upversion the data to this CT version.

Identifying Non-standard Domains

- A dataset is considered non-standard if either:
  - It is a sponsor defined custom domain, or
  - It is a domain based on an un-published draft of a CDISC dataset.
- For nonstandard domain definitions, the dataset must include a **def:IsNonStandard="Yes"** attribute.
- For Define-XML documents used for submissions, the dataset must either include a reference to a standard (**def:StandardOID**) or must include the **def:IsNonStandard="Yes"** attribute

Define-XML 2.1

Identifying Non-standard Domains

```
<MetaDataVersion OID="MDV.CDISC01.SDTMIG.3.1.3.SDTM.1.3
  Name="Study CDISC01, Data Definitions"
  Description="Study CDISC01, Data Definitions"
  def:DefineVersion="2.1"
  def:CommentOID="COM.MDV">
  <Standards>
    <Standard OID="1" Name="SDTMIG" Type="IG" Version="3.1.3" Status="Final" />
    <Standard OID="2" Name="SDTMIG-MD" Type="IG" Version="1.0" Status="Provisional"/>
  </Standards>

  <ItemGroupDef OID="IG.DE"
    Domain="DE" Name="DE" Repeating="Yes" IsReferenceData="No"
    SASDatasetName="DE"
    Purpose="Tabulation"
    def:Structure="One record per event per device"
    def:Class="EVENTS"
    def:ArchiveLocationID="LF.DE"
    def:StandardOID="2">
    <Description>
      <TranslatedText xml:lang="en">Device Events</TranslatedText>
    </Description>
```

Define-XML 2.1 Identifying Multiple CT Packages

- For Define-XML documents used for submissions, the Standards Element should include references to published controlled terminology versions.
- Every CodeList in the Define-XML that references a CDISC published Controlled Terminology must identify the controlled terminology publication that serves as the source (**def:StandardOID**).
- Sponsor defined controlled terminologies should be identified as non-standard, by specifying a **def:IsNonStandard="Yes"** attribute.

Identifying Non-standard Variables

- Non-standard variables in a dataset can use the def:IsNonStandard attribute.
- This **enables** non-standard variables to be part of the parent domain (instead of Supplemental Qualifiers)
  - ... which does not mean that it can be used now in eSubmissions
    Keep in mind that Define-XML is not only for eSubmissions

Dataset Class and SubClass

- The SDTM, SEND and ADaM standards use Class as a way to identify each dataset in relation to its respective model
- There is no way to identify specific applications of these classes
- Beginning in version 2.1, the Class concept has been expanded to include a SubClass
- Subclasses adhere to the definition of the “Parent” Class, but have additional requirements and rules to be considered
- Facilitates validation

Dataset Class and SubClass

- Initial uses:
  - Identify Adverse Events Analysis datasets (SubClass = “ADVERSE EVENT”) within the ADaM OCCURRENCE DATA STRUCTURE Class
  - Identify Time-to-Event Analysis datasets (SubClass = “TIME-TO-EVENT”) within the ADaM BASIC DATA STRUCTURE Class

- There is no requirement that a SubClass is defined for every ADaM dataset

Define-XML 2.0 Dataset Class and SubClass

```
<ItemGroupDef OID="IG.AE" Domain="AE" Name="AE" def:Class="EVENTS"
  Repeating="Yes" IsReferenceData="No" SASDatasetName="AE"
  def:Structure="One record per adverse event per subject"
  Purpose="Tabulation" def:ArchiveLocationID="LF.AE">
```

```
<ItemGroupDef OID="IG.ADAE" Name="ADAE" SASDatasetName="ADAE"
  def:Class="OCCURRENCE DATA STRUCTURE"
  Repeating="Yes" IsReferenceData="No" Purpose="Analysis"
  def:Structure="one record per subject per adverse event"
  def:ArchiveLocationID="LF.ADAE">
```

Define-XML 2.1 Dataset Class and SubClass

```
<ItemGroupDef OID="IG.AE" Domain="AE" Name="AE"
  Repeating="Yes" IsReferenceData="No" SASDatasetName="AE"
  def:Structure="One record per adverse event per subject"
  Purpose="Tabulation" def:ArchiveLocationID="LF.AE">
  <Description>
    <TranslatedText xml:lang="en">Adverse Events</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.STUDYID" OrderNumber="1" Mandatory="Yes" KeySequence="1"/>
    ...
  <ItemRef ItemOID="IT.AE.AEENRF" OrderNumber="18" Mandatory="No"/>
  <def:Class Name="EVENTS"/>
  <def:leaf ID="LF.AE" xlink:href="ae.xpt">
    <def:title>ae.xpt</def:title>
  </def:leaf>
</ItemGroupDef>
```

Define-XML 2.1 Dataset Class and SubClass

```
<ItemGroupDef OID="IG.ADAE" Name="ADAE" SASDatasetName="ADAE"
  Repeating="Yes" IsReferenceData="No" Purpose="Analysis"
  def:Structure="one record per subject per adverse event"
  def:ArchiveLocationID="LF.ADAE">
  <Description>
    <TranslatedText xml:lang="en">Adverse Events Analysis Dataset</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.ADAE.STUDYID" OrderNumber="1" Mandatory="No"  KeySequence="1"/>
    ...
  <ItemRef ItemOID="IT.ADAE.AOCC01FL" OrderNumber="55" Mandatory="No" />
  <def:Class Name="OCCURRENCE DATA STRUCTURE">
    <def:SubClass Name="ADVERSE EVENT"/>
  </def:Class>
  <def:leaf ID="LF.ADAE" xlink:href="adae.xpt">
    <def:title>adae.xpt </def:title>
  </def:leaf>
</ItemGroupDef>
```

Origin - Define-XML v2.0

- Define-XML **v2.0** **-** Origin Type:
  - CRF
  - Derived
  - Assigned
  - Protocol
  - eDT
  - Predecessor
- Mixes type and source in Type attribute
- SEND values (COLLECTED, DERIVED, OTHER, NOT AVAILABLE) were added later with an erratum

Enhanced Origin Define-XML v2.1 - Type and Source (Clinical)

Type	Definition	Source (*)			
		Subject	Investigator	Vendor	Sponsor
Collected	Data that were actually observed or recorded by a person or received from an instrument.	ePro	CRF	Lab data, ECG	X
Derived	Data that is not directly collected, but is calculated by an algorithm or reproducible rule, which is dependent upon other data values.	X	X	Lab data, ECG	SDTM ADaM
Assigned	Data that is determined by individual judgment as provided by an evaluator other than the subject or investigator.	X	X	X	SDTM ADaM
Protocol	Data that is defined as part of the trial design preparation.	X	X	X	SDTM
Predecessor	Data that is copied from a variable in another dataset.	X	X	X	SDTM ADaM

In specification, table is provided separately for SDTM, SEND and ADaM

(*) Source is not used by SEND

Define-XML 2.1

Enhanced Origin Define-XML v2.1 - Type and Source (Clinical)

```
<ItemDef OID="IT.AE.AEACN" Name="AEACN" DataType="text" Length="30" SASFieldName="AEACN">
  <Description>
    <TranslatedText xml:lang="en">Action Taken with Study Treatment</TranslatedText>
  </Description>
  <CodeListRef CodeListOID="CL.ACN"/>
  <def:Origin Type="Collected" Source="Investigator">
    <def:DocumentRef leafID="LF.blankcrf">
      <def:PDFPageRef PageRefs="21" Type="PhysicalRef" Title="aCRF Page"/>
    </def:DocumentRef>
  </def:Origin>
</ItemDef>

<ItemDef OID="IT.ADQSADAS.STUDYID" Name="STUDYID" SASFieldName="STUDYID" DataType="text" Length="12">
  <Description>
    <TranslatedText xml:lang="en">Study Identifier</TranslatedText>
  </Description>
  <def:Origin Type="Predecessor" Source="Sponsor">
    <Description>
      <TranslatedText xml:lang="en">ADSL.STUDYID</TranslatedText>
    </Description>
  </def:Origin>
</ItemDef>
```

Define-XML 2.1 Multiple Origins

- Already supported in Define-XML v2.0 with the use of Value Level Metadata. Example:
  - Origin/@Type="CRF" when LBNAM EQ "VENDOR_A"
  - Origin/@Type="eDT" when LBNAM NE "VENDOR_A"
- This is still the best solution in Define-XML v2.1

- However, in cases where there is no variable (like LBNAM) to differentiate, the standard allows multiple def:Origin elements for a variable.
  - A description should explain when each origin applies.
  - This should be a last resort solution, as there is no machine readable way to indicate when each origin is applicable.

Define-XML 2.1 Use of Alias for longer SAS names

- Define-XML has several attributes that are used in conjunction with SAS Version 5 XPT files:
  - SASDatasetName
  - SASFieldName
  - SASFormatName
- These attributes are restricted by ODM to a maximum length of 8 characters
- When using longer names, the SAS name can be specified by using the Alias child element with Context="SAS"

```
<Alias Name="VERYLONGNAME" Context="SAS"/>
```

Define-XML 2.1 XML Schema enumerations

- Various attributes in Define-XML have a list of allowable values
- Examples:
  - def:Standard/@Name
  - def:Standard/@Type
  - def:Standard/@Status
  - def:Standard/@PublishingSet
  - ItemGroupDef/@def:Class
  - def:Origin/@Type
  - def:Origin/@Source
  - def:PDFPageRef/@Type
- These allowed values (enumerations) are now part of the XML schema
- An updated schema will be published when values are added (2.1.1, 2.2.2, ...)

Define-XML 2.1 Various

- ODM/@def:**Context** attribute can be used for validation
  Values: **Submission** or **Other**
  (some business rules are only required in the context of a submission)
- **def:HasNoData="Yes"** attribute added to datasets and variables
  - Included in study definition, but not present in data
  - Needs to be explained with comment
- **Description** elements were added to:
  - def:ValueListDef
  - CodeList, CodeListItem, EnumeratedItem
- **Comments** can now be added to MetaDataVersion and CodeList

Define-XML 2.1 Various

- An optional def:DocumentRef/def:PDFPageRef/@Title attribute was added.
  This title can be a **more specific reference** to a page or named destination than the **generic document title** that is defined by the def:leaf/def:title element.
- This avoids proliferation of def:leaf elements

```
<def:DocumentRef leafID="LF.CSR">
    <def:PDFPageRef PageRefs="2" Type="PhysicalRef" Title="Table 14-3.01"/>
 </def:DocumentRef>

<def:DocumentRef leafID="LF.CSR">
    <def:PDFPageRef PageRefs="5" Type="PhysicalRef" Title="Table 14-3.05"/>
 </def:DocumentRef>

 <def:leaf ID="LF.CSR" xlink:href="../dummy-csr/dummy-csr.pdf">
   <def:title>Clinical Study Report</def:title>
 </def:leaf>
```

Thank You !
Questions ?