

# Define-XML v2: Good for ADaM!

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# Agenda

- Define-XML History and Background
- What is Define-XML?
- Issues with Define-XML 1.0
- What's new in Define-XML 2.0?
- Displaying Define-XML (*stylesheet*)
- Next steps (*Analysis Results Metadata*)
- Questions

# DEFINE-XML – HISTORY AND BACKGROUND



## Define-XML HISTORY AND BACKGROUND

- **July 2004** - FDA adds Study Data Specifications v1.0 to draft eCTD Guidance. This specification references the CDISC SDTM for data tabulation datasets

### Electronic Common Technical Document (eCTD)

- Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions. (Posted 8/28/2003)
  - *Federal Register Notice* [\[TXT\]](#) [\[PDF\]](#)
  - [The Draft Guidance](#) 

#### Specifications

- [eCTD Backbone Files Specification for Module 1](#) 
- [eCTD Backbone File Specification for Modules 2 through 5](#) 
- [eCTD Backbone File Specification for Study Tagging Files](#) 
- [FDA eCTD Table of Contents Headings and Hierarchy](#) 
- [Study Data Specifications](#)  **New!!** (Posted 7/21/2004)

## Define-XML HISTORY AND BACKGROUND

- **March 2005** - Study Data Specifications v1.1 Update: Specifications for Data Set Documentation includes:
  - Data definitions
  - Annotated Case Report Forms (CRFs)

*“The specification for the data definitions for datasets provided using the **CDISC SDTM** is included in the Case Report Tabulation Data Definition Specification (**define.xml**) developed by the CDISC define.xml Team”*

- For datasets not prepared using the CDISC SDTM specifications, consult Appendix 2 for information concerning the preparation of a define.pdf data definition file.

## Define-XML HISTORY AND BACKGROUND

- **June 2011** – Study Data Specifications v1.6:  
The specification for the data definitions for datasets provided using the *CDISC SDTM IG* or *SEND IG* is included in the Case Report Tabulation Data Definition Specification ...”
- **July 2012** – Study Data Specifications v2.0:  
The specification for the data definitions for datasets provided using *CDISC* is included in the Case Report Tabulation Data Definition Specification ...”

## **Define-XML** HISTORY AND BACKGROUND

- **December 2011** CDER Common Data Standards Issues Document (Version 1.1):

“A critical component of data submission is the define file. A properly functioning define.xml file is an important part of the submission of standardized electronic datasets and should not be considered optional.”

“Additionally, sponsors should make certain that every data variable’s code list, origin, and derivation is clearly and easily accessible from the define file. An insufficiently documented define file is a common deficiency that reviewers have noted.”

# Define-XML HISTORY AND BACKGROUND

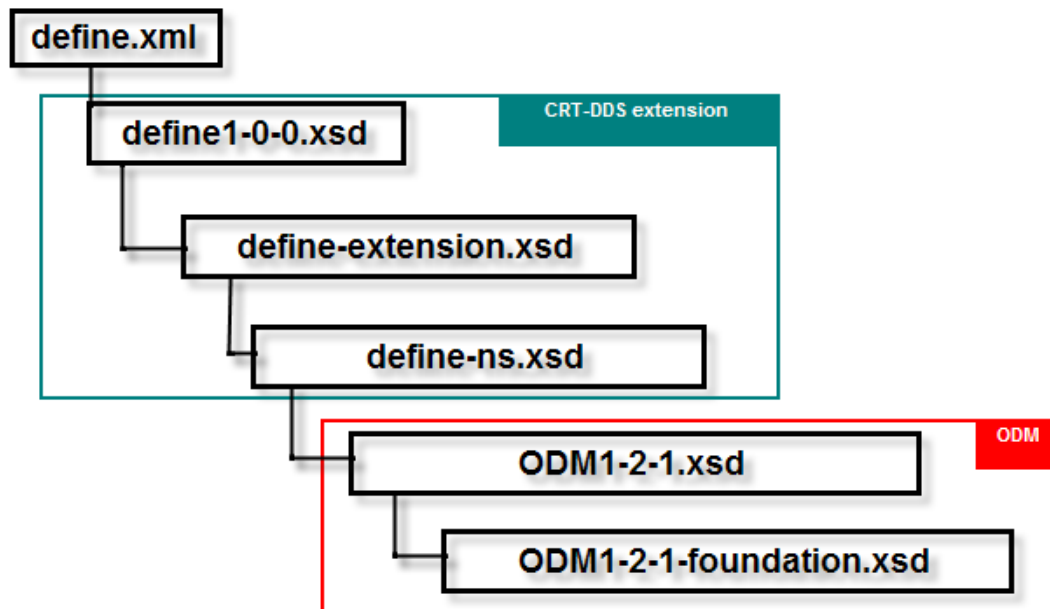


# WHAT IS DEFINE-XML ?



## Define-XML WHAT IS IT ?

- Extension of the CDISC Operational Data Model (ODM), an XML specification to facilitate the archival and interchange of the metadata and data for clinical research
- Define-XML: **metadata** structures to describe data sets
- Maintained by CDISC's **XML Technologies Team**



## Define-XML WHAT IS IT ?

- Case Report Tabulation Data Definition Specification, (CRT-DDS), or commonly known as “define.xml”, is not just for SDTM, SEND or ADaM but can even be used for non-submission, proprietary data sets.
- In version 2 the standard is called “**Define-XML**”
- **define.xml** is the file, an instance of the Define-XML standard.

## Define-XML WHAT IS IT ?

- Provides **metadata** about:
  - **Study**
    - Name, Description Protocol name
  - **Domains**
    - Name, Description, Structure, Dataset Location, ...
  - **Variables**
    - Name, Label, Data Type, Length, ...
  - **Controlled Terminology**
  - **Derivations** (computations, methods)
  - Supporting **Documents** (aCRF, Supplemental Data Definitions, ..)
  - (Parameter) **Value Level Metadata**
  - Concepts as **SuppQuals**, **Split domains** ...

# Define-XML WHAT IS IT ?

- Specification for describing data sets
- Does **not** describe how this metadata should be displayed - that is not part of the standard

| Dataset | Description                             | Structure                                                                                             | Purpose    | Keys                                  | Location                                                   |
|---------|-----------------------------------------|-------------------------------------------------------------------------------------------------------|------------|---------------------------------------|------------------------------------------------------------|
| AE      | <a href="#">Adverse Events</a>          | Events - One record per adverse event per subject                                                     | Tabulation | STUDYID USUBJID<br>AEECOD<br>AESTDTC  | <a href="#">Adverse Events SAS transport file</a>          |
| CE      | <a href="#">Clinical Events</a>         | Events - One record per event per subject                                                             | Tabulation | STUDYID USUBJID<br>CETERM CESTDTC     | <a href="#">Clinical Events SAS transport file</a>         |
| CM      | <a href="#">Concomitant Medications</a> | Interventions - One record per recorded medication occurrence or constant-dosing interval per subject | Tabulation | STUDYID USUBJID<br>CMTR1 CMSTDTC      | <a href="#">Concomitant Medications SAS transport file</a> |
| CO      | <a href="#">Comments</a>                | Special Purpose Domains - One record per comment per subject                                          | Tabulation | STUDYID USUBJID<br>COSEQ              | <a href="#">Comments SAS transport file</a>                |
| DA      | <a href="#">Drug Accountability</a>     | Findings - One record per drug accountability finding per subject                                     | Tabulation | STUDYID USUBJID<br>DATESTCD DADTC     | <a href="#">Drug Accountability SAS transport file</a>     |
| DM      | <a href="#">Demographics</a>            | Special Purpose Domains - One record per subject                                                      | Tabulation | STUDYID USUBJID                       | <a href="#">Demographics SAS transport file</a>            |
| DS      | <a href="#">Disposition</a>             | Events - One record per disposition status or protocol milestone per subject                          | Tabulation | STUDYID USUBJID<br>DSDECOD<br>DSSTDTC | <a href="#">Disposition SAS transport file</a>             |

|                            |
|----------------------------|
| Annotated Case Report Form |
| Reviewers Guide            |
| Datasets                   |
| Value Level Metadata       |
| Computational Algorithms   |
| Controlled Terms           |

| Dataset | Description                                        | Class           | Structure                                    | Purpose    | Keys                     |
|---------|----------------------------------------------------|-----------------|----------------------------------------------|------------|--------------------------|
| TA      | <a href="#">Trial Arms</a>                         | Trial Design    | One record per planned Element per Arm       | Tabulation | STUDYID, ARMCD, TAETORD  |
| TE      | <a href="#">Trial Elements</a>                     | Trial Design    | One record per planned Element               | Tabulation | STUDYID, ETCD            |
| TI      | <a href="#">Trial Inclusion/Exclusion Criteria</a> | Trial Design    | One record per I/E criterion                 | Tabulation | STUDYID, IETESTCD        |
| TS      | <a href="#">Trial Summary</a>                      | Trial Design    | One record per trial summary parameter value | Tabulation | STUDYID, TSPARMCD, TSSEQ |
| TV      | <a href="#">Trial Visits</a>                       | Trial Design    | One record per planned Visit per Arm         | Tabulation | STUDYID, VISITNUM, ARMCD |
| DM      | <a href="#">Demographics</a>                       | Special Purpose | One record per subject                       | Tabulation | STUDYID, FIRSTTRTID      |

|                            |
|----------------------------|
| Annotated Case Report Form |
| SDTM Datasets              |
| Value Level Metadata       |
| Controlled Terms           |
| External Dictionaries      |
| Computational Algorithms   |

SDTM Datasets for Study CDISCPILOT01

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

# Define-XML WHAT IS IT ?



```
<ItemGroupDef OID="ADSL" Name="ADSL" Repeating="No" IsReferenceData="No"
  Purpose="Analysis" def:Label="Subject-Level Analysis"
  def:Structure="one record per subject" def:DomainKeys="USUBJID"
  def:Class="ADSL" def:ArchiveLocationID="Location.ADSL">
  <ItemRef ItemOID="ADSL.STUDYID" OrderNumber="1" Mandatory="No"/>
  <ItemRef ItemOID="ADSL.USUBJID" OrderNumber="2" Mandatory="No"/>
  <ItemRef ItemOID="ADSL.SUBJID" OrderNumber="3" Mandatory="No"/>
  ...

  <ItemRef ItemOID="ADSL.ARM" OrderNumber="6" Mandatory="No" />
  ...

  <def:leaf ID="Location.ADSL" xlink:href="adsl.xpt">
    <def:title>adsl.xpt </def:title>
  </def:leaf>
</ItemGroupDef>
...

<ItemDef OID="ADSL.ARM" Name="ARM" DataType="text" Length="20"
  Origin="Derived" Comment="DM.ARM" def:Label="Description of Planned Arm">
  <CodeListRef CodeListOID="ARM"/>
</ItemDef>
```

# ISSUES WITH DEFINE-XML 1.0



## Define-XML 1.0 ISSUES – 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
  - 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 1.0 ISSUES – VALUE LEVEL METADATA

```
<ItemDef OID="I.VSTESTCD"
  Name="VSTESTCD" DataType="text"
  Length="8" Origin="CRF Page 9"
  def:Label="Vital Signs Test Short Name">
  <def:ValueListRef ValueListOID="VL.VSTESTCD" />
</ItemDef>
```

| USUBJID | VSTESTCD | VSTEST          | VSORRES | VSTRESN | VSTRESC | VISITNUM |
|---------|----------|-----------------|---------|---------|---------|----------|
| 00001   | HEIGHT   | Height in cm    | 183     | 183     |         | 1        |
| 00001   | WEIGHT   | Weight in kg    | 88.5    | 88.5    |         | 1        |
| 00001   | FRAME    | Body Frame Size | Large   |         | Large   | 1        |

| Value Level Metadata |                 |        |              |         |                            |            |
|----------------------|-----------------|--------|--------------|---------|----------------------------|------------|
| Source Dataset       | Source Variable | Value  | Label        | Type    | Controlled Terms or Format | Origin     |
| VS                   | VSTESTCD        | HEIGHT | Height in cm | integer | 3.0                        | CRF Page 5 |
| VS                   | VSTESTCD        | WEIGHT | Weight in kg | float   | 5.1                        | CRF Page 5 |
| VS                   | VSTESTCD        | FRAME  | Frame        | text    | Small, Medium, Large       | CRF Page 6 |

# Define-XML 1.0 ISSUES – VALUE LEVEL METADATA

```
<ItemDef OID="I.VSTESTCD"  
  Name="VSTESTCD" DataType="text"  
  Length="8" Origin="CRF Page 9"  
  def:Label="Vital Signs Test Short Name">  
    <def:ValueListRef ValueListOID="VL.VSTESTCD" />  
</ItemDef>
```

```
<def:ValueListDef OID="VL.VSTESTCD">  
  <ItemRef ItemOID="I.VSTESTCD.HEIGHT" OrderNumber="1" Mandatory="No" />  
  <ItemRef ItemOID="I.VSTESTCD.WEIGHT" OrderNumber="2" Mandatory="No" />  
  ...  
</def:ValueListDef>
```

```
<ItemDef OID="I.VSTESTCD.HEIGHT"  
  Name="HEIGHT" DataType="integer" Length="3"  
  Origin="CRF Page 18" def:Label="Height" />
```

```
<ItemDef OID="I.VSTESTCD.WEIGHT"  
  Name="WEIGHT" DataType="float" SignificantDigits="1" Length="5"  
  Origin="CRF Page 18" def:Label="Weight" />
```

## Define-XML 1.0 ISSUES – VALUE LEVEL METADATA

Which variable are we really describing ?  
VSORRES, VSSTRESN, VSSTRESC ???

```
<ItemDef OID="I.VSTESTCD.HEIGHT"  
  Name="HEIGHT" DataType="integer" Length="3"  
  Origin="CRF Page 18" def:Label="Height" />
```

```
<ItemDef OID="I.VSTESTCD.WEIGHT"  
  Name="WEIGHT" DataType="float" SignificantDigits="1" Length="5"  
  Origin="CRF Page 18" def:Label="Weight" />
```

| USUBJID | VSTESTCD | VSTEST          | VSORRES | VSSTRESN | VSSTRESC | VISITNUM |
|---------|----------|-----------------|---------|----------|----------|----------|
| 00001   | HEIGHT   | Height in cm    | 183     | 183      |          | 1        |
| 00001   | WEIGHT   | Weight in kg    | 88.5    | 88.5     |          | 1        |
| 00001   | FRAME    | Body Frame Size | Large   |          | Large    | 1        |

# Define-XML 1.0 ISSUES – VALUE LEVEL METADATA

## Analysis Dataset Lab Hy's Law (ADLBHY) [adlbhy.xpt](#)

| Variable             | Label                            | Type  | Length | Display Format | Code List / Controlled Terms | Source/Derivation |
|----------------------|----------------------------------|-------|--------|----------------|------------------------------|-------------------|
| STUDYID              | Study Identifier                 | text  | 12     |                |                              | ADSL.STUDYID      |
| SUBJID               | Subject Identifier for the Study | text  | 4      |                |                              | ADSL.SUBJID       |
| USUBJID              | Unique Subject Identifier        | text  | 11     |                |                              | ADSL.USUBJID      |
| <a href="#">AVAL</a> | Analysis Value                   | float | 8      |                |                              |                   |
| <a href="#">BASE</a> | Baseline Value                   | float | 8      |                |                              |                   |
| <a href="#">A1LO</a> | Analysis Range 1 Lower Limit     | float | 8      |                |                              |                   |

## Parameter Value List - ADLBHY [AVAL]

| Source Variable | Where PARAMCD= | Where PARAM=                     | Type    | Length | Display Format | Code List / Controlled Term | Source/Derivation/Comments                                       |
|-----------------|----------------|----------------------------------|---------|--------|----------------|-----------------------------|------------------------------------------------------------------|
| AVAL            | ALT            | Alanine Aminotransferase (U/L)   | integer | 8      |                |                             | ADLBC.AVAL                                                       |
| AVAL            | AST            | Aspartate Aminotransferase (U/L) | integer | 8      |                |                             | ADLBC.AVAL                                                       |
| AVAL            | BILI           | Bilirubin (umol/L)               | float   | 8      | 6.2            |                             | ADLBC.AVAL                                                       |
| AVAL            | BILIH          | Bilirubin 1.5 x ULN              | integer | 8      |                | <a href="#">YNN</a>         | for a given visit, if param='BILI' and param='BILIH' then aval=0 |

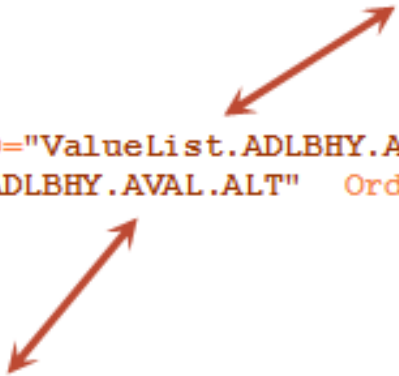
# Define-XML 1.0 ISSUES – VALUE LEVEL METADATA

```
<ItemDef OID="ADLBHY.PARAMCD" Name="PARAMCD" DataType="text"
  Length="8" Origin="Derived" def:Label="Parameter Code" >

<ItemDef OID="ADLBHY.AVAL" Name="AVAL" DataType="float"
  Length="8" SignificantDigits="2" Origin="Derived" def:Label="Analysis Value" >
  <def:ValueListRef ValueListOID="ValueList.ADLBHY.AVAL"/>
</ItemDef>

<def:ValueListDef OID="ValueList.ADLBHY.AVAL">
  <ItemRef ItemOID="ADLBHY.AVAL.ALT" OrderNumber="13" Mandatory="No"/>
  ...
</def:ValueListDef>

<ItemDef OID="ADLBHY.AVAL.ALT" Name="ALT" DataType="integer" Length="8"
  Origin="Derived" Comment="ADLBC.AVAL" def:Label="Alanine Aminotransferase (U/L)" />
```



“Where PARAMCD=“ and “Where PARAM=“  
were hardcoded in the stylesheet.

## Define-XML 1.0 ISSUES – VALUE LEVEL METADATA

- Define-XML 1.0 does not fully support the use cases in SDTM and ADaM in a fully machine readable way:
  - Variable Level Metadata for more than one variable in a domain
  - Variable Level Metadata based on a condition more complicated condition than equal to one variable value
- This can lead to operability problems

## Define-XML 1.0 ISSUES – CODE LISTS

- In Define-XML 1.0 Code Lists always need **Codes** and **Decodes**
- SDTM and ADaM only need a list of allowed values in most cases
- The solution in 1.0 is to have identical **Codes** and **Decodes**

```
<CodeList OID="ACN" Name="ACN" DataType="text">
  <CodeListItem CodedValue="DOSE NOT CHANGED">
    <Decode>
      <TranslatedText>DOSE NOT CHANGED</TranslatedText>
    </Decode>
  </CodeListItem>
```

## Define-XML 1.0 ISSUES – CODE LISTS

- In Define-XML 1.0 there is no link with the CDISC / NCI Controlled Terminology

### *CDISC Controlled Terminology ADaM - 2011-01-07*

**C81224** - DTYPE - Derivation Type

Codelist **extensible: Yes**

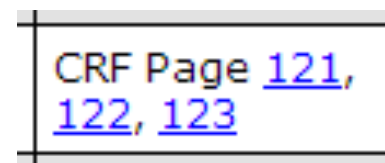
| NCI Code | CDISC Submission Value | CDISC Synonym | CDISC Definition                                                                                                                                     | NCI Preferred Term                                        |
|----------|------------------------|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| C81209   | AVERAGE                |               | Average: A data derivation technique which calculates a subject's average value over a defined set of records.                                       | Average of Value Derivation Technique                     |
| C92225   | BC                     |               | Best Case: A data imputation technique which populates missing values with the best possible outcome.                                                | Best Case Imputation Technique                            |
| C81201   | BLOCF                  |               | Baseline Observation Carried Forward: A data imputation technique which populates missing values with the subject's nonmissing baseline observation. | Baseline Observation Carried Forward Imputation Technique |
| C92226   | BOCF                   |               | Best Observation Carried Forward: A data imputation technique which populates missing values with the subject's best-case nonmissing value.          | Best Observation Carried Forward Imputation Technique     |
| C82866   | ENDPOINT               |               | Endpoint: A data derivation technique which calculates a subject's analysis end point value.                                                         | Endpoint Value Derivation Technique                       |

## Define-XML 1.0 ISSUES – EXTERNAL DOCUMENT LINKS

- Define-XML 1.0 has very limited support for linking
- How do we get from:

Origin = “CRF Pages 121, 122, 123” to real links ?

.... parsing and hardcoding



- How can we link from datasets, variables or methods to supporting documents ?  
Comment = “See Data Guide page 14”
- How about linking to Named Destinations or ranges of pages ?

## Define-XML 1.0 ISSUES – SPECIFICATION

- The Define-XML 1.0 specification is ambiguous in several aspects:
  - Datatypes – is a date “date” or “text” ?
  - Do we need a code list reference for ISO8601
- There is no specification for “split domains”, which were introduced after the release of 1.0
- Not many examples in the Define-XML 1.0 specification

# WHAT'S NEW IN DEFINE-XML 2.0 ?



## Define-XML 2.0 | WHAT'S NEW

- Based on ODM 1.3.2
- Define-XML version 2.0 can be used to transmit metadata for the following CDISC standards:
  - SDTM Implementation Guide Versions 3.1.2 and higher
  - ADaM Implementation Guide Versions 1.0 and higher
  - SEND Implementation Guide Versions 3.0 and higher
- Not completely backward compatible to allow for a clearer and less ambiguous model

## Define-XML 2.0 WHAT'S NEW

- Deprecated: replaced by ODM 1.3.2 or enhanced

| Element         | Component                | Replaced by             |
|-----------------|--------------------------|-------------------------|
| MetaDataVersion | def:ComputationalMethod  | MethodDef element       |
| ItemGroupDef    | def:Label                | Description element     |
| ItemGroupDef    | def:DomainKeys           | @KeySequence attribute  |
| ItemDef         | def:Label                | Description element     |
| ItemDef         | def:ComputationMethodOID | @MethodOID attribute    |
| ItemDef         | Origin                   | New def:Origin element  |
| ItemDef         | Comment                  | New def:Comment element |
| CodeListItem    | def:Rank                 | ODM Rank attribute      |

## Define-XML 2.0 WHAT'S NEW – VALUE LEVEL METADATA

- Can now be provided for any dataset variable
- Condition can be based on values of multiple variables with more complicated conditions (not just EQUAL)
- Examples:
  - VSTESTCD=SYSBP and VSPOS=STANDING
  - PARAMCD IN (ACITM01, ACITM012, ACITM02, ACITM04)
  - PARAMCD NE ACTTOT
- Available: LT, LE, GT, GE, EQ, NE, IN, NOTIN
- Unambiguous interpretation by a computer

# Define-XML 2.0 WHAT'S NEW – VALUE LEVEL METADATA

## Parameter Value List - ADQSADAS [AVAL]

| Variable | Where                                                                                                              | Type    | Length / Display Format | Controlled Terms or Format | Origin  | Derivation/Comment                                                                                                                                                                                                                                    |
|----------|--------------------------------------------------------------------------------------------------------------------|---------|-------------------------|----------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AVAL     | <a href="#">PARAMCD</a> IN ( "ACITM01" (Word Recall Task) , "ACITM02" (Naming Objects And Fingers (Refer To 5 C) . | integer | 8                       |                            | Derived | QS.QSSTRESN where QSTESTCD=PARAMCD                                                                                                                                                                                                                    |
|          | speed) , "ACITM14" (Recall Of Test Instructions) )                                                                 |         |                         |                            |         |                                                                                                                                                                                                                                                       |
| AVAL     | <a href="#">PARAMCD</a> 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.<br>Analysis Data Reviewer's Guide ( <a href="#">analysis-data-reviewers-guide.pdf</a> ) |

## Define-XML 2.0 WHAT'S NEW – 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 2.0 WHAT'S NEW – VALUE LEVEL METADATA

```
<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 2.0 WHAT'S NEW – CODE LISTS

- Controlled Terminology can now be defined by using Enumerated Items
- Also notice the new OrderNumber attribute for defining display order

```
<CodeList OID="CL.DISCREAS" Name="DISCREAS" DataType="text">
  <EnumeratedItem CodedValue="Completed" OrderNumber="1"/>
  <EnumeratedItem CodedValue="Adverse Event" OrderNumber="2"/>
  <EnumeratedItem CodedValue="Death" OrderNumber="3"/>
  <EnumeratedItem CodedValue="I/E Not Met" OrderNumber="4"/>
  <EnumeratedItem CodedValue="Lack of Efficacy" OrderNumber="5"/>
  <EnumeratedItem CodedValue="Lost to Follow-up" OrderNumber="6"/>
  <EnumeratedItem CodedValue="Physician Decision" OrderNumber="7"/>
  <EnumeratedItem CodedValue="Protocol Violation" OrderNumber="8"/>
  <EnumeratedItem CodedValue="Sponsor Decision" OrderNumber="9"/>
  <EnumeratedItem CodedValue="Withdrew Consent" OrderNumber="10"/>
</CodeList>
```

## Define-XML 2.0 WHAT'S NEW – CODE LISTS

- Linking Code Lists to CDISC / NCI Controlled Terminology

### SDTM-IG 3.1.2

Annotated Case Report Form

Reviewers Guide

Complex Algorithms

► Tabulation Datasets

► Value Level Metadata

▼ Controlled Terminology

▼ Controlled Terms

Action Taken with Study T

Domain Abbreviation (AE)

Epoch

Ethnic Group

Domain Abbreviation (EX)

### Trial Summary Parameter Test Code [CL.TSPARMCD, C66738]

| Permitted Value (Code) | Display Value (Decode)               |
|------------------------|--------------------------------------|
| ADDON [C49703]         | Added on to Existing Treatments      |
| AGEMAX [C49694]        | Planned Maximum Age of Subjects      |
| AGEMIN [C49693]        | Planned Minimum Age of Subjects      |
| AGESPAN [C20587]       | Age Span                             |
| AGEU [*]               | Age Unit                             |
| DOSE [C25488]          | Dose per Administration              |
| INT [C41101]           | Investigational Therapy or Treatment |
| TTYPE [C49660]         | Trial Type                           |

\* Extended Value

## Define-XML 2.0 WHAT'S NEW – CODE LISTS

- Linking Code Lists to CDISC / NCI Controlled Terminology

```
<CodeList OID="CL.TSPARMCD" Name="Trial Summary Parameter Test Code"
  DataType="text" SASFormatName="$TSPARMC">
  <CodeListItem CodedValue="ADDON">
    <Decode>
      <TranslatedText xml:lang="en">Added on to Existing Treatments</TranslatedText>
    </Decode>
    <Alias Name="C49703" Context="nci:ExtCodeID"/>
  </CodeListItem>
  <CodeListItem CodedValue="AGEU" def:ExtendedValue="Yes">
    <Decode>
      <TranslatedText xml:lang="en">Age Unit</TranslatedText>
    </Decode>
  </CodeListItem>
  ...

  <CodeListItem CodedValue="TTYE">
    <Decode>
      <TranslatedText xml:lang="en">Trial Type</TranslatedText>
    </Decode>
    <Alias Name="C49660" Context="nci:ExtCodeID"/>
  </CodeListItem>
  <Alias Name="C66738" Context="nci:ExtCodeID"/>
</CodeList>
```

## Define-XML 2.0 WHAT'S NEW – LINKING TO DOCUMENTS

- Linking from a derivation to an external document

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

```
<MethodDef OID="MT.ADQSADAS.AVAL.ACTOT"
  Name="CM.ADQSADAS.AVAL.ACTOT" Type="Computation">
  <Description>
    <TranslatedText xml:lang="en">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.</TranslatedText>
  </Description>
  <def:DocumentRef leafID="LF.ADRG">
    <def:PDFPageRef PageRefs="3" Type="PhysicalRef"/>
  </def:DocumentRef>
</MethodDef>
```

## Define-XML 2.0 WHAT'S NEW – LINKING TO DOCUMENTS

- Linking from a dataset or variable to an external document

```
<ItemGroupDef OID="IG.ADSL" Name="ADSL" SASDatasetName="ADSL"
...
  <def:CommentOID="COM.ADSL" def:ArchiveLocationID="LF.ADSL">
    <Description>
      <TranslatedText xml:lang="en">Subject-Level Analysis</TranslatedText>
    </Description>
  ...
</def:CommentDef OID="COM.ADSL">
  <Description>
    <TranslatedText>Screen Failures are excluded since they are not needed for
      this study analysis. See Reviewers Guide, section 2.1 for more
      details.</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 2.0 WHAT'S NEW – LINKING TO VARIABLES

- Linking from an ADaM variable to a Predecessor (traceability)

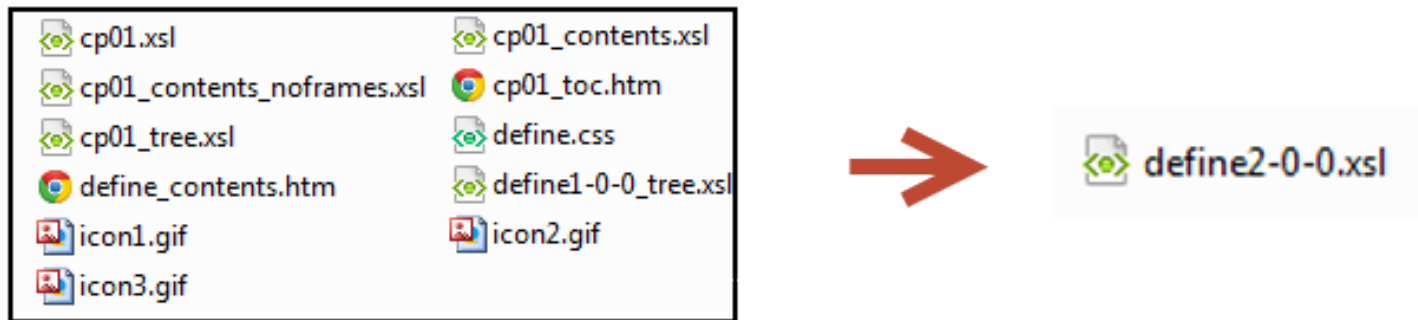
```
<ItemDef OID="IT.ADQSADAS.TRTP" Name="TRTP"  
  SASFieldName="TRTP" DataType="text" Length="20">  
  <Description>  
    <TranslatedText xml:lang="en">Planned Treatment</TranslatedText>  
  </Description>  
  <CodeListRef CodeListOID="CL.ARM" />  
  <def:Origin Type="Predecessor">  
    <Description>  
      <TranslatedText xml:lang="en">ADSL.TRT01P</TranslatedText>  
    </Description>  
  </def:Origin>  
</ItemDef>
```

# DISPLAYING DEFINE-XML



## 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 stylesheet conforms to web standards and follows accessibility guidelines
- 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

# NEXT STEPS



## Define-XML NEXT STEPS

- Validation Rules for FDA submissions
  - Define unambiguous business rules, that tools can implement
- Implementation Guide
  - No massive document, but incremental
- Pilot
- Analysis Results Metadata extension
  - Under development

## Define-XML ANALYSIS RESULTS METADATA

- **Traceability** from **results** used in a statistical display to analysis **data** used to create it
- Analysis results metadata are not required
- Assists a reviewer by
  - identifying the critical analyses
  - providing links between results, documentation, and datasets
  - documenting the analyses performed
- Sponsor determines which analyses should have analysis results metadata

## Define-XML ANALYSIS RESULTS METADATA

| Analysis Results Metadata Fields | Description                                                         |
|----------------------------------|---------------------------------------------------------------------|
| DISPLAY IDENTIFIER               | Unique Identifier                                                   |
| DISPLAY NAME                     | Title, description                                                  |
| RESULT IDENTIFIER                | Unique Identifier                                                   |
| PARAM / PARAMCD                  | Analysis parameter                                                  |
| ANALYSIS VARIABLE                | Analysis variable being analyzed                                    |
| REASON                           | AnalysisPurpose / Reason                                            |
| DATASET                          | Dataset(s) used to generate the result                              |
| SELECTION CRITERIA               | 'WHERE CLAUSE'                                                      |
| DOCUMENTATION                    | Textual description, pseudo code, link to document or program       |
| PROGRAMMING STATEMENTS           | The software programming code used to perform the specific analysis |

# Define-XML ANALYSIS RESULTS METADATA

## Data Guide

### ▼ Analysis Results Metadata

Table\_14-1.01

Table\_14-1.02

Table\_14-2.01

Table\_14-3.01

Table\_14-3.02

Table\_14-3.12

Table\_14-5.02

Table\_14-6.01

Table\_14-6.02

Table\_14-6.03

Table\_14-6.04

Table\_14-6.05

Table\_14-6.06

Figure\_14-1

### ► Analysis Datasets

### ► Parameter Value Level Meta

## Analysis Results Metadata (Summary) for Study CDISCPILLOT01

[Table\\_14-1.01](#) Summary of Populations

[Table\\_14-1.02](#) Summary of End of Study Data (ITT population)

[Table\\_14-2.01](#) Summary of Demographic and Baseline Characteristics (ITT population)  
[treatment group comparison for continuous variables](#)  
[treatment group comparison for categorical variables](#)

[Table\\_14-3.01](#) Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Pop)  
[dose response analysis for ADAS-Cog changes from baseline](#)  
[pairwise comparisons to placebo for ADAS-Cog changes from baseline](#)

[Table\\_14-3.02](#) Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF (Efficacy Popula)  
[dose response analysis for CIBIC+ values](#)  
[pairwise comparisons to placebo for CIBIC+ values](#)

[Table\\_14-3.12](#) Mean NPI-X total score from Weeks 4 through Week 24 - Windowed (Efficacy Pop)  
[Descriptive statistics \(n, mean, standard deviation, median, min, and max\)](#)

# Define-XML ANALYSIS RESULTS METADATA

## Data Guide

### ▼ Analysis Results Metadata

Table\_14-1.01

Table\_14-1.02

Table\_14-2.01

Table\_14-3.01

Table\_14-3.02

Table\_14-3.12

Table\_14-5.02

Table\_14-6.01

Table\_14-6.02

Table\_14-6.03

Table\_14-6.04

Table\_14-6.05

Table\_14-6.06

Figure\_14-1

► Analysis Datasets

► Parameter Value Level Metadata

► Controlled Terms

► External Dictionaries

|                                                   |                                                                                                                                            |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Display</b>                                    | <a href="#">Table 14-3.01</a> Primary Endpoint Analysis: ADAS-Cog -                                                                        |
| <b>AnalysisResult</b>                             | <b>dose response analysis for ADAS-Cog changes from</b>                                                                                    |
| <b>Analysis Parameter(s)</b>                      | ACTOT=Adas-Cog(11) Subscore                                                                                                                |
| <b>Analysis Variable(s)</b>                       | <a href="#">CHG</a>                                                                                                                        |
| <b>Reason</b>                                     | Primary Endpoint Analysis; pre-specified in SAP                                                                                            |
| <b>Data References (incl. Selection Criteria)</b> | <a href="#">ADQSADAS</a> [ EFFFLL="Y" and ANL01FL="Y" and AVISIT=                                                                          |
| <b>Documentation</b>                              | <a href="#">SAP Section 10.1.1</a> Linear model analysis of CHG for dose; 81 for high dose) and site group in model. Used treatment dose). |
| <b>Programming Statements</b>                     | <pre>proc glm data = ADQSADAS;   where EFFFLL='Y' and ANL01FL='Y' and AVISIT='Wee   class sitegr1;   model CHG = trtpn sitegr1; run;</pre> |
| <b>AnalysisResult</b>                             | <b>pairwise comparisons to placebo for ADAS-Cog chan</b>                                                                                   |
| <b>Analysis Parameter(s)</b>                      | ACTOT=Adas-Cog(11) Subscore                                                                                                                |
| <b>Analysis Variable(s)</b>                       | <a href="#">CHG</a>                                                                                                                        |
| <b>Reason</b>                                     | Primary Endpoint Analysis; pre-specified in SAP                                                                                            |



**Thank You !**

**Questions ?**



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