Creating Define-XML version 2
including Analysis Results Metadata
with the SAS® Clinical Standards Toolkit

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Why Analysis Results Metadata?

- Analysis Results Metadata provides **traceability** from **results** in a statistical display to the **data** in the analysis datasets.
- Facilitates documentation and reproduction of the analysis results.
- Not needed - or even advisable - for every analysis in a submission.
- Analysis Results Metadata v1.0 for Define-XML v2.0 has been available at CDISC since January 2015.
- PMDA (Japan) is already asking for it.
- FDA is interested.
**ADaM Results Metadata v1 for Define-XML v2**

**Protocol:** CDISCPILOT01  
**Population:** Efficacy

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=79)</th>
<th>Low Dose (N=81)</th>
<th>High Dose (N=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SD)</td>
<td>79</td>
<td>81</td>
<td>74</td>
</tr>
<tr>
<td>(Range)</td>
<td>24.1 (12.19)</td>
<td>24.4 (12.92)</td>
<td>21.3 (11.74)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>79</td>
<td>81</td>
<td>74</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>26.7 (13.79)</td>
<td>26.4 (13.18)</td>
<td>22.8 (12.48)</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>79</td>
<td>81</td>
<td>74</td>
</tr>
<tr>
<td>(SD)</td>
<td>2.5 (5.80)</td>
<td>2.0 (5.55)</td>
<td>1.5 (4.26)</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>2.0 (-11;16)</td>
<td>2.0 [-11;17]</td>
<td>1.0 [-7;13]</td>
</tr>
</tbody>
</table>

**p-value (Dose Response)**  
1. [1][2]  
2. 0.245

**p-value (Xan - Placebo)**  
1. [1][3]  
2. 0.569

**Diff of LS Means (SE)**  
1. 0.5 (0.82)  
2. -1.0 (0.84)  
3. (-2.1;1.1)

**p-value (Xan High - Xan Low)**  
1. [1][3]  
2. 0.520

**Diff of LS Means (SE)**  
1. -0.5 (0.84)

2. (-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
### Table 14-3.01

<table>
<thead>
<tr>
<th>Display</th>
<th>Secondary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis Result</td>
<td>Dose response analysis for ADAS-Cog changes from baseline</td>
</tr>
<tr>
<td>Analysis Parameter(s)</td>
<td>PARAMCD = &quot;ACTOT&quot; (Adas-Cog(11) Subscore)</td>
</tr>
<tr>
<td>Analysis Variable(s)</td>
<td>CHG (Change from Baseline)</td>
</tr>
<tr>
<td>Analysis Reason</td>
<td>SPECIFIED IN SAP</td>
</tr>
<tr>
<td>Analysis Purpose</td>
<td>PRIMARY OUTCOME MEASURE</td>
</tr>
</tbody>
</table>

**Data References (incl. Selection Criteria)**

ADOSSADAS [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]

```sas
proc glm data = ADQSSADAS;
   where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT";
   class SITEGR1;
   model CHG = TRIPN SITEGR1;
run;
```

**Analysis Result**

Pairwise comparisons to placebo for ADAS-Cog changes from baseline

**Analysis Parameter(s)**

PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
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
Creating the Define-XML v2 (incl. ARM) with CST
• **Framework** to primarily support Clinical Research activities (CDISC).

• A collection of metadata and "tools" (SAS macros, XML schemas, some Java code, ...)

• Provides SAS representation of published CDISC standards as SAS data sets and catalogs
  
  • Contents standards: SDTM, ADaM, SEND
  
  • XML standards: Define-XML, Dataset-XML and ODM
  
  • Controlled Terminology (CDISC/NCI)
• Hotfix for Toolkit 1.7 (CST 1.7.1):
  • Support for Analysis Results Metadata v1.0 for Define-XML v2
  • Implemented as an update to the existing CDISC Define-XML 2.0 standard

• CST 1.7.1 expected availability May/June 2016.

• CST is available at no additional charge to currently licensed SAS customers.

• Contact your SAS Account Representative concerning availability
From Study Source Metadata to Define-XML v2

1. Column Metadata
2. Value Level Metadata
3. Codelist Metadata
4. Table Metadata
5. Study Metadata
6. Document Metadata
7. Analysis Results Metadata

Internal SAS representation of Define-XML
(54 SAS data sets*)

XML Validation Process

*Define-XML v2 uses 39 data sets
Creating Source Metadata for Define-XML v2

Internal SAS representation of Define-XML

Excel

MDR

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Source Metadata - `source_analysisresults` (ADaM) - One record per `DisplayIdentifier`, `ResultIdentifier`, Table

<table>
<thead>
<tr>
<th><code>DisplayIdentifier</code></th>
<th><code>ResultIdentifier</code></th>
<th><code>AnalysisReason</code></th>
<th><code>AnalysisPurpose</code></th>
<th><code>ResultDescription</code></th>
</tr>
</thead>
<tbody>
<tr>
<td>RD.Table_14-3.01</td>
<td>AR.Table_14-3.01.R.1</td>
<td>SPECIFIED IN SAP</td>
<td>PRIMARY OUTCOME MEASURE</td>
<td>Dose response analysis for ADAS-Cog changes from baseline</td>
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<td>RD.Table_14-3.01</td>
<td>AR.Table_14-3.01.R.2</td>
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<td>Pairwise comparisons to placebo for ADAS-Cog changes from baseline</td>
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<td>RD.Table_14-5.02</td>
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<td>PRIMARY OUTCOME MEASURE</td>
<td>Incidence of Treatment Emergent Serious Adverse Events by Treatment Group</td>
</tr>
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<table>
<thead>
<tr>
<th><code>DisplayIdentifier</code></th>
<th><code>ResultIdentifier</code></th>
<th><code>ParameterColumn</code></th>
<th><code>Table</code></th>
<th><code>AnalysisVariables</code></th>
<th><code>WhereClause</code></th>
</tr>
</thead>
<tbody>
<tr>
<td>RD.Table_14-3.01</td>
<td>AR.Table_14-3.01.R.1</td>
<td>PARAMCD</td>
<td>ADQSADAS</td>
<td>CHG</td>
<td>(PARAMCD EQ &quot;ACTOT&quot;) AND (AVISIT EQ &quot;Week 24&quot;) AND (EFFFL EQ &quot;Y&quot;) AND (ANL01FL EQ &quot;Y&quot;)</td>
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<td>RD.Table_14-3.01</td>
<td>AR.Table_14-3.01.R.2</td>
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<td>RD.Table_14-5.02</td>
<td>AR.Table_14-5.02.R.1</td>
<td>ADAE</td>
<td>AEBODSYS AEDECOD</td>
<td></td>
<td>(TRTEMFL EQ &quot;Y&quot;) AND (AESER EQ &quot;Y&quot;)</td>
</tr>
<tr>
<td>RD.Table_14-5.02</td>
<td>AR.Table_14-5.02.R.1</td>
<td>ADSL</td>
<td></td>
<td></td>
<td>SAFFFL EQ &quot;Y&quot;</td>
</tr>
</tbody>
</table>
### Source Metadata - source_analysisresults (ADaM)
- One record per DisplayIdentifier, ResultIdentifier, Table

**Code**

```sas
proc glm data = ADQSADAS;
  where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD='ACTOT';
  class SITEGR1;
  model CHG = TRTPN SITEGR1;
run;
```

Whitespace and "\n" or Carriage Return ('0D'x) in Code metadata will be honored in Define-XML file and HTML display.
### Source Metadata - source_documents (ADaM)

- One record per table, column, `whereclause` or
- One record per `DisplayIdentifier`, `ResultIdentifier`
%define_sourcetodefine(
   _cstOutLib=srcdata, 
   _cstSourceStudy=sampdata.source_study, 
   _cstSourceTables=sampdata.source_tables, 
   _cstSourceColumns=sampdata.source_columns, 
   _cstSourceCodeLists=sampdata.source_codelists, 
   _cstSourceValues=sampdata.source_values, 
   _cstSourceDocuments=sampdata.source_documents, 
   _cstSourceAnalysisResults=sampdata.source_analysisresults, 
   _cstFullModel=N, 
   _cstCheckLengths=Y, 
   _cstLang=en
);

%define_write();
%cstutilxmlvalidate();

proc xsl
   in=extxml
   xsl=xslt01
   out=html;
run;
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** Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)

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<tr>
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<td>[PARAMCD = &quot;ACTOT&quot; and AVISIT = &quot;Week 24&quot; and EFFFL = &quot;y&quot; and ANL01FL = &quot;y&quot;]</td>
</tr>
</tbody>
</table>
Define-XML v2 with Analysis Results Metadata
Thank You!
Questions?