

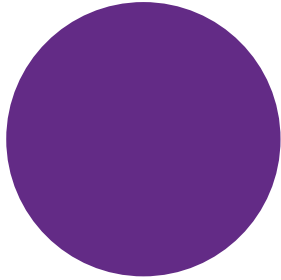


Generating define.xml and Analysis Results Metadata using Specifications, Datasets and TFL Annotation

Mark Crangle

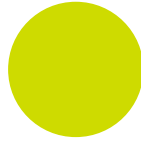
ICON Clinical Research

Key points



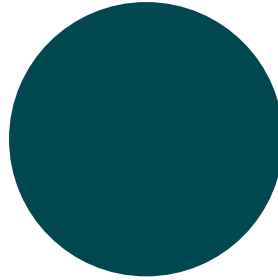
Define.xml

Define.xml is a key part of a regulatory submission



Dataset Metadata

Dataset Metadata has been a key part of define.xml since inception



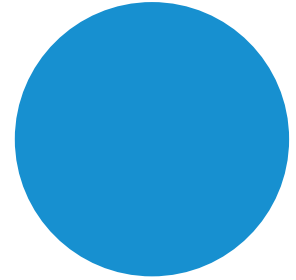
Analysis Results Metadata

More recently, Analysis Results Metadata (ARM) has been added to define.xml requirements



Collecting Information

ICON uses standard templates to collect information needed to populate define.xml



Standard Macros

Standard macros convert templates into define.xml files

Steps

ADaM Datasets

- Compliance with ADaM standards already assessed
- Ensure consistency of variable lengths
- Assess size of xpt files for compliance with eCTD requirements

Dataset Specifications

- Dataset specifications created to support development of datasets
- User friendly excel template
- Re-using this information ensures consistency and minimises rework
- Programmers don't need xml knowledge

Annotated TFLs

- User friendly excel template collects annotations needed for Analysis Results Metadata
- Undergoes statistical review prior to use in define.xml
- Programmers don't need xml knowledge

Creating define.xml

- Macros create define.xml from datasets, specifications and TFL annotations
- Macros ensure consistency with define-xml standard
- Identifies errors if datasets don't contain items referenced in specifications, or vice versa

ADaM Datasets

Dataset Compliance



- CDISC compliance assessed during dataset development and validation process
- Prior to creating define.xml, the package is again validated using Pinnacle 21 and other in house tools to ensure compliance
- Any unresolved issues are documented in the Analysis Data Reviewers Guide

Trim Variable Lengths



- Character variable lengths are trimmed to the maximum length of any value within that variable
- Eg. If longest value for RACE is “AMERICAN INDIAN OR ALASKA NATIVE” which has length 32, then the variable length is set to 32
- Ensures the dataset size is kept to a minimum
- Variables that are common between ADSL and other ADaM datasets have lengths applied consistently

Assess Dataset Size



- Datasets submitted to FDA have a maximum size of 5gb
- The standard macros assess the datasets used in the package to identify any that are above this limit
- The user would need to manually decide how the datasets should be split
- Having the macros flag any non-compliant datasets ensures this step is not missed

ADaM Dataset Specifications

Used in Dataset Development



- Specifications are a key document for the development and validation of datasets
- Reviewed by sponsors and study statisticians
- Revised when new requirements, raw data changes come to light
- Constantly updated, and reviewed and approved prior to deliverables ensuring it is consistent with programming

User Friendly Template



- Template is designed to capture all information needed for dataset development:
 - Dataset metadata
 - Variable metadata
 - Value level metadata
 - Controlled terminology
- This is the same information that is needed for define.xml

Re-used to create define.xml



- Ensures information in define.xml is consistent with datasets
- Efficient re-use of information that has already been collected
- Information entered by study experts and converted to define.xml by define.xml experts
- Study programmers don't need detailed xml knowledge

Analysis Results Metadata

User Friendly Template



- User friendly Excel template to collect information needed from ARM
- Allows for agreement with study teams and statisticians about information to be included in ARM
- Separate from the dataset specifications template as ARM is not always needed

Macros Combine With Dataset Information



- Macros optionally include ARM information with dataset information from specifications
- Validates information in ARM to ensure correct controlled terms have been used where applicable
- Cross reference between datasets and ARM to provide links between elements required by standard

Output to Define.xml



- Combines information from specifications and ARM template to produce Define.xml
- References different version of xsl style-sheet if ARM is included
- Macros validated to ensure compliant xml file is produced
- Compliance of define.xml also assessed using Pinnacle 21

Analysis Results Metadata – Basic Structure

```
<arm:AnalysisResultDisplays>
  <arm:ResultDisplay>
    <arm:AnalysisResult>
      <arm:AnalysisDatasets>
        <arm:AnalysisDataset>
          <arm:AnalysisVariable/>
        </arm:AnalysisDataset>
      </arm:AnalysisDatasets>
    </arm:AnalysisResult>
  </arm:ResultDisplay>
</arm:AnalysisResultDisplays>
```

- Basic xml definitions
 - An element defines an item in the xml file
 - An item attribute defines something about that item
- In define.xml, attributes are often used to link one element to another
 - Eg. In ARM, attributes are used to link analyses to the datasets that support those analyses

Analysis Results Metadata – Basic Structure

<arm:AnalysisResultDisplays>

```
<arm:ResultDisplay>
```

```
<arm:AnalysisResult>
```

```
<arm:AnalysisDatasets>
```

```
<arm:AnalysisDataset>
```

```
<arm:AnalysisVariable/>
```

```
</arm:AnalysisDataset>
```

```
</arm:AnalysisDatasets>
```

```
</arm:AnalysisResult>
```

```
</arm:ResultDisplay>
```

</arm:AnalysisResultDisplays>

- AnalysisResultDisplays element defines the Analysis Results Metadata section of the xml file
- There will be only one closing and one opening element within each xml file containing an ARM section

Analysis Results Metadata – Basic Structure

```
<arm:AnalysisResultDisplays>  
  <arm:ResultDisplay>  
    <arm:AnalysisResult>  
      <arm:AnalysisDatasets>  
        <arm:AnalysisDataset>  
          <arm:AnalysisVariable/>  
        </arm:AnalysisDataset>  
      </arm:AnalysisDatasets>  
    </arm:AnalysisResult>  
  </arm:ResultDisplay>  
</arm:AnalysisResultDisplays>
```

- Each table or figure described in the ARM has one ResultDisplay element
- There can be any number of ResultDisplay elements depending on how many tables/figures are included in the ARM
- Attributes for the ResultDisplay element define the name (number) of the table/figure, the title and a link to the location of that result in the CSR

Analysis Results Metadata – Basic Structure

```
<arm:AnalysisResultDisplays>
  <arm:ResultDisplay>
    <arm:AnalysisResult>
      <arm:AnalysisDatasets>
        <arm:AnalysisDataset>
          <arm:AnalysisVariable/>
        </arm:AnalysisDataset>
      </arm:AnalysisDatasets>
    </arm:AnalysisResult>
  </arm:ResultDisplay>
</arm:AnalysisResultDisplays>
```

- Each result described in the ARM has a AnalysisResult element
- There can be more than one AnalysisResult element per ResultDisplay element
- Attributes for this element define the purpose of the result, a description of the result
- If the result is supported by a specific PARAMCD in a BDS dataset this is also defined in an attribute of the AnalysisResult element

Analysis Results Metadata – Basic Structure

```
<arm:AnalysisResultDisplays>
  <arm:ResultDisplay>
    <arm:AnalysisResult>
      <arm:AnalysisDatasets>
        <arm:AnalysisDataset>
          <arm:AnalysisVariable/>
        </arm:AnalysisDataset>
      </arm:AnalysisDatasets>
    </arm:AnalysisResult>
  </arm:ResultDisplay>
</arm:AnalysisResultDisplays>
```

- Each AnalysisResult contains one AnalysisDatasets element
- Within each AnalysisDatasets element, there is at least one AnalysisDataset element defining the datasets used for each analysis
- If there is more than one AnalysisDataset element then an attribute to the AnalysisDatasets element will define how they are combined to support the analysis
- The attributes for the AnalysisDataset element define a link back to that dataset definition
- The AnalysisDataset element also contains a link to a where clause element that defines how the dataset is subset to support the analysis

Analysis Results Metadata – Basic Structure

```
<arm:AnalysisResultDisplays>
  <arm:ResultDisplay>
    <arm:AnalysisResult>
      <arm:AnalysisDatasets>
        <arm:AnalysisDataset>
          <arm:AnalysisVariable/>
        </arm:AnalysisDataset>
      </arm:AnalysisDatasets>
    </arm:AnalysisResult>
  </arm:ResultDisplay>
</arm:AnalysisResultDisplays>
```

- Each AnalysisDataset element contains one or more AnalysisVariable elements
- One AnalysisVariable element for each variable used in the analysis
- The attributes for this element define a link to the variable definition elsewhere in the xml file

Analysis Results Metadata – Basic Structure

```
<arm:AnalysisResultDisplays>
  <arm:ResultDisplay>
    <arm:AnalysisResult>
      <arm:AnalysisDatasets>
        <arm:AnalysisDataset>
          <arm:AnalysisVariable/>
        </arm:AnalysisDataset>
      </arm:AnalysisDatasets>
    </arm:AnalysisResult>
  </arm:ResultDisplay>
</arm:AnalysisResultDisplays>
```

- ARM also uses elements to define where clauses or subsets for each analysis, and to define references to external documents
- The dataset metadata sections also use these elements so information from the ARM template is combined with the dataset metadata template and output together in the xml file.

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

- Analysis tab collects information about the analysis being described in the Analysis Results Metadata
- One row for each analysis
 - Can be more than one row per table if multiple analyses on one table is described
 - Eg. If response by treatment and comparison of response between treatment is described
- Multiple datasets and variables can be included, separated by a space
 - Comment describing the dataset merge if more than one is used

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Number and title of the table or figure being described.

In the xml file, each table/figure has a ResultDisplay element which is then contains the each analysis result described. The ID for each ResultDisplay is derived by the macro.

```
<arm:ResultDisplay OID="RD.Table 14-3.01" Name="Table 14-3.01">
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Number and title of the table or figure being described.

In the xml file, each table/figure has a ResultDisplay element which is then contains the each analysis result described. The ID for each ResultDisplay is derived by the macro.

```
<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  
    Population)</TranslatedText>  
  </Description>
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Reference to the CSR section and page where the table is used. Information is in two parts, separated by “/”, with the first part being the document reference and the second part being the page number within the document where the table is used

The first part is used for the leafID attribute of the def:DocumentRef
The second part is used for the def:PDFPageRef element to define a link to the specific page of the CSR.

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

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Reference to the CSR section and page where the table is used. Information is in two parts, separated by “/”, with the first part being the document reference and the second part being the page number within the document where the table is used

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 ANLO1FL = "Y" and AVISIT = "Week 24" and EFFFL = "Y") SAP Section 10.1.1
Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and Type III SS for treatment dose).
Programming Statements	[SAS Version 9.2] <pre>proc glm data = ADQSADAS; where EFFFL='Y' and ANLO1FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;</pre>

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	proc glm data = ADQSADAS; ...

Description of the analysis result

Each analysis result is represented by an AnalysisResult element in the xml file. A unique ID for each analysis result for each table is derived by the macro

Entry in the spreadsheet is used for the Description element of the arm:AnalysisResult element

```
<arm:AnalysisResult  
OID="AR.Table 14-3.01.R.1">  
<Description>  
<TranslatedText xml:lang="en">Dose  
response analysis for ADAS-Cog changes  
from baseline  
</TranslatedText>  
</Description>
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	proc glm data = ADQSADAS; ...

Reason and Purpose for the analysis

Acceptable values are covered by controlled terminology but are extensible if required. The macro will output a message to the user if values outside the codelist are used.

Used to populate the attributes of the AnalysisResult element

```
<arm:AnalysisResult  
OID="AR.Table 14-3.01.R.1"  
ParameterOID="IT.ADQSADAS.PARAMCD"  
AnalysisReason="SPECIFIED IN SAP"  
AnalysisPurpose="PRIMARY OUTCOME  
MEASURE">
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Dataset name.

In the xml file this is a link to the data definition in the analysis datasets section.

Populates the ItemGroupOID attribute of the arm:AnalysisDataset element

```
<arm:AnalysisResult>  
  <arm:AnalysisDataset  
    ItemGroupOID="IG.ADQSADAS">  
</arm:AnalysisDataset>  
</arm:AnalysisResult>
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Dataset name.

In the xml file this is a link to the data definition in the analysis datasets section.

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 ANLO1FL = "Y" and AVISIT = "Week 24" and EFFFL = "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 Type III SS for treatment dose). SAP Section 10.1.1
Programming Statements	[SAS Version 9.2] <pre>proc glm data = ADQSADAS; where EFFFL='Y' and ANLO1FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;</pre>

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Analysis variables used in the analysis. If more than one variable is used then these should be specified together, separated by a space.

In the xml file this is used to create a link to the variable definition in the variable metadata section and to display the variable label.

Populates the ItemOID attribute of the arm:AnalysisVariable element.

```
<arm:AnalysisResult>  
  <arm:AnalysisVariable  
    ItemOID="IT.ADQSADAS.CHG"/>  
</arm:AnalysisResult>
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Analysis variables used in the analysis. If more than one variable is used then these should be specified together, separated by a space.

In the xml file this is used to create a link to the variable definition in the variable metadata section and to display the variable label

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 ANLO1FL = "Y" and AVISIT = "Week 24" and EFFFL = "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 Type III SS for treatment dose). SAP Section 10.1.1
Programming Statements	[SAS Version 9.2] <pre>proc glm data = ADQSADAS; where EFFFL='Y' and ANLO1FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;</pre>

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Y/N flag to identify whether a single parameter in a BDS-type dataset is used to support this analysis.

Define.xml file includes an extra reference to the specific parameter definition using information from the Where Clause definition

Used to populate the ParameterOID attribute of the AnalysisResult element. If flag is set to N this attribute is not added

```
<arm:AnalysisResult  
OID="AR.Table 14-3.01.R.1"  
ParameterOID="IT.ADQSADAS.PARAMCD"  
AnalysisReason="SPECIFIED IN SAP"  
AnalysisPurpose="PRIMARY OUTCOME  
MEASURE">
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Y/N flag to identify whether a single parameter in a BDS-type dataset is used to support this analysis.

Define.xml file includes an extra reference to the specific parameter definition using information from the Where Clause definition

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 ANLO1FL = "Y" and AVISIT = "Week 24" and EFFFL = "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 Type III SS for treatment dose). SAP Section 10.1.1
Programming Statements	[SAS Version 9.2] <pre>proc glm data = ADQSADAS; where EFFFL='Y' and ANLO1FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;</pre>

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Text description of the statistical methods describing how the analysis result is created

Used in the arm:Documentation element

```
<Description>  
<TranslatedText xml:lang="en">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).  
</TranslatedText>  
</Description>
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Reference to the SAP section and page where this analysis is specified. This is done in two parts, separated by "/" with the first part being a reference to the document and the second part being a reference to the page number.

Used within the arm:AnalysisResult element. The first part is used for the leafID attribute of the def:DocumentRef
The second part is used for the def:PDFPageRef element to define a link to the specific page of the SAP.

```
<def:DocumentRef leafID="LF.SAP-SEC-10.1.1">  
<def:PDFPageRef PageRefs="4"  
Type="PhysicalRef"/>  
</def:DocumentRef>
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Text entered in Description goes into the Documentation row of the xml file, along with a hyperlink to the SAP

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 ANLO1FL = "Y" and AVISIT = "Week 24" and EFFFL = "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 Type III SS for treatment dose). SAP Section 10.1.1
Programming Statements	[SAS Version 9.2] <pre>proc glm data = ADQSADAS; where EFFFL='Y' and ANLO1FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;</pre>

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
Table Title	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
CSR Ref	LF.Table-14-3.01 / 2
Analysis	Dose response analysis for ADAS-Cog changes from baseline
Reason	SPECIFIED IN SAP
Purpose	PRIMARY OUTCOME MEASURE
Dataset	ADQSADAS
Analysis Variable	CHG
PARAMCD	Y
Description	Linear model analysis of CHG...
SAP	LF.SAP-SEC-10.1.1 / 4
Code	<pre>proc glm data = ADQSADAS; ...</pre>

Details of the statistical procedure which can either be code itself or a reference to a separate SAS program file which is included in the submission package.

Used for the arm:ProgrammingCode element. If code is used then an arm:Code element is added, or if a reference to separate SAS file is used then a def:DocumentRef is added.

```
<arm:ProgrammingCode Context="SAS  
Version 9.2">  
<arm:Code>  
proc glm data = ADQSADAS;  
...  
</arm:Code>  
</arm:ProgrammingCode>
```

Analysis Results Metadata - Analysis

Table Number	Table 14-3.01
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PARAMCD	Y
Description	Linear model analysis of CHG...
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Programming Statements	[SAS Version 9.2] <pre>proc glm data = ADQSADAS; where EFFFL='Y' and ANLO1FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTFL SITEGR1; run;</pre>

Analysis Results Metadata – Where Clause

Table Number	Analysis	Dataset	Variable	Value
Table 14-3.01	Dose response analysis...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Dose response analysis...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Dose response analysis...	ADQSADAS	EFFL	Y
Table 14-3.01	Pairwise comparison...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Pairwise comparison...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Pairwise comparison...	ADQSADAS	EFFL	Y

- Where Clause tab collects the subset conditions used for each analysis result described
- One row per Table Number and Analysis Result described
 - Then one row for each dataset, variable and value used in the condition
- If more than one value is entered per Variable then this is represented as an “IN” condition in the xml file, otherwise an “EQ” condition is used
- Table Number and Analysis are used to match Where Clause information to Analysis information within the macro

Analysis Results Metadata – Where Clause

Table Number	Analysis	Dataset	Variable	Value
Table 14-3.01	Dose response analysis...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Dose response analysis...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Dose response analysis...	ADQSADAS	EFFL	Y
Table 14-3.01	Pairwise comparison...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Pairwise comparison...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Pairwise comparison...	ADQSADAS	EFFL	Y

Dataset used for the where clause subset criteria which provides a link to the dataset and variable definition sections of the define.xml

Matches with the Dataset Name defined on the analysis tab.

Matches with the Dataset Name defined on the analysis tab. Also used to populate the OID attribute of the def:WhereClauseDef element and the def:ItemOID attribute of the RangeCheck element.

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

Analysis Results Metadata – Where Clause

Table Number	Analysis	Dataset	Variable	Value
Table 14-3.01	Dose response analysis...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Dose response analysis...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Dose response analysis...	ADQSADAS	EFFL	Y
Table 14-3.01	Pairwise comparison...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Pairwise comparison...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Pairwise comparison...	ADQSADAS	EFFL	Y

Variable used for the where clause subset criteria which provides a link to the dataset and variable definition sections of the define.xml

Used to populate the OID attribute of the def:WhereClauseDef element and the def:ItemOID attribute of the RangeCheck element.

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

Analysis Results Metadata – Where Clause

Table Number	Analysis	Dataset	Variable	Value
Table 14-3.01	Dose response analysis...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Dose response analysis...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Dose response analysis...	ADQSADAS	EFFL	Y
Table 14-3.01	Pairwise comparison...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Pairwise comparison...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Pairwise comparison...	ADQSADAS	EFFL	Y

Value used in the subset criteria. The Where Clause tab should contain one row for each value that the variable in question is subset on. If more than one row per variable exists, this is converted to an “IN” condition for the define.xml, otherwise it is handled as an “EQ” condition

Used to generate CheckValue elements within the def:WhereClauseDef element.

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

Analysis Results Metadata – Where Clause

Table Number	Analysis	Dataset	Variable	Value
Table 14-3.01	Dose response analysis...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Dose response analysis...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Dose response analysis...	ADQSADAS	EFFL	Y
Table 14-3.01	Pairwise comparison...	ADQSADAS	PARAMCD	ACTOT
Table 14-3.01	Pairwise comparison...	ADQSADAS	AVISIT	Week 24
Table 14-3.01	Pairwise comparison...	ADQSADAS	EFFL	Y

Table 14-3.01

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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 ANLO1FL = "Y" and AVISIT = "Week 24" and EFFL = "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 Type III SS for treatment dose). SAP Section 10.1.1
Programming Statements	[SAS Version 9.2] proc glm data = ADQSADAS; where EFFL='Y' and ANLO1FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;

Analysis Results Metadata – Document References

- Specifies the external documents referenced within the Analysis Results Metadata
- These include references to the location of the table within the CSR or reference to a specific section of the SAP where the analysis is described
- Actual page numbers for each document are specified in the Analysis tab

ID	Title	href
LF.Table-14-3.01	Table 14-3.01	../dummy-csr/dummy-csr.pdf
LF.SAP-SEC-10.1.1	SAP Section 10.1.1	../dummy-csr/dummy-csr.pdf

Analysis Results Metadata – Document References

- Specifies the external documents referenced within the Analysis Results Metadata
- These include references to the location of the table within the CSR or reference to a specific section of the SAP where the analysis is described
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ID	Title	href
LF.Table-14-3.01	Table 14-3.01	../dummy-csr/dummy-csr.pdf
LF.SAP-SEC-10.1.1	SAP Section 10.1.1	../dummy-csr/dummy-csr.pdf

Populates the ID attribute of the def:leaf element

```
<def:leaf ID="LF.Table-14-3.01" xlink:href="../dummy-csr/dummy-csr.pdf">  
<def:title>Table 14-3.01</def:title>  
</def:leaf>
```

Analysis Results Metadata – Document References

- Specifies the external documents referenced within the Analysis Results Metadata
- These include references to the location of the table within the CSR or reference to a specific section of the SAP where the analysis is described
- Actual page numbers for each document are specified in the Analysis tab

ID	Title	href
LF.Table-14-3.01	Table 14-3.01	../dummy-csr/dummy-csr.pdf
LF.SAP-SEC-10.1.1	SAP Section 10.1.1	../dummy-csr/dummy-csr.pdf

Used for the def:title element of the def:leaf element

```
<def:leaf ID="LF.Table-14-3.01" xlink:href="../dummy-csr/dummy-csr.pdf">  
<def:title>Table 14-3.01</def:title>  
</def:leaf>
```

Analysis Results Metadata – Document References

- Specifies the external documents referenced within the Analysis Results Metadata
- These include references to the location of the table within the CSR or reference to a specific section of the SAP where the analysis is described
- Actual page numbers for each document are specified in the Analysis tab

ID	Title	href
LF.Table-14-3.01	Table 14-3.01	../dummy-csr/dummy-csr.pdf
LF.SAP-SEC-10.1.1	SAP Section 10.1.1	../dummy-csr/dummy-csr.pdf

Populates the xlink:ref attribute of the def:leaf element

```
<def:leaf ID="LF.Table-14-3.01" xlink:href="../dummy-csr/dummy-csr.pdf">  
<def:title>Table 14-3.01</def:title>  
</def:leaf>
```

Conclusion



Data-driven Approach to Define.xml creation

Ensures metadata consistency between datasets and information in define.xml

Re-use of Dataset Specifications

Efficient use of information necessary for dataset creation

Consistency between derivations used in datasets and described in define.xml

Template for TFL Annotations

TFL Annotations for ARM collected in template

Populated by study teams who don't need detailed knowledge of xml language

Standard Macros to Create Define.xml

Macros are run by teams that are expert in define.xml

Ensures define.xml output meets the CDISC standard

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