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

Lex Jansen
Principal Software Developer @ SAS

PharmaSUG 2016

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

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
SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.74)
(Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;57)
	79	81	74
Mean (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 change 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 TRTDOSE SITEGR1;
	model CHG = BASE SITEGR1 TRTDOSE;
	run;

Analysis Result	Pairwise

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

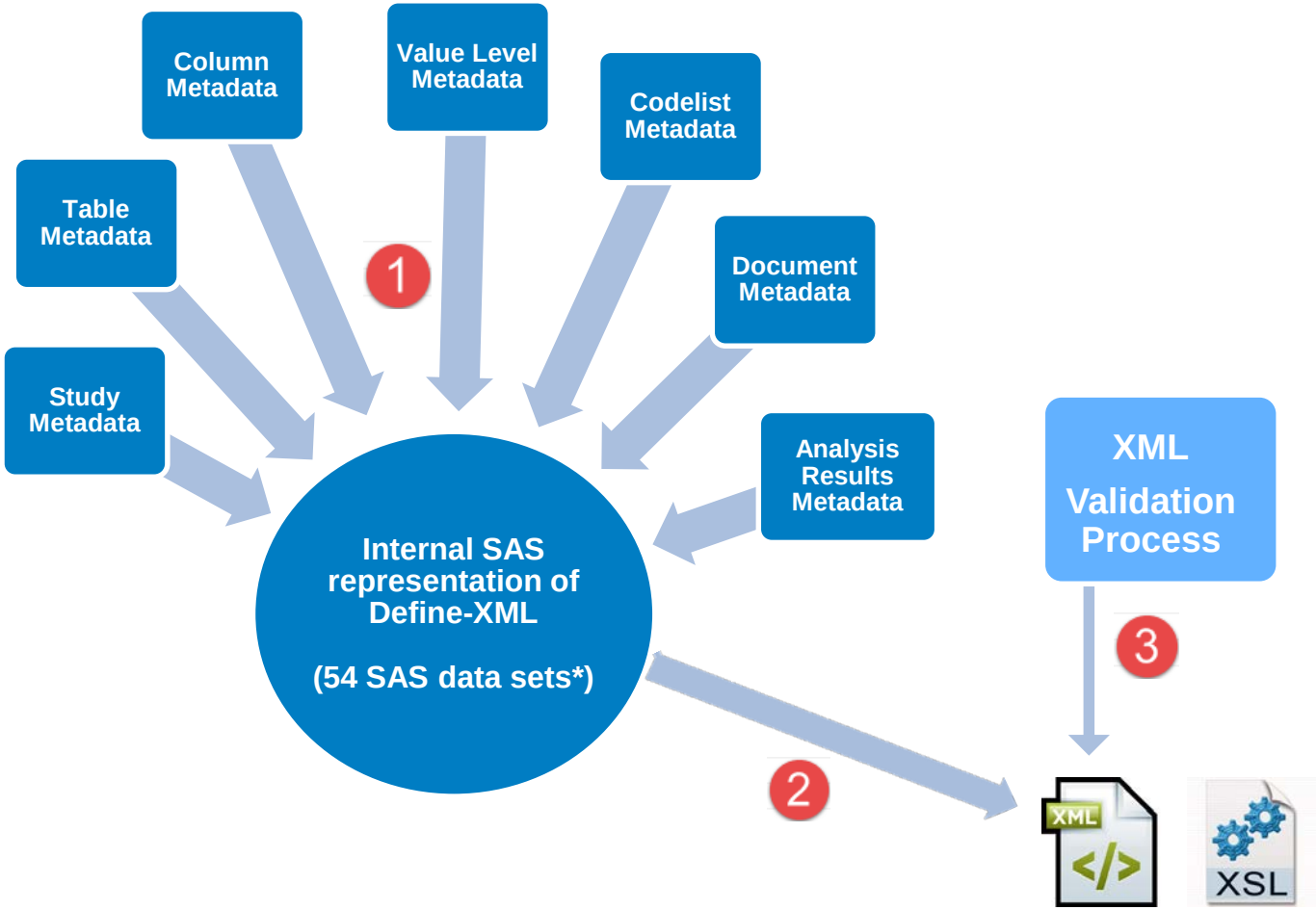
Introduction

- **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)

Introduction

- 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

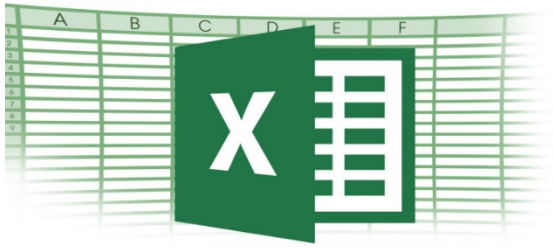
From Study Source Metadata to Define-XML v2

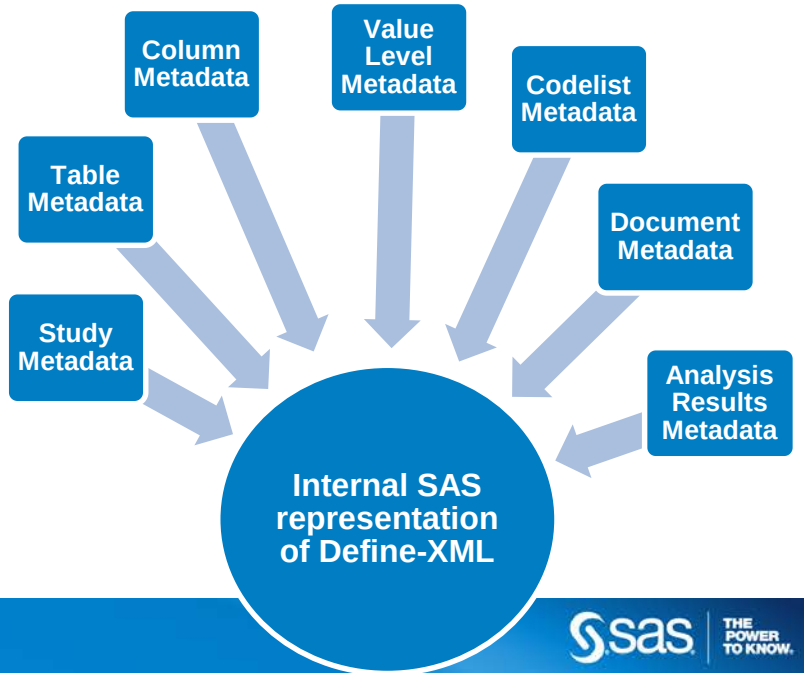


*Define-XML v2 uses 39 data sets

Creating Source Metadata for Define-XML v2

Excel





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

VIEWTABLE: Sampdata.Source_analysisresults (Source Analysis Results Metadata)

	DisplayIdentifier	DisplayName	DisplayDescription	ResultIdentifier
1	RD.Table_14-3.01	Table 14-3.01	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)	AR.Table_14-3.01.R.1
2	RD.Table_14-3.01	Table 14-3.01	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)	AR.Table_14-3.01.R.2
3	RD.Table_14-5.02	Table 14-5.02	Incidence of Treatment Emergent Serious Adverse Events by Treatment Group	AR.Table_14-5.02.R.1
4	RD.Table_14-5.02	Table 14-5.02	Incidence of Treatment Emergent Serious Adverse Events by Treatment Group	AR.Table_14-5.02.R.1

VIEWTABLE: Sampdata.Source_analysisresults (Source Analysis Results Metadata)

	DisplayIdentifier	ResultIdentifier	AnalysisReason	AnalysisPurpose	ResultDescription
1	RD.Table_14-3.01	AR.Table_14-3.01.R.1	SPECIFIED IN SAP	PRIMARY OUTCOME MEASURE	Dose response analysis for ADAS-Cog changes from baseline
2	RD.Table_14-3.01	AR.Table_14-3.01.R.2	SPECIFIED IN SAP	PRIMARY OUTCOME MEASURE	Pairwise comparisons to placebo for ADAS-Cog changes from baseline
3	RD.Table_14-5.02	AR.Table_14-5.02.R.1	SPECIFIED IN SAP	PRIMARY OUTCOME MEASURE	Incidence of Treatment Emergent Serious Adverse Events by Treatment Group
4	RD.Table_14-5.02	AR.Table_14-5.02.R.1	SPECIFIED IN SAP	PRIMARY OUTCOME MEASURE	Incidence of Treatment Emergent Serious Adverse Events by Treatment Group

	DisplayIdentifier	ResultIdentifier	ParameterColumn	Table	AnalysisVariables	WhereClause
1	RD.Table_14-3.01	AR.Table_14-3.01.R.1	PARAMCD	ADQSADAS	CHG	(PARAMCD EQ "ACTOT") AND (AVISIT EQ "Week 24") AND (EFFFL EQ "Y") AND (ANL01FL EQ "Y")
2	RD.Table_14-3.01	AR.Table_14-3.01.R.2	PARAMCD	ADQSADAS	CHG	(PARAMCD EQ "ACTOT") AND (AVISIT EQ "Week 24") AND (EFFFL EQ "Y") AND (ANL01FL EQ "Y")
3	RD.Table_14-5.02	AR.Table_14-5.02.R.1		ADAE	AEBODSYS AEDECOD	(TRTEMFL EQ "Y") AND (AESER EQ "Y")
4	RD.Table_14-5.02	AR.Table_14-5.02.R.1		ADSL		SAFFL EQ "Y"

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

VIEWTABLE: Sampdata.Source_analysisresults (Source Analysis Results Metadata)

	DisplayIdentifier	ResultIdentifier	ResultDocumentation	CodeContext	Code
1	RD.Table_14-3.01	AR.Table_14-3.01.R.1	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). See page 4 (section 10.1.1) in the Statistical Analysis Plan.	SAS version 9.2	proc glm data = ADQSADAS;\n where EFFFL="Y" and ANL01FL="Y" and AVISIT="Week 24" and PARAMCD="ACTOT";\n class SITEGR1;\n model CHG = TRTPN SITEGR1;\nrun;
2	RD.Table_14-3.01	AR.Table_14-3.01.R.2	ANCOVA analysis of CHG performed to provide pairwise comparisons among treatment groups and adjusted means; using randomized treatment as class variable and site group as class variable in model and the baseline value as a covariate. See page 4 (section 10.1.1) in the Statistical Analysis Plan.	SAS version 9.2	proc glm data = ADQSADAS;\n where EFFFL="Y" and ANL01FL="Y" and AVISIT="Week 24" and PARAMCD="ACTOT";\n class TRTPN SITEGR1;\n model CHG = TRTPN SITEGR1 BASE;\n means TRTPN;\n lsmeans TRTPN / OM STDERR PDIFF CL;\nrun;
3	RD.Table_14-5.02	AR.Table_14-5.02.R.1	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. See page 5 (section 11.2) in the Statistical Analysis Plan.	SAS version 9.2	

Code
proc glm data = ADQSADAS;\n where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT";\n class SITEGR1;\n model CHG = TRTPN SITEGR1;\nrun;

Whitespace and "\n" or Carriage Return ('0D'x) in Code metada will be honored in Define-XML file and HTML display.

[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;
```

Source Metadata - source_documents (ADaM)

- One record per table, column, whereclause

or

- One record per DisplayIdentifier, ResultIdentifier

VIEWTABLE: Sampdata.Source_documents (Source Document Metadata)

	doctype	href	title	pdfpagereftype	pdfpagerefs	table	column	whereclause
1	COMMENT	'adae-sas.txt	adae.sas			ADAE		
2	COMMENT	'adqsadas-sas.txt	adqsadas.sas			ADQSADAS		
3	COMMENT	'analysis-data-reviewers-guid	Analysis Data Reviewer's Guide	NamedDestination	Section2.1	ADQSADAS		
4	COMMENT	'analysis-data-reviewers-guid	Analysis Data Reviewer's Guide	PhysicalRef	6	ADSL		
7	METHOD	'analysis-data-reviewers-guid	Analysis Data Reviewer's Guide	PhysicalRef	3	ADQSADAS	AVAL	PARAMCD EQ "ACTOT"

VIEWTABLE: Sampdata.Source_documents (Source Document Metadata)

	doctype	href	title	pdfpagerefty	pdfpageref	displayidentifier	resultidentifier
5	DISPLAY	dummy-csr.pdf	Table 14-3.01	PhysicalRef	2	RD.Table_14-3.01	
6	DISPLAY	dummy-csr.pdf	Table 14-5.02	PhysicalRef	3	RD.Table_14-5.02	
8	RESULTCODE	at14-5-02-sas.txt	at14-5-02.sas			RD.Table_14-5.02	AR.Table_14-5.02.R.1
9	RESULTDOC	dummy-sap.pdf	Statistical Analysis Plan	PhysicalRef	4	RD.Table_14-3.01	AR.Table_14-3.01.R.2
10	RESULTDOC	dummy-sap.pdf	Statistical Analysis Plan	PhysicalRef	5	RD.Table_14-5.02	AR.Table_14-5.02.R.1
11	RESULTDOC	dummy-sap.pdf	Statistical Analysis Plan	PhysicalRef	4	RD.Table_14-3.01	AR.Table_14-3.01.R.1
12	SUPPDOC	analysis-data-reviewers-guide.pdf	Analysis Data Reviewer's Guide				
13	SUPPDOC	dummy-csr.pdf	Clinical Study Report				
14	SUPPDOC	dummy-sap.pdf	Statistical Analysis Plan				

From Study Source Metadata to Define-XML v2

1
```
%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
  );
```

2
```
%define_write();
```

3
```
%cstutilxmlvalidate();
```

4
```
proc xsl
  in=extxml
  xsl=xslt01
  out=html;
run;
```

SAS Clinical Standards Toolkit 1.7.1

Define-XML v2 with Analysis Results Metadata

ADaM-IG 1.0

- Analysis Data Reviewer's Guide
- Clinical Study Report
- Statistical Analysis Plan
- ▸ Analysis Results Metadata
- ▸ Analysis Datasets
- ▸ Parameter Value Level Metadata
- ▸ Controlled Terminology
- ▸ Analysis Derivations
- ▸ Comments

Date of Define-XML document generation: 2016-03-30T12:22:27-04:00

Stylesheet version: 2016-02-11

Standard	ADaM-IG 1.0
Study Name	CDISC-Sample
Study Description	CDISC-Sample Data Definition
Protocol Name	CDISC-Sample
Metadata Name	Data Definitions for CDISC-Sample, ADaM-IG 1.0
Metadata Description	Data Definitions for CDISC-Sample, ADaM-IG 1.0

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

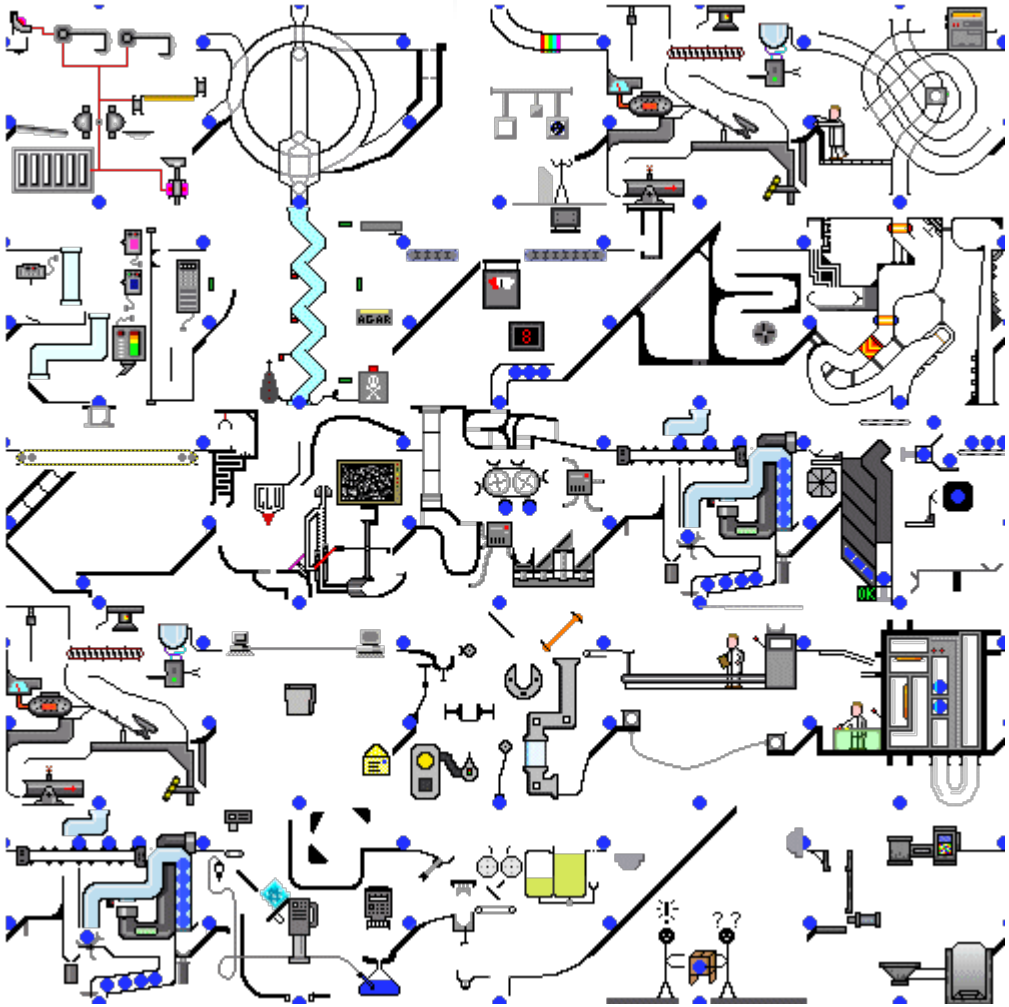
Analysis Results Metadata (Detail) for Study CDISC-Sample

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

SAS Clinical Standards Toolkit 1.7.1

Define-XML v2 with Analysis Results Metadata



Demo

Thank You !
Questions ?

sas | THE POWER TO KNOW.

sas

SAS Institute Inc.
World Headquarters
SAS Campus Drive
Cary, NC 27513 USA
Tel: +1 919 677 8000
Fax: +1 919 677 4444
www.sas.com

Lex Jansen
Principal Software Developer
Health and Life Sciences
Tel: +1 919 531 9860

E-mail: lex.jansen@sas.com

THE POWER TO KNOW.