# Business & Decision Life Sciences

## *What's new in ADaM*

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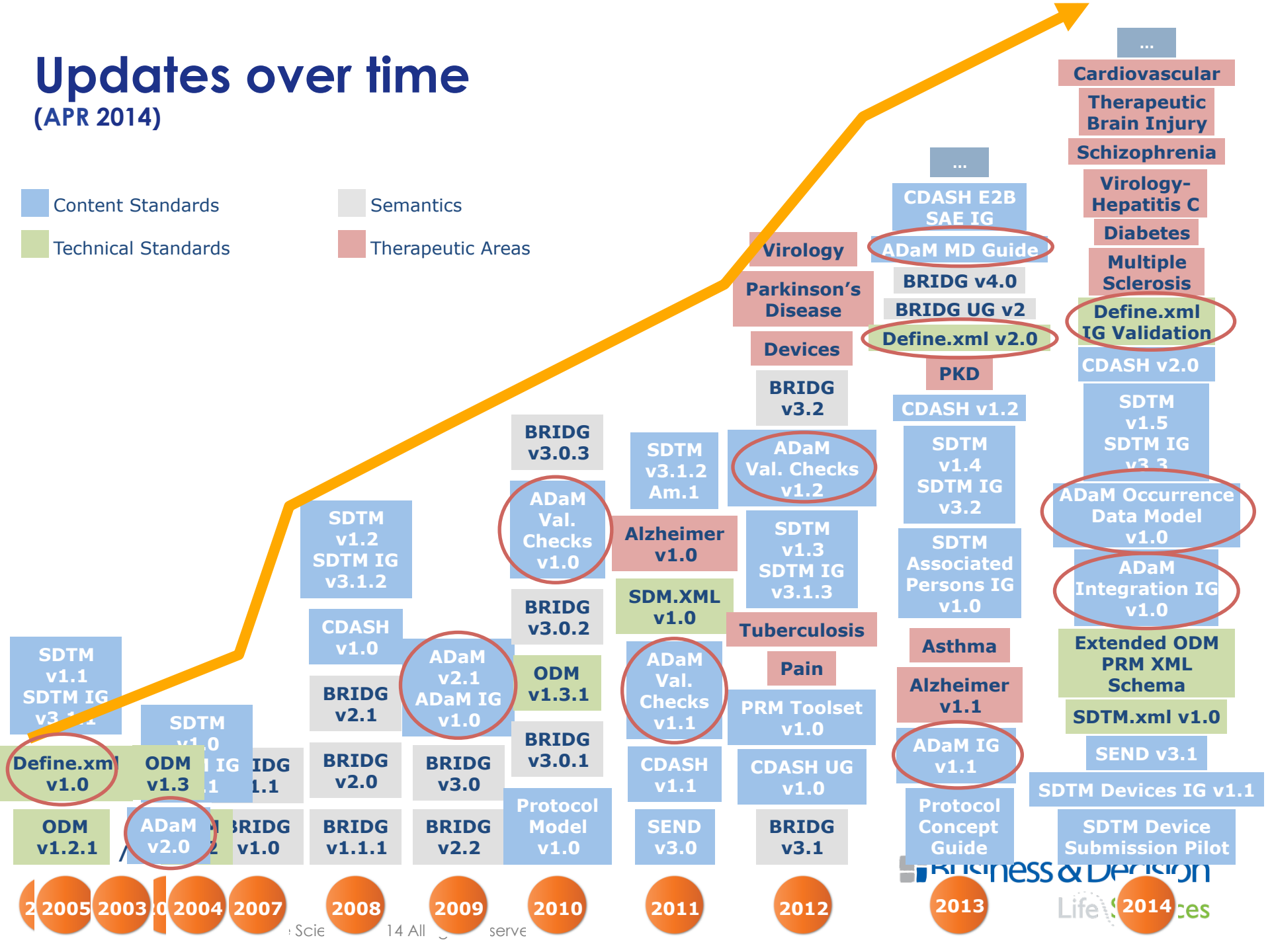
18 September 2014

# Agenda

- CDISC and Regulatory Submission Landscape
- What's Happening: ADaM Implementation Guide
- What's Happening: ADaM Occurrence Data Structure (ODS)
- What's Happening: Define-XML v2 and Analysis Results Metadata Specification
- What's Happening: Analysis Data Reviewer's Guide
- Q&A

# Updates over time
(APR 2014)



# Regulatory Position

- FDA CDER draft guidance for Study Data Technical Conformation Guide contains the statements:
  - *4.1.7.2. General Considerations (page 12)*:
    "One of the expected benefits of analysis datasets that conform to ADaM is that they simplify the programming steps necessary for performing an analysis. ADaM datasets should be derived from the data contained in the SDTM datasets. There are features built into the ADaM standard that promote traceability from analysis results to ADaM datasets and from ADaM datasets to SDTM. **Sponsors who provide the software programs used to create ADaM datasets help reviewers to better understand how the datasets were created** (see section 4.1.7.8). Each analysis dataset that is shown in the define.xml file should be described."

# CDISC ADaM Team 2014 Goals


Goals

- Document on the introduction of ADaM methodologies to support ISS/ISE and an integrated ADSL structure
- Explore integrating ADaM in SHARE
- Development of CFAST/Therapeutic Area ADaM standards
- Development of ADaM examples and best practices for questionnaire data which can be applied across TA standards
- Update Compliance rules for consistency with the current version of ADaM-IG
- Harmonize ADaM model document with Define 2.0 and better address representation of results-level metadata
- Continued work on ADaM-IG updates
- Publication of final versions of ODS v1 and ADaMIG v1.1

# Planned SHARE Milestones (June 2014)

| # | Milestone Description | Date |
|---|---|---|
| 1 | Production eSHARE content download site | July 25 |
| 2a | SDTM 3.1.3 Available | June 13 |
| 2b | SDTM 3.2 Available | July 25 |
| 3 | Initial Value Level Metadata content in eSHARE | August 29 |
| 4 | SEND 3.0 Available | September 26 |
| 5 | Research concepts prototype | September 26 |
| 6 | Initial ADaM content Available | Q4 |
| 7 | Research concepts meta-model and initial content | Q4 |
| 8 | RDF/OWL export format available | Q4 |

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# CDISC ADaM Implementation Guide (Version 1.1 Draft)


- Appendix B of the document details the changes made - generally fairly minor, with some additions, clarifications, tidying up.
- Announced retirement of PARAMTYP variable
  - Indicates whether parameter is derived as a function of one or more other parameters.
  - Retired from the ADaM IG in next update as it is confused with the concept of DTYPE.
- Increased padding of 'x' to "xx" in a variable names (e.g., TRTxxP, APxxSDT) where "xx" is replaced with a zero-padded two-digit [01-99].
- Increased padding of 'z' to 'zz' in a variable name (e.g., ANLzzFL) where "zz" is replaced with a zero-padded two-digit integer [01-99].
  - Note that the 'zz' convention represents a simple counter, while the 'xx' convention represents a specific period

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# CDISC ADaM Implementation Guide (Version 1.1 Draft)

- Noted that length can vary between SDTM and ADaM variable
- Added variables for ADSL:
  - AGEGRy ACTARM,  TSEQPGy, DOSE
- Added variables for BDS datasets:
  - ASEQ, dose variables, MCRITy and corresponding flags
- Made RFL and PFL Population flag variables permissible instead of conditional
- Clarification regarding when certain timing variables should be included in ADSL vs. BDS
- Clarifications regarding use of DTYPE, PARAM

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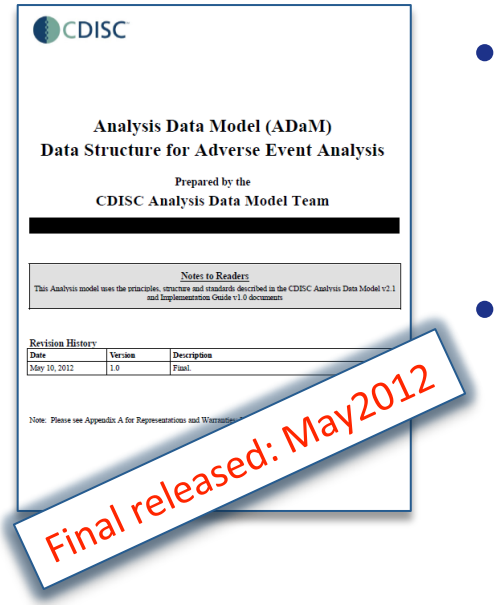
# CDISC ADaM ODS (Draft)




- ADAE structure document released May 2012
- Intended to support analysis of AEs, and structurally similar to SDTM's AE.
- **Issue:**

  Other occurrence event data and analysis needs are very similar to AEs, and the structure is being applied outside its original remit to support these in custom domains.

# CDISC ADaM ODS v1.0 (Draft)


- **Solution:**
  Expanded AE structure to also support Occurrence Data Models such as Medical History, Concomitant Medications, Lab Events.
- **Input data:**
  Usually events and interventions

- **Analysis need:**
  Subject count analysis, where a subject may be represented multiple times in a category. => AVAL or AVALC are not required.

# CDISC ADaM ODS: AE

- ADAE under ODS structure – mapped and backwards compatible. Examples from ADAE Structure document are copied into new ODS structure document

- Minor label changes to make them general rather than specific to AE, and Class of Dataset made non-specific.

**Table 4.1 Example of ADaM ADAE Dataset Metadata**

| Dataset Name | Dataset Description | Dataset Location | Key Variables of Dataset | Class of Dataset | Documentation |
|---|---|---|---|---|---|
| ADAE | Adverse Event Analysis Dataset | pathname/analysis/datasets/adae.xpt | USUBJID, AEDECOD, AESEQ, (optional: | ADAE* | ADAE.SAS<br>*Example: Dictionary used is* |

**Table 4.1.1 Example of ADaM ODS Dataset Metadata**

| Dataset Name | Dataset Description | Dataset Location | Key Variables of Dataset | Class of Dataset | Documentation |
|---|---|---|---|---|---|
| ADXXXXXX | <Dataset label> | adxxxxxx.xpt | *List variables, such as USUBJID, --SEQ* | ODS | *Example: Dictionary used is MedDRA V11.1* |

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# CDISC ADaM ODS: ConMeds

- Most variables are from CM + SUPPCM + ADSL
  - Include any variables needed for analysis

**Table 9.2.1 Example of ADCM Variable Metadata**

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|---|---|---|---|---|---|---|
| ADCM | STUDYID | Study Identifier | text | $3 | | CM.STUDYID |
| ADCM | USUBJID | Unique Subject Identifier | text | $11 | | CM.USUBJID |
| ADCM | CMSEQ | Sequence Number | integer | 3.0 | | CM.CMSEQ |
| ADCM | CMTRT | Reported Name of Drug, Med or Therapy | text | $200 | | CM.CMTRT |
| ADCM | CMMODIFY | Modified Reported Name | text | $200 | | CM.CMMODIFY |
| ADCM | CMDECOD | Standardized Medication Name | text | $200 | WHODRUG | CM.CMDECOD<br>WHO Drug Dictionary March 2012 |
| ADCM | PREFCODE | Preferred Term Code | text | $200 | WHODRUG | CM.PREFCODE<br>WHO Drug Dictionary March 2012 |
| ADCM | ATC1C | ATC Level 1 Code | text | $200 | WHODRUG | ATC Level 1 Code<br>WHO Drug Dictionary March 2012 |
| ADCM | ATC2C | ATC Level 2 Code | text | $200 | WHODRUG | ATC Level 2 Code<br>WHO Drug Dictionary March 2012 |
| ADCM | ATC3C | ATC Level 3 Code | text | $200 | WHODRUG | ATC Level 3 Code<br>WHO Drug Dictionary March 2012 |
| ADCM | ATC1T | ATC Level 1 Text | text | $200 | WHODRUG | ATC Level 1 Text<br>WHO Drug Dictionary March 2012 |
| ADCM | ATC2T | ATC Level 2 Text | text | $200 | WHODRUG | ATC Level 2 Text<br>WHO Drug Dictionary March 2012 |
| ADCM | ATC3T | ATC Level 3 Text | text | $200 | WHODRUG | ATC Level 3 Text<br>WHO Drug Dictionary March 2012 |
| ADCM | AOCCFL | 1st Occurrence of Any AE Flag | text | $1 | Y | <Sponsor will insert derivation here> |
| ADCM | ATC1FL | ATC Level 1 – First Occurrence Flag | text | $1 | Y | <Sponsor will insert derivation here> |
| ADCM | ATC2FL | ATC Level 2 – First Occurrence Flag | text | $1 | Y | <Sponsor will insert derivation here> |
| ADCM | ATC3FL | ATC Level 3 – First Occurrence Flag | text | $1 | Y | <Sponsor will insert derivation here> |
| ADCM | AOCCPFL | 1st Occurrence of Preferred Term Flag | text | $1 | Y | <Sponsor will insert derivation here> |

# CDISC ADaM ODS: ConMeds

- Additional derived variables
  - Indicator and Occurrence flags needed for analysis have been provided.

**Table 4.2.5.4 Concomitant Medications Indicator Variables**

| Variable Name | Variable Label | Type | Code List / Controlled Terms | Core | CDISC Notes |
|---|---|---|---|---|---|
| ONTRTFL | On-Treatment Flag | Char | Y | Cond | Character indicator of whether the observation occurred while the subject was on treatment.<br>Example derivation:<br>If ADSL.TRTSDT <= ASTDT <= ADSL.TRTEDT then ONTRTFL = 'Y'<br>This variable is conditional on whether the concept of on-treatment is a feature of the study and used in analysis. |
| PREFL | Pre-treatment Flag | Char | Y | Cond | Character indicator of whether the observation occurred before the subject started treatment.<br>Example derivation:<br>If ASTDT < ADSL.TRTSDT then PREFL='Y'<br>This variable is conditional on whether the concept of pre-treatment is a feature of the study and used in analysis. |
| FUPFL | Follow-up Flag | Char | Y | Cond | Character indicator of whether the observation occurred while the subject was on follow-up.<br>Example derivation:<br>If ASTDT > ADSL.TRTEDT then FUPFL='Y'<br>This variable is conditional on whether the concept of follow-up is a feature of the study and used in analysis. |

# CDISC ADaM ODS: ConMeds

**Table 9.3.1 Sample ADCM Data**

| Row | STUDYID | USUBJID | CMSEQ | CMTRT | CMMODIFY |
|---|---|---|---|---|---|
| 1 | ABC | ABC-001 | 1 | TYLENOL | TYLENOL |
| 2 | ABC | ABC-001 | 2 | TYLENOL | TYLENOL |
| 3 | ABC | | | | |
| 4 | ABC | | | | |
| 5 | ABC | | | | |
| 6 | ABC | | | | |

| Row | CMDECOD | PREFCODE | ATC1C | ATC2C | ATC3C | ATC1T |
|---|---|---|---|---|---|---|
| 1 | PARACETAMOL | N02BE | N | N02 | N02B | NERVOUS SYSTEM |
| 2 | PARACETAMOL | N02BE | N | N02 | N02B | NERVOUS SYSTEM |
| 3 | PARACETAMOL | N02BE | N | N02 | N02B | NERVOUS SYSTEM |
| 4 | PARACETAMOL | N0 | | | | |
| 5 | CONTACMS | N0 | | | | |
| 6 | FLUTICASONE PROPIONATE | R0 | | | | |

| Row | ATC2T | ATC3T |
|---|---|---|
| 1 | ANALGESICS | OTHER ANALGESICS AND ANTIPYRETICS |
| 2 | ANALGESICS | OTHER ANALGESICS AND ANTIPYRETICS |
| 3 | ANALG | RETICS |
| 4 | ANALG | RETICS |
| 5 | ANALG | RETICS |
| 6 | NASAL | SAL |

| Row | ATC1FL | ATC2FL | ATC3FL | AOCCFL | AOCCPFL | CMINDC |
|---|---|---|---|---|---|---|
| 1 | Y | Y | Y | Y | Y | HEADACHE |
| 2 | | | | | | HEADACHE |
| 3 | | | | | | HEADACHE |
| 4 | | | | | | HEADACHE |
| 5 | | | | | Y | COLD |
| 6 | Y | Y | Y | | Y | CHOLESTEROL |

- The Occurrence Flags (AOCCzzFL) are permissible, and not required.
- The main purpose of these flags is to facilitate data point traceability between records in the dataset and unique counts in the summary displays.

# CDISC ADaM ODS: Medical History

- Most variables are from MH + ADSL
  - Include any variables needed for analysis (e.g. could add severity of the History event).

**Table 10.2.1 Example of ADMH Variable Metadata**

| Dataset Name | Variable Name | Variable Label | Variable Type | Display Format | Codelist / Controlled Terms | Source / Derivation |
|---|---|---|---|---|---|---|
| ADMH | USUBJID | Unique Subject Identifier | text | $11. | | MH.USUBJID |
| ADMH | MHSEQ | Sequence Number | integer | 3. | | MH.MHSEQ |
| ADMH | MHCAT | Category for Medical History | text | $200. | | MH.MHCAT |
| ADMH | MHSCAT | Sub Category for Medical History | text | $200. | | MH.MHSCAT |
| ADMH | MHDECOD | Dictionary-Derived Term | text | $200. | | MH.MHDECOD |
| ADMH | MHBODSYS | Body System or Organ Class | text | $200. | | MH.MHBODSYS |
| ADMH | MHTERM | Reported Term for the Medical History | text | $200. | | MH.MHTERM |
| ADMH | MHSTDTC | Start Date/Time of Medication | datetime | $16. | ISO 8601 | MH.MHSTDTC |
| ADMH | ASTDT | Analysis Start Date | integer | date9. | | From MHSTDTC, converted to SAS Date. Any derivations to derive partial start dates are applied here and listed in comments. |
| ADMH | ASTTM | Analysis Start Time | integer | time5. | | From MH.MHSTDTC, converted to SAS Time. |
| ADMH | ASTDTM | Analysis Start Date/Time | integer | datetime16. | | From MH.MHSTDTC, converted to SAS Datetime. |
| ADMH | MHENDTC | End Date/Time of Medication | datetime | $16. | ISO 8601 | MH.MHENDTC |
| ADMH | AENDT | Analysis End Date | integer | date9. | | From MHENDTC, converted to SAS Date. Any derivations to derive partial start dates are applied here and listed in comments. |
| ADMH | AENTM | Analysis End Time | integer | time5. | | From MHENDTC, converted to SAS Time. |
| ADMH | AENDTM | Analysis End Date/Time | integer | datetime16. | | From MHENDTC, converter to SAS Datetime. |
| ADMH | MHENRF | Continuation Flag | text | $20. | | MH.MHENRF |

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# CDISC Define-XML v2


- Specification describes an updated Define-XML 2.0.0 model that is used to describe CDISC SDTM, SEND and ADaM datasets for the purpose of submissions to the FDA, as well as any proprietary (non-CDISC) dataset structure.

- Define-XML version 2.0.0 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

# CDISC Define-XML v2 features

- Value ("parameter" in ADaM) level metadata improved.
  - Instead of just pointing at AVAL the value level metadata can point at any variable if needed.
- Provides where clause machine metadata and "slices" (collection of where clauses) for parameter level metadata definitions
- Old ADaM "source/derivation" metadata can be broken into smaller and more useful chunks.
  - New machine readable "Formal Expression" element as part of Method Definitions.
  - Define.xml 2.0 says, "Comments are not intended to replace a properly defined computational algorithm, which is expected for derived variables."

# CDISC AResM Specification (Version 1.0)(Draft) for Define-XML (Version 2)


CDISC

Analysis Results Metadata Specification
Version 1.0
for
Define-XML Version 2

DRAFT

Prepared by
CDISC ADaM Metadata Sub-Team

Note to Readers

Revision History

Draft release: 14Sep2014
Review Period closes: 14Oct2014

- ADaM Results Metadata
  - Unique to ADaM and not formalized in define.xml 2.0

Document package can be downloaded from: http://portal.cdisc.org/CT/Review%20Documents/AResM-for-Define-XML-1.zip

- Comments can be uploaded to: http://portal.cdisc.org/CT/Review%20Documents/Forms/Active%20Documents.aspx

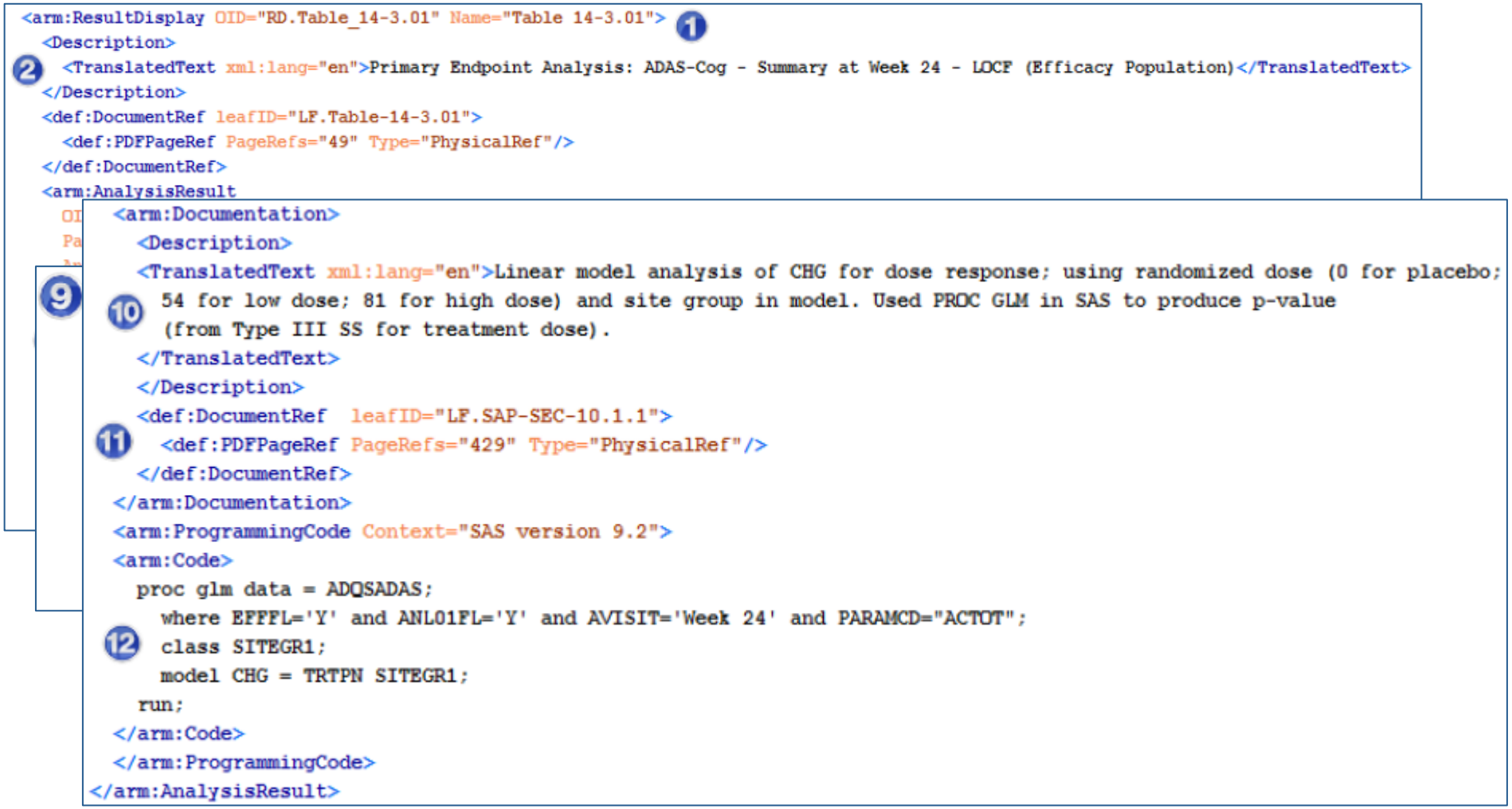
# CDISC ADaM Results Metadata

**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) | 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;
```

# CDISC ADaM Results Metadata



```
<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>
  <def:DocumentRef leafID="LF.Table-14-3.01">
    <def:PDFPageRef PageRefs="49" Type="PhysicalRef"/>
  </def:DocumentRef>
  <arm:AnalysisResult
    <arm:Documentation>
      <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>
      <def:DocumentRef  leafID="LF.SAP-SEC-10.1.1">
        <def:PDFPageRef PageRefs="429" Type="PhysicalRef"/>
      </def:DocumentRef>
    </arm:Documentation>
    <arm:ProgrammingCode Context="SAS version 9.2">
    <arm:Code>
      proc glm data = ADQSADAS;
        where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT";
        class SITEGR1;
        model CHG = TRTPN SITEGR1;
      run;
    </arm:Code>
    </arm:ProgrammingCode>
</arm:AnalysisResult>
```

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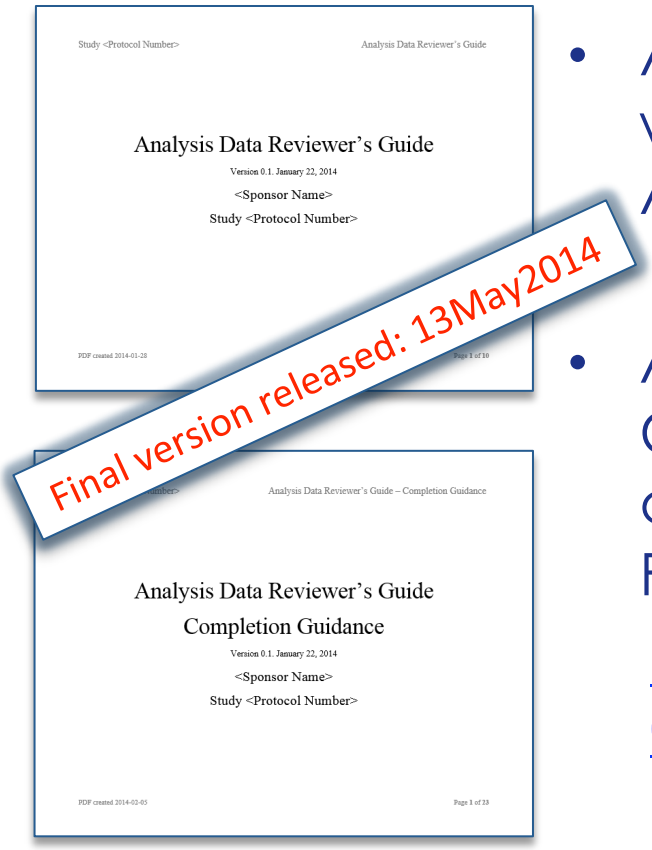
# Analysis Data Reviewer's Guide




- At PhUSE CSS symposium in 2013, PhUSE working group formed to create an Analysis Data Reviewer's Guide (ADRG)
- Analysis Data Reviewer's Guide plus Completion Guidance documents drafted during 2013, and released as Final on PhUSE Wiki Website:

  http://www.phusewiki.org/wiki/images/0/0d/ADRG_V1.0_2014-05-13.zip

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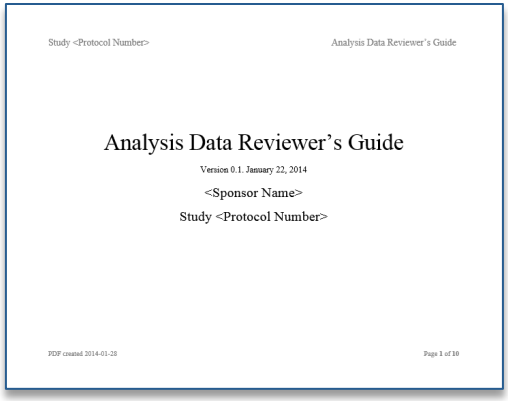
# Analysis Data Reviewer's Guide


Study <Protocol Number> Analysis Data Reviewer's Guide

Analysis Data Reviewer's Guide

Version 0.1. January 22, 2014

<Sponsor Name>

Study <Protocol Number>

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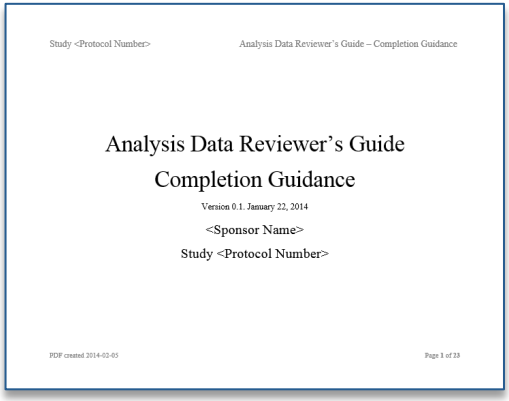
Study <Protocol Number> Analysis Data Reviewer's Guide – Completion Guidance

Analysis Data Reviewer's Guide

Completion Guidance

Version 0.1. January 22, 2014

<Sponsor Name>

Study <Protocol Number>

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- ADaM "provides a framework that enables analysis of the data, while at the same time allowing reviewers to have a clear understanding of the data's lineage.
- FDA Reviewers benefit from additional, human-readable, documentation of analysis methods, datasets, and programs.
- The development of an Analysis Data Reviewer's Guide (ADRG) template will ensure this documentation is provided to the agency in consistent and usable format.

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***Thank you for your attention.***

***Join us for a coffee at our stand.***

London, United Kingdom, 13 OCT 2014

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