

Business & Decision Life Sciences

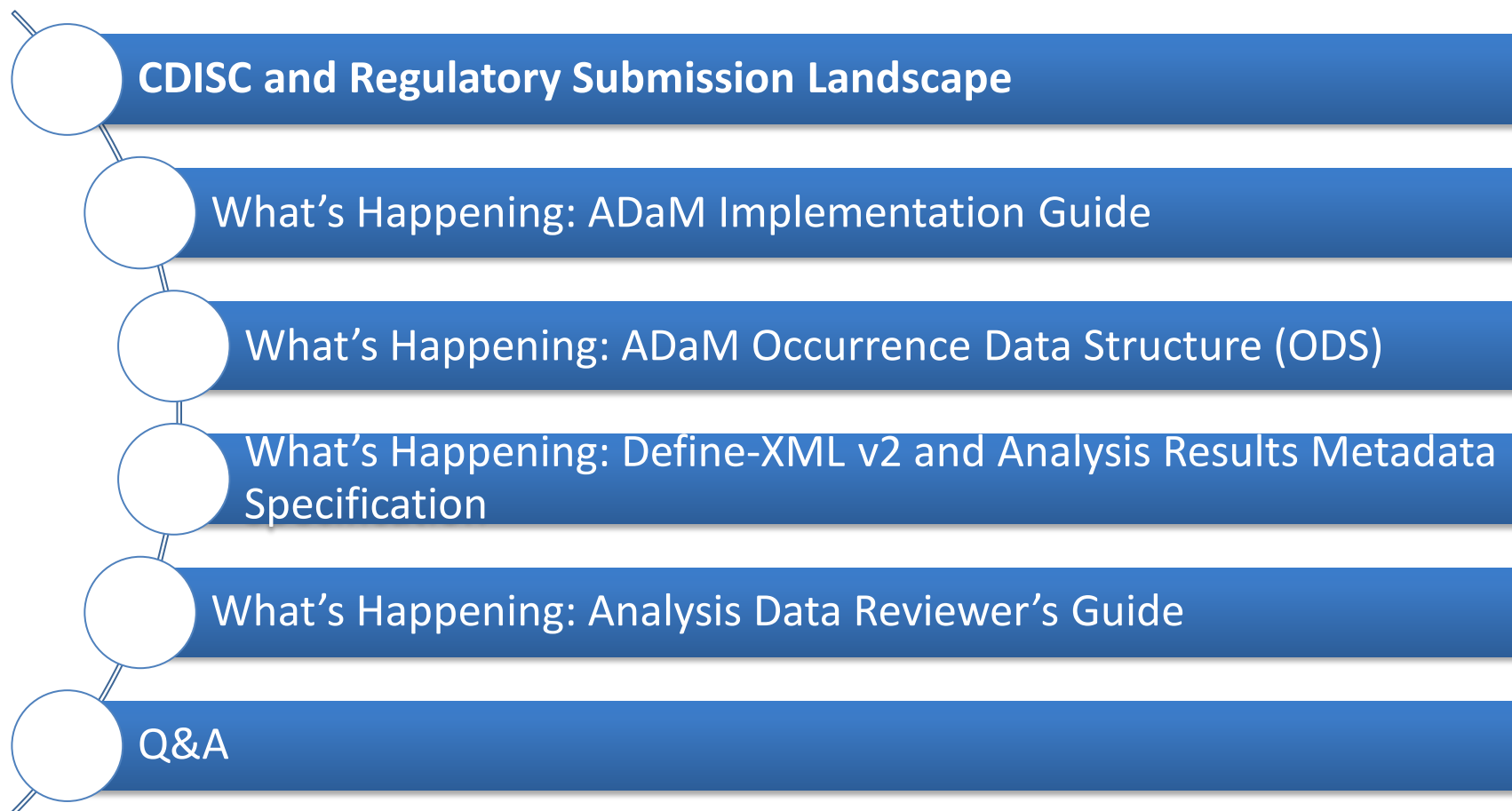
CD03: What's new in ADaM

Gavin Winpenny

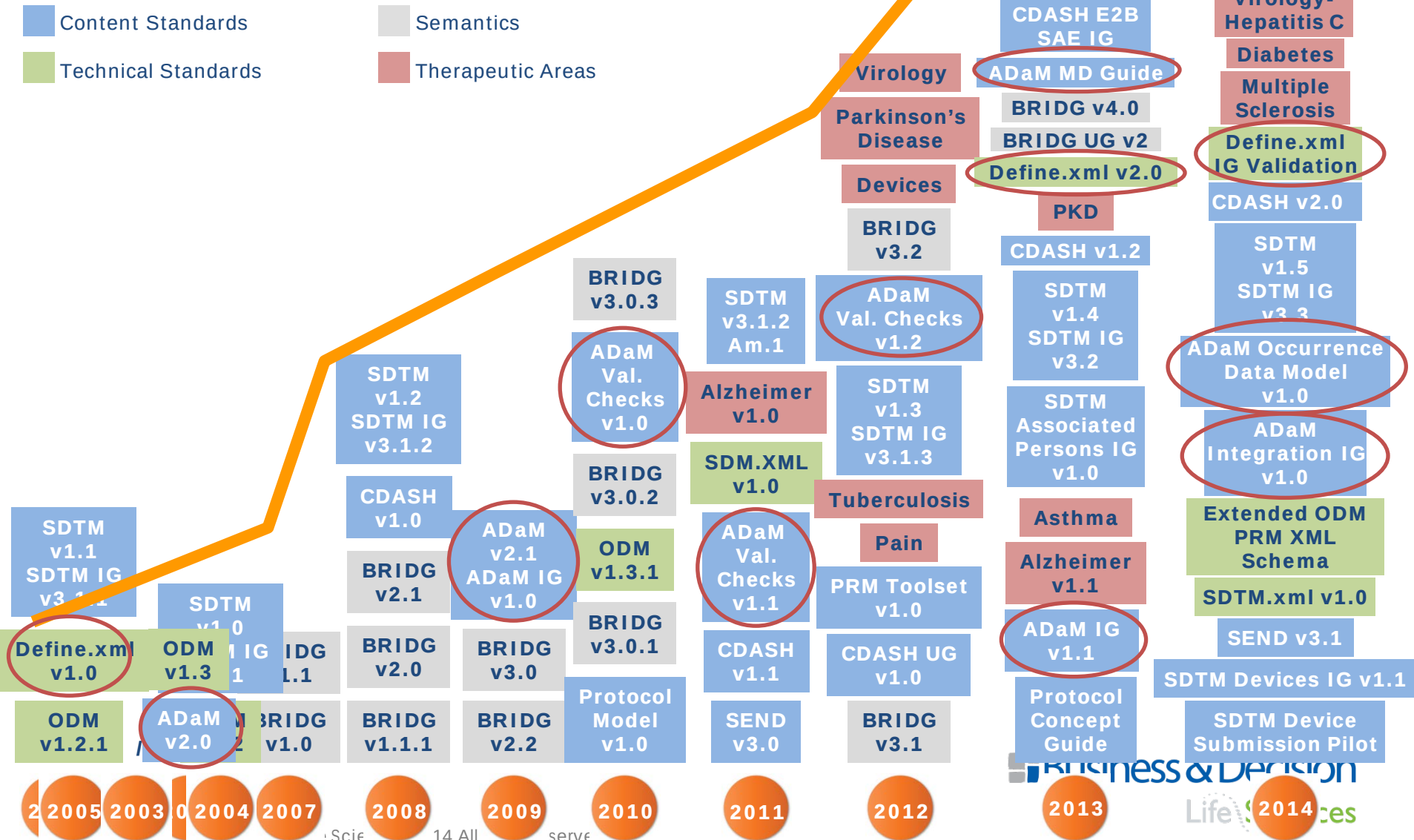
13 October 2014



Agenda



(APR 2014)



- FDA CDER draft guidance for [Study Data Technical Conformation Guide](#) contains the statements: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
- Harmonize ADaM model document with Define 2.0 and better address representation of results-level metadata
- Update Compliance rules for consistency with the current version of ADaM-IG
- 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

Agenda



CDISC ADaM Implementation Guide (Version 1.1 Draft)



Draft Release: 23 May 2014
Final Release: Q4 2014 ?

- 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

CDISC ADaM Implementation Guide (Version 1.1 Draft)

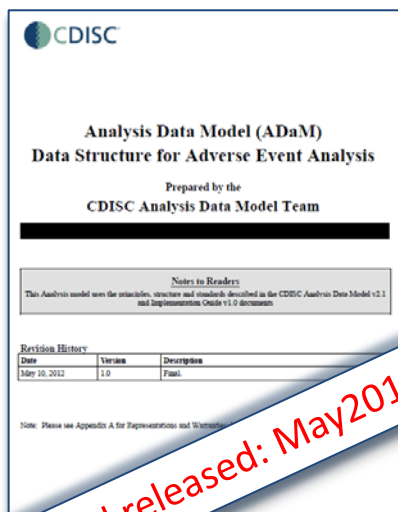


- Noted that length can vary between SDTM and ADaM variable
- Added variables for ADSL:
 - AGEGRy ACTARM, TSEQPGy, DOSE
- Added variables for BDS datasets:
 - ASEQ, dose variables, MCRITy and corresponding flags
- Made record-level Population flags (RFL) and parameter-level Population flags (PFL) variables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

Agenda



CDISC ADaM ODS (Draft)



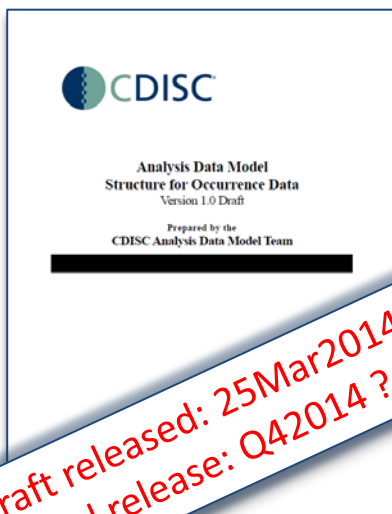
Final released: May 2012

- [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 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

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 WHO Drug Dictionary March 2012
ADCM	PREFCODE	Preferred Term Code	text	\$200	WHODRUG	CM.PREFCODE WHO Drug Dictionary March 2012
ADCM	ATC1C	ATC Level 1 Code	text	\$200	WHODRUG	ATC Level 1 Code WHO Drug Dictionary March 2012
ADCM	ATC2C	ATC Level 2 Code	text	\$200	WHODRUG	ATC Level 2 Code WHO Drug Dictionary March 2012
ADCM	ATC3C	ATC Level 3 Code	text	\$200	WHODRUG	ATC Level 3 Code WHO Drug Dictionary March 2012
ADCM	ATC1T	ATC Level 1 Text	text	\$200	WHODRUG	ATC Level 1 Text WHO Drug Dictionary March 2012
ADCM	ATC2T	ATC Level 2 Text	text	\$200	WHODRUG	ATC Level 2 Text WHO Drug Dictionary March 2012
ADCM	ATC3T	ATC Level 3 Text	text	\$200	WHODRUG	ATC Level 3 Text 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. Example derivation: If ADSL.TRTSDT <= ASTDT <= ADSL.TRTEDT then ONTRTFL = 'Y' 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. Example derivation: If ASTDT < ADSL.TRTSDT then PREFL='Y' 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. Example derivation: If ASTDT > ADSL.TRTEDT then FUPFL='Y' 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	ABC-001	3	TYLENOL	TYLENOL			
Row	CMDECODE	PREFCODE	ATC1C	ATC2C	ATC3C	ATC1T		
4	ABC	1	PARACETAMOL	N02BE	N	N02	N02B	NERVOUS SYSTEM
5	ABC	2	PARACETAMOL	N02BE	N	N02	N02B	NERVOUS SYSTEM
6	ABC	3	PARACETAMOL	N02				
		4	PARACETAMOL	N02				
		5	CONTACMS	N02				
		6	FLUTICASONE PROPIONATE	R01				
Row	ATC2T	ATC3T						
1	ANALGESICS	OTHER ANALGESICS AND ANTIPYRETICS						
2	ANALGESICS	OTHER ANALGESICS AND ANTIPYRETICS						
3	ANALGESICS	OTHER ANALGESICS AND ANTIPYRETICS						
4	ANALGESICS	OTHER ANALGESICS AND ANTIPYRETICS						
5	ANALGESICS	OTHER ANALGESICS AND ANTIPYRETICS						
6	NASAL	NASAL						
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 **Occurrence** Flags (AOCCEFL) 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

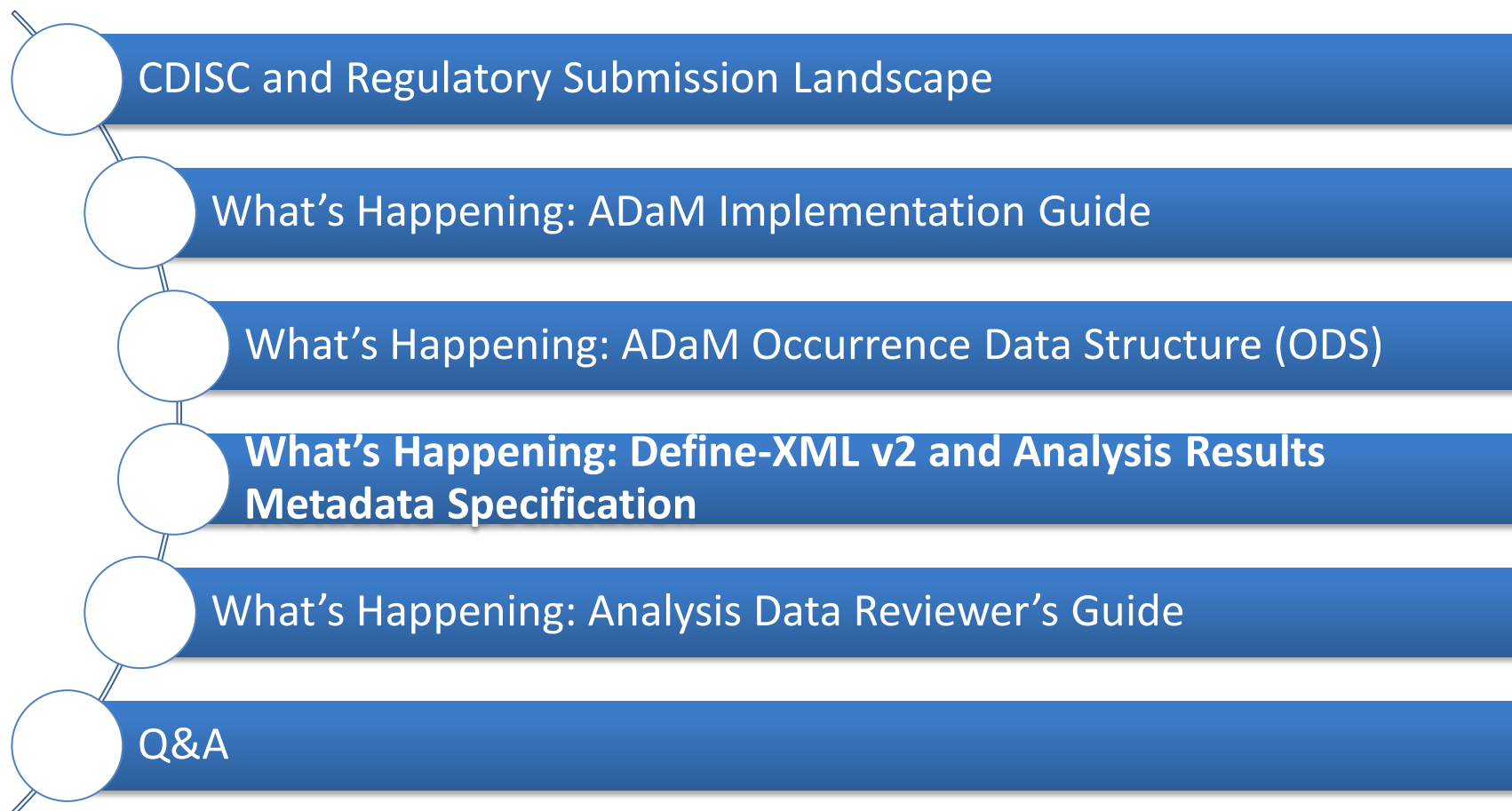


- Most variables are from MH + ADSL
 - Include any variables needed for analysis (e.g. could add severity of the History event).

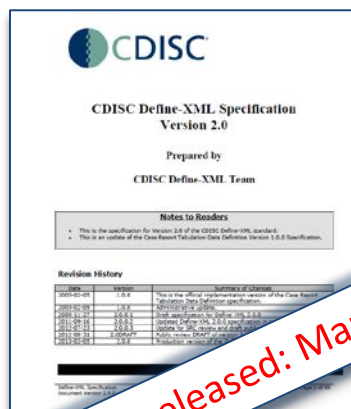
Table 10.2.1 Example of ADMH Variable Metadata

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 MH.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 MH.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 MH.MHENDTC, converted to SAS Time.
ADMH	AENDTM	Analysis End Date/Time	integer	datetime16.		From MH.MHENDTC, converted to SAS Datetime.
ADMH	MHENRF	Continuation Flag	text	\$20.		MH.MHENRF

Agenda



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.

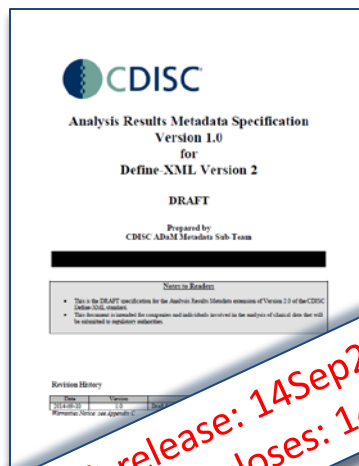
- Define-XML version 2.0.0 can be used to transmit metadata for the following CDISC standards:
 - SDTM Implementation Guide Versions 3.1.2 and higher
 - ADaM Implementation Guide Versions 1.0 and higher
 - SEND Implementation Guide Versions 3.0 and higher

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)



- 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>

Draft release: 14Sep2014
Review period closes: 14Oct2014

CDISC ADaM Results Metadata



Analysis Results Display for Study CDISC-Sample
Table 14-3.01

Analysis Results Display Description

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"]
Analysis 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 = TRIPN SITEGR1; run;

Analysis Results Description

Analysis Results Parameter

Analysis Dataset Variable

Analysis Results Reason

Analysis Results Analysis Purpose

Analysis Results Dataset

Analysis Results Where Clause

Analysis Results Documentation hyperlink

Analysis Results
Programming Statements

CDISC ADaM Results Metadata

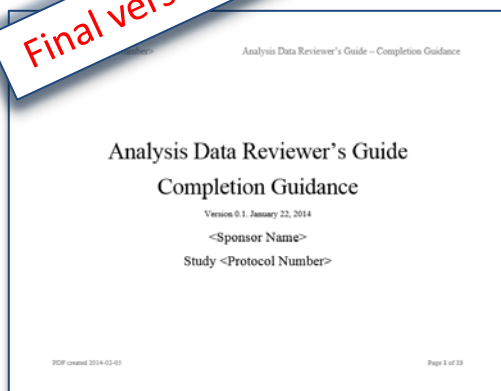
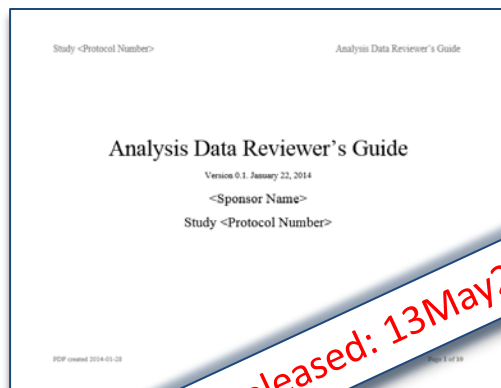


```
<arm:ResultDisplay OID="RD.Table_14-3.01" Name="Table 14-3.01"> 1
  <Description>
2  <TranslatedText xml:lang="en">Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)</TranslatedText>
  </Description>
  <def:DocumentRef leafID="LF.Table-14-3.01">
    <def:PDFPageRef PageRefs="49" Type="PhysicalRef"/>
  </def:DocumentRef>
  <arm:AnalysisResult
    <arm:Documentation
      <Description>
10  <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">
11  <def:PDFPageRef PageRefs="429" Type="PhysicalRef"/>
    </def:DocumentRef>
  </arm:Documentation>
  <arm:ProgrammingCode Context="SAS version 9.2">
    <arm:Code>
12  proc glm data = ADQSADAS;
    where EFFF1='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT";
    class SITEGR1;
    model CHG = TRTPN SITEGR1;
    run;
  </arm:Code>
  </arm:ProgrammingCode>
</arm:AnalysisResult>
```

Agenda



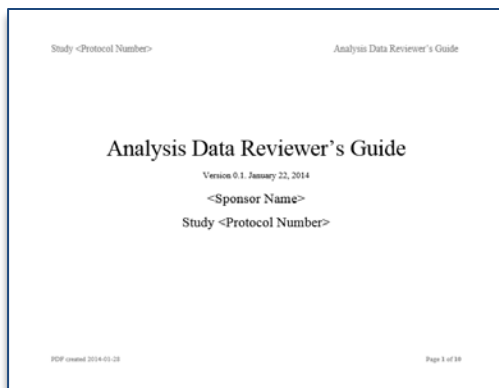
Analysis Data Reviewer's Guide



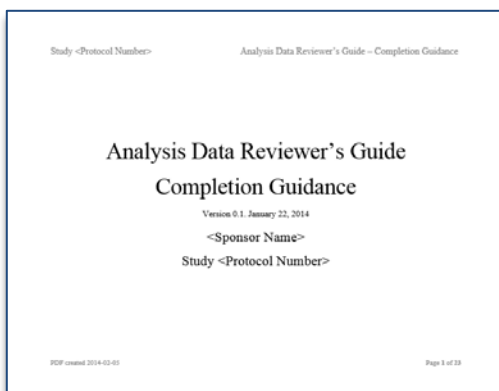
- At PhUSE CSS symposium in 2013, PhUSE working group formed to create an Analysis Data Reviewer's Guide (ADRG)
- Analysis Data Reviewer's Guide plus Completion Guidance documents drafted during 2013, and released as Final on PhUSE Wiki Website:

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

Analysis Data Reviewer's Guide



- 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.

Agenda



Thank you for your attention.

Join us for a coffee at our stand.

London, United Kingdom, 13 OCT 2014





Gavin Winpenny | Line Manager Statistical Projects | +32 (0)2 774 11 52 | +44 (0) 1843 850 928 |
gavin.winpenny@businessdecision.com

Business & Decision Life Sciences
Sint-Lambertusstraat 141 rue Saint-Lambert
B-1200 Brussels
T: +32 2 774 11 00
F: +32 2 774 11 99
lifesciences@businessdecision.com
<http://www.businessdecision-lifesciences.com/>