BetterManagement Presents

Results and Lessons from the CDISC SDTM/ADaM Pilot Project

Technical Requirements

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BetterManagement Presents

Results and Lessons from the CDISC SDTM/ADaM Pilot Project

Featuring:

Cathy Barrows, Ph.D.
Chris Holland
Edward D. Helton, Ph.D.
Tanyss Mason

Visionary perspectives for management insights

Results and Lessons from the CDISC SDTM/ADaM Pilot Project

CDISC®

Setting the Global Standard for Medical Research

CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

Presenters
Cathy Barrows, GSK
Chris Holland, FDA

Moderators
Tanyss Mason, CDISC
Ed Helton, SAS

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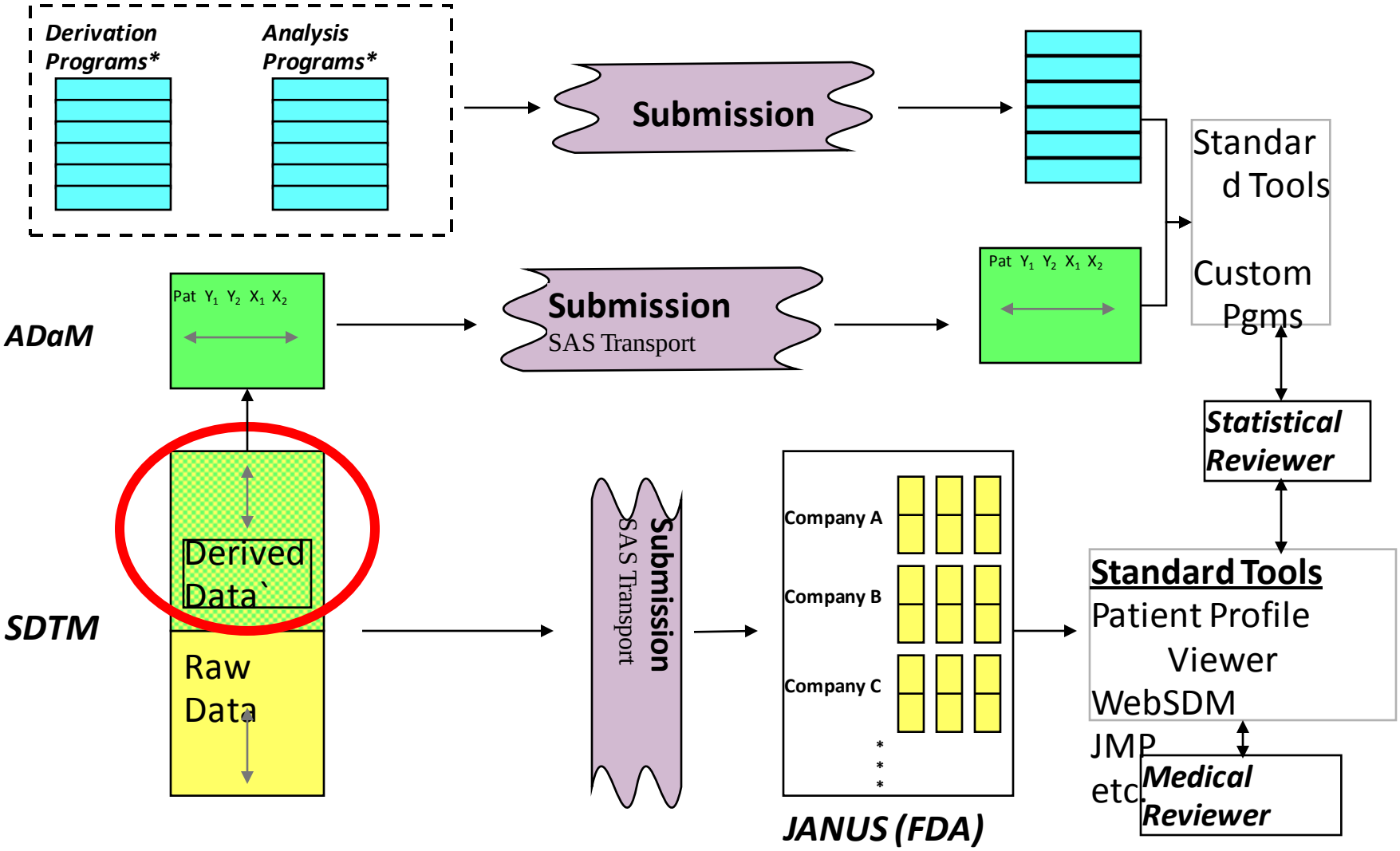
Harmonizing CDISC Submission Models

Edward Helton, Ph.D.
Chief Strategist, Pharmaceutical & Regulatory Affairs
SAS Institute, Inc.

Stephen J. Ruberg, Ph.D.
Director, Medical Information Sciences
Eli Lilly & Company

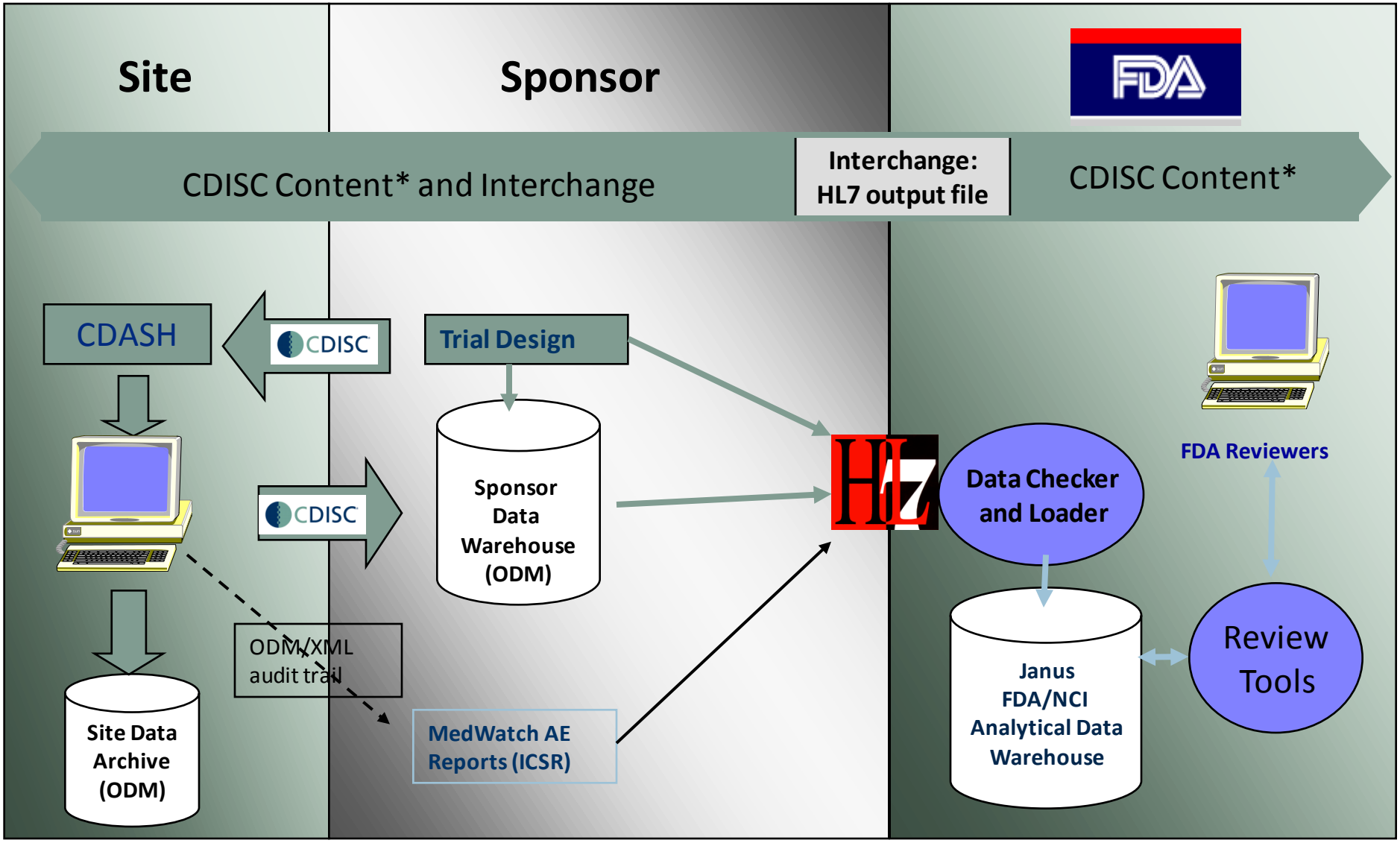
CDISC Interchange
21 Sep 2005

Figure 1B Submission Data Flow – Emerging State



*Structure and process is the discretion of the Sponsor.

Site to Sponsor to FDA Data Flow



*SDTM, ADaM, et al.

Results and Lessons from the CDISC SDTM / ADaM Pilot Project

Cathy Barrows

Global Strategies for Clinical Research Information Series Webcast

Sponsored by CDISC and AMIA

February 25, 2008

Outline

- Overview of the CDISC SDTM/ADaM Pilot
- Learnings from the Pilot
- The published report and package

Will not be discussing what CDISC, SDTM, and ADaM are - assume listeners have that basic background.

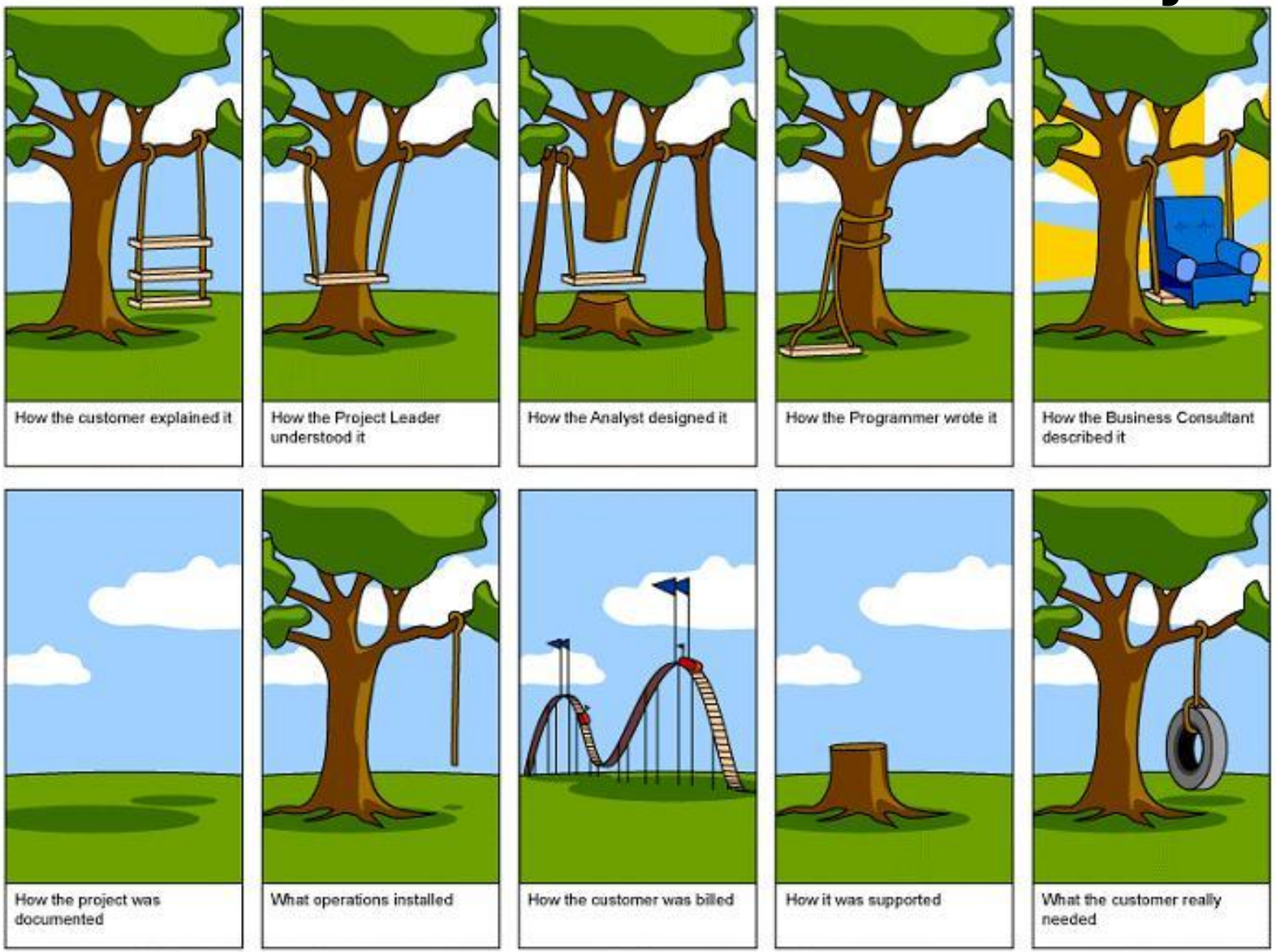
Disclaimer

- All comments, statements, and opinions attributed in this presentation to the regulatory (FDA) review team reflect views of those individuals conveyed as informal feedback to the pilot project team, and must not be taken to represent guidance, policy, or evaluation from the Food and Drug Administration.

CDISC SDTM / ADaM Pilot Project

- Goal for the Pilot was to get initial answers to key questions
  - What does a CDISC-format submission look like, including both SDTM and ADaM datasets?
  - Where are the overlaps and differences between SDTM and ADaM?
  - Do the current CDISC standards and models meet the FDA's requirements and expectations (both medical and statistical reviewers)?
  - What improvements can be considered to optimize the SDTM and ADaM models?
- And to produce a worked example implementation of the available CDISC standards.

The Reason for the Pilot Project



http://philhord.com/phord/wp-content/development.jpg

How?

- Conduct a case study
  - legacy data (real clinical trial data, warts and all) → CDISC SDTM domains and ADaM datasets and associated metadata
  - submission of case study package to FDA for mock review
- Identify issues to be resolved in SDTM and ADaM models

SDTM / ADaM Pilot Focus

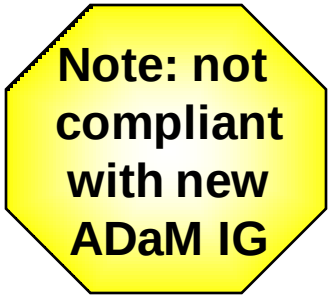
- Focus on the package and not on the process
- Choices/decisions guided by
  - timeline
  - realities of a team of volunteers from multiple companies
  - goal was the submission package and the FDA review
  - quick, efficient, effective - not necessarily the most preferred option

SDTM / ADaM Pilot Focus

- Attention to the process would detract from pilot objectives:
  - Do current standards result in package that meets expectations?
- The Pilot results should be reviewed with project objective in mind
  - Utilize information on the process as a basis for discussion within your organization

SDTM / ADaM Pilot CDISC Tools

- Used the CDISC standards available at that time (with very minor modifications if any) to produce the pilot submission.
  - SDTM IG Version 3.1.1
  - SDTM Version 1.1
  - ADaM Version 2.0
  - CRT-DDS version 3.1.1
  - ODM version 1.3
    - (public comment closed May 2, 2006)
  - Custom stylesheet
    - developed by team members
  - Datasets as XPT not XML



SDTM / ADaM Pilot Deliverables

1. **Submission package**
   - Includes SDTM datasets, ADaM datasets, all relevant metadata, analysis tables and figures, abbreviated final study report, annotated CRF's
   - Review package tied together using metadata in Define.xml

SDTM / ADaM Pilot Deliverables

2. **Summary report of the pilot submission project**
   - issues encountered, strengths and weaknesses
   - incorporate what we learned from the FDA feedback

Both the Package and the Report are available via the CDISC website

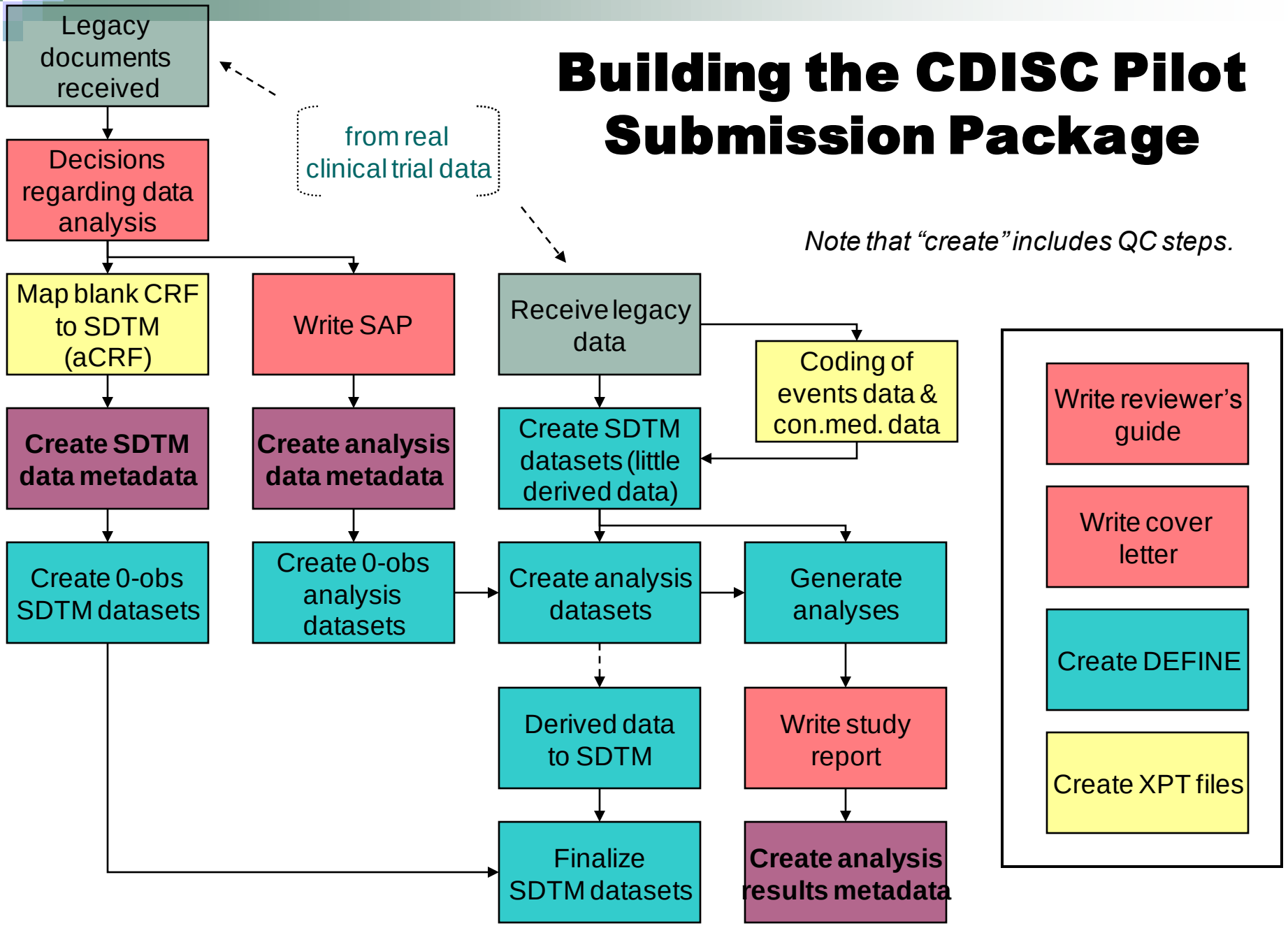
SDTM / ADaM Pilot Team

- Cathy Barrows (GSK)
- Musa Nsereko (Cephalon / Shire)
- FDA Co-Leaders:
  - Lonnie Smith (previous)
  - Chris Holland
  - Mina Hohlen
- Greg Anglin (Lilly)
- T Friebel (SAS)
- John Gorden (Quintiles)
- Tom Guinter (Octagon)
- Joel Hoffman (Insightful)
- Susan Kenny (Inspire Pharm.)
- Sandy Lei (J&J)
- Richard Lewis (Octagon)
- Arline Nakanishi (Amgen)
- Gregory Steffens (Lilly)
- Gary Walker (Quintiles)
- Aileen Yam (sanofi-aventis)
- Yuguang Zhao(sanofi-aventis)

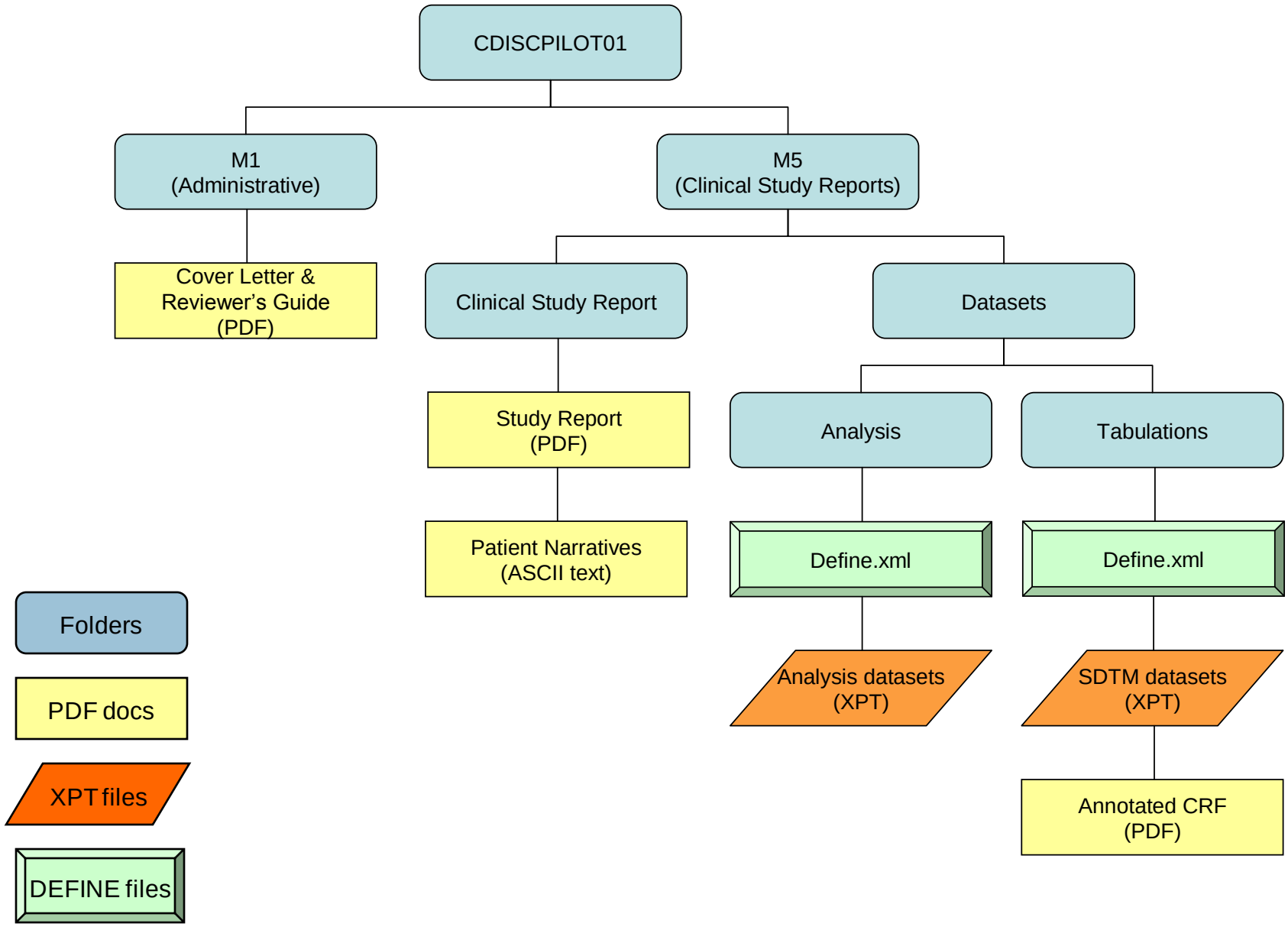
FDA Participation

- Unprecedented level of involvement
- Co-Leadership of the project
- Included medical and statistical reviewers
- ≈ 12 consistently in contact with team

Building the CDISC Pilot Submission Package



Content and General Structure of Pilot Submission Package



FDA Review Team Comments After Reviewing 1st Submission

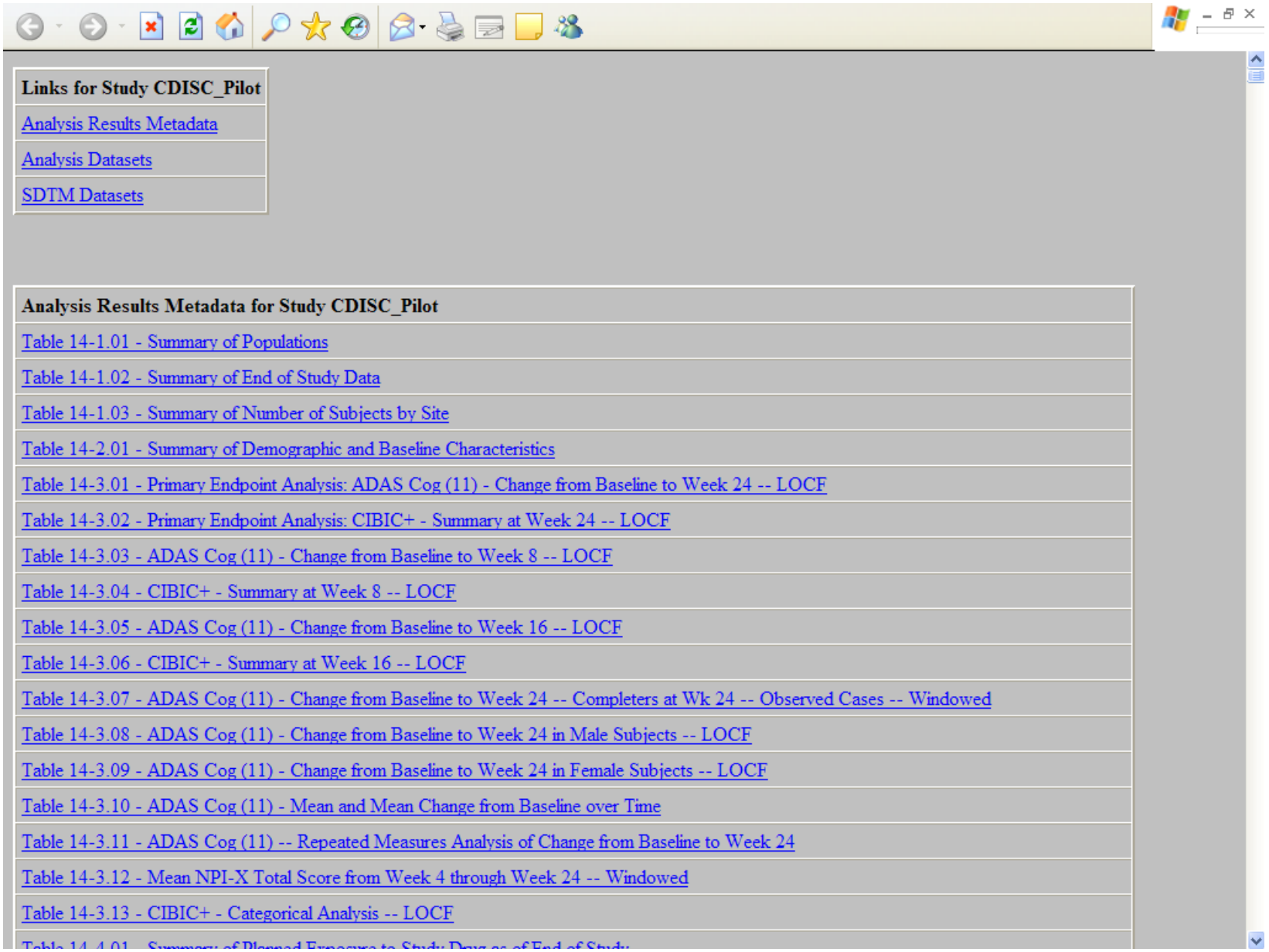
- Overall favorable impression
  - Expect learning curve to be less steep when standards are being followed
- Severable notable comments
  - ADaM datasets were important component since SDTM datasets are not analysis ready
  - ADaM ADSL was very useful for both medical and statistical reviewer
- Some issues…
  - Difficulties with transparency in some analysis datasets
  - Difficulties with Define.xml file - primarily navigation

Changes Made to Define.xml File

- Modifications to style sheet took care of numerous issues
  - navigation
  - back button
  - additional links
- Printing issue remains

Top of Define.xml

Original

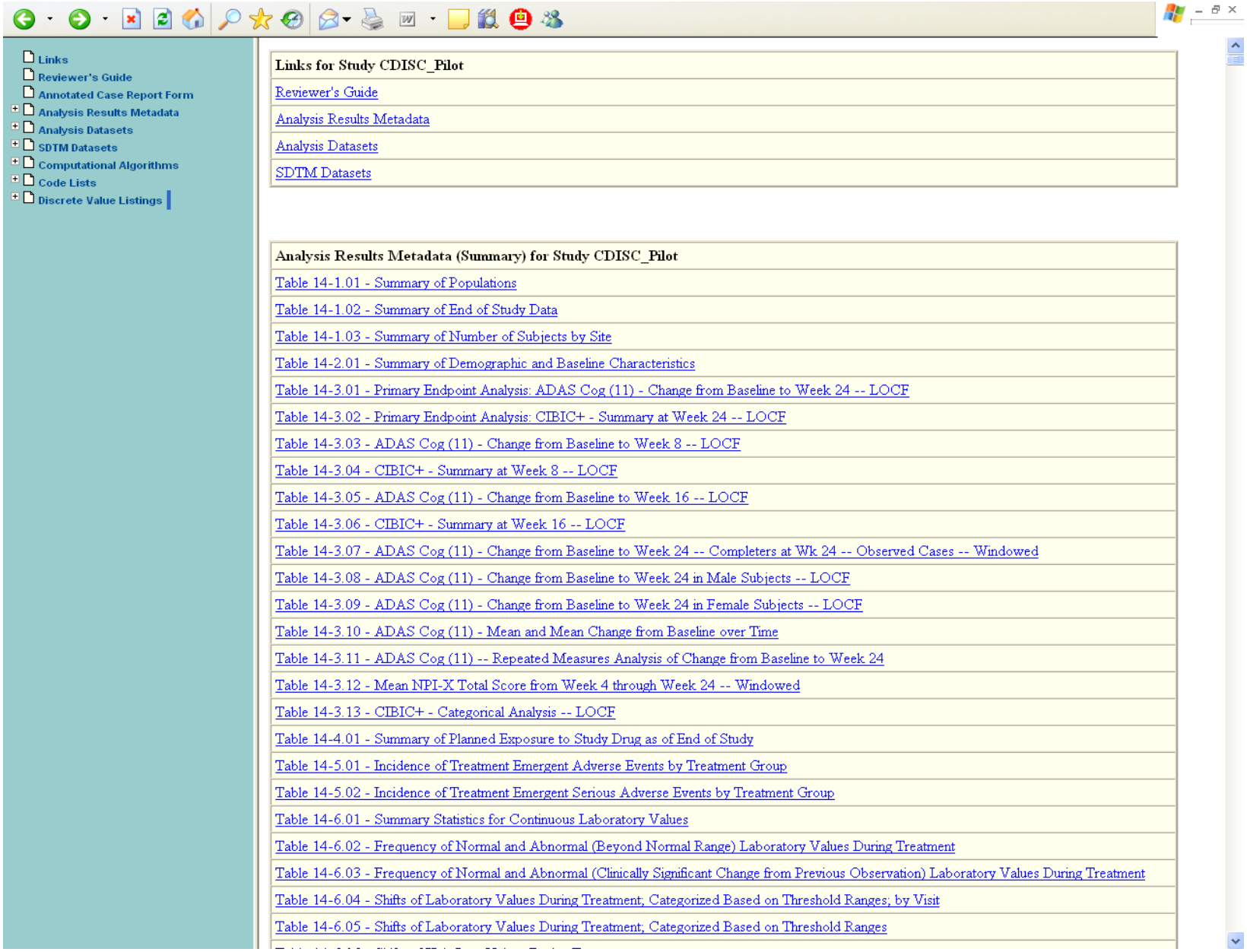


Links for Study CDISC_Pilot
Analysis Results Metadata
Analysis Datasets
SDTM Datasets

Analysis Results Metadata for Study CDISC_Pilot
Table 14-1.01 - Summary of Populations
Table 14-1.02 - Summary of End of Study Data
Table 14-1.03 - Summary of Number of Subjects by Site
Table 14-2.01 - Summary of Demographic and Baseline Characteristics
Table 14-3.01 - Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 -- LOCF
Table 14-3.02 - Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 -- LOCF
Table 14-3.03 - ADAS Cog (11) - Change from Baseline to Week 8 -- LOCF
Table 14-3.04 - CIBIC+ - Summary at Week 8 -- LOCF
Table 14-3.05 - ADAS Cog (11) - Change from Baseline to Week 16 -- LOCF
Table 14-3.06 - CIBIC+ - Summary at Week 16 -- LOCF
Table 14-3.07 - ADAS Cog (11) - Change from Baseline to Week 24 -- Completers at Wk 24 -- Observed Cases -- Windowed
Table 14-3.08 - ADAS Cog (11) - Change from Baseline to Week 24 in Male Subjects -- LOCF
Table 14-3.09 - ADAS Cog (11) - Change from Baseline to Week 24 in Female Subjects -- LOCF
Table 14-3.10 - ADAS Cog (11) - Mean and Mean Change from Baseline over Time
Table 14-3.11 - ADAS Cog (11) -- Repeated Measures Analysis of Change from Baseline to Week 24
Table 14-3.12 - Mean NPI-X Total Score from Week 4 through Week 24 -- Windowed
Table 14-3.13 - CIBIC+ - Categorical Analysis -- LOCF
Table 14-4.01 - Summary of Planned Exposure to Study Drug as of End of Study

Top of Define.xml

Revised



- Links
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- SDTM Datasets
- Computational Algorithms
- Code Lists
- Discrete Value Listings

Links for Study CDISC_Pilot

Reviewer's Guide

Analysis Results Metadata

Analysis Datasets

SDTM Datasets

Analysis Results Metadata (Summary) for Study CDISC_Pilot

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Table 14-5.01 - Incidence of Treatment Emergent Adverse Events by Treatment Group

Table 14-5.02 - Incidence of Treatment Emergent Serious Adverse Events by Treatment Group

Table 14-6.01 - Summary Statistics for Continuous Laboratory Values

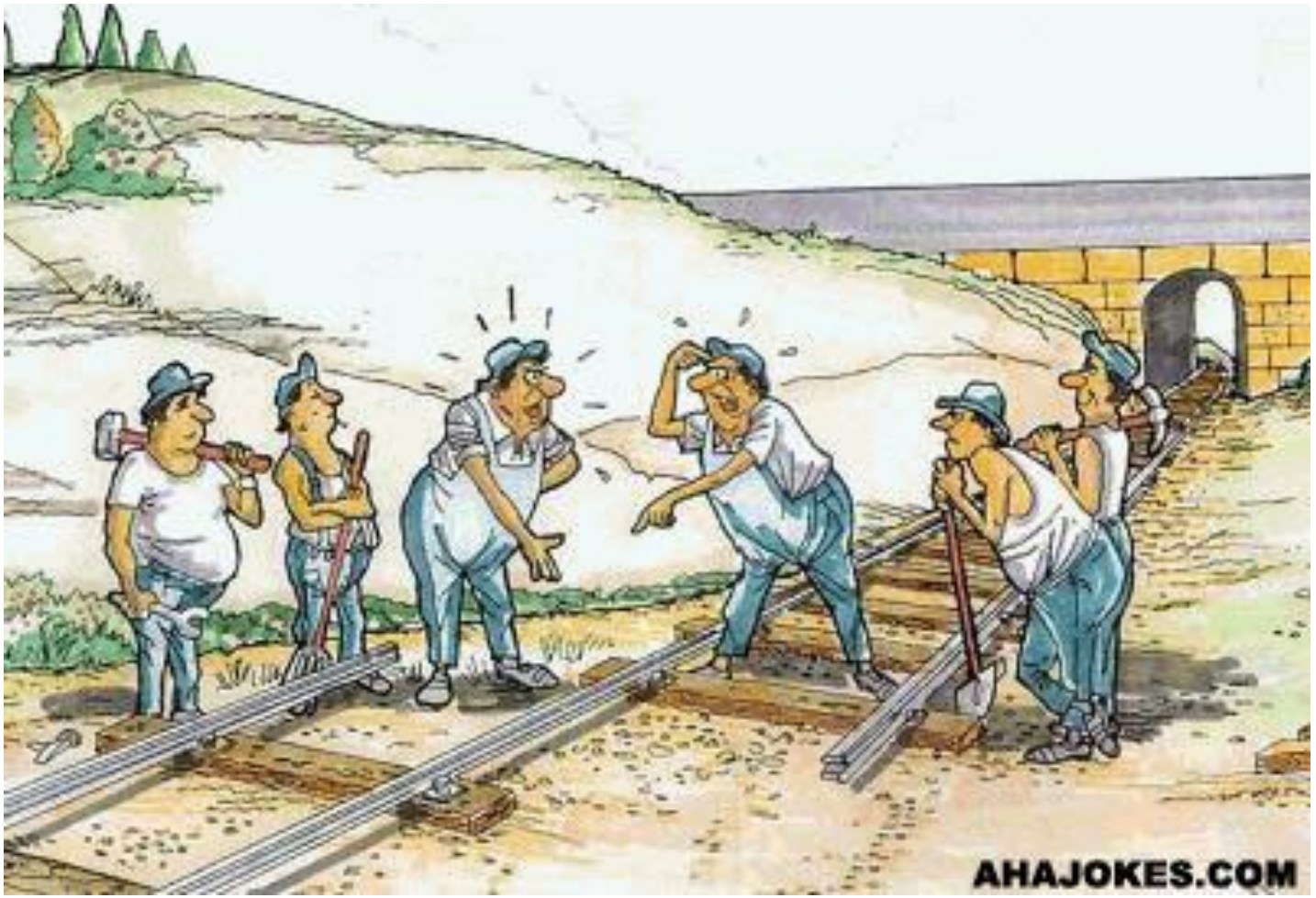
Table 14-6.02 - Frequency of Normal and Abnormal (Beyond Normal Range) Laboratory Values During Treatment

Table 14-6.03 - Frequency of Normal and Abnormal (Clinically Significant Change from Previous Observation) Laboratory Values During Treatment

Table 14-6.04 - Shifts of Laboratory Values During Treatment; Categorized Based on Threshold Ranges; by Visit

Table 14-6.05 - Shifts of Laboratory Values During Treatment; Categorized Based on Threshold Ranges

Issues with analysis datasets??



Regarding Analysis Datasets

- Need a clear data lineage from CRF to analysis
- Traceability and Transparency are key
  - Allows reviewers to understand (and trust) what was done
  - Allows reviewers to examine the sensitivity of what was done to alternative methodologies
- Through data (e.g. flag variables) and metadata
  - Clear, unambiguous communication of decisions, analysis and results

What Was Lacking -

- Though the algorithm for performing windowing and selecting LOCF'ed visits was pre-specified in the SAP, verifying the procedure followed was not clear without significant investigative work
  - Corrected by revising the metadata significantly, rather than relying solely on the text written in the SAP
  - Also added variables that allowed reviewers to trace the lineage
- Reviewers were unable to test other strategies (e.g., including all data in the LOCF imputation rather than only the windowed visits)
  - Corrected by including all data records in the analysis dataset and using flags to select appropriate records for an analysis

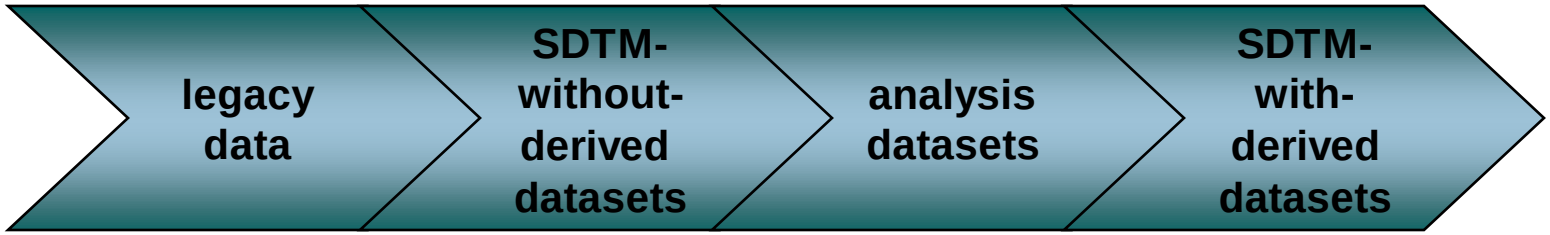
FDA Feedback after 2nd Submission

- Define file much improved
- The analysis dataset modifications met their needs
- The new structure and metadata provide a good model of what information is critical to a reviewer's understanding of the data lineage from CRF to analysis

Lessons Learned / Key Points

- Communication between sponsor and regulatory reviewers is essential
  - Provide a “sample” submission
    - verify that the Define file renders as expected
    - verify the level of detail in the content is appropriate
  - Agree which analysis results are “key”
    - impacts the metadata to be provided
  - Agree on issues regarding datasets
    - including elements to include at request of reviewers
    - location of certain components, e.g. MedDRA coded terms

Lessons Learned / Key Points



- Sequence followed in pilot project for creating datasets
  - How to provide metadata links between the derived data in SDTM and analysis datasets?
  - How much and how to put derived data in SDTM?
  - Essential to maintain consistency between corresponding variables in SDTM and analysis datasets

Lessons Learned / Key Points

- CRT-DDS provided in a Define.xml file
  - Develop a style sheet
    - no standard currently exists
    - ensure the Define.xml file renders correctly
  - Consider issue of printing
    - Style sheet was intended for web browser viewing, not for printing
  - Define file included
    - analysis datasets data definition tables
    - analysis results metadata
    - tabulation data definition tables
  - Analysis results metadata involved extra effort
    - technical aspects of the XML and style sheet
    - content (documentation and links) for the Define file

Lessons Learned / Key Points

- Addressing requests/expectations of the regulatory review team
  - Navigation in the Define file
    - bookmark pane
    - table of contents
  - Reviewer's guide
    - orient reviewers to various aspects of the pilot submission package
    - link provided from annotated CRF and from Define file, as well as within the PDF file
  - Links in Define file to PDF files
    - (e.g. annotated CRF, SAP, study report)

Lessons Learned / Key Points

- Prescriptive use of metadata
  - Dataset specifications entered once:
    - use as metadata content
    - use to support automation of the data set creation
    - use to support automation of order of variables in data sets to be the same as in the define
    - use to maintain consistency with datasets and support automation of data set validation
  - Resulted in significant efficiencies

The suite of SAS macros is also available via the CDISC website

Lessons Learned / Key Points

- Some issues to be aware of in creating package
  - Define file is crucial, must be accurate and consistent with the data
  - Consider how to provide links between the derived data in SDTM and analysis datasets
  - Definition of the term “derived data”
  - Design and implementation of style sheet
  - Ordering of variables in the data is important, must be consistent with ordering in Define file
  - Verify transparency regarding how data were derived and analyzed
  - Structure analysis datasets to facilitate reviewers performing sensitivity analyses as well as verifying analysis results

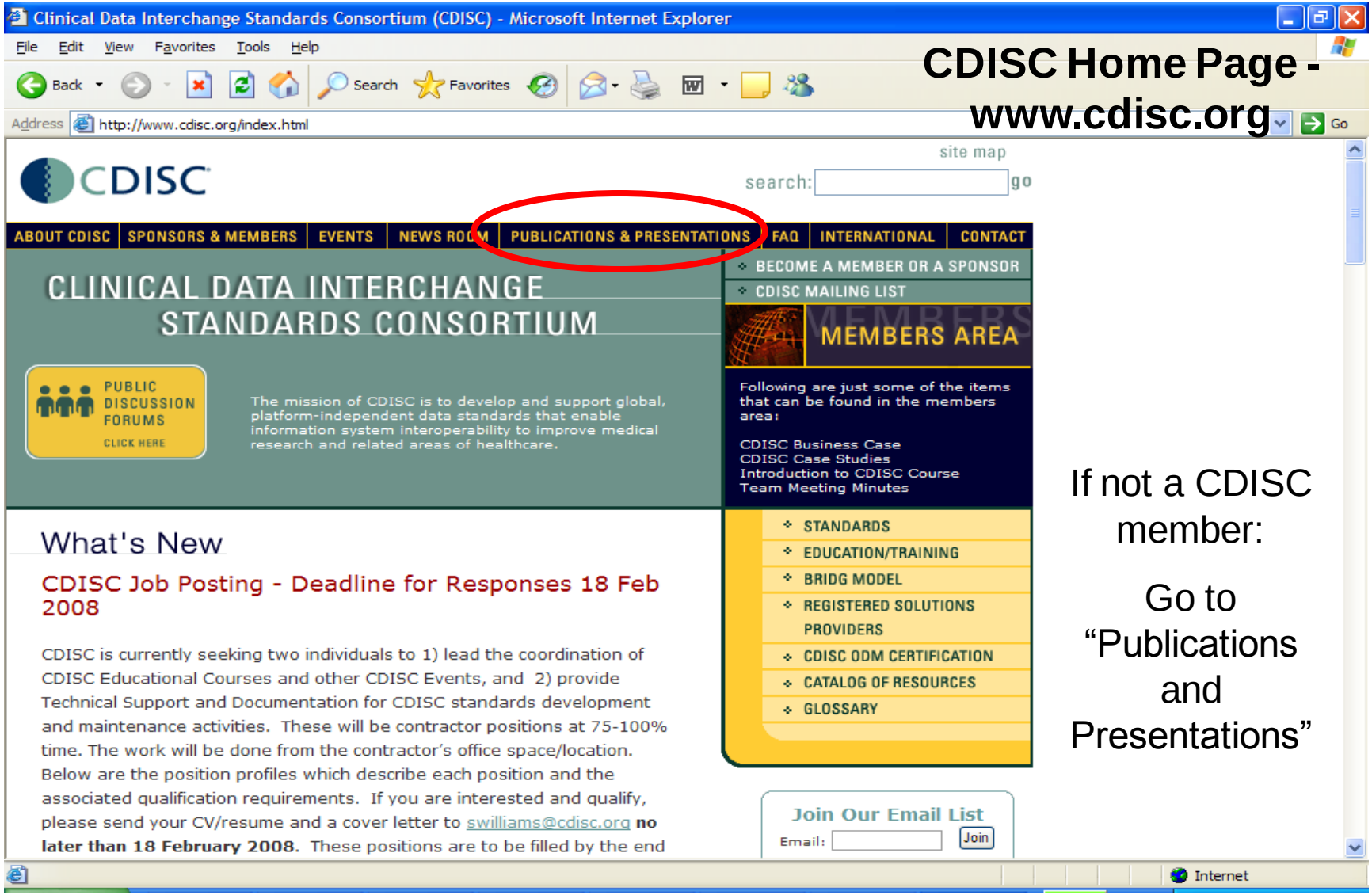
Pilot Results Available on the CDISC Website

- Pilot submission package
  - Contains the final version of the submission package
  - Does not contain all analysis datasets
- Pilot project report
- Suite of metadata macros

In Using the Report and Package…

- Keep in mind the various caveats - detailed in the report
- Key points:
  - One should not interpret the processes described in this report as the only, or the best, way to proceed with the creation of a submission using the CDISC standards
  - The package does not necessarily represent a future version of the standards.
  - The versions of the standards used may no longer be the current versions (e.g., ADaM)
  - NOT meant to be a guidance!
- Report is a sharing of learnings
- Package is a worked example
    - an illustration
    - one way of applying the CDISC standards
    - did meet the expectations and requirements of pilot review team

Finding the Pilot Results



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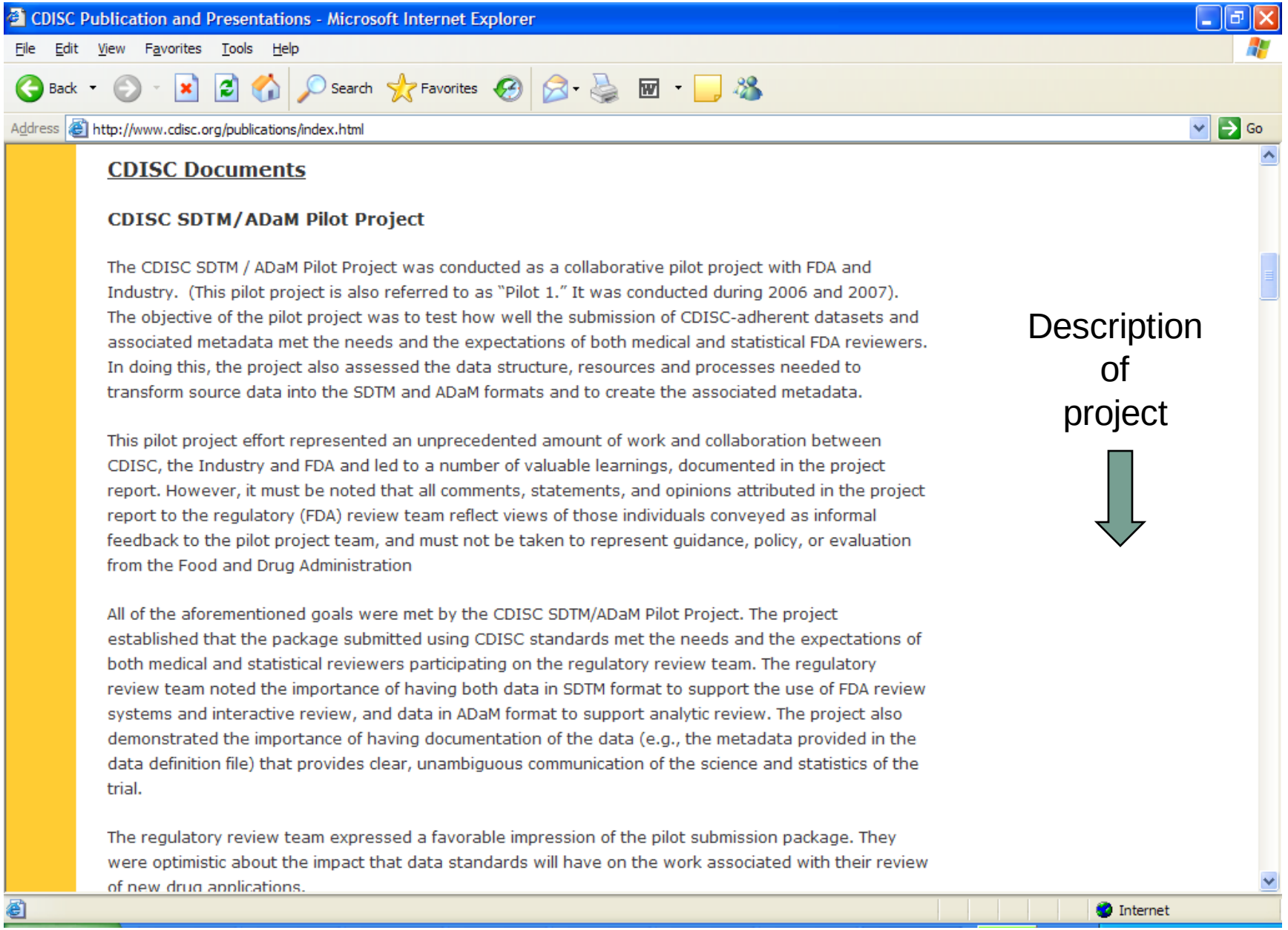
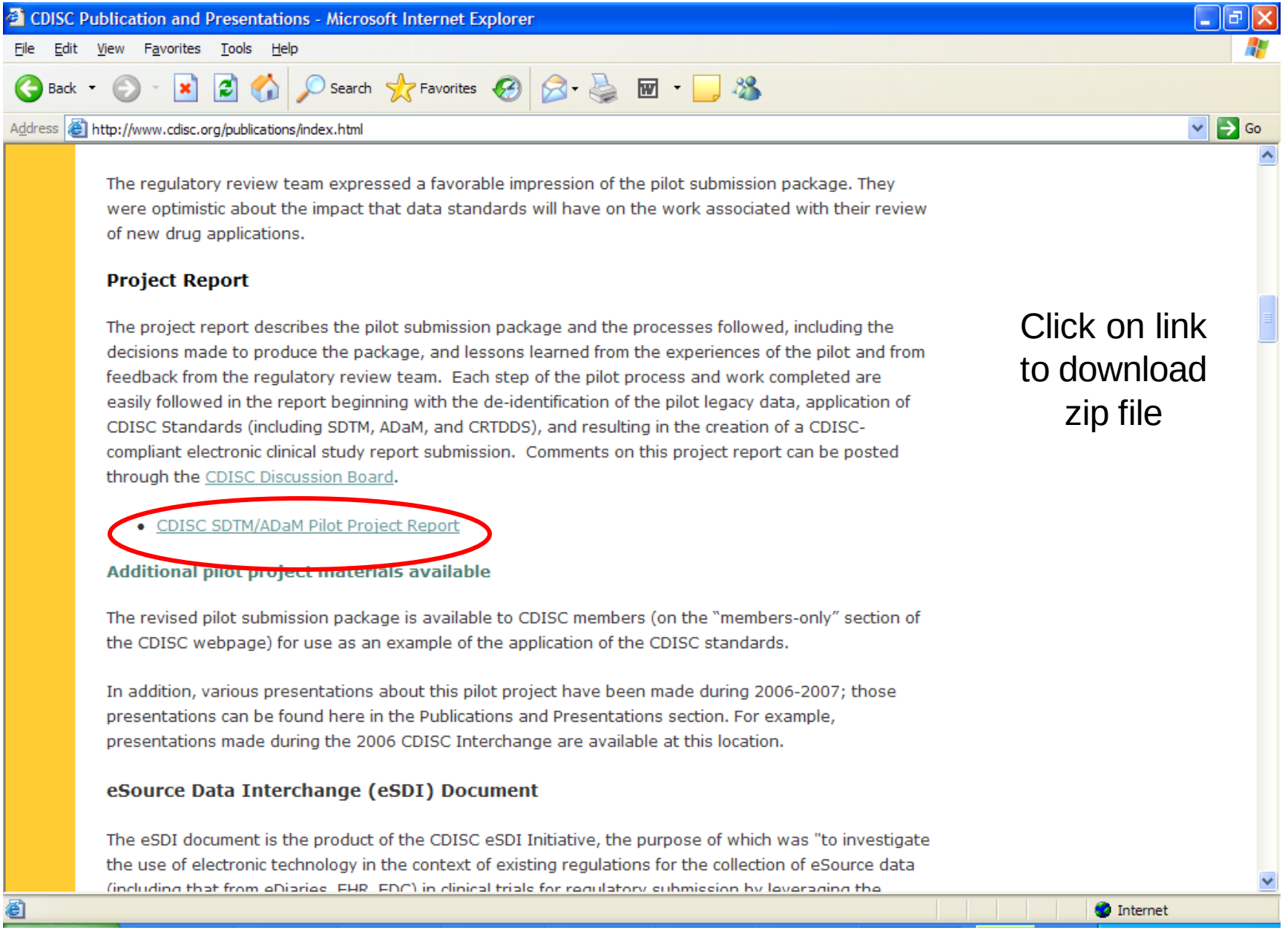
http://www.cdisc.org/publications/index.html

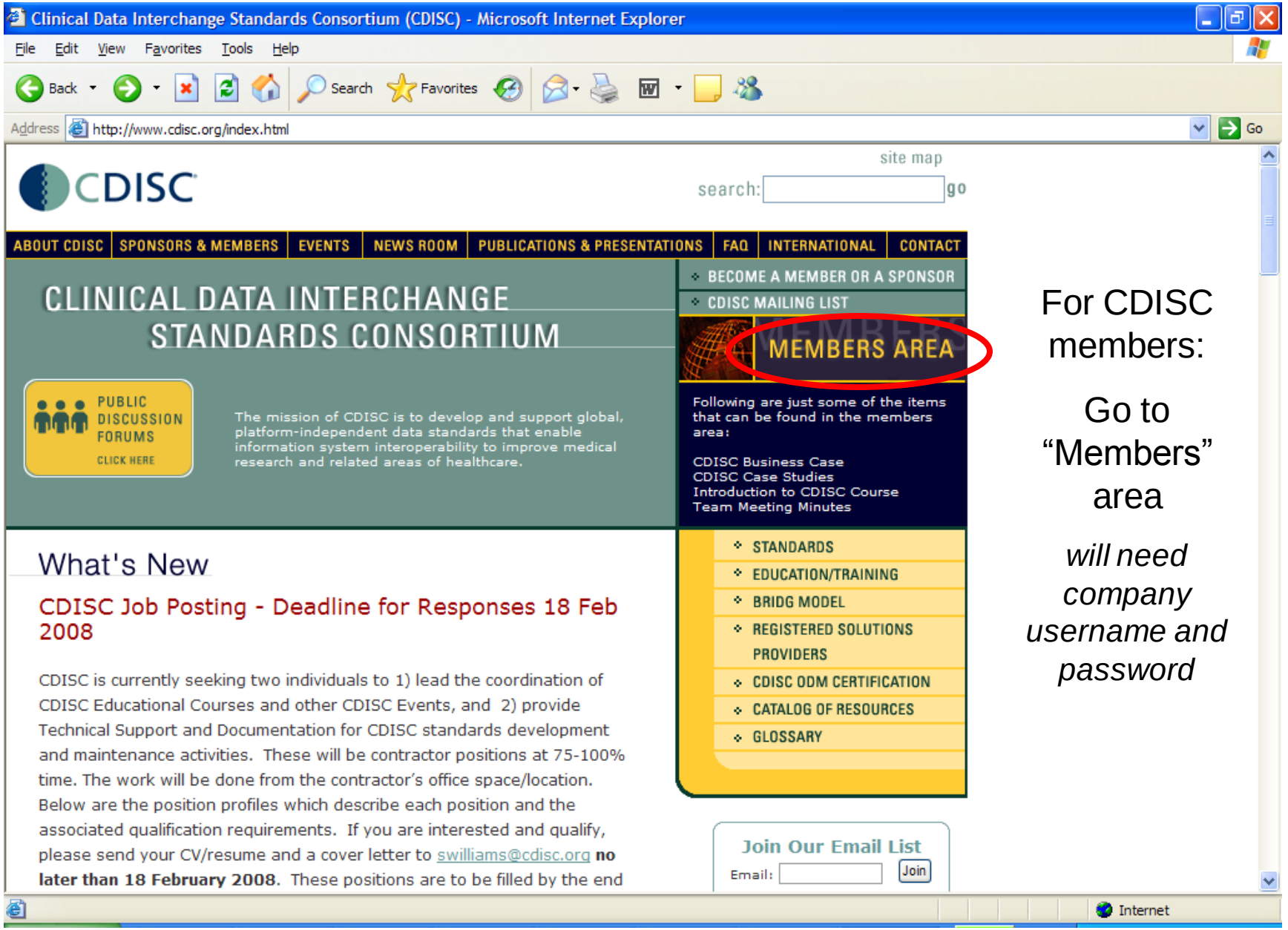
Scroll down



Description of project



Click on link to download zip file



For CDISC members:

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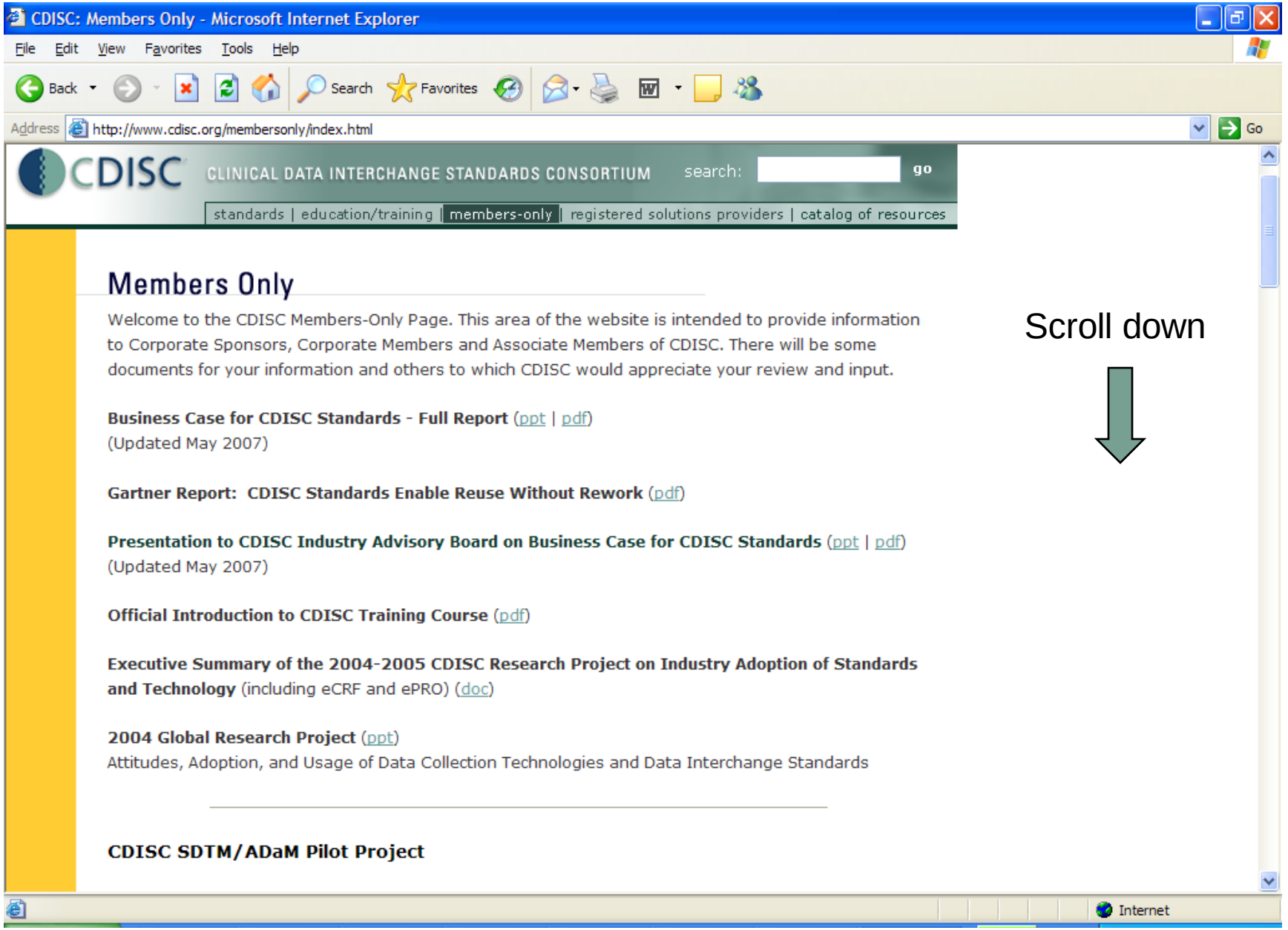
will need company username and password


CDISC: Members Only - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.cdisc.org/membersonly/index.html
Go
CDISC
CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM
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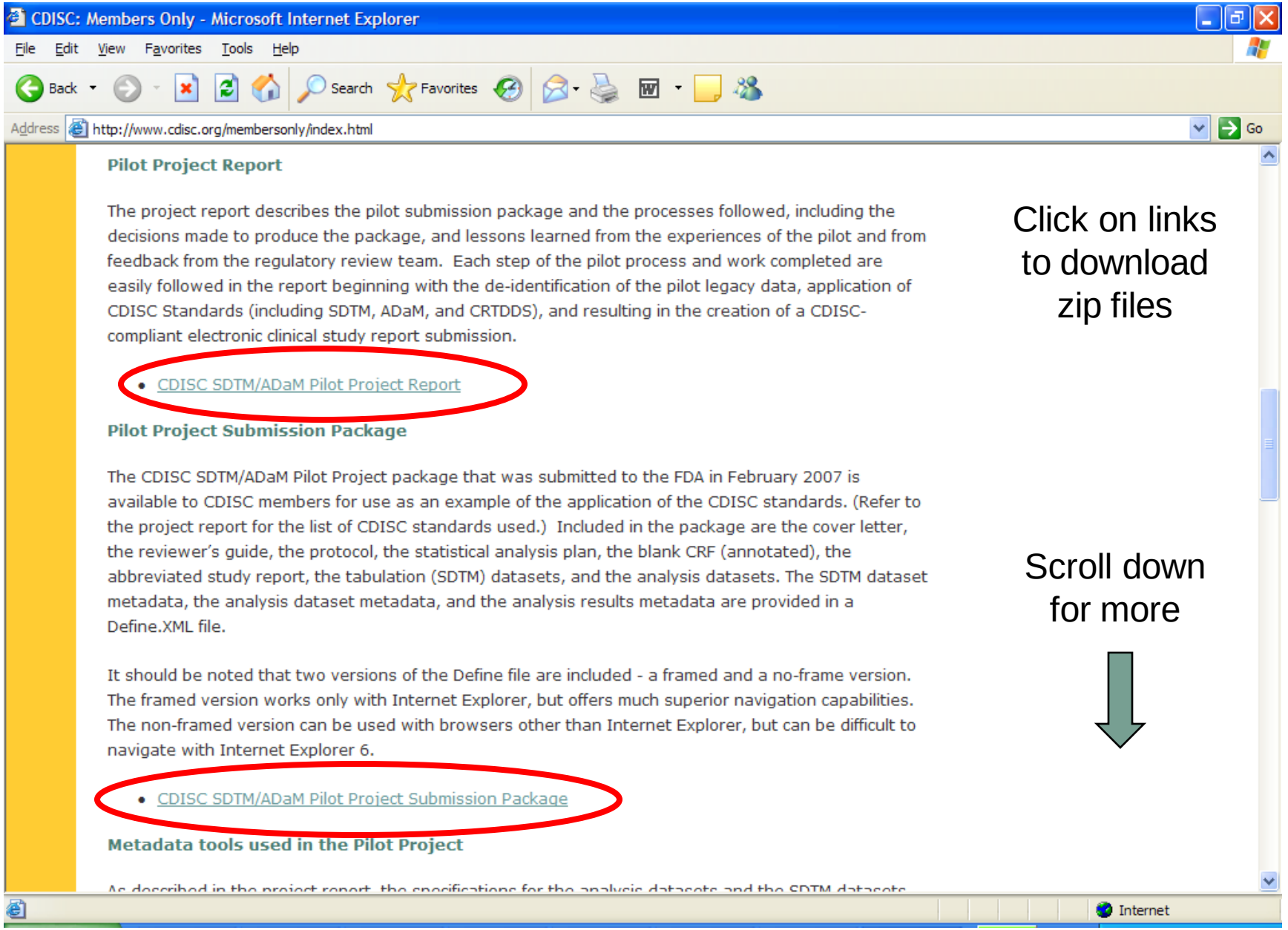
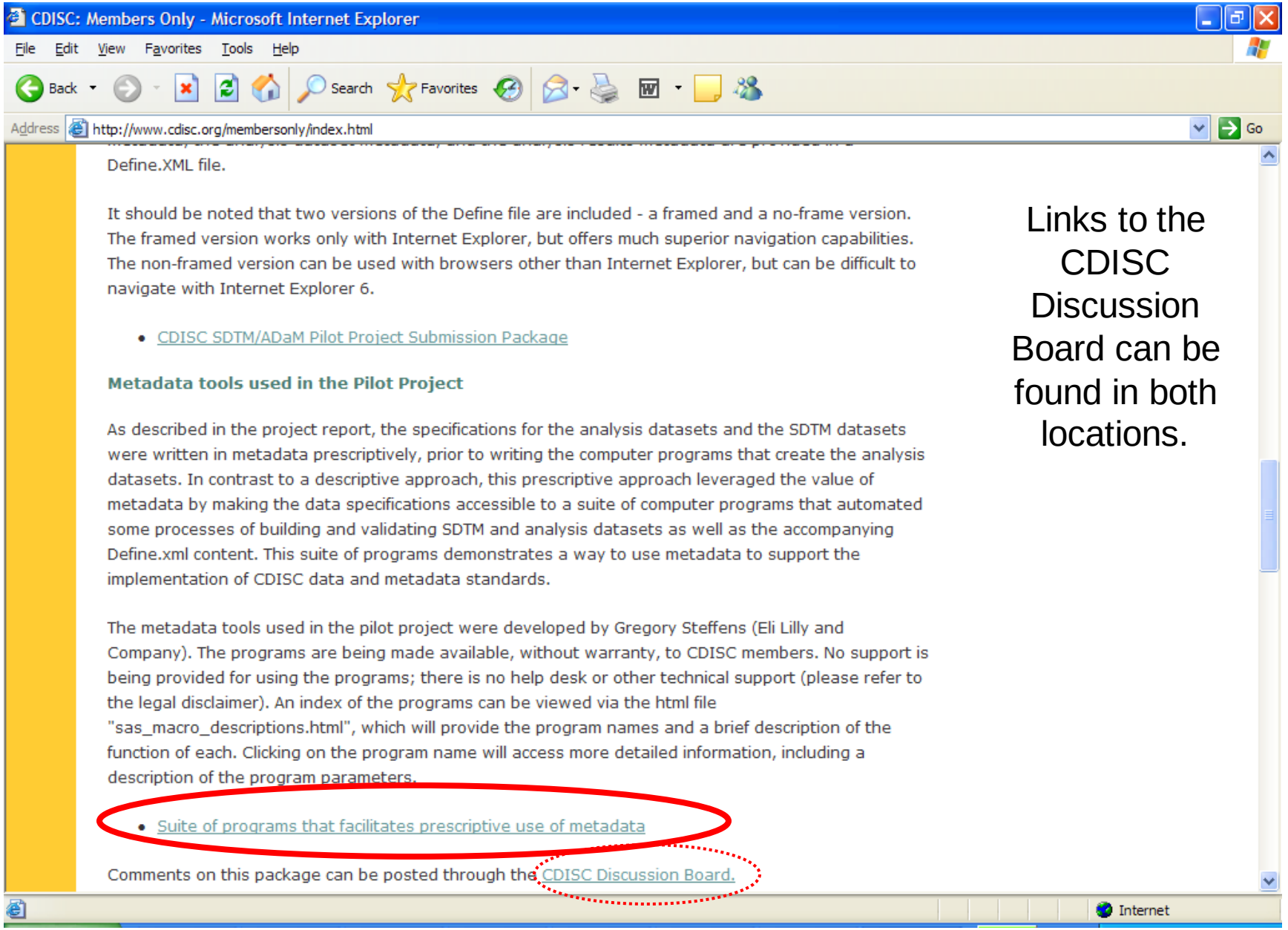
standards | education/training | members-only | registered solutions providers | catalog of resources
Members Only
Welcome to the CDISC Members-Only Page. This area of the website is intended to provide information to Corporate Sponsors, Corporate Members and Associate Members of CDISC. There will be some documents for your information and others to which CDISC would appreciate your review and input.
Business Case for CDISC Standards - Full Report (ppt | pdf)
(Updated May 2007)
Gartner Report: CDISC Standards Enable Reuse Without Rework (pdf)
Presentation to CDISC Industry Advisory Board on Business Case for CDISC Standards (ppt | pdf)
(Updated May 2007)
Official Introduction to CDISC Training Course (pdf)
Executive Summary of the 2004-2005 CDISC Research Project on Industry Adoption of Standards and Technology (including eCRF and ePRO) (doc)
2004 Global Research Project (ppt)
Attitudes, Adoption, and Usage of Data Collection Technologies and Data Interchange Standards
CDISC SDTM/ADaM Pilot Project
Scroll down
Internet

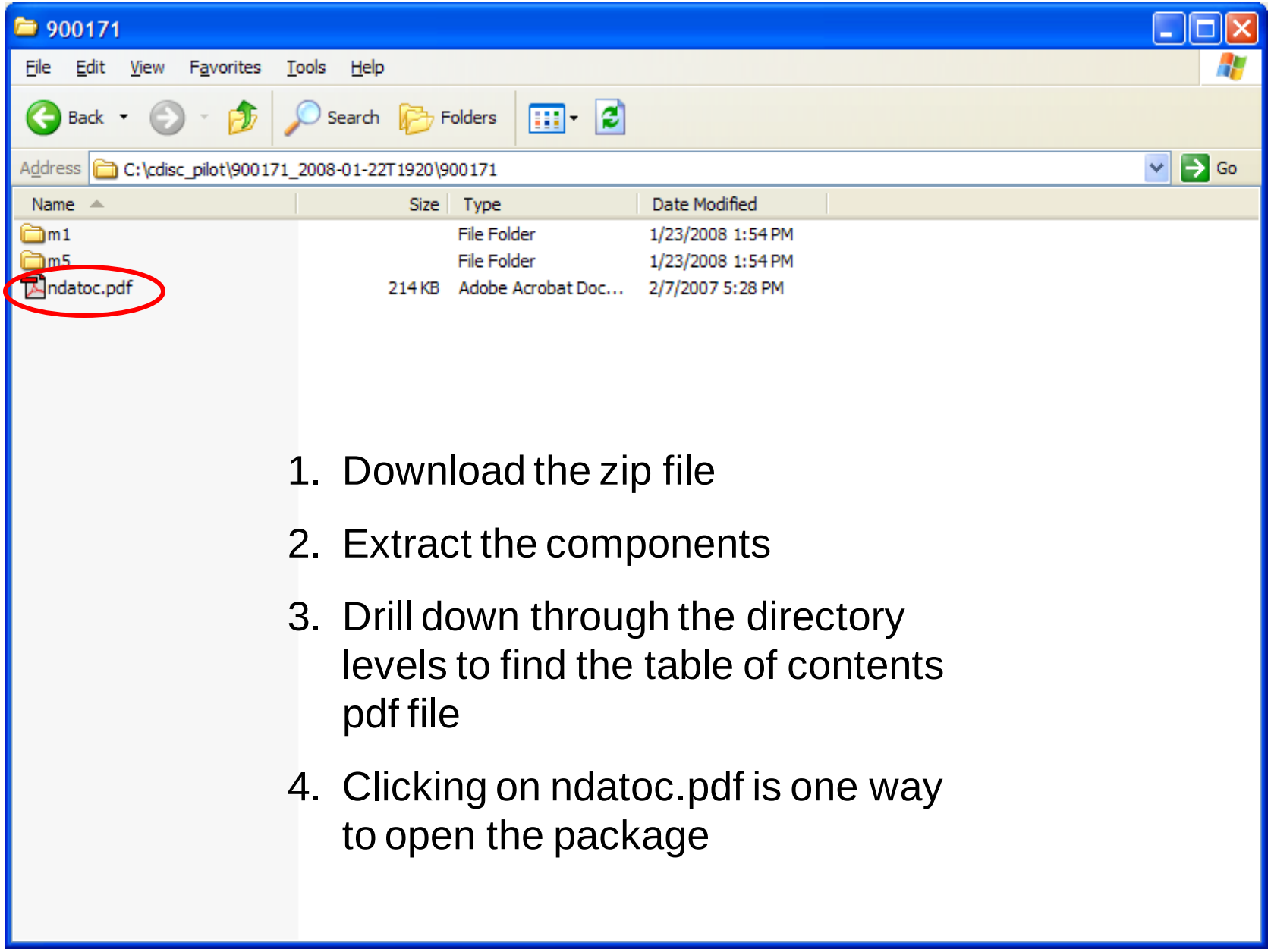


Click on links to download zip files

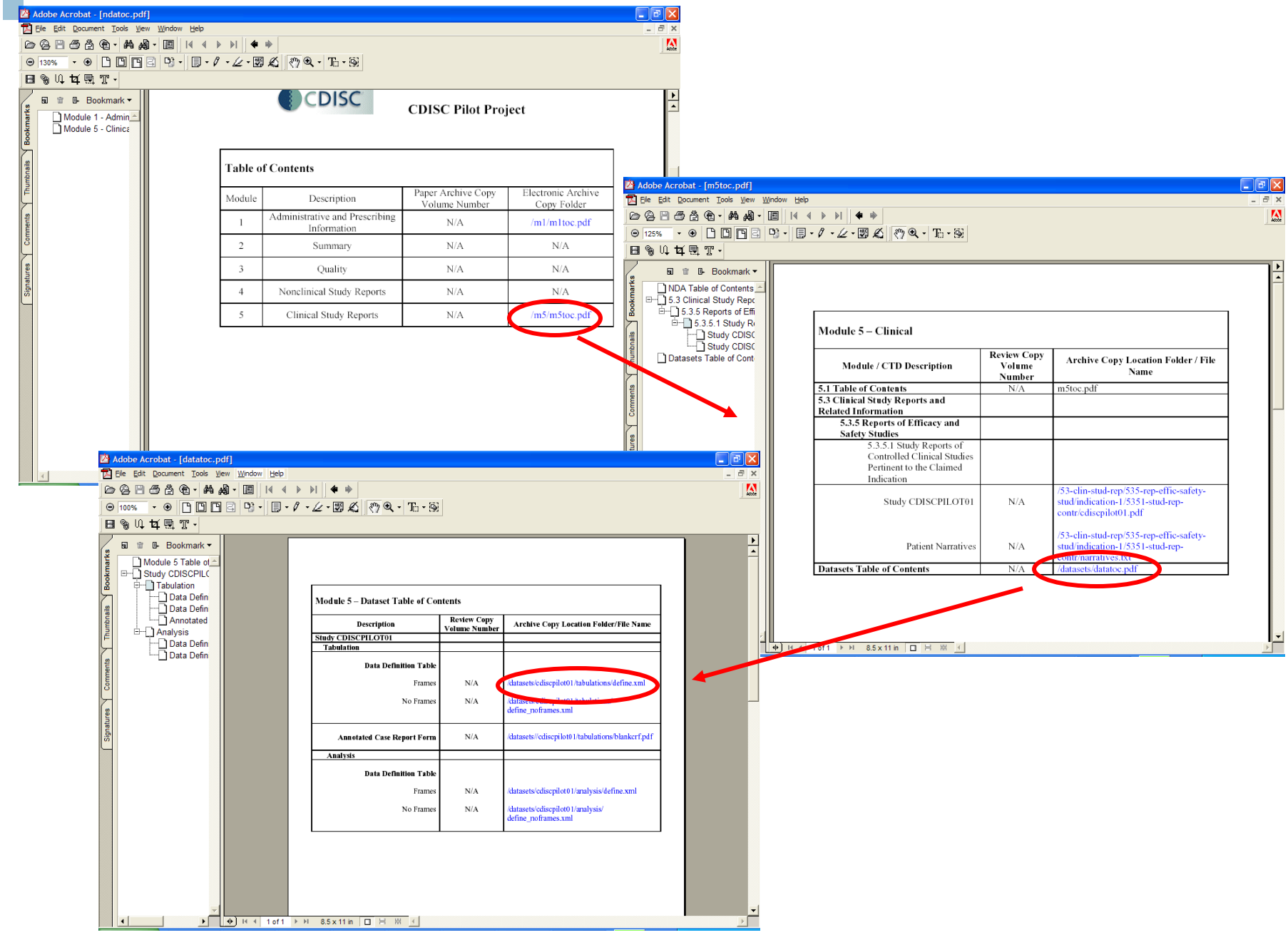
Scroll down for more



Links to the CDISC Discussion Board can be found in both locations.



1. Download the zip file
2. Extract the components
3. Drill down through the directory levels to find the table of contents pdf file
4. Clicking on ndatoc.pdf is one way to open the package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CDISC
CDISC Pilot Project
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Electronic Archive Copy Folder
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Administrative and Prescribing Information
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2
Summary
N/A
N/A
3
Quality
N/A
N/A
4
Nonclinical Study Reports
N/A
N/A
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Clinical Study Reports
N/A
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Module 5 – Clinical
Module / CTD Description
Review Copy Volume Number
Archive Copy Location Folder / File Name
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N/A
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5.3 Clinical Study Reports and Related Information
5.3.5 Reports of Efficacy and Safety Studies
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
Study CDISCPILOT01
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Module 5 – Dataset Table of Contents
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Annotated Case Report Form
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Analysis
Data Definition Table
Frames
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No Frames
N/A
/datasets/cdiscpilot01/analysis/define_noframes.xml

Top of Define.xml

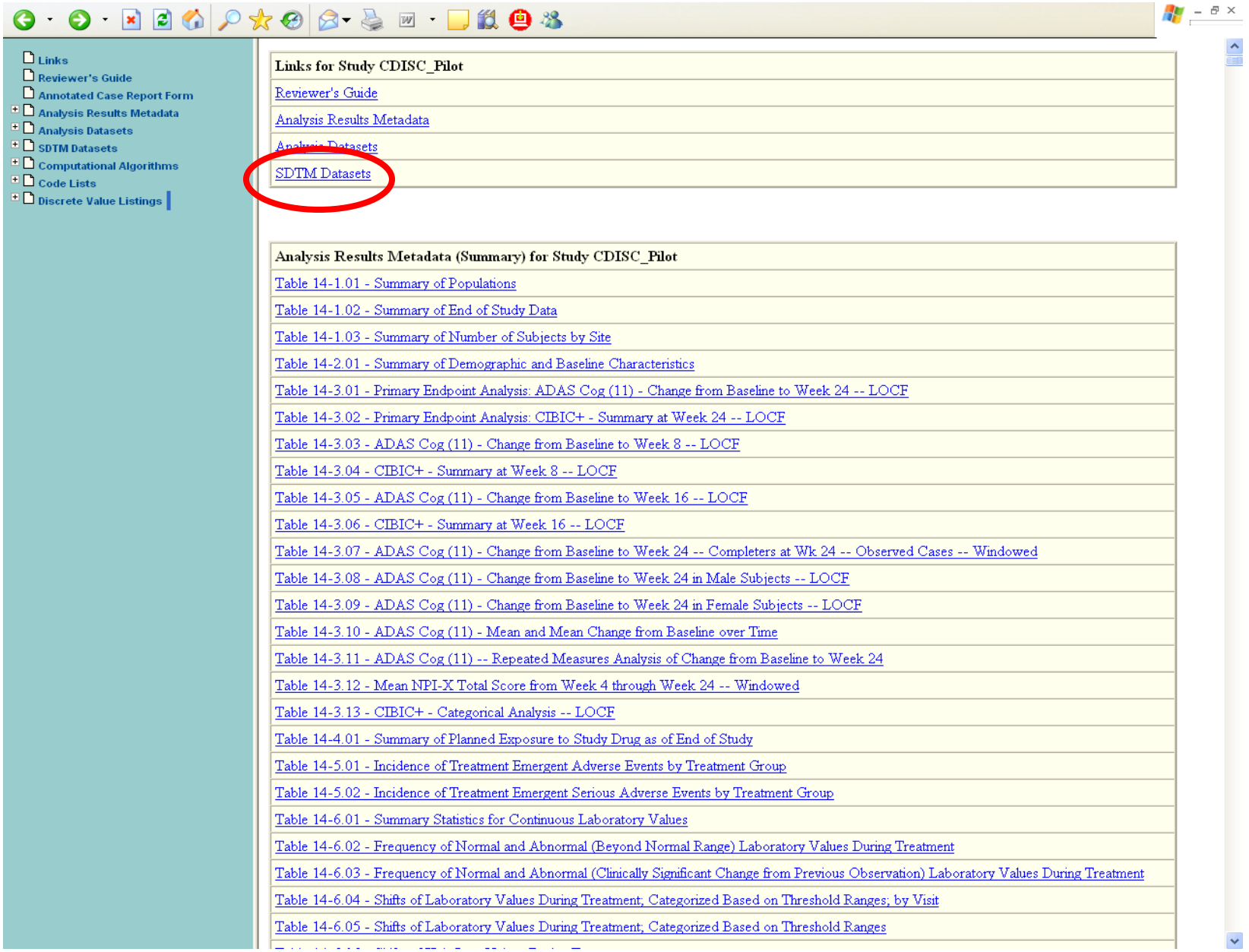

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Table 14-3.06 - CIBIC+ - Summary at Week 16 -- LOCF
Table 14-3.07 - ADAS Cog (11) - Change from Baseline to Week 24 -- Completers at Wk 24 -- Observed Cases -- Windowed
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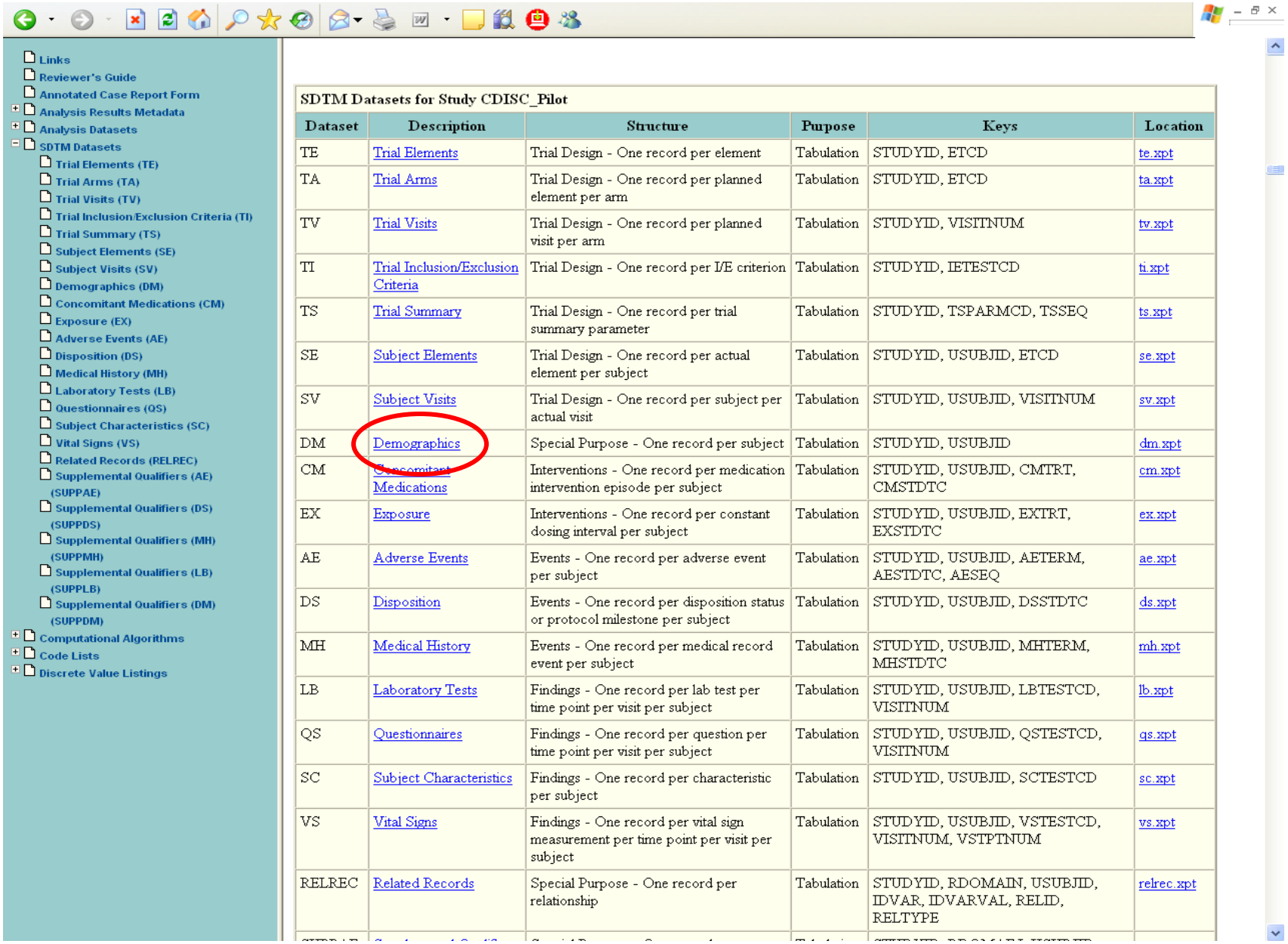
SDTM Dataset Metadata



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  - Related Records (RELREC)
  - Supplemental Qualifiers (AE) (SUPPAE)
  - Supplemental Qualifiers (DS) (SUPPDS)
  - Supplemental Qualifiers (MH) (SUPPMH)
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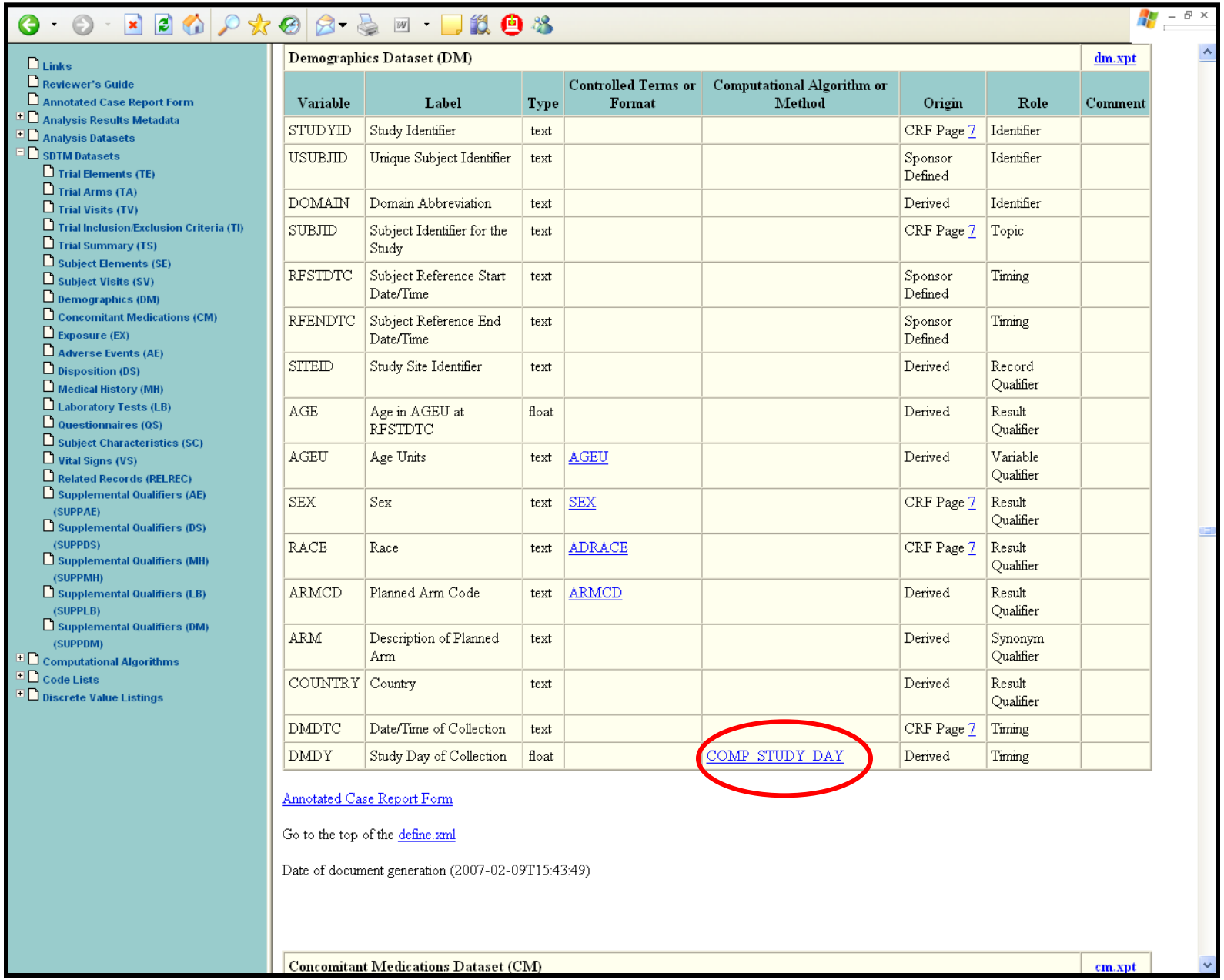
SDTM Datasets for Study CDISC_Pilot

Dataset	Description	Structure	Purpose	Keys	Location
TE	Trial Elements	Trial Design - One record per element	Tabulation	STUDYID, ETCD	te.xpt
TA	Trial Arms	Trial Design - One record per planned element per arm	Tabulation	STUDYID, ETCD	ta.xpt
TV	Trial Visits	Trial Design - One record per planned visit per arm	Tabulation	STUDYID, VISITNUM	tv.xpt
TI	Trial Inclusion/Exclusion Criteria	Trial Design - One record per I/E criterion	Tabulation	STUDYID, IETESTCD	ti.xpt
TS	Trial Summary	Trial Design - One record per trial summary parameter	Tabulation	STUDYID, TSPARMCD, TSSEQ	ts.xpt
SE	Subject Elements	Trial Design - One record per actual element per subject	Tabulation	STUDYID, USUBJID, ETCD	se.xpt
SV	Subject Visits	Trial Design - One record per subject per actual visit	Tabulation	STUDYID, USUBJID, VISITNUM	sv.xpt
DM	Demographics	Special Purpose - One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt
CM	Concomitant Medications	Interventions - One record per medication intervention episode per subject	Tabulation	STUDYID, USUBJID, CMTRT, CMSTDTC	cm.xpt
EX	Exposure	Interventions - One record per constant dosing interval per subject	Tabulation	STUDYID, USUBJID, EXTRT, EXSTDTC	ex.xpt
AE	Adverse Events	Events - One record per adverse event per subject	Tabulation	STUDYID, USUBJID, AETERM, AESTDTC, AESEQ	ae.xpt
DS	Disposition	Events - One record per disposition status or protocol milestone per subject	Tabulation	STUDYID, USUBJID, DSSTDTC	ds.xpt
MH	Medical History	Events - One record per medical record event per subject	Tabulation	STUDYID, USUBJID, MHTERM, MHSTDTC	mh.xpt
LB	Laboratory Tests	Findings - One record per lab test per time point per visit per subject	Tabulation	STUDYID, USUBJID, LBTESTCD, VISITNUM	lb.xpt
QS	Questionnaires	Findings - One record per question per time point per visit per subject	Tabulation	STUDYID, USUBJID, QSTESTCD, VISITNUM	qs.xpt
SC	Subject Characteristics	Findings - One record per characteristic per subject	Tabulation	STUDYID, USUBJID, SCTESTCD	sc.xpt
VS	Vital Signs	Findings - One record per vital sign measurement per time point per visit per subject	Tabulation	STUDYID, USUBJID, VSTESTCD, VISITNUM, VSTPTNUM	vs.xpt
RELREC	Related Records	Special Purpose - One record per relationship	Tabulation	STUDYID, RDOMAIN, USUBJID, IDVAR, IDVARVAL, RELID, RELTYPE	relrec.xpt

Individual Domain Metadata



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  - Supplemental Qualifiers (MH) (SUPPMH)
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Demographics Dataset (DM) — dm.xpt

Variable	Label	Type	Controlled Terms or Format	Computational Algorithm or Method	Origin	Role	Comment
STUDYID	Study Identifier	text			CRF Page 7	Identifier	
USUBJID	Unique Subject Identifier	text			Sponsor Defined	Identifier	
DOMAIN	Domain Abbreviation	text			Derived	Identifier	
SUBJID	Subject Identifier for the Study	text			CRF Page 7	Topic	
RFSTDTC	Subject Reference Start Date/Time	text			Sponsor Defined	Timing	
RFENDTC	Subject Reference End Date/Time	text			Sponsor Defined	Timing	
SITEID	Study Site Identifier	text			Derived	Record Qualifier	
AGE	Age in AGEU at RFSTDTC	float			Derived	Result Qualifier	
AGEU	Age Units	text	AGEU		Derived	Variable Qualifier	
SEX	Sex	text	SEX		CRF Page 7	Result Qualifier	
RACE	Race	text	ADRACE		CRF Page 7	Result Qualifier	
ARMCD	Planned Arm Code	text	ARMCD		Derived	Result Qualifier	
ARM	Description of Planned Arm	text			Derived	Synonym Qualifier	
COUNTRY	Country	text			Derived	Result Qualifier	
DMDTC	Date/Time of Collection	text			CRF Page 7	Timing	
DMDY	Study Day of Collection	float		COMP_STUDY_DAY	Derived	Timing	

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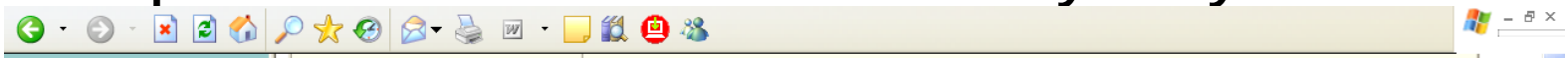
Concomitant Medications Dataset (CM) — cm.xpt

Computational Methods for Study Day



COMP_ADVS_VSWK24CH	VSWK24-VSBLRESN
COMP_QSAD_QSSTRESN	if QSCAT="ALZHEIMER'S DISEASE ASSESSMENT SCALE" and QSDRVFL = "Y" then QSSTRESN=ADQSADAS.ACTOT where avisflgn=1, if QSCAT= "NEUROPS YCHIATRIC INVENTORY - REVISED (NPI-X)" and QSDRVFL = "Y" then QSSTRESN=ADQSNPIX.NPTOT where avisflgn=1, else if QSDRVFL = "
COMP_STUDY_DAY	(date portion of --DTC) minus (date portion of RFSTDTC) , add 1 if -- DTC >= RFSTDC
ITTV	If the observed data are eligible for analysis (i.e., QS.VISITNUM in 3,8,10,12,201) and if QS.VISIT = the name of the visit window containing ADQSADAS.ANLDY then ITTV='Y'; ITTV='N' otherwise
ITYPE	ITYPE='LOCF' if record was created to replace missing value
ONTRTFL	If TRTSTDT<=AESTDT<=LSTDOSDT then ONTRTFL='Y'. ONTRTFL='N' otherwise
PARAM	Hardcoded to 'ADAS-Cog11 Total'
PARAMCD	Hardcoded to 'ACTOT'
TTPU	TTPU='DAYS' for all records

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Code Lists

ADRACEN, Reference Name (CODELISTN1)

Code Value	Code Text
1	CAUCASIAN
2	AFRICAN DESCENT
3	EAST/SOUTHEST ASIAN
4	WESTERN ASIAN
5	HISPANIC
6	OTHER

AECAUS, Reference Name (CODELISTC2)

Code Value	Code Text
NONE	NONE
POSSIBLE	POSSIBLE
PROBABLE	PROBABLE
REMOTE	REMOTE
	N/A

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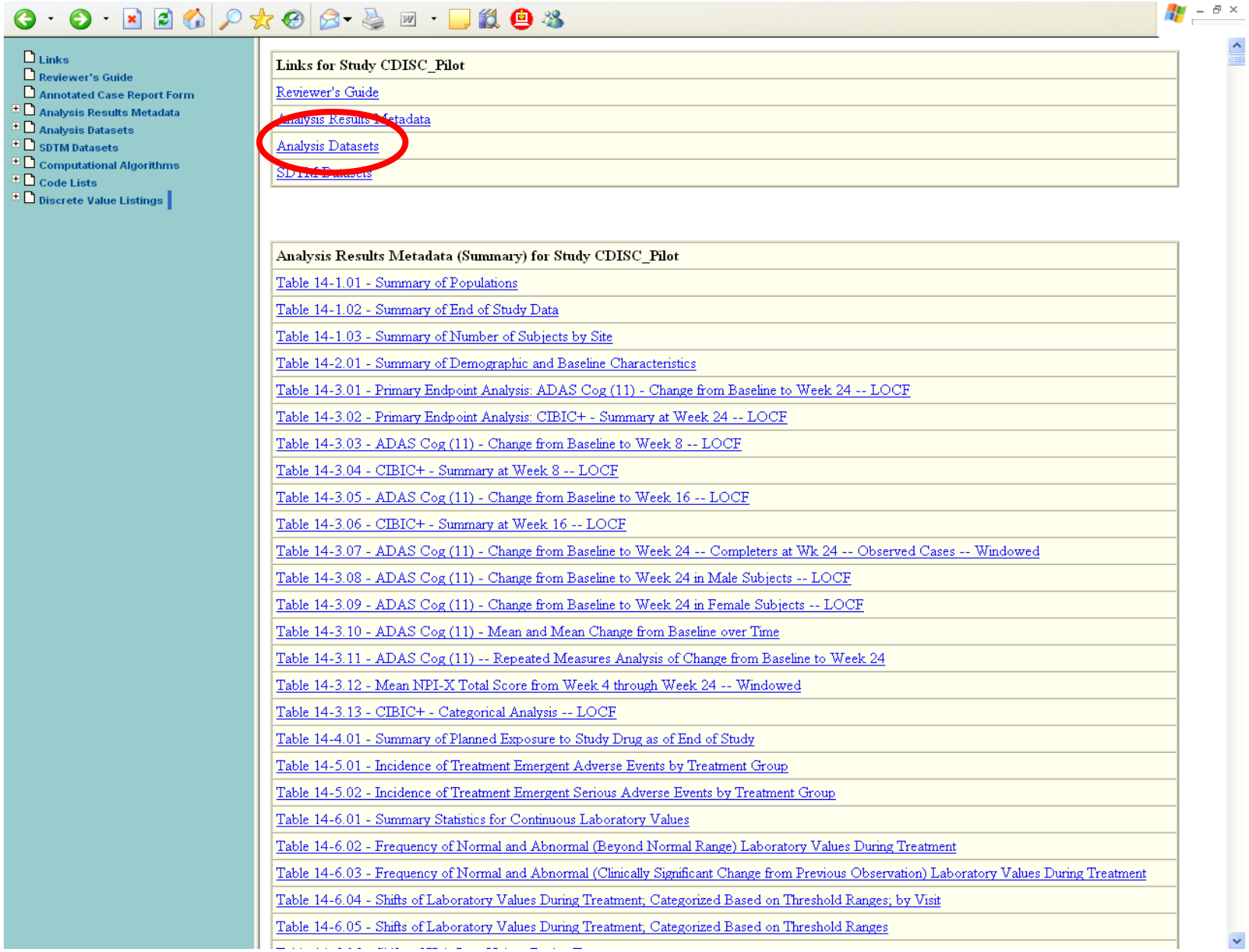

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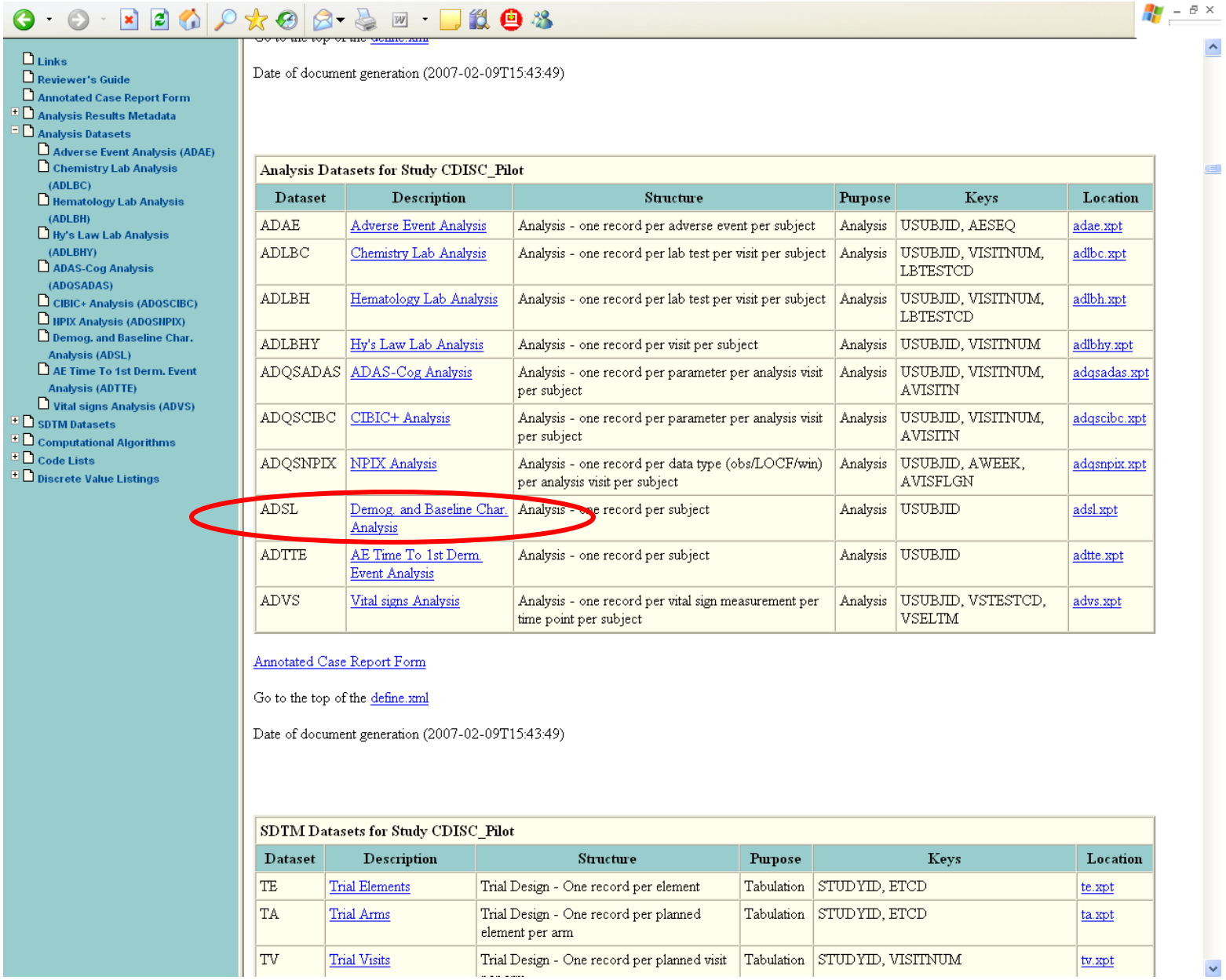
ADaM Dataset Metadata



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  - IIPIX Analysis (ADQSNPIX)
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Analysis Datasets for Study CDISC_Pilot

Dataset	Description	Structure	Purpose	Keys	Location
ADAE	Adverse Event Analysis	Analysis - one record per adverse event per subject	Analysis	USUBJID, AESEQ	adae.xpt
ADLBC	Chemistry Lab Analysis	Analysis - one record per lab test per visit per subject	Analysis	USUBJID, VISITNUM, LBTESTCD	adlbc.xpt
ADLBH	Hematology Lab Analysis	Analysis - one record per lab test per visit per subject	Analysis	USUBJID, VISITNUM, LBTESTCD	adlbh.xpt
ADLBHY	Hy's Law Lab Analysis	Analysis - one record per visit per subject	Analysis	USUBJID, VISITNUM	adlbhy.xpt
ADQSADAS	ADAS-Cog Analysis	Analysis - one record per parameter per analysis visit per subject	Analysis	USUBJID, VISITNUM, AVISITN	adqsadas.xpt
ADQSCIBC	CIBIC+ Analysis	Analysis - one record per parameter per analysis visit per subject	Analysis	USUBJID, VISITNUM, AVISITN	adqscibc.xpt
ADQSNPIX	NPIX Analysis	Analysis - one record per data type (obs/LOCF/win) per analysis visit per subject	Analysis	USUBJID, AWEEK, AVISFLGN	adqsnpix.xpt
ADSL	Demog. and Baseline Char. Analysis	Analysis - one record per subject	Analysis	USUBJID	adsl.xpt
ADTTE	AE Time To 1st Derm. Event Analysis	Analysis - one record per subject	Analysis	USUBJID	adtte.xpt
ADVS	Vital signs Analysis	Analysis - one record per vital sign measurement per time point per subject	Analysis	USUBJID, VSTESTCD, VSELTM	advs.xpt

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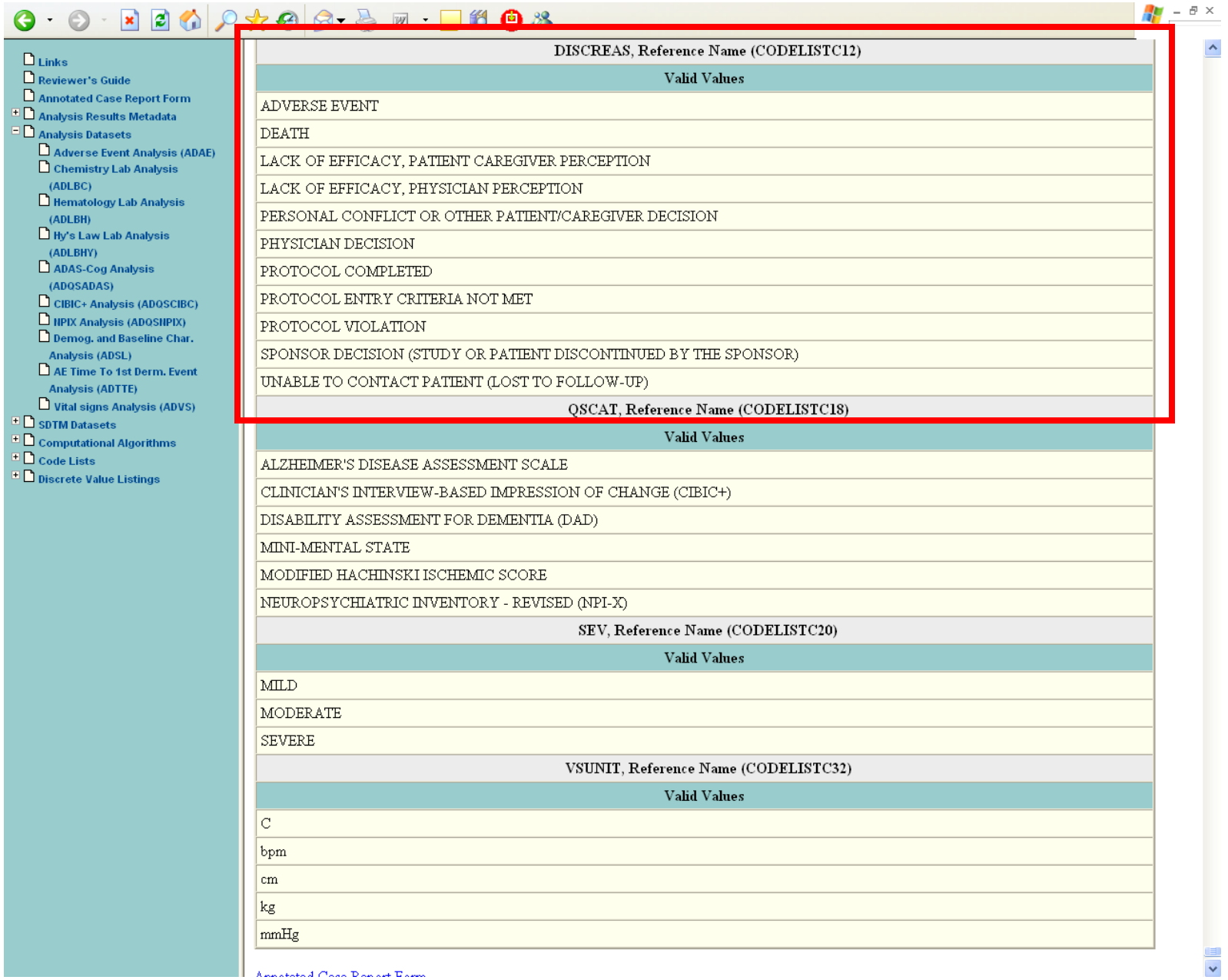
Dataset	Description	Structure	Purpose	Keys	Location
TE	Trial Elements	Trial Design - One record per element	Tabulation	STUDYID, ETCD	te.xpt
TA	Trial Arms	Trial Design - One record per planned element per arm	Tabulation	STUDYID, ETCD	ta.xpt
TV	Trial Visits	Trial Design - One record per planned visit	Tabulation	STUDYID, VISITNUM	tv.xpt

ADSL Metadata

Demog. and Baseline Char. Analysis Dataset (ADSL) — adsl.xpt

Variable	Label	Type	Controlled Terms or Format	Computational Algorithm or Method	Origin	Role	Comment
USUBJID	Unique Subject Identifier	text			DM	Identifier	Data from DM
STUDYID	Study Identifier	text			DM	Identifier	Data from DM
DOMAIN	Domain Abbreviation	text		COMP_ADSL_DOMAIN	created here	Identifier	Data from ADSL
SITEID	Study Site Identifier	text			DM	Identifier	Data from DM
SITEGRP	Pooled Site	text		COMP_ADSL_SITEGRP	created here	Identifier	Data from ADSL
SUBJID	Subject Identifier for the Study	text			DM	Identifier	Data from DM
VISIT1DT	Date of Visit 1	date		COMP_ADSL_VISIT1DT	created here	Support	Data from SV
RANDDT	Date of Randomization (Visit 3)	date		COMP_ADSL_RANDDT	created here	Support	Data from ADSL
TRTSTDT	Start Date of Treatment	date		COMP_ADSL_TRTSTDT	created here	Support	Data from SV
RFSTDTC	Subject Reference Start Date/Time	text			DM	Support	Data from DM
LSTDOSDT	Date of Last Dose	date		COMP_ADSL_LSTDOSDT	created here	Support	Data from EX
ENDDT	Date of Discontinuation/Completion	date		COMP_ADSL_ENDDT	created here	Support	Data from ADSL
RFENDTC	Subject Reference End Date/Time	text			DM	Support	Data from DM
VISNUMEN	End of Trt Visit (Vis 12 or Early Term.)	float		COMP_ADSL_VISNUMEN	created here	Support	Data from DS
DISCONT	Did the Subject Discontinue the Study?	text	Y_BLANK	COMP_ADSL_DISCONT	created here	Analysis	Data from ADSL
DSDECOD	Standardized Disposition Term	text	DISCREAS		DS	Analysis	Data from DS
DSREASAE	Discontinued due to AE?	text	Y_BLANK	COMP_ADSL_DSREASAE	created here	Analysis	Data from ADSL
DSREASCD	Reason for Discontinuation	text	DISCCD	COMP_ADSL_DSREASCD	created here	Analysis	Data from ADSL
DEATH	Subject Died?	text	Y_BLANK	COMP_ADSL_DEATH	created here	Selection	Data from ADSL
TRTDUR	Duration of Treatment (days)	float		COMP_ADSL_TRTDUR	created here	Support	Data from ADSL
TRTP	ADaM Description of Planned Arm	text	ARM	COMP_ADSL_TRTP	created here	Analysis	Data from ADSL

Value list for DSREAS



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  - NPIX Analysis (ADQSNPIX)
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DISCREAS, Reference Name (CODELISTC12)
Valid Values
ADVERSE EVENT
DEATH
LACK OF EFFICACY, PATIENT CAREGIVER PERCEPTION
LACK OF EFFICACY, PHYSICIAN PERCEPTION
PERSONAL CONFLICT OR OTHER PATIENT/CAREGIVER DECISION
PHYSICIAN DECISION
PROTOCOL COMPLETED
PROTOCOL ENTRY CRITERIA NOT MET
PROTOCOL VIOLATION
SPONSOR DECISION (STUDY OR PATIENT DISCONTINUED BY THE SPONSOR)
UNABLE TO CONTACT PATIENT (LOST TO FOLLOW-UP)
QSCAT, Reference Name (CODELISTC18)
Valid Values
ALZHEIMER'S DISEASE ASSESSMENT SCALE
CLINICIAN'S INTERVIEW-BASED IMPRESSION OF CHANGE (CIBIC+)
DISABILITY ASSESSMENT FOR DEMENTIA (DAD)
MINI-MENTAL STATE
MODIFIED HACHINSKI ISCHEMIC SCORE
NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)
SEV, Reference Name (CODELISTC20)
Valid Values
MILD
MODERATE
SEVERE
VSUNIT, Reference Name (CODELISTC32)
Valid Values
C
bpm
cm
kg
mmHg

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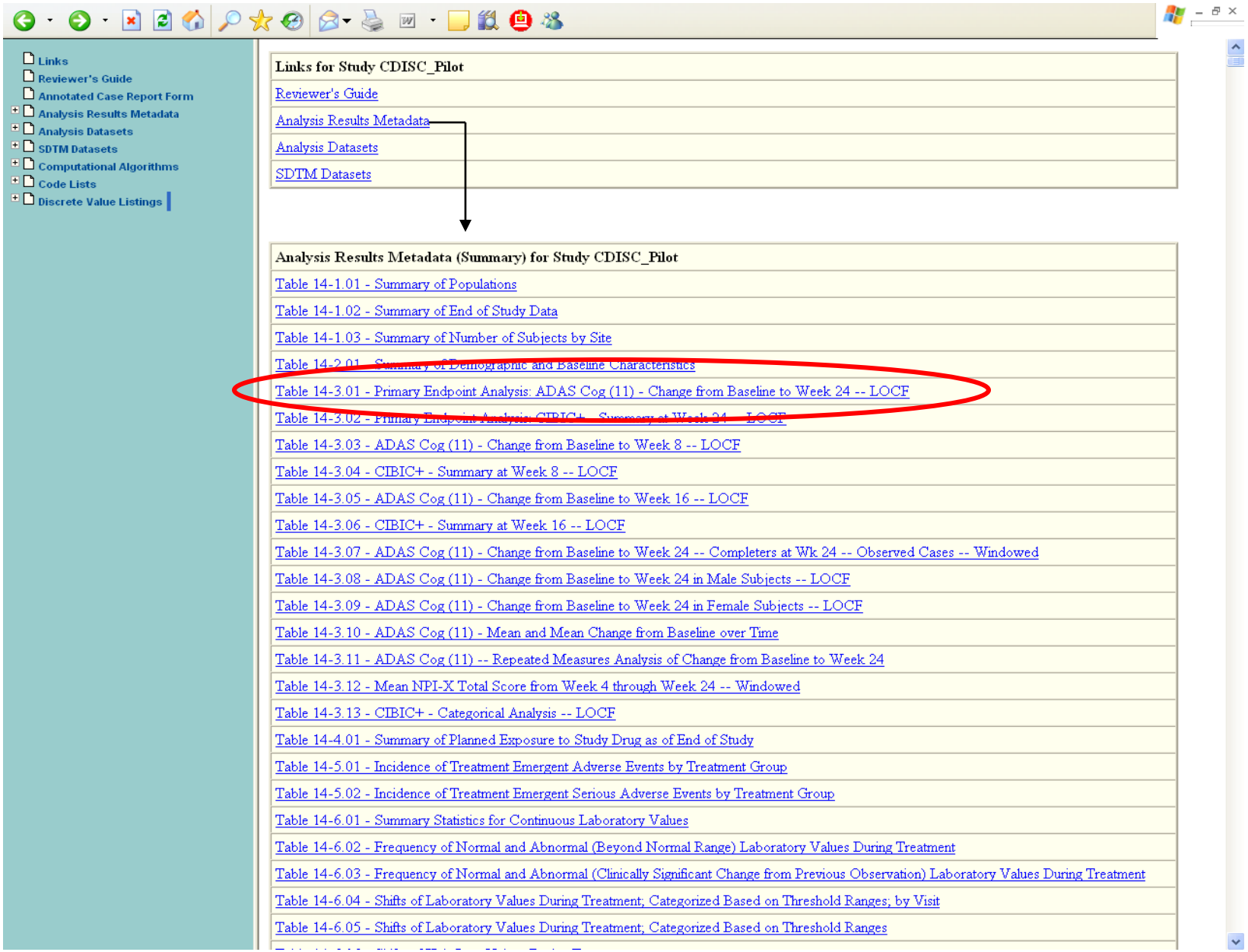

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Analysis Results Metadata

Data References	Demog. and Baseline Char. Analysis (ADSL) [where ITT='Y']
Documentation	SAP Section 9.2, SAP Template 3

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Analysis	**Table 14-3.01 - Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 -- LOCF**
Description	Summary of ADAS-Cog(11) total score at baseline and at Week 24, and change from baseline at Week 24, includes analysis of dose response and pairwise comparisons between treatment groups - missing values imputed using LOCF, Efficacy population
Reason	Primary Endpoint Analysis; pre-specified in protocol
Data References	ADAS-Cog Analysis (ADQSADAS) [where EFFICACY='Y' and ITTV='Y' and AVISITCD='Wk24' and PARAMCD='ACTOT']
Documentation	SAP Section 10.1.1, SAP Template 5, Summary statistics of BASE; VAL at Week 24; and CHG at Week 24. Linear model analysis of CHG for dose response; model included randomized dose; site group; and baseline ADAS-Cog score (i.e. BASE). Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose); Independent terms in model are TRTDOSE (0 for placebo; 54 for low dose; 81 for high dose) SITEGRP (as a class variable) and BASE. Linear model analysis of CHG for pairwise treatment comparisons and adjusted means; using randomized treatment as class variable; site group as class variable; and baseline ADAS-Cog score in model. Used PROC GLM in SAS to produce LSMEANS for treatment differences and associated statistics. Independent terms in model are TRTPCD (as class variable); SITEGRP (as class variable); and BASE. Estimate statements and the statement LSMEANS TRTPCD / OM STDERR PDIFF CL were used to produce the adjusted means of the pairwise treatment differences.

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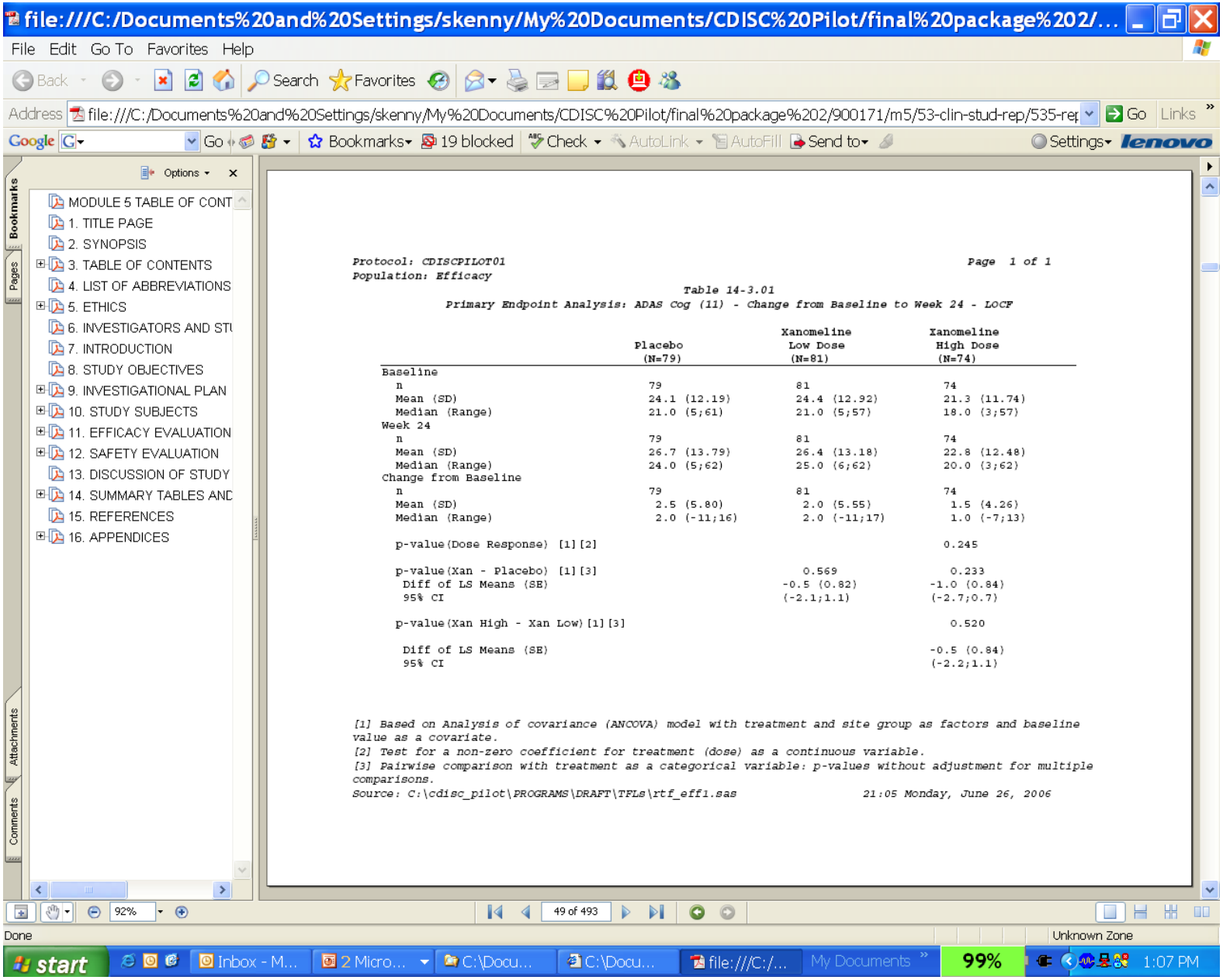
Analysis	**Table 14-3.02 - Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 -- LOCF**
Description	Summary of CIBIC at Week 24, includes analysis of dose response and pairwise comparisons between treatment groups - missing values imputed using LOCF, Efficacy population
Reason	Primary Endpoint Analysis; pre-specified in protocol
Data References	CIBIC+ Analysis (ADQSCIBC) [where EFFICACY='Y' and ITTV='Y' and AVISITCD='Wk24' and PARAMCD='CIBICVAL']
Documentation	SAP Section 10.1.2, SAP Template 6, Summary statistics of VAL at Week 24. Linear model analysis of VAL for dose response; using randomized dose and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose); Independent terms in model are TRTDOSE (0 for placebo; 54 for low dose; 81 for high dose) and SITEGRP (as a class variable). Linear model analysis of VAL 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. Used PROC GLM in SAS to produce LSMEANS for treatment differences and associated statistics. Independent terms in model are TRTPCD (as class variable) and SITEGRP (as class variable). Estimate statements and the statement LSMEANS TRTPCD / OM STDERR PDIFF CL were used to produce the adjusted means of the pairwise treatment differences

Go to the Analysis Results Metadata Summary

Analysis	**Table 14-3.03 - ADAS Cog (11) - Change from Baseline to Week 8 -- LOCF**
Description	Summary of ADAS-Cog(11) total score at baseline and at Week 8, and change from baseline at Week 8, includes analysis of dose response and pairwise comparisons between treatment groups - missing values imputed using LOCF, Efficacy population
Reason	pre-specified in protocol

Analysis Results Metadata



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

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Baseline			
n	79	81	74
Mean (SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.74)
Median (Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;57)
Week 24			
n	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*

Conclusion

- The goals of the CDISC SDTM/ADaM pilot project were met
- Package using CDISC standards met the needs and expectations of both regulatory review team medical and statistical reviewers
- Demonstrated the importance of having metadata and data that provide clear, unambiguous communication of the science and statistics of the trial

Wisdom is scar tissue in disguise

Or, as one FDA Team Member said:

In order to get a standard we have to suffer

FDA Review Process and Reviewer Experience

For the SDTM/ADaM Pilot Project

P. Chris Holland, MS
For the Pilot Project FDA Review Team
February 25, 2008

Disclaimer

Views expressed in this presentation are those of the SDTM/ADaM Pilot Project FDA Review Team and not, necessarily, of the Food and Drug Administration and must not be taken to represent policy or guidance on behalf of the FDA.

Outline

- FDA Team and Review Process
- Reviewer Experiences
  - Overall Impression/general comments
  - Dataset Documentation/Metadata
  - Datasets
    - Tabulation Data (SDTM)
    - Analysis Datasets (ADaM)
  - Use of Review Tools
- Project Limitations
- Conclusions

FDA Review Team and Review Process…

- US Food and Drug Administration

FDA Review Team

- 16 Active Review Participants
  - 10 Statisticians, 3 Medical Officers, 3 Technical Staff Members
  - 14 from CDER, 2 from CBER
- Experience ranged from <1 year to >18 years
- Review Areas
  - Neurology
  - Drug Safety
  - Antimicrobials
  - Gene Therapy and Blood Products
  - Metabolism/Endocrinology
  - Dermatology/Dental Products
  - Pulmonary and Allergy

Review Process

- Reviewers volunteered to examine certain aspects of the submission
  - E.g. Safety data, efficacy data, narratives, general review tool issues
- 20 Questions were submitted to the Pilot Project Team for Comment
  - Reviewers posted responses to questions that pertained to their review by posting comments in an eRoom
- Weekly meetings were held to discuss comments and compile feedback

FDA Reviewer Experiences…

- US Food and Drug Administration

Overall Impression/General Comments

- Submission was well done
- Standards have great promise!
  - Most reviewers on the team had no problems with the submitted data
    - Review team was, however, a potentially "biased" sample
  - Other reviewers will need experience with standardized data
  - Tools will be needed to assist with reviewer needs
- The pilot project package can serve as a helpful example

Dataset Documentation/Metadata

- Data definition file (Define.XML)
  - Framed version found to be much easier than the version without frames
    - Requires an extension to the ODM, however
  - Concept and content were very good:
    - Analysis results table:

Analysis	Table 14-1.01 - **Summary of Populations**
Description	Summary of number of subjects in each analysis population
Reason	pre-specified in SAP
Data References	Demog. and Baseline Char. Analysis (ADSL)
Documentation	SAP Section 9.1, SAP Template 1

Go to the Analysis Results Metadata Summary

    - Computational Algorithms Table
    - Controlled Terminology (Codelist) Table

Tabulation Datasets (SDTM)

- Overall, data were suitable to reviewer needs
- Data appeared to be CDISC compliant
- Derived variables were helpful
  - Derived data flag (QSDRVFL)
  - ADAS-Cog(11) total score (in QS)
  - Baseline flags (QSBLFL)
  - Endpoint flags (in SUPPLB)
- Comments/documentation could be used to explain that these fields might *not*, necessarily, allow one to reproduce analysis results.

Tabulation Datasets (SDTM)

- Comments and/or labels should explain what the variables represent
  - Assume reviewers are not familiar with CDISC concepts and jargon
- MedDRA coding levels added to SUPPAE (LLTERM, HLTERM, and HLGTERM)
- Dictionary names and versions are important
  - Included in TS domain
  - Useful in the AE and CM domains as well

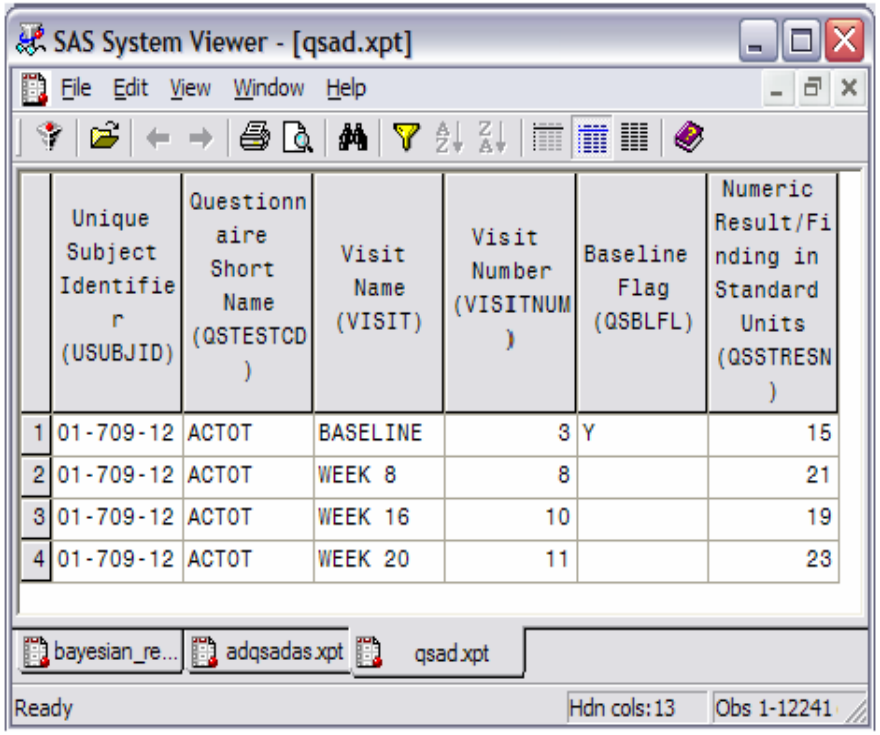
Analysis Datasets (ADaM)

- Essential component since SDTM datasets are not analysis ready!
  - Core variables such as treatment group, center, age, gender, etc. are not within each SDTM file.
- Overall, the data sets were very useful
  - Many analyses were “one PROC away”
- Structure of some files were changed based on FDA review team feedback
  - Changes facilitated “traceability”

Analysis Datasets

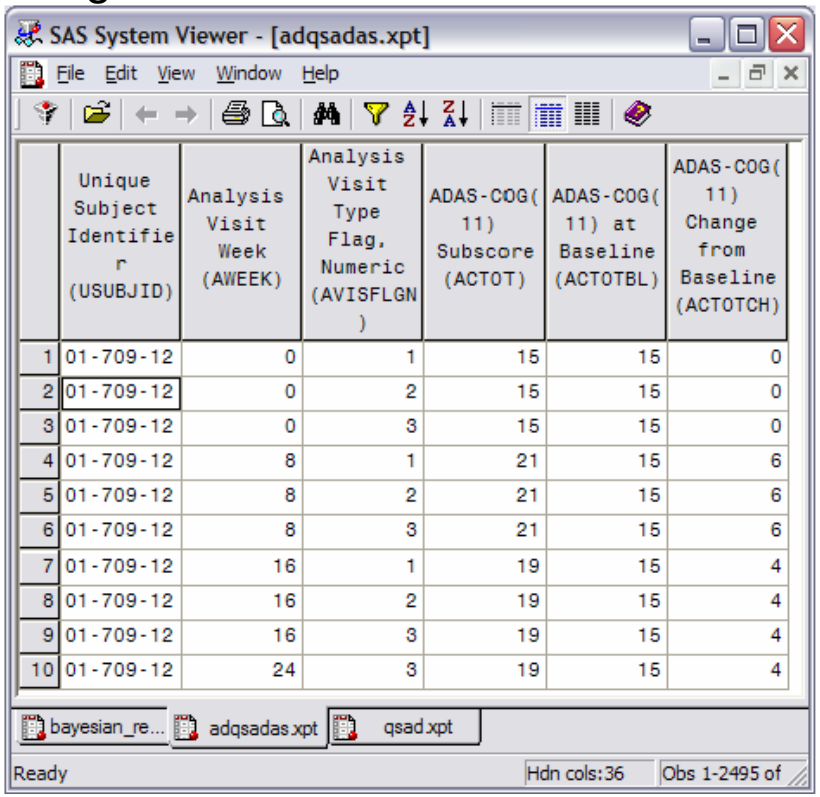
- Efficacy Data Structures:

SDTM data:



	Unique Subject Identifier (USUBJID)	Questionnaire Short Name (QSTESTCD)	Visit Name (VISIT)	Visit Number (VISITNUM)	Baseline Flag (QSBLFL)	Numeric Result/Finding in Standard Units (QSSTRESN)
1	01-709-12	ACTOT	BASELINE	3	Y	15
2	01-709-12	ACTOT	WEEK 8	8		21
3	01-709-12	ACTOT	WEEK 16	10		19
4	01-709-12	ACTOT	WEEK 20	11		23

Original ADaM data:



	Unique Subject Identifier (USUBJID)	Analysis Visit Week (AWEEK)	Analysis Visit Type Flag, Numeric (AVISFLGN)	ADAS-COG(11) Subscore (ACTOT)	ADAS-COG(11) at Baseline (ACTOTBL)	ADAS-COG(11) Change from Baseline (ACTOTCH)
1	01-709-12	0	1	15	15	0
2	01-709-12	0	2	15	15	0
3	01-709-12	0	3	15	15	0
4	01-709-12	8	1	21	15	6
5	01-709-12	8	2	21	15	6
6	01-709-12	8	3	21	15	6
7	01-709-12	16	1	19	15	4
8	01-709-12	16	2	19	15	4
9	01-709-12	16	3	19	15	4
10	01-709-12	24	3	19	15	4

AVISFLGN: 1="Observed", 2="Windowed", and 3="LOCF"

Analysis Datasets

- Efficacy Analysis Background:
  - The SAP designated the primary analysis as the one that used the last observation carried forward (LOCF) missing value imputation.
  - Data were to be excluded if there had been >3 days since the last dose
  - Windows were constructed around each planned visit in order to determine the visit with which data would be summarized
  - If more than one datum fell into a visit window, then the one closest to the target time was to be used for analysis.

Analysis Datasets

- Efficacy Data Structures:

SAS System Viewer - [qsad.xpt]

File Edit View Window Help

	Unique Subject Identifier (USUBJID)	Questionnaire Short Name (QSTESTCD)	Visit Name (VISIT)	Visit Number (VISITNUM)	Baseline Flag (QSBLFL)	Numeric Result/Finding in Standard Units (QSSTRESN)
1	01-709-12	ACTOT	BASELINE	3	Y	15
2	01-709-12	ACTOT	WEEK 8	8		21
3	01-709-12	ACTOT	WEEK 16	10		19
4	01-709-12	ACTOT	WEEK 20	11		23

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SAS System Viewer - [adqsadas.xpt]

File Edit View Window Help

	Unique Subject Identifier (USUBJID)	Analysis Visit Week (AWEEK)	Analysis Visit Type Flag, Numeric (AVISFLGN)	ADAS-COG(11) Subscore (ACTOT)	ADAS-COG(11) at Baseline (ACTOTBL)	ADAS-COG(11) Change from Baseline (ACTOTCH)
1	01-709-12	0	1	15	15	0
2	01-709-12	0	2	15	15	0
3	01-709-12	0	3	15	15	0
4	01-709-12	8	1	21	15	6
5	01-709-12	8	2	21	15	6
6	01-709-12	8	3	21	15	6
7	01-709-12	16	1	19	15	4
8	01-709-12	16	2	19	15	4
9	01-709-12	16	3	19	15	4
10	01-709-12	24	3	19	15	4

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Ready Hdn cols:36 Obs 1-2495 of

Why does the Week 24 LOCF value equal 19 and not 23?

Revised ADQSADAS

- Flags were added so that the analysis data's lineage is transparent to reviewers
- Flags also make it easier for reviewers to test the sensitivity of results to alternative methodologies

SAS System Viewer - [adqsadas.xpt]

File Edit View Window Help

	Unique Subject Identifier (USUBJID)	Analysis Visit Number (AVISITN)	Analysis Visit Description (AVISITC)	Visit Name (VISIT)	Analysis Visit Short Name (AVISITCD)	Analysis Visit Week (AWEEK)	Imputation Type (ITYPE)	Intent to Treat Visit Flag (ITTV)	Analysis Parameter Short Name (PARAMCD)	Numeric value of PARAM (VAL)	Baseline value of VAL (BASE)	Change from baseline (VAL - BASE) (CHG)
1	01-709-1259	3	BASELINE	BASELINE	BL	0		Y	ACTOT	15	15	0
2	01-709-1259	8	WEEK 8	WEEK 8	Wk8	8		Y	ACTOT	21	15	6
3	01-709-1259	10	WEEK 16	WEEK 16	Wk16	16		Y	ACTOT	19	15	4
4	01-709-1259	12	WEEK 24	WEEK 16	Wk24	24	LOCF	Y	ACTOT	19	15	4
5	01-709-1259	.	WEEK 20	WEEK 20		.		N	ACTOT	23	15	8

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Note that the forthcoming ADaM guidelines refer to a similar variable named DTYPE

Analysis Datasets

- General comments
  - Be consistent with what “core” variables are used in each file
  - Adding the drug start and stop dates to every file can be helpful
    - Helps reviewers to determine what events (e.g. lab abnormalities) occurred while on or off treatment
  - Place variables in a logical order
    - Some reviewers may prefer alphabetical ordering, but this can be achieved with tools– logical ordering can not
  - Ensure clarity with data documentation, comments, and variable labels
    - Avoid CDISC jargon that reviewers may not be familiar with

Review Tools

- Many different review tools and software were used:
  - WebSDM™, Integrated Review™ (iReview), CrossGraphs®, S-PLUS Graphlets™, R, JMP®, SAS®
- These were used for various review functions
  - Patient profiles
  - Safety summaries (AE tables, Lab shifts)
  - Efficacy analyses
  - Review of demographics, enrollment, and study disposition
- Many of the tools were used for data visualization

Review Tools

- The submitted data worked well with the tools
- WebSDM made specific use of the SDTM data
  - SDTM compliance checking
  - Creation of graphical patient profiles
  - Automatic merging of "core" (e.g. treatment group, gender, age, etc.) and SUPPQUAL variables into domains
    - The modified domains could then be downloaded as new data files for use with other software and tools
- Other review tools were non-SDTM specific
  - ADaM files could therefore be used
  - More familiar to reviewers since they are used on all data types

Project Limitations…

Despite the successes, there are some project limitations to keep in mind…

•US Food and Drug Administration

Project Limitations

- This was a CDER/CBER project
  - The standards may not meet the needs of CDRH, CVM, CFSAN
- Limited scope
  - Other therapeutic areas or study designs may face more (or different) challenges
    - e.g. non-questionnaire efficacy data, cross-over designs, adaptive designs, etc.
  - Does not address multiple-study submissions
  - Demonstrated that the SDTM *can* be useful, but not that it will always be useful in it's current state
- Implementer and reviewer "selection bias"
  - Implementation and review by those with less CDISC familiarity might produce less successful results

Conclusions

- Great job overall
  - Very useful example for future submissions
- ADaM files are critical when submitting SDTM data
  - Maintaining transparency is key
- Standards have great promise
  - Efficiencies will come with:
    - Training (for reviewers *and* implementers)
    - Experience (for reviewers *and* implementers)
    - Adaptation and development of review tools

Conclusions (continued)

- FDA is committed to standards
  - CDISC is mentioned throughout the FDA's draft PDUFA IV IT Plan
    - (a rolling 5-year plan on how FDA will automate business processes and develop IT systems to support PDUFA IV performance goals)
    - http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0481-gdl0001.pdf
    - ADaM datasets specifically referred to as being "pilot tested by CDER review staff" (page 26).

Question & Answer Session

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