

BetterManagement Presents

Results and Lessons from the CDISC SDTM/ADaM Pilot Project

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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



*Setting the
Global Standard
for Medical Research*

Results and Lessons from the CDISC SDTM/ADaM Pilot Project

**CLINICAL DATA INTERCHANGE
STANDARDS CONSORTIUM**

Presenters

**Cathy Barrows, GSK
Chris Holland, FDA**

Moderators

**Tanyss Mason, CDISC
Ed Helton, SAS**

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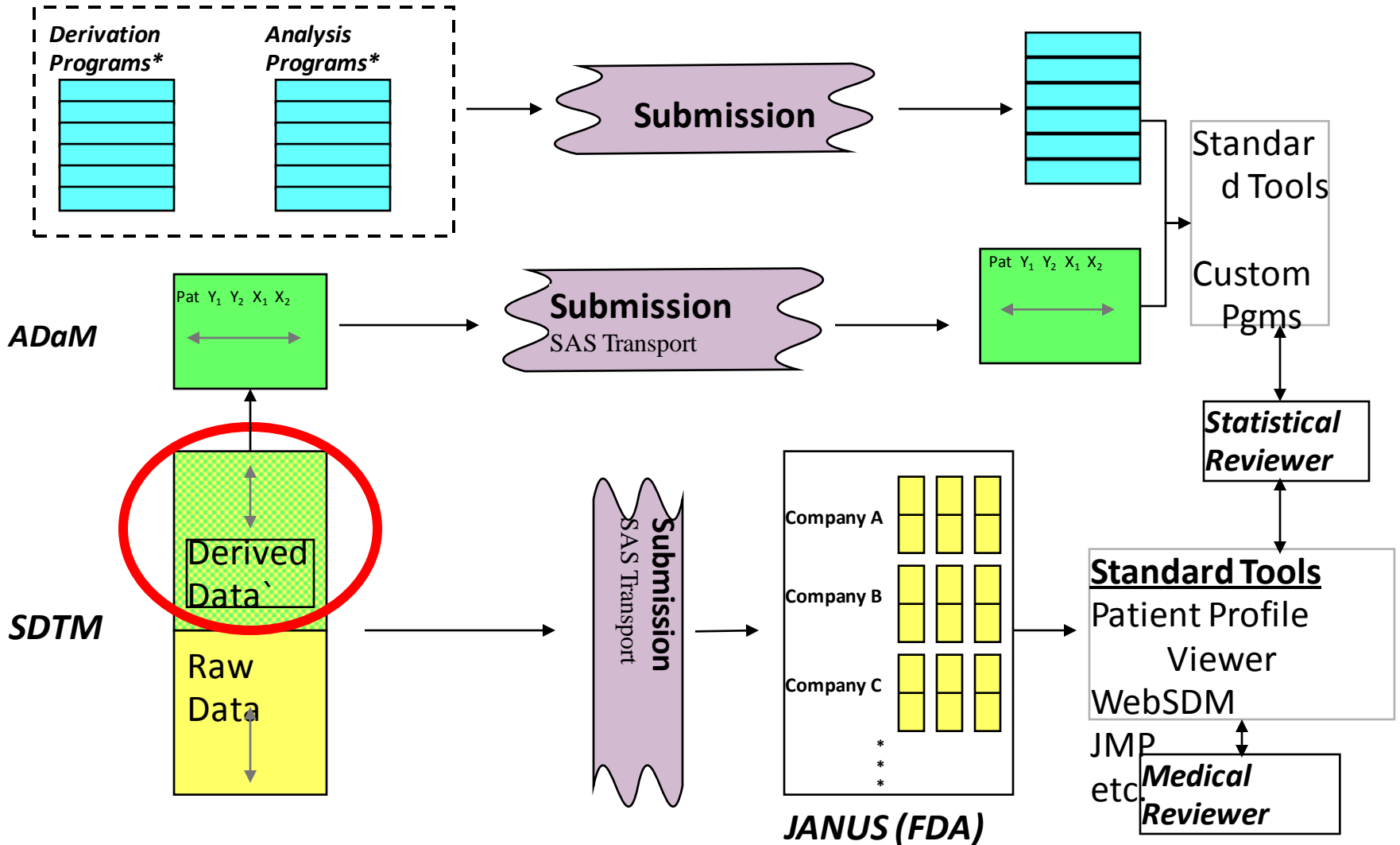


Harmonizing CDISC Submission Models

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

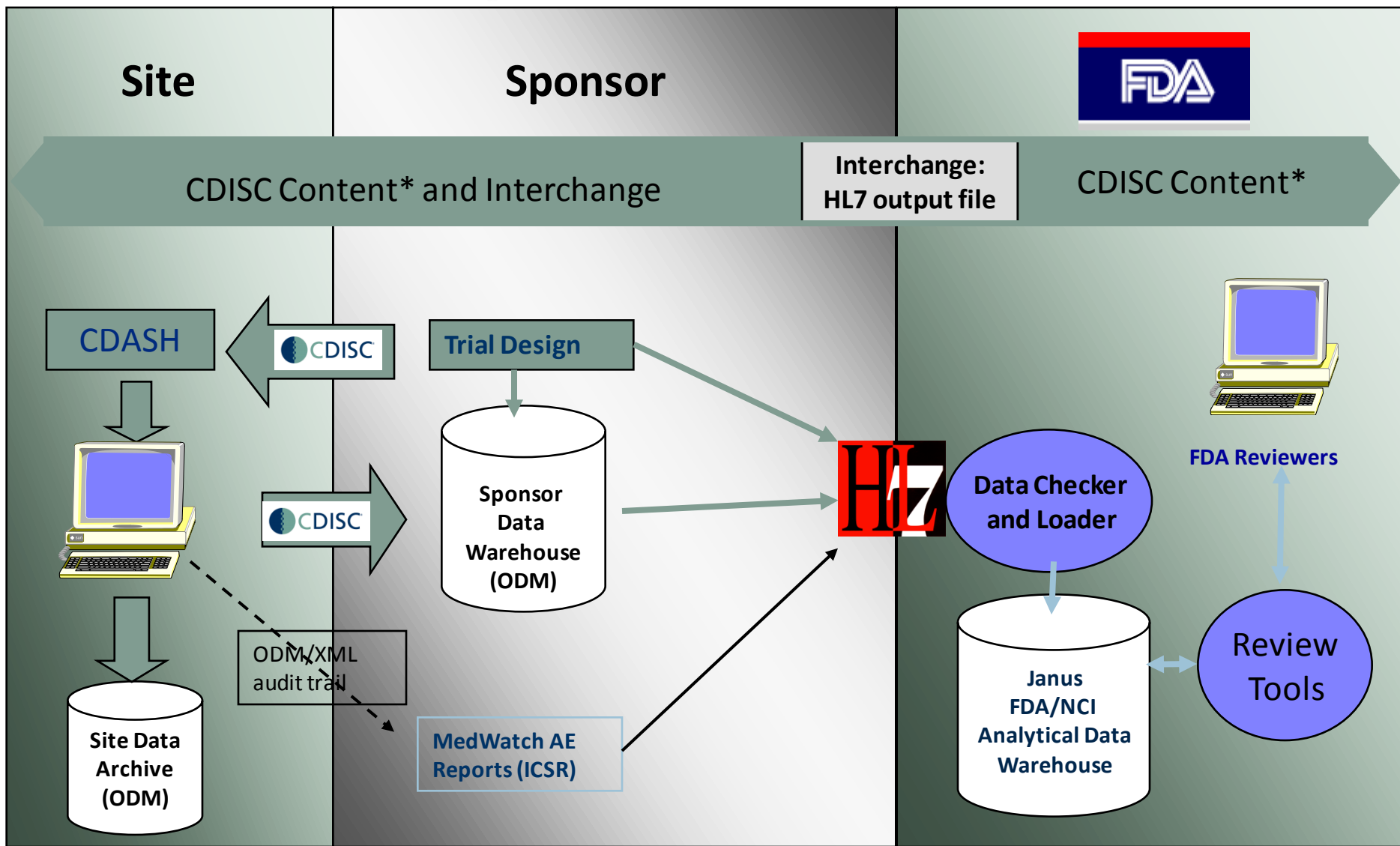
Stephen J. Ruberg, Ph.D.
Director, Medical Information Sciences
Eli Lilly & Company
CDISC Interchange
21 Sep 2005

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



How the customer explained it



How the Project Leader understood it



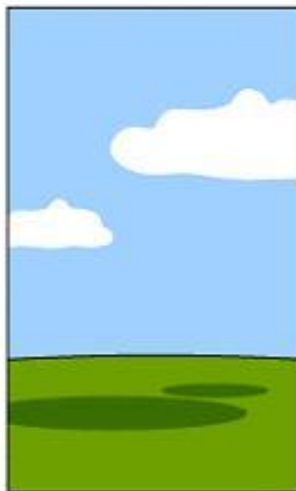
How the Analyst designed it



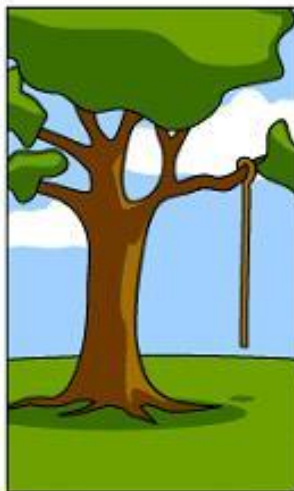
How the Programmer wrote it



How the Business Consultant described it



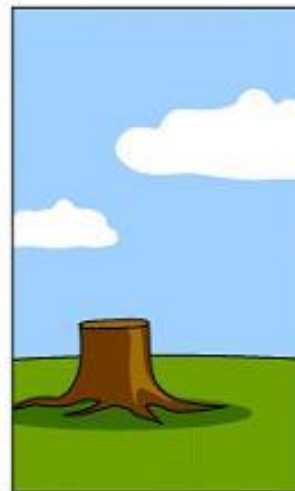
How the project was documented



What operations installed



How the customer was billed



How it was supported



What the customer really needed



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

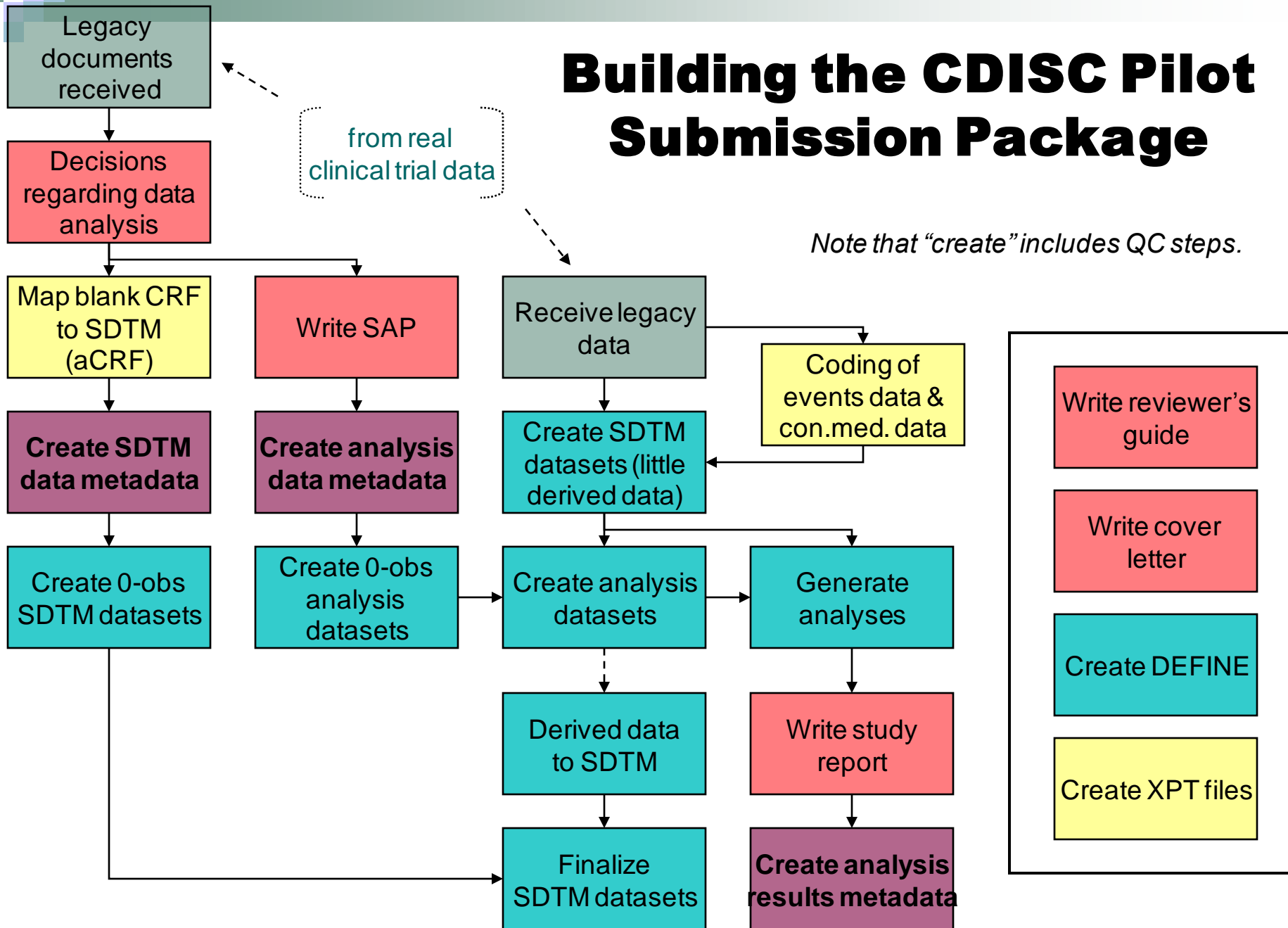
- Cathy Barrows (GSK)
- Musa Nsereko (Cephalon / Shire)
- FDA Co-Leaders:
 - Lonnie Smith (previous)
 - Chris Holland
 - Mina Hohlen
- Greg Anglin (Lilly)
- T Friebel (SAS)
- John Gorden (Quintiles)
- Tom Guinter (Octagon)
- Joel Hoffman (Insightful)
- Susan Kenny (Inspire Pharm.)
- Sandy Lei (J&J)
-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



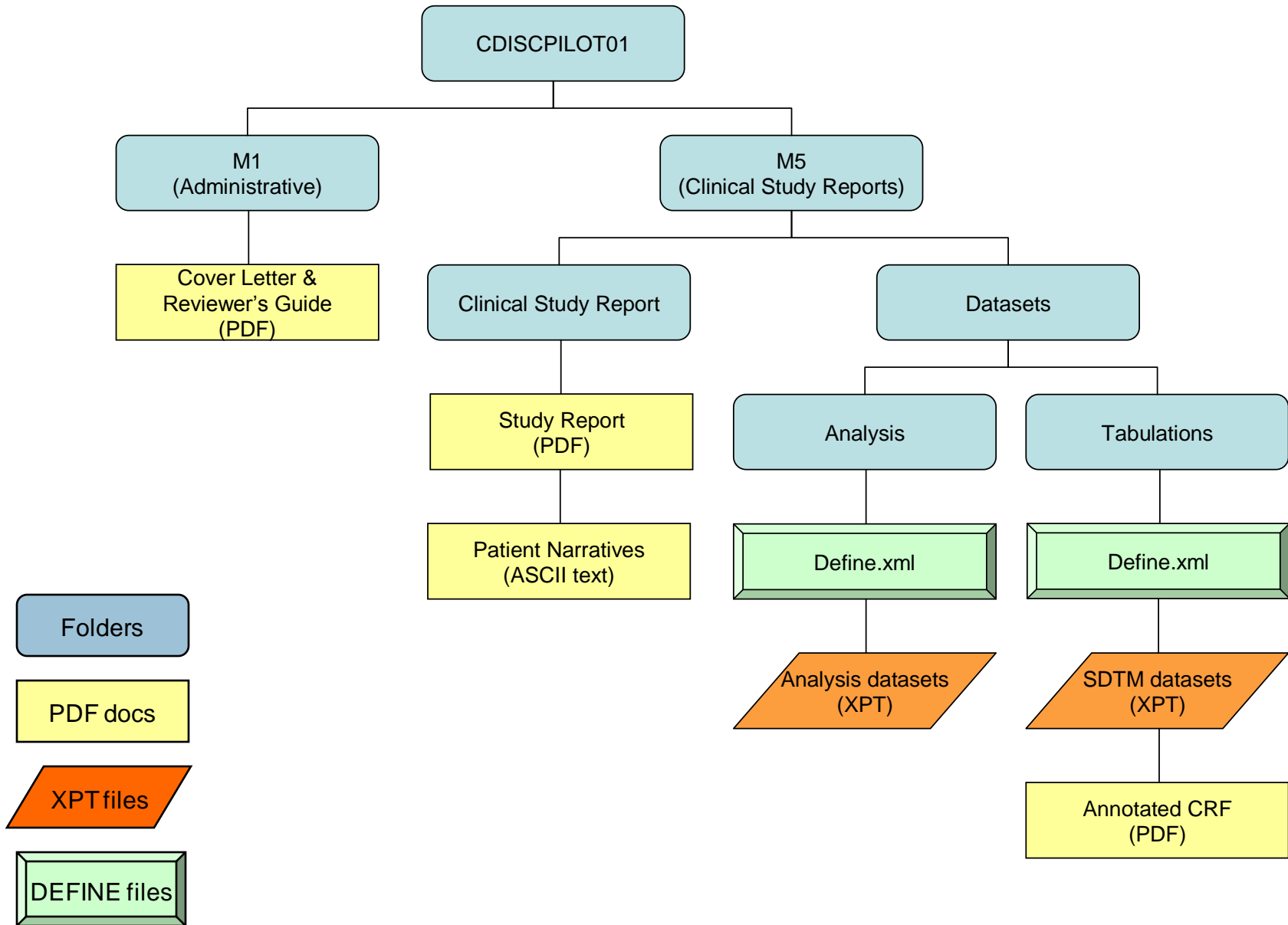
FDA Participation


- Unprecedented level of involvement
- Co-Leadership of the project
- Included medical and statistical reviewers
- \approx 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

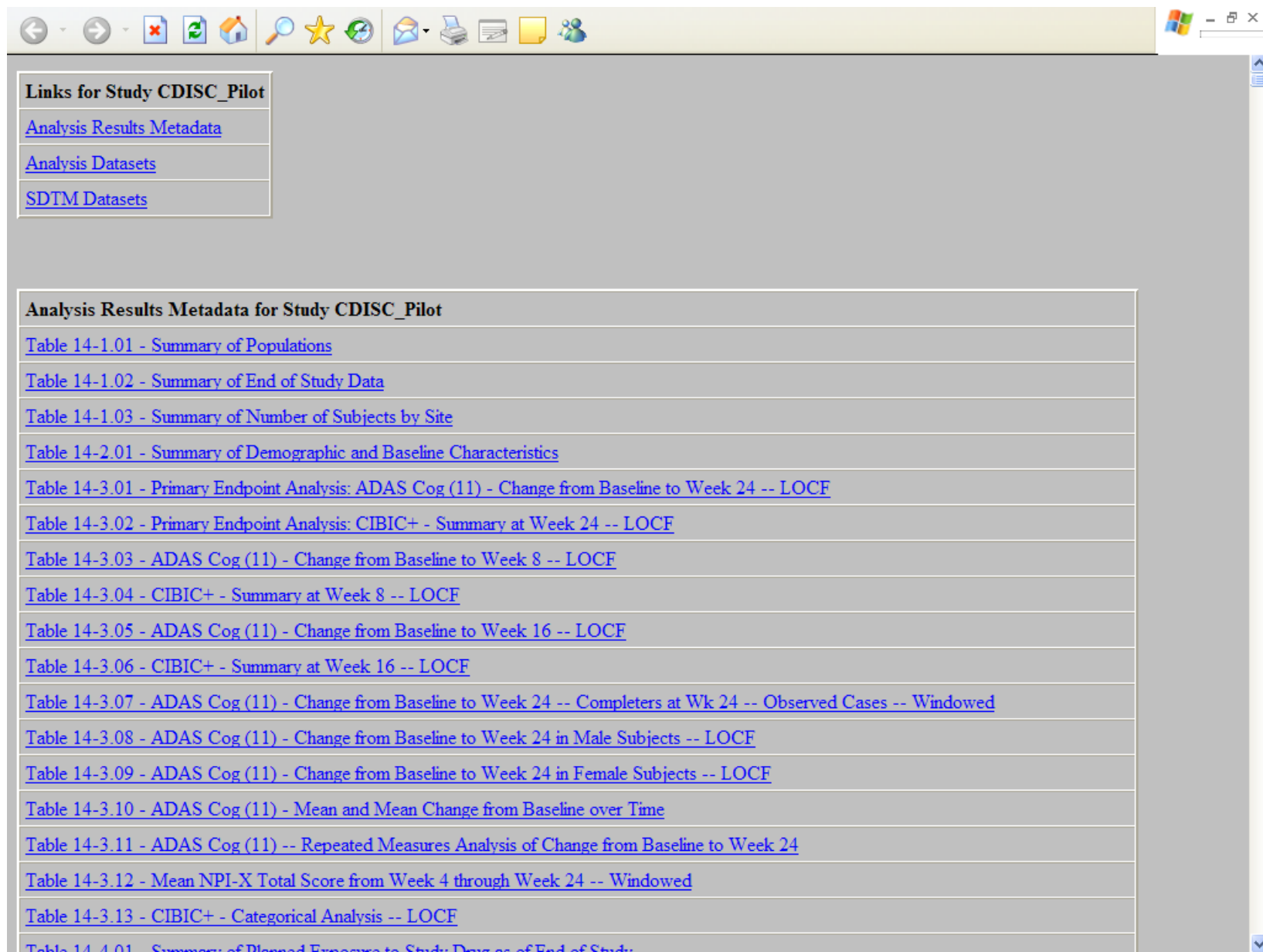
- Overall favorable impression
 - Expect learning curve to be less steep when standards are being followed
- Severable notable comments
 - ADaM datasets were important component since SDTM datasets are not analysis ready
 - ADaM ADSL was very useful for both medical and statistical reviewer
- Some issues...
 - 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

Original



The screenshot shows a web browser window with a toolbar at the top. The main content area displays a table with the following structure:

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 at End of Study

Revised

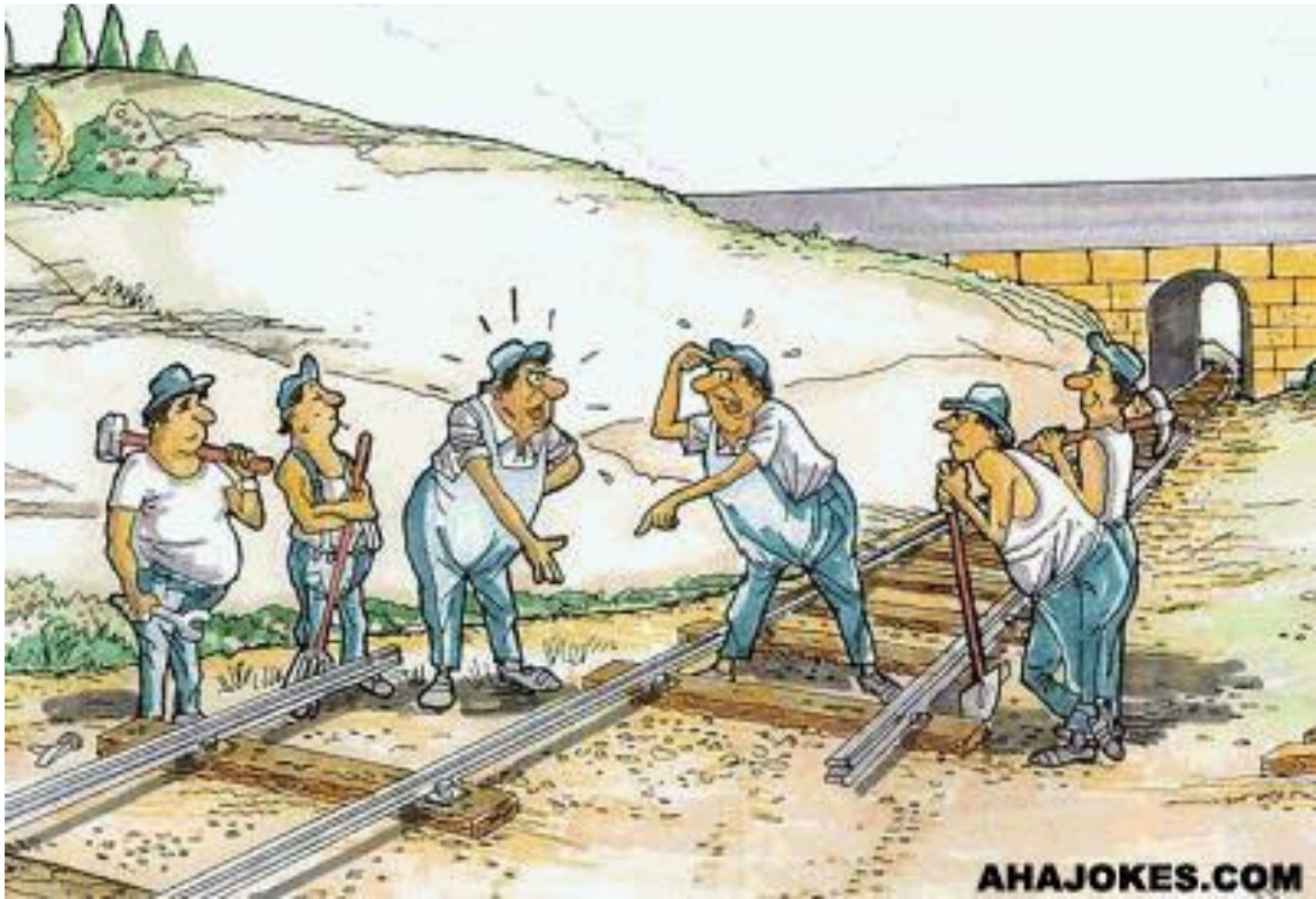
Links for Study CDISC_Pilot

- [Reviewer's Guide](#)
- [Analysis Results Metadata](#)
- [Analysis Datasets](#)
- [SDTM Datasets](#)

Analysis Results Metadata (Summary) 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](#)
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- [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](#)
- [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

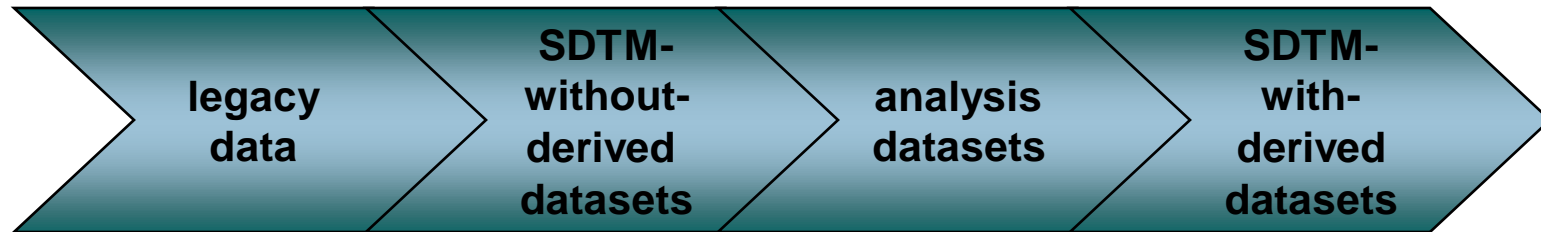
- Define file much improved
- The analysis dataset modifications met their needs
- The new structure and metadata provide a good model of what information is critical to a reviewer's understanding of the data lineage from CRF to analysis



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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CDISC is currently seeking two individuals to 1) lead the coordination of CDISC Educational Courses and other CDISC Events, and 2) provide Technical Support and Documentation for CDISC standards development and maintenance activities. These will be contractor positions at 75-100% time. The work will be done from the contractor's office space/location. Below are the position profiles which describe each position and the associated qualification requirements. If you are interested and qualify, please send your CV/resume and a cover letter to swilliams@cdisc.org **no later than 18 February 2008**. These positions are to be filled by the end

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Publications and Presentations

Unless otherwise noted, the following publications and presentations are available in in Adobe Acrobat PDF format, and can be read using the Adobe Acrobat Reader or by a browser that supports viewing of PDF files. [Download the free Adobe Acrobat Reader.](#)

FDA Information/Documents Relevant to CDISC

[For abstracts of the following, click here.](#)

- PROPOSED RULE and SDTM ([DOC](#))
- [Electronic Submission of Data from Studies Evaluating Human Drugs and Biologics](#)
- Guidances on Providing Regulatory Submissions in Electronic Format; Withdrawal of Guidances (PDF vs. XML) ([PDF](#))
- [ODM Pilot - Electronic Case Report Form Submission; Notice of Pilot Project](#)
- FDA Critical Path Opportunities and CDASH
The Critical Path Initiative, "[Innovation vs. Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products](#)"
 - [For the entire update report](#)

EMA Information/Documents Relevant to CDISC

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CDISC Documents

CDISC SDTM/ADaM Pilot Project

The CDISC SDTM / ADaM Pilot Project was conducted as a collaborative pilot project with FDA and Industry. (This pilot project is also referred to as "Pilot 1." It was conducted during 2006 and 2007). The objective of the pilot project was to test how well the submission of CDISC-adherent datasets and associated metadata met the needs and the expectations of both medical and statistical FDA reviewers. In doing this, the project also assessed the data structure, resources and processes needed to transform source data into the SDTM and ADaM formats and to create the associated metadata.

This pilot project effort represented an unprecedented amount of work and collaboration between CDISC, the Industry and FDA and led to a number of valuable learnings, documented in the project report. However, it must be noted that all comments, statements, and opinions attributed in the project report 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

All of the aforementioned goals were met by the CDISC SDTM/ADaM Pilot Project. The project established that the package submitted using CDISC standards met the needs and the expectations of both medical and statistical reviewers participating on the regulatory review team. The regulatory review team noted the importance of having both data in SDTM format to support the use of FDA review systems and interactive review, and data in ADaM format to support analytic review. The project also demonstrated the importance of having documentation of the data (e.g., the metadata provided in the data definition file) that provides clear, unambiguous communication of the science and statistics of the trial.

The regulatory review team expressed a favorable impression of the pilot submission package. They were optimistic about the impact that data standards will have on the work associated with their review of new drug applications.

Description
of
project



The regulatory review team expressed a favorable impression of the pilot submission package. They were optimistic about the impact that data standards will have on the work associated with their review of new drug applications.

Project Report

The project report describes the pilot submission package and the processes followed, including the decisions made to produce the package, and lessons learned from the experiences of the pilot and from feedback from the regulatory review team. Each step of the pilot process and work completed are easily followed in the report beginning with the de-identification of the pilot legacy data, application of CDISC Standards (including SDTM, ADaM, and CRTDDS), and resulting in the creation of a CDISC-compliant electronic clinical study report submission. Comments on this project report can be posted through the [CDISC Discussion Board](#).

- [CDISC SDTM/ADaM Pilot Project Report](#)

Additional pilot project materials available

The revised pilot submission package is available to CDISC members (on the "members-only" section of the CDISC webpage) for use as an example of the application of the CDISC standards.

In addition, various presentations about this pilot project have been made during 2006-2007; those presentations can be found here in the Publications and Presentations section. For example, presentations made during the 2006 CDISC Interchange are available at this location.

eSource Data Interchange (eSDI) Document

The eSDI document is the product of the CDISC eSDI Initiative, the purpose of which was "to investigate the use of electronic technology in the context of existing regulations for the collection of eSource data (including that from eDiaries, EHR, EDC) in clinical trials for regulatory submission by leveraging the

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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

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Pilot Project Report

The project report describes the pilot submission package and the processes followed, including the decisions made to produce the package, and lessons learned from the experiences of the pilot and from feedback from the regulatory review team. Each step of the pilot process and work completed are easily followed in the report beginning with the de-identification of the pilot legacy data, application of CDISC Standards (including SDTM, ADaM, and CRTDDS), and resulting in the creation of a CDISC-compliant electronic clinical study report submission.

- [CDISC SDTM/ADaM Pilot Project Report](#)

Pilot Project Submission Package

The CDISC SDTM/ADaM Pilot Project package that was submitted to the FDA in February 2007 is available to CDISC members for use as an example of the application of the CDISC standards. (Refer to the project report for the list of CDISC standards used.) Included in the package are the cover letter, the reviewer's guide, the protocol, the statistical analysis plan, the blank CRF (annotated), the abbreviated study report, the tabulation (SDTM) datasets, and the analysis datasets. The SDTM dataset metadata, the analysis dataset metadata, and the analysis results metadata are provided in a Define.XML file.

It should be noted that two versions of the Define file are included - a framed and a no-frame version. The framed version works only with Internet Explorer, but offers much superior navigation capabilities. The non-framed version can be used with browsers other than Internet Explorer, but can be difficult to navigate with Internet Explorer 6.

- [CDISC SDTM/ADaM Pilot Project Submission Package](#)

Metadata tools used in the Pilot Project

As described in the project report, the specifications for the analysis datasets and the SDTM datasets

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- [CDISC SDTM/ADaM Pilot Project Submission Package](#)

Metadata tools used in the Pilot Project

As described in the project report, the specifications for the analysis datasets and the SDTM datasets were written in metadata prescriptively, prior to writing the computer programs that create the analysis datasets. In contrast to a descriptive approach, this prescriptive approach leveraged the value of metadata by making the data specifications accessible to a suite of computer programs that automated some processes of building and validating SDTM and analysis datasets as well as the accompanying Define.xml content. This suite of programs demonstrates a way to use metadata to support the implementation of CDISC data and metadata standards.

The metadata tools used in the pilot project were developed by Gregory Steffens (Eli Lilly and Company). The programs are being made available, without warranty, to CDISC members. No support is being provided for using the programs; there is no help desk or other technical support (please refer to the legal disclaimer). An index of the programs can be viewed via the html file "sas_macro_descriptions.html", which will provide the program names and a brief description of the function of each. Clicking on the program name will access more detailed information, including a description of the program parameters.

- [Suite of programs that facilitates prescriptive use of metadata](#)

Comments on this package can be posted through the [CDISC Discussion Board](#).

Internet

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

The screenshot shows a Windows Explorer window titled '900171'. The address bar displays the path 'C:\cdisc_pilot\900171_2008-01-22T1920\900171'. The main pane shows a list of files and folders:

Name	Size	Type	Date Modified
m1		File Folder	1/23/2008 1:54 PM
m5		File Folder	1/23/2008 1:54 PM
ndatoc.pdf	214 KB	Adobe Acrobat Doc...	2/7/2007 5:28 PM

The file 'ndatoc.pdf' is circled in red. Below the screenshot is a list of four numbered steps:

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

Adobe Acrobat - [ndatoc.pdf]

CDISC Pilot Project

Table of Contents

Module	Description	Paper Archive Copy Volume Number	Electronic Archive Copy Folder
1	Administrative and Prescribing Information	N/A	/m1/m1toc.pdf
2	Summary	N/A	N/A
3	Quality	N/A	N/A
4	Nonclinical Study Reports	N/A	N/A
5	Clinical Study Reports	N/A	/m5/m5toc.pdf

Adobe Acrobat - [m5toc.pdf]

NDA Table of Contents

- 5.3 Clinical Study Reports
 - 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 CDISCPLOT01
 - Study CDISC
 - Datasets Table of Contents

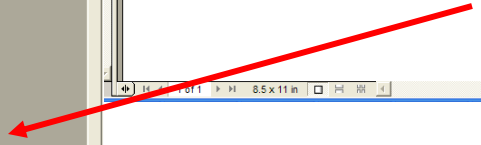
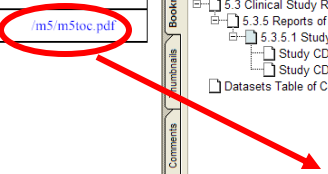
Module 5 – Clinical

Module / CTD Description	Review Copy Volume Number	Archive Copy Location Folder / File Name
5.1 Table of Contents	N/A	m5toc.pdf
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 CDISCPLOT01	N/A	/53-elin-stud-rep/535-rep-efic-safety-stud/indication-1/5351-stud-rep-contr/cdiscpilot01.pdf
Patient Narratives	N/A	/53-elin-stud-rep/535-rep-efic-safety-stud/indication-1/5351-stud-rep-contr/narratives.txt
Datasets Table of Contents	N/A	/datasets/datatoc.pdf

Adobe Acrobat - [datatoc.pdf]

Module 5 – Dataset Table of Contents

Description	Review Copy Volume Number	Archive Copy Location Folder/File Name
Study CDISCPLOT01		
Tabulation		
Data Definition Table		
Frames	N/A	/datasets/cdiscpilot01/tabulations/define.xml
No Frames	N/A	/datasets/cdiscpilot01/tabulations/define_noframes.xml
Annotated Case Report Form	N/A	/datasets/cdiscpilot01/tabulations/blankerf.pdf
Analysis		
Data Definition Table		
Frames	N/A	/datasets/cdiscpilot01/analysis/define.xml
No Frames	N/A	/datasets/cdiscpilot01/analysis/define_noframes.xml



Top of Define.xml

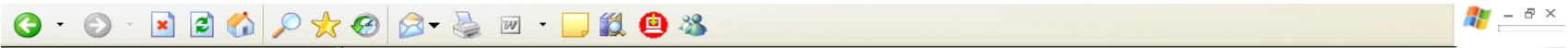
Links for Study CDISC_Pilot

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- [Analysis Results Metadata](#)
- [Analysis Datasets](#)
- [SDTM Datasets](#)

Analysis Results Metadata (Summary) for Study CDISC_Pilot

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SDTM Dataset Metadata



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 - Trial Visits (TV)
 - Trial Inclusion/Exclusion Criteria (TI)
 - Trial Summary (TS)
 - Subject Elements (SE)
 - Subject Visits (SV)
 - Demographics (DM)
 - Concomitant Medications (CM)
 - Exposure (EX)
 - Adverse Events (AE)
 - Disposition (DS)
 - Medical History (MH)
 - Laboratory Tests (LB)
 - Questionnaires (QS)
 - Subject Characteristics (SC)
 - Vital Signs (VS)
 - Related Records (RELREC)
 - Supplemental Qualifiers (AE) (SUPPAE)
 - Supplemental Qualifiers (DS) (SUPPDS)
 - Supplemental Qualifiers (MH) (SUPPMH)
 - Supplemental Qualifiers (LB) (SUPPLB)
 - Supplemental Qualifiers (DM) (SUPPDM)
 - Computational Algorithms
 - Code Lists
 - Discrete Value Listings

SDTM Datasets for Study CDISC_Pilot					
Dataset	Description	Structure	Purpose	Keys	Location
TE	Trial Elements	Trial Design - One record per element	Tabulation	STUDYID, ETCDCD	te.xpt
TA	Trial Arms	Trial Design - One record per planned element per arm	Tabulation	STUDYID, ETCDCD	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, ETCDCD	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

Windows Explorer interface showing a tree view on the left and a table of metadata on the right.

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	
STTEID	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-Y)" 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 >= RFSTDTC

ITTV If the observed data are eligible for analysis (e.g., QSVISFNUM is 3,8,10,12,20) and if QSVISIT = 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

ONIRIFL If TRTSTDT<=AESTDT<=LSTDOSDT then ONIRIFL='Y'. ONIRIFL='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/SOUTHEAST 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

Top of Define.xml

The screenshot shows a web browser window with a navigation menu on the left and a main content area. The navigation menu includes the following items:

- Links
- Reviewer's Guide
- Annotated Case Report Form
- Analysis Results Metadata
- Analysis Datasets
- SDTM Datasets
- Computational Algorithms
- Code Lists
- Discrete Value Listings

The main content area is titled "Links for Study CDISC_Pilot" and contains the following links:

- [Reviewer's Guide](#)
- [Analysis Results Metadata](#)
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Below this, there is a section titled "Analysis Results Metadata (Summary) for Study CDISC_Pilot" which contains a list of table links:

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- [Table 14-1.03 - Summary of Number of Subjects by Site](#)
- [Table 14-2.01 - Summary of Demographic and Baseline Characteristics](#)
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ADaM Dataset Metadata



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 - CIBIC+ Analysis (ADQSCIBC)
 - NPIX Analysis (ADQSNPIX)
 - Demog. and Baseline Char. Analysis (ADSL)
 - AE Time To 1st Derm. Event Analysis (ADTTE)
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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, A WEEK, 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	adv.s.xpt

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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, ETC	te.xpt
TA	Trial Arms	Trial Design - One record per planned element per arm	Tabulation	STUDYID, ETC	ta.xpt
TV	Trial Visits	Trial Design - One record per planned visit	Tabulation	STUDYID, VISITNUM	tv.xpt

ADSL Metadata



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 - Chemistry Lab Analysis (ADLBC)
 - Hematology Lab Analysis (ADLBH)
 - Hy's Law Lab Analysis (ADLBHY)
 - ADAS-Cog Analysis (ADOSADAS)
 - CIBIC+ Analysis (ADOSCIBC)
 - NPfX Analysis (ADOSHPIX)
 - Demog. and Baseline Char. Analysis (ADSL)
 - AE Time To 1st Derm. Event Analysis (ADTTE)
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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
RFSTDT	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

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	

Analysis Results Metadata



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Analysis Results Metadata (Summary) for Study CDISC_Pilot

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[Table 14-3.05 - ADAS Cog \(11\) - Change from Baseline to Week 16 -- LOCF](#)

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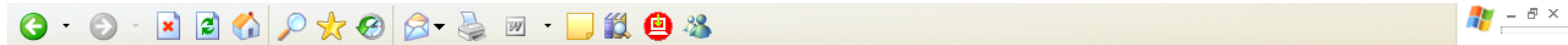
[Table 14-6.02 - Frequency of Normal and Abnormal \(Beyond Normal Range\) Laboratory Values During Treatment](#)

[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](#)

Analysis Results Metadata



- Links
- Reviewer's Guide
- Annotated Case Report Form
- Analysis Results Metadata
- Analysis Datasets
- SDTM Datasets
- Computational Algorithms
- Code Lists
- Discrete Value Listings

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

Go to the [Analysis Results Metadata Summary](#)

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 (ADQCADAS) [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.

Go to the [Analysis Results Metadata Summary](#)

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

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- 12. SAFETY EVALUATION
- 13. DISCUSSION OF STUDY
- 14. SUMMARY TABLES ANC
- 15. REFERENCES
- 16. APPENDICES

Pages

Attachments

Comments

Protocol: CDISCPIL01 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

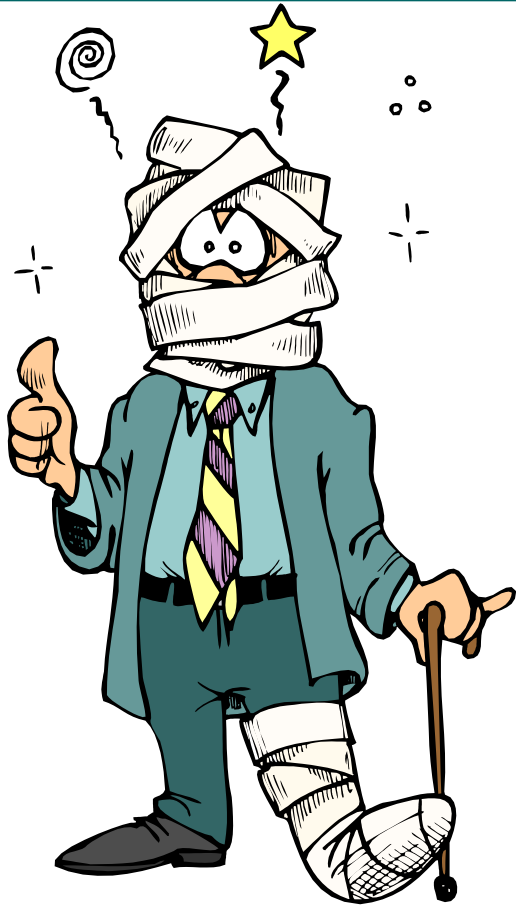
49 of 493 92% Unknown Zone 1:07 PM



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

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- 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...

FDA Review Team

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- 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

•66

- 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...

Overall Impression/General Comments

•68

- 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

•69

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

Go to the [Analysis Results Metadata Summary](#)

- Computational Algorithms Table
- Controlled Terminology (Codelist) Table

Tabulation Datasets (SDTM)

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- 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)

•71

- 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)

•72

- 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

•73

□ Efficacy Data Structures: SDTM data:

SAS System Viewer - [qsad.xpt]

	Unique Subject Identifier (USUBJID)	Questionnaire Short Name (QSTESTCD)	Visit Name (VISIT)	Visit Number (VISITNUM)	Baseline Flag (QSBFL)	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

Ready Hdn cols:13 Obs 1-12241

Original ADaM data:

SAS System Viewer - [adqsadas.xpt]

	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

Ready Hdn cols:36 Obs 1-2495 of

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

•US Food and Drug Administration

Analysis Datasets

•74

- 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

•75

□ Efficacy Data Structures:

	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

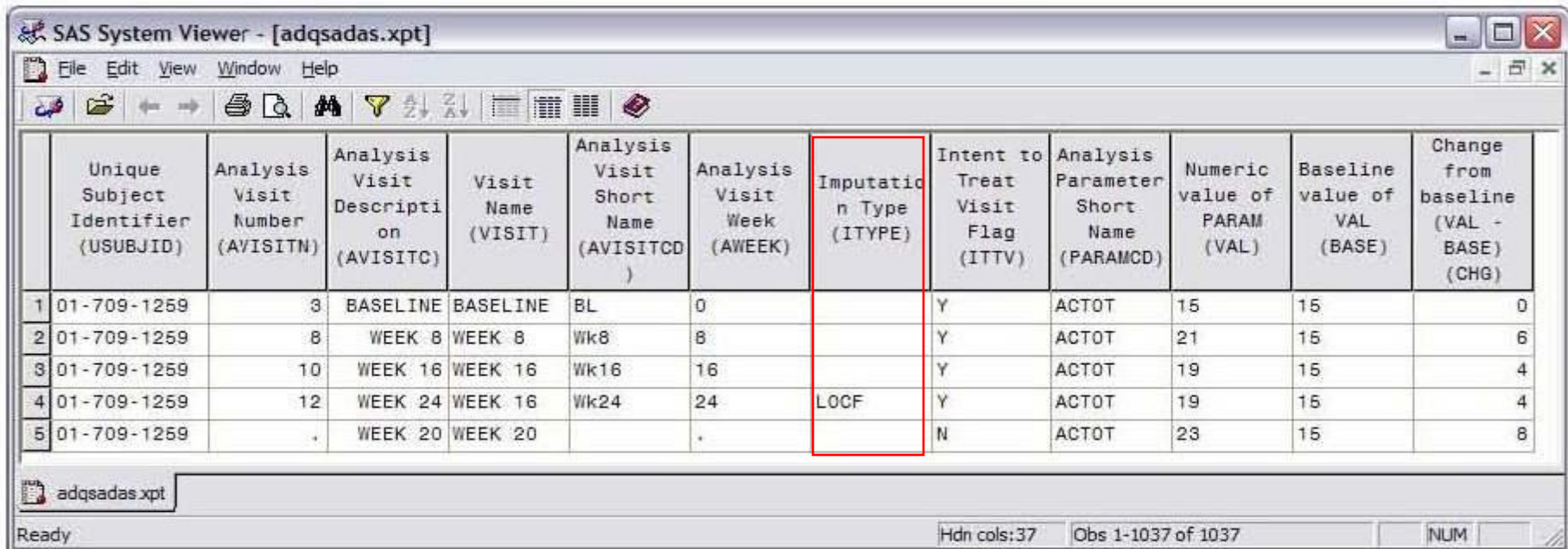
	Unique Subject Identifier (USUBJID)	Analysis Visit Week (AWEEK)	Analysis Visit Type Flag, Numeric (AVISFLGN)	ADAS-COG(11) Subscore (ACTOT)	ADAS-COG(11) at Baseline (ACTOTBL)	ADAS-COG(11) Change from Baseline (ACTOTCH)
1	01-709-12	0	1	15	15	0
2	01-709-12	0	2	15	15	0
3	01-709-12	0	3	15	15	0
4	01-709-12	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

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

•US Food and Drug Administration

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

adqsadas.xpt

Ready Hdn cols:37 Obs 1-1037 of 1037 NUM

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

Analysis Datasets

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- 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

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- 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

•79

- 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...

Project Limitations

•81

- 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

•82

- 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)

•83

- 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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