Prequel 1: October 2, 2003

- *Public Meeting on Clinical Data Interchange Standard Consortium (CDISC) Version 3 Submission Data Standards and Electronic Case Report Tabulations*
- "Web Submission Data Manager (WebSDM) DEMONSTRATION"
- eDR vs. WebSDM

Prequel 2: Standards Development – Unprecedented Collaboration

An FDA Statistical Reviewer Perspective:

Analysis Data Submissions & Wrap-up of FDA perspectives

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Update on the Study Data Tabulation Model for FDA Submissions Public Meeting

Rockville, MD
Tuesday, February 1, 2005

Disclaimer

Views expressed in this presentation are those of the speaker and not, necessarily, of the Food and Drug Administration.

Acknowledgements

- Rafia Bhore
- Andrea James
- Wayne Kubick
- Becky Kush
- Randy Levin
- Cynthia Liu
- Ed Nevius
- Armando Oliva
- Tom Papoian
- Norm Stockbridge
- CDISC SDM and ADaM Teams

Outline

- Analysis Data Submissions
  - Statistical Review
  - Current Guidance
  - First Experience
  - ADaM – General Considerations
- Wrap-up of FDA Perspectives
  - Standards development
  - SDTM Review
  - Challenges

Why Standards?

Improve time to market for safe and effective treatments (increased patient safety and reduced costs)

- Improve efficiency for clinical research
  - Facilitates design and conduct of clinical trials
  - Facilitates communication between researchers and study sponsor (e.g., between CRO and drug company)
- Improves efficiency of evaluation of safety and efficacy of investigational treatments
  - Facilitates communication between regulatory authority and applicant
  - Facilitates development of efficient review environment (e.g., training, analysis tools)

Efficient Review Environment

- Standards provide:
  - Common structure and terminology
  - Single data source for review (less redundant data)
- Standards allow:
  - Use of common tools and techniques
  - Common training
  - Single validation of data

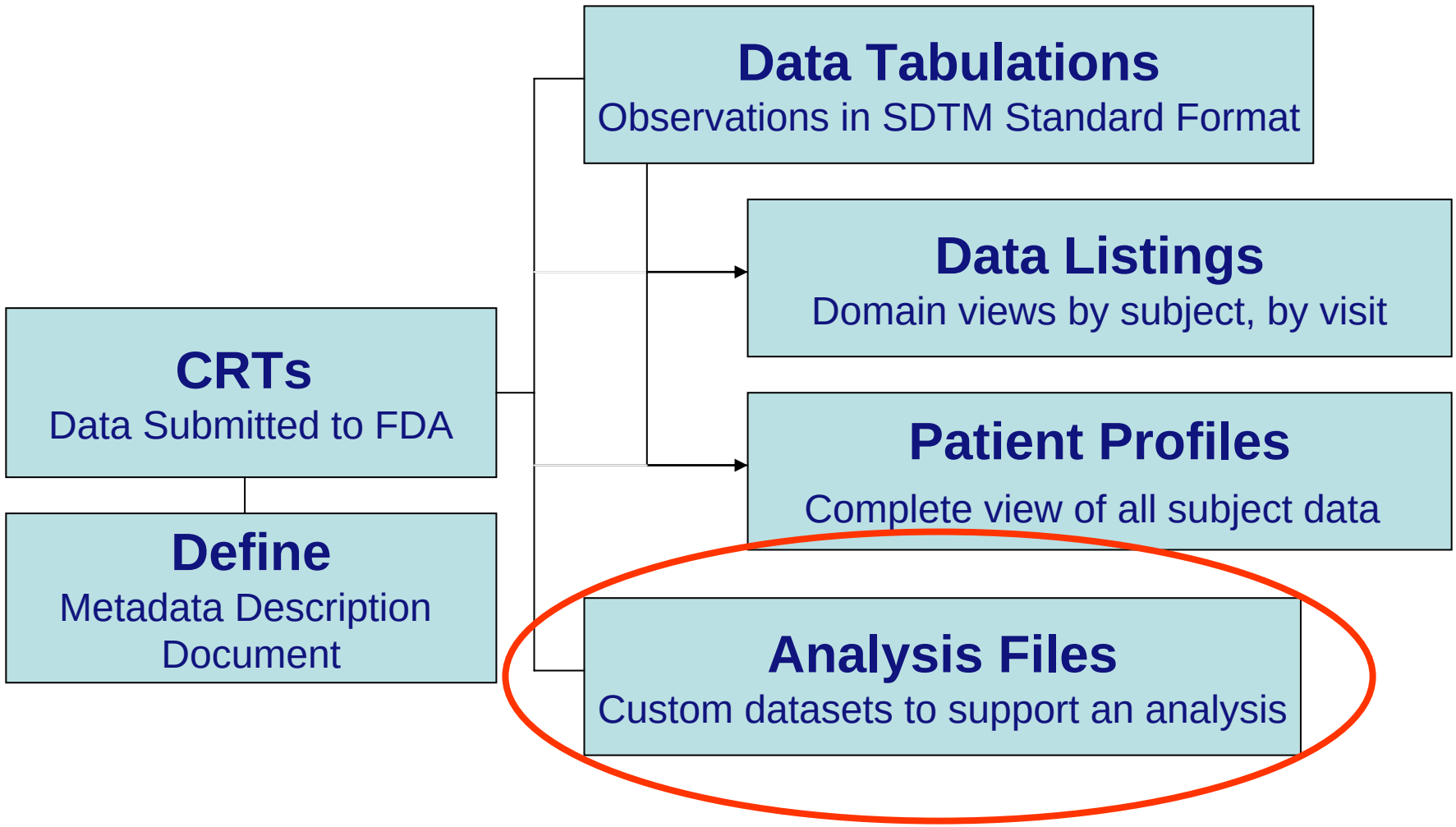
Statistical Review of Clinical Trials Data

- Efficacy and safety
- Confirmatory/Exploratory– focus on evaluating sponsor's results
- Check appropriateness of statistical models and conclusions – programs & analysis datasets
- Assess quality/completeness of data
- Evaluate the impact of sponsor's analytical decisions – derived variables, missing/messy data ("quirks" – R. Helms) – sensitivity analyses
- Answer new, review-related statistical questions
- Communication with sponsors
- Archive results

Statistical Review Environment

- No programmers
- Multiple projects
- Increasingly electronic world
- Understaffed
- Good review practice not well described
- Without standards every review is an adventure
- Communication with sponsor

Submission Files



CDISC

Today's Mantra

SDTM and Analysis Datasets

BOTH

ARE NEEDED FOR REVIEW!

(for now)

Current Guidance

- Guidance, 1999
  - *Providing Regulatory Submissions in Electronic Format — NDAs*
- *Data Specifications*, 2004
  - "Study Data Tabulation Model (SDTM) developed by the Submission Data Standard working group of the Clinical Data Interchange Standard Consortium (CDISC)"

Electronic Submission NDA, 1999

K. Item 11: Case Report Tabulations (CRTs)

"…Prior to the submission, you should discuss with the review division the datasets to be provided and the data elements that should be included in each dataset…

The data organization varies from indication to indication. Prior to the submission, you should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset, and the organization of the data within the file."

Study Data Specifications

- Individual subject data listings
  - –Data tabulations
    - +Data tabulations datasets
    - +Data definitions
  - –Data listing
    - +Data listing datasets
    - +Data definitions
  - –Analysis datasets
    - +Analysis datasets
    - +Analysis programs
    - +Data definitions

Data Specifications: Analysis Datasets

Definition

- Analysis datasets are datasets created to support specific analyses.
- Programs are scripts used with selected software to produce reported analyses based on these datasets.

Data Specifications: Analysis Datasets

Specifications

- Each dataset is provided as a SAS Transport (XPORT) file.
- Programs should be provided as both ASCII text and PDF files and should include sufficient documentation to allow a reviewer to understand the submitted programs.
- It is not necessary to provide analysis datasets and programs that will enable the reviewer to directly reproduce reported results using agency hardware and software.
- Currently, there are no other additional specifications for creating analysis datasets.

CDISC-it! A First Experience: Some Lessons Learned

- Submission with SDTM Datasets
  - Statistical Reviewer
  - Analysis Datasets
  - Training

CDISC-it! A First Experience: SDTM Submission: Statistical Review

- Shortly after submission -- training for medical reviewers and statisticians on WebSDM provided by Lincoln
- Statistician not able to start review until recently
- Good SAS skills
- Now looking at statistical review using both SDTM files and analysis files
- Use experience in developing additional feedback

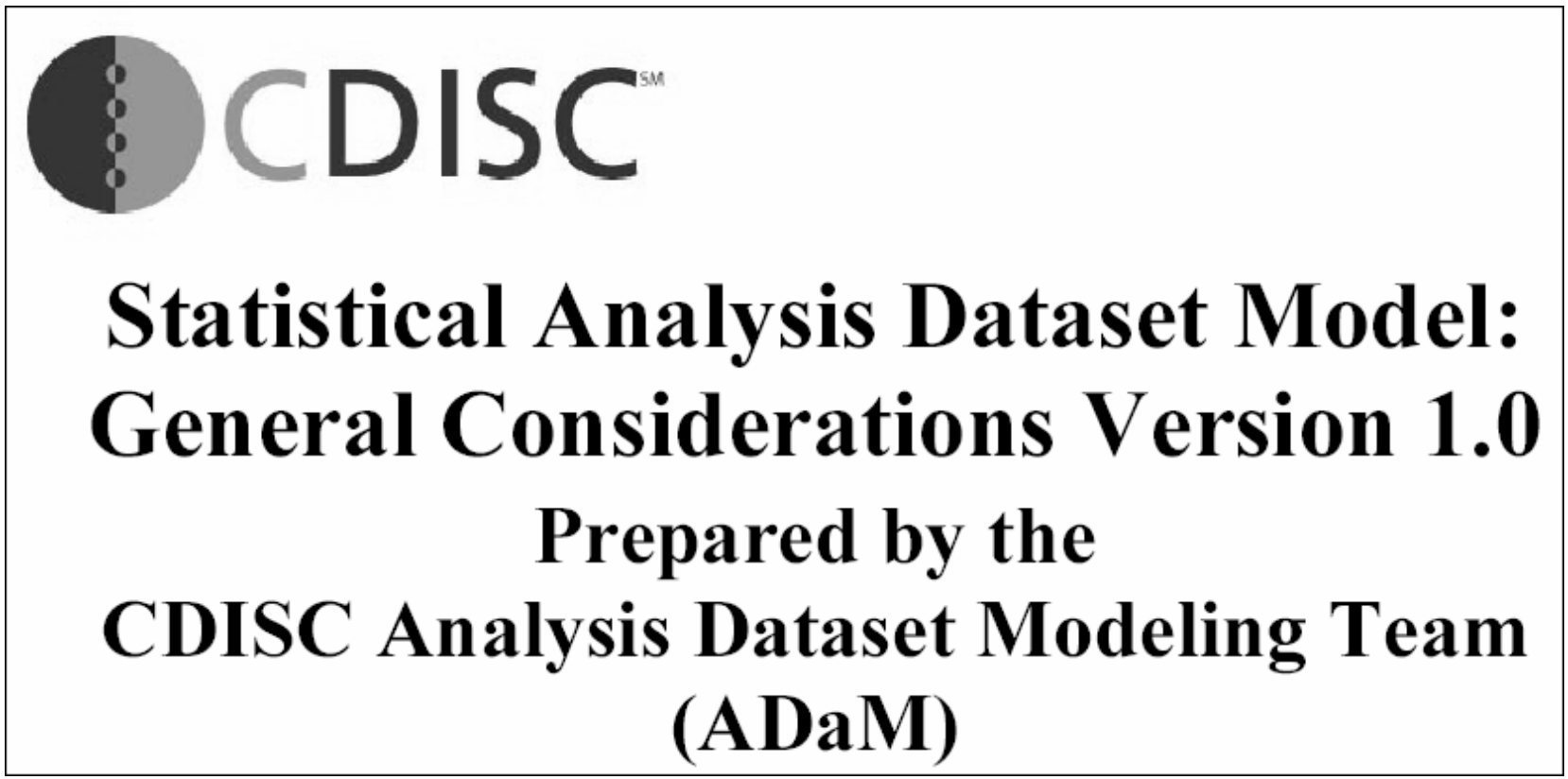
CDISC-it! A First Experience: Some Lessons Learned

- Familiarity with standard data
- FDA Tools needed to work with SDTM datasets – SDTM with WebSDM is big advantage over eDR data
- Need more experience – More resources devoted to on-time training, hand-holding – we need and want to work with you!
- Give SDTM submissions "special attention"
- Does not eliminate need for communication between sponsor and reviewers during review
- Need more real world test of SDTM and "real" trial data

SDTM & Analysis Datasets

- Currently, SDTM describes observations from a clinical trial
- SDTM (with appropriate tools) is particularly useful in medical officer evaluation of safety
- It is well recognized that datasets that are used in the analysis have been restructured and contain additional information (derived variables, flags, comments, etc.)
- To facilitate communication between statistical reviewers and sponsors, there is a need to standardize the documentation and content of these datasets
- The CDISC/ADaM Team has a guidance describing the documentation of analysis files.

Progress: New Guidance from CDISC/ADaM Team



- http://www.cdisc.org

ADaM Guidance: Guiding Principle

- "The overall principle in designing Statistical Analysis Datasets and related metadata is that there must be clear and unambiguous communication of the content, source and quality of the datasets submitted in support of the statistical analysis performed by the sponsor."
- Would support the machine-readable description for the JANUS data repository

ADaM Guidance

- Build on SDTM: "Statistical analysis Dataset Metadata conforms to the CDISC Submission Metadata Model"
- Include proposed descriptions of:
  - Analysis-level metadata
  - Dataset-level metadata
  - Variable-level metadata
  - Value-level metadata

ADaM Guidance: Analysis-level Metadata

- **ANALYSIS NAME –** A unique identifier for this analysis. May include a table number or other sponsor-specific reference.
- **DOCUMENTATION –** A text description documenting the analysis performed.
- **REASON –** The reason for performing this analysis. Examples may include Pre-specified, Data-driven, Exploratory, and Regulatory Request.
- **DATASET –** the name of the analysis dataset used should be linked to the analysis dataset used for this analysis. In most cases, this will be a single dataset. If multiple datasets are used, they should all be listed here.
- **PROGRAM –** Analysis programs using the DATASET above as input can be described or included here.

ADaM Guidance:
Dataset-level Metadata

Example Statistical Analysis Dataset Metadata					
Dataset	**Description of Dataset**	**Structure**	**Purpose**	**Keys**	**Location**
sbc	Subject/Baseline Characteristics	One record per subject	Analysis	USUBJID	crt/datasets/111/sbc.xpt
vsstat	Vital Signs Stat Analysis	One record per subject per visit	Analysis	USUBJID VISITNUM	crt/datasets/111/vsstat.xpt

ADaM Guidance: Variable-level Metadata

- Identifier and Qualifier Variables
- Statistical Analysis Variable Roles
- Analysis Population Indicator Variables
- Imputation Indicator Variables
- Statistical Analysis Date Variables
- Statistical Analysis Study Day Variables
- Visit Timing Variables
- Numeric Code Variables
- Statistical Analysis Treatment Variables

ADaM Guidance: Value-level Metadata

- For variables containing more than one type of measure
- Allow transformation of data back and forth between “vertical” and “horizontal” dataset structures.
- Part of proposed CDISC DEFINE.XML standard

Regulation

Guidance

Adapted from S. Woollen

Wrap-Up of FDA Perspectives

- Standards Development—Big Picture – Healthcare/Clinical Trials
  - Patient Record / HL7
  - Protocol
  - Operational Data Model
  - eSDI
- FDA Data Standards Council – Coordinating activities of all Centers
  - CBER Pilot – Gene Therapy, Vaccines
  - CVM, CFSAN - evaluating

Wrap-Up of FDA Perspectives

- It's ALL SDTM
  - Medical review — SDTM/SDS
  - Statistical review—SDTM/ADaM
  - PharmTox review — SDTM/SEND
- Review not dependent on specific tool(s) – "It's all data"
- Future development—JANUS
- Requirements – Rule-making

Challenges

- Still need to do the work -- get reviews done
- Work with minimal resources
- Good review practice
- Moving target – efficacy and safety
- Science – therapeutic areas
- Communication: External and Internal
- Buy-in (CDISC-it!)
- Lessons learned – evaluation
- Training – experience (no missed opportunities)
- Next Steps vs. "Vision" Thing
- Adopting Change
- Effective/Efficient Collaboration
- Guidance/Communication

That Fast Efficient, High Quality Review Machine

CDISC-it!

Thank You