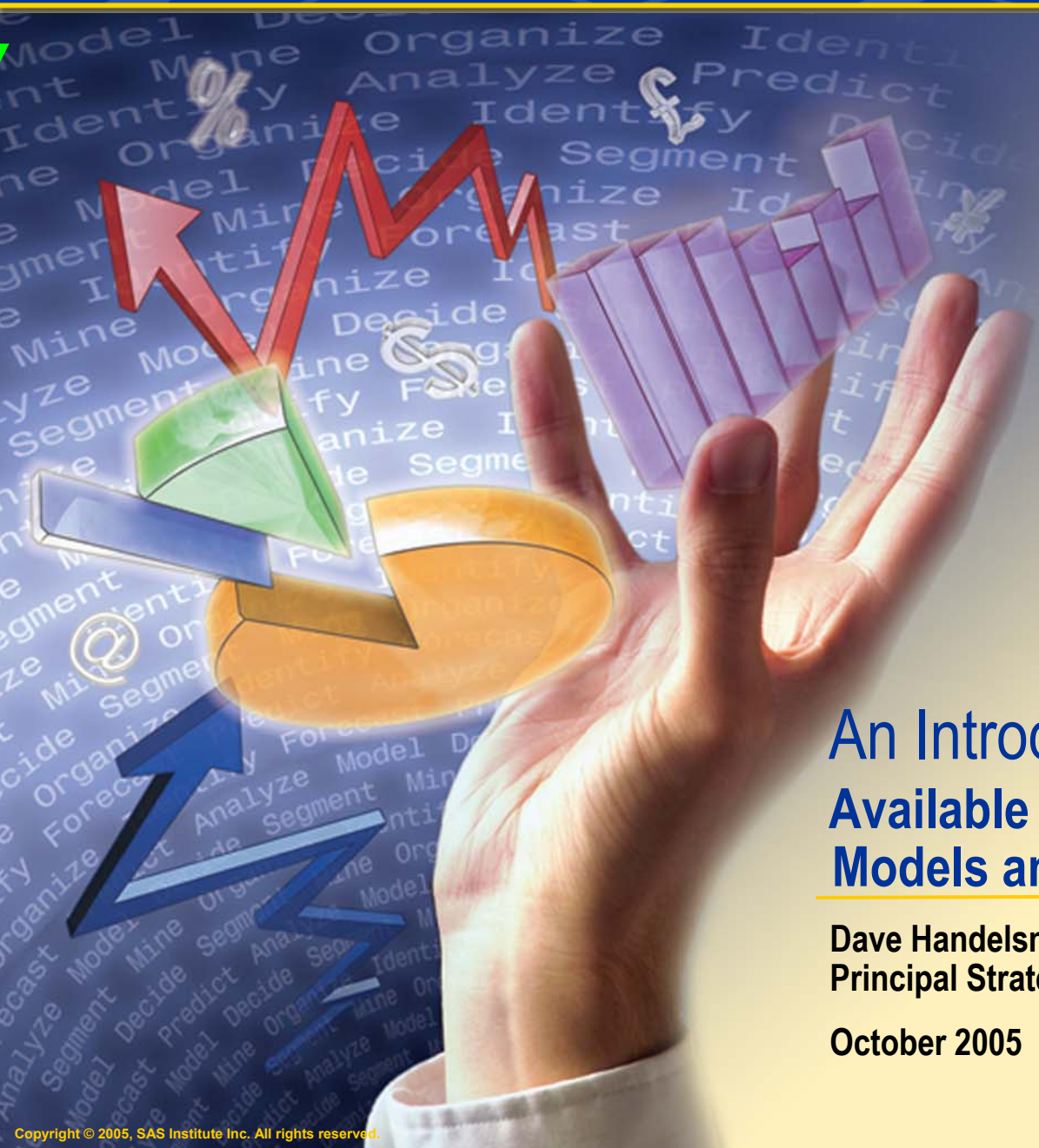


An Introduction to CDISC:

Available CDISC Standards and Models and How SAS Supports These

Dave Handelsman
Principal Strategist, Clinical R&D, SAS

October 2005

Agenda

- Part I: What is CDISC and Why Standards?
- **Part II: Available CDISC Standards and Models and How SAS Supports These**
- Part III: CDISC Collaborations and Standards in Progress

Clinical Data Interchange Standards Consortium

CDISC is an open, multidisciplinary, non-profit organization committed to the development of worldwide industry standards to support the electronic acquisition, exchange, submission and archiving of clinical trials data and metadata for medical and biopharmaceutical product development.

The mission of CDISC is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare.

CDISC Standards

- **Operational Data Model (ODM)**
- **Submission Domain Standard (SDS)**
  - Study Data Tabulation Model (SDTM)
  - Standard for Exchange of Non-clinical Data (SEND)
- **Analysis Data Model (ADaM)**
- **Laboratory Data Model (Lab)**
- Case Report Tabulation Data Definition Specification (CRTDDS - aka define.xml)
- Protocol Representation Standard
- Biomedical Research Integrated Domain Group (BRIDG)

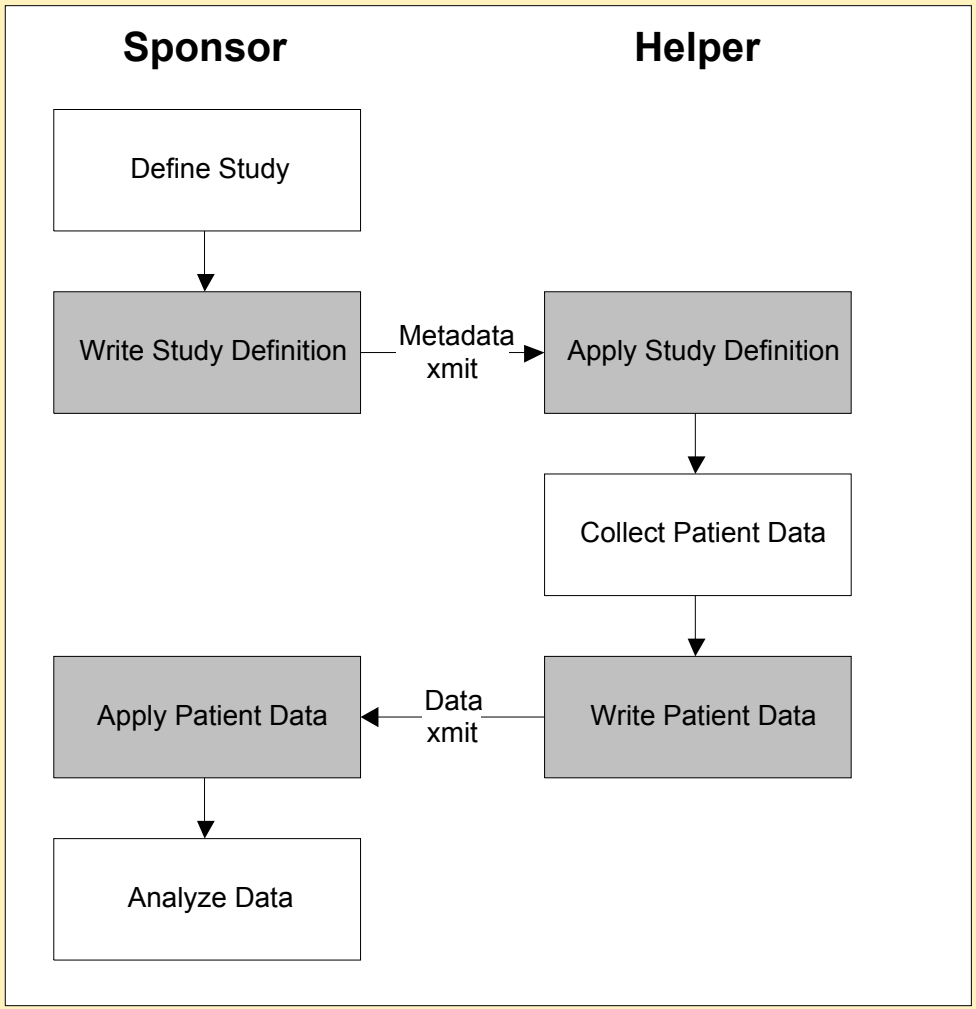
ODM – Operational Data Model

- Written in XML
- Clinical trials data recording / transfer / archive
- Contains both study metadata and clinical data

Model Features:

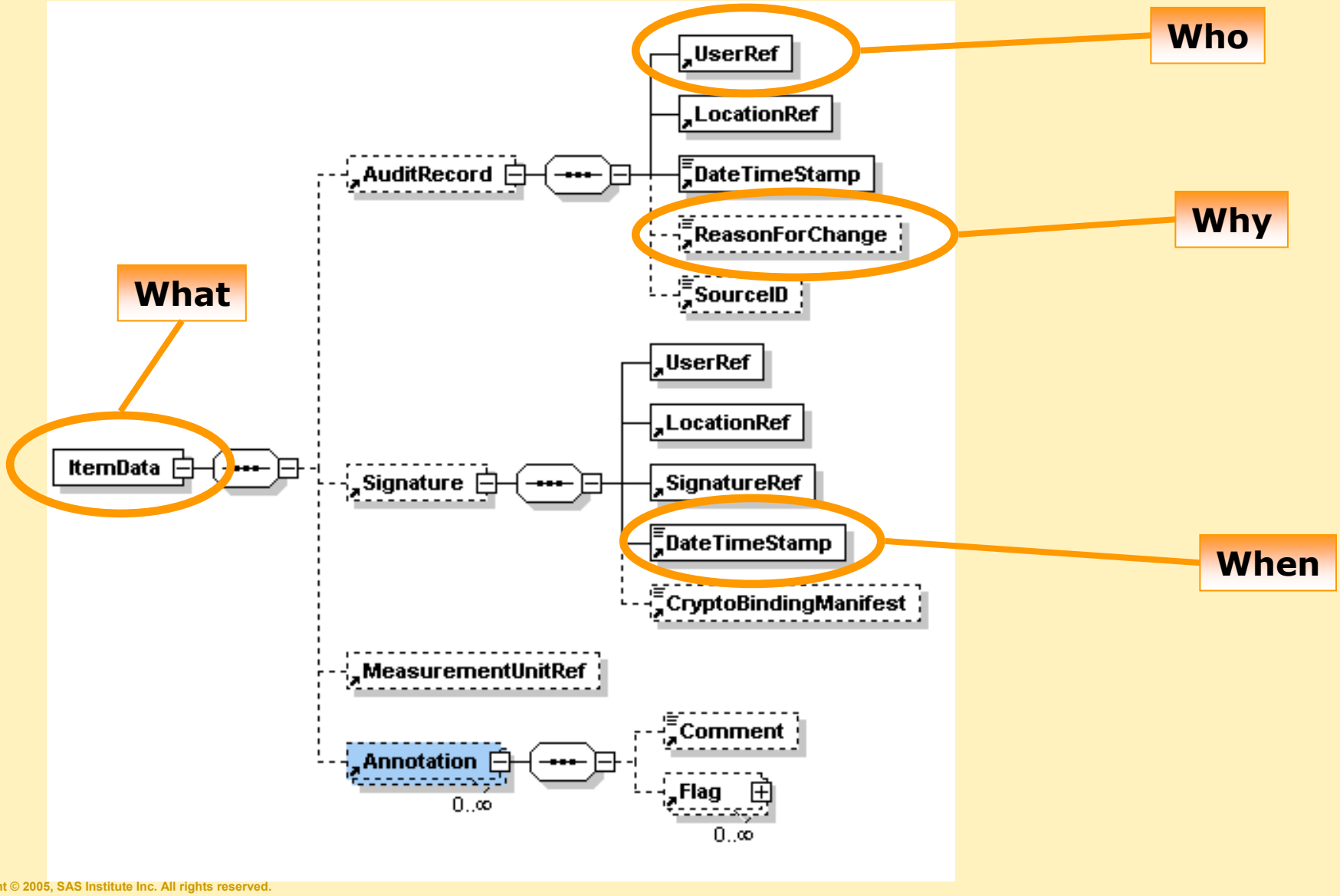
- Framework can be used by any clinical data management (CDM) system or clinical application
- Supports 21 CFR Part 11 audit trail and electronic signatures
- Supports archiving & data retention guidance
- Provides for incremental transfers
- Includes vendor extension capability

Interchange cycle – move to ODM



- Traditional approach
  - MetaData Xmit = Excel spreadsheet
  - Data Xmit = SAS Datasets
- **CDISC approach**
  - **MetaData Xmit = ODM XML**
  - **Data Xmit = ODM XML**
- **CDISC Benefits**
  - **More information exchange**
  - **Increased automation**

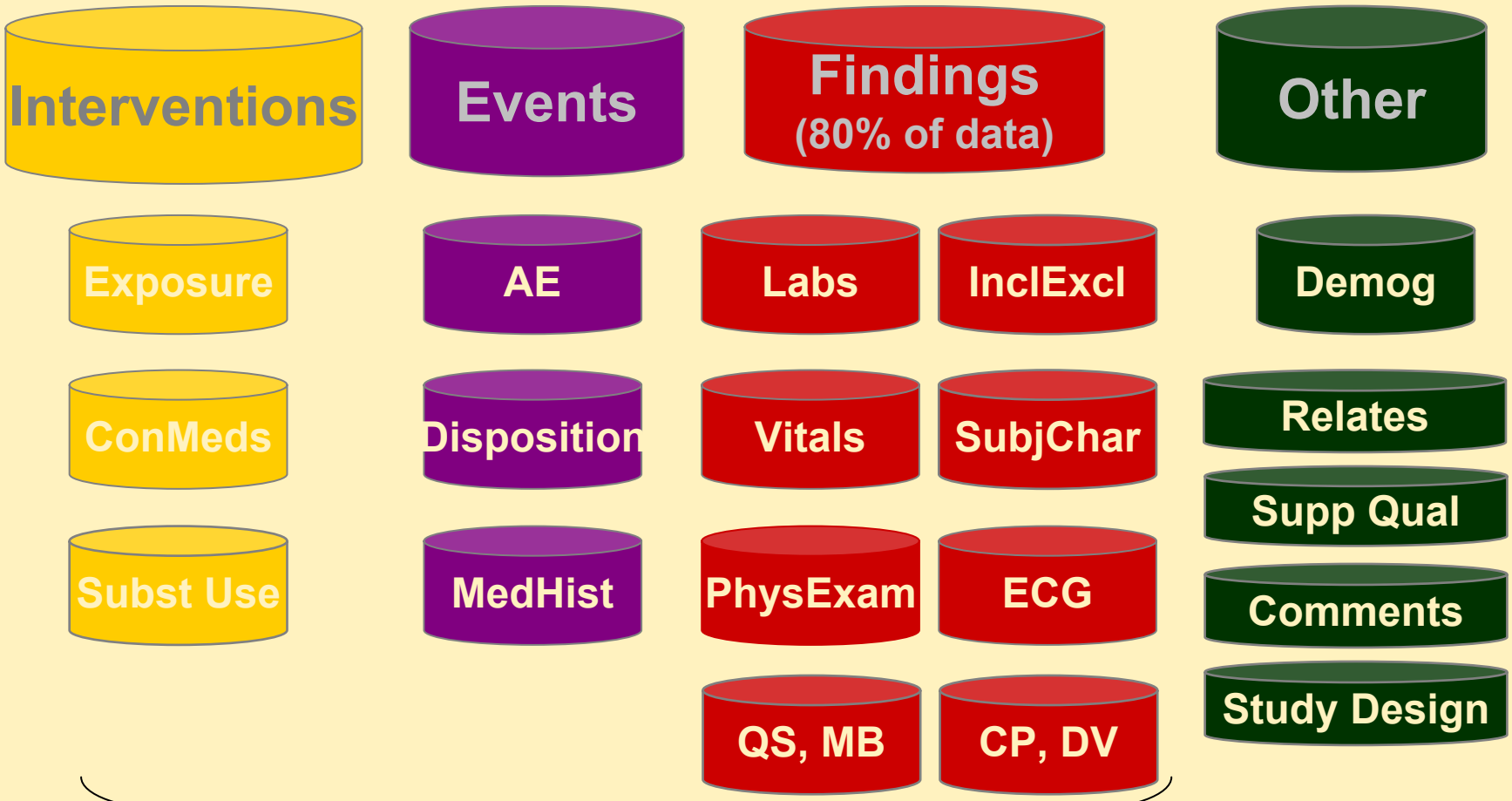
ODM & Audit Trail



SDS, SDTM and SEND – Submission Standards

- **SDS: Submissions Data Standards**
  - Refers to the ***implementation*** of the model for ***clinical submissions*** (e.g. SDS v3.1.1)
- **SDTM: Study Data Tabulation Model**
  - Refers to the **model** that supports ***clinical and preclinical submissions*** data
- **SEND: Standard for Exchange of Nonclinical Data**
  - Defines ***domains and variables*** for ***submitting*** all data generated from **animal toxicity studies**

SDS V3.1.1: CDISC Standard Domain Models Observation Classes



SDTM Basic Concepts

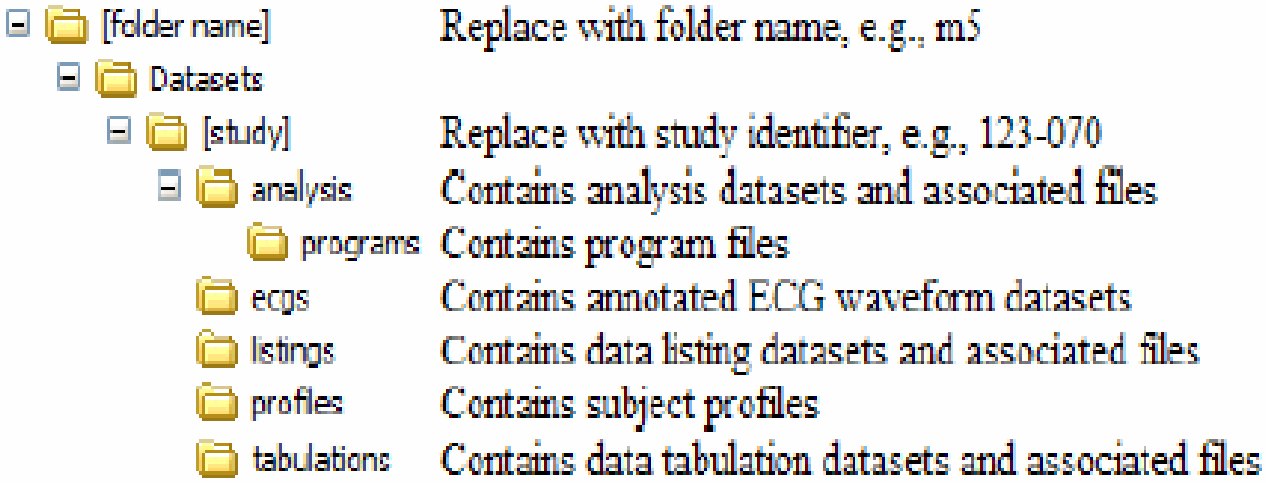
- Utilizes standard variable names, metadata, and data structure
- Each domain has required, expected, and permitted variables
- No redundancy (other than identifying variables)
- SDS team has developed standards, containing specific metadata for >20 domains

SDTM

- 3 general observation classes
  - Interventions
  - Events
  - Findings
- Special domains
  - Demographics
  - Comments
  - Relationship between records in multiple domains
  - Supplemental qualifier domains

Specifications For Organizing The Datasets

http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf



SDTM Benefits

- Increase in efficiency
  - Data transfers
  - Data reviews
  - Creation of analysis files
- Flexible
  - Supplemental domains
  - Can accommodate a mixture of raw and derived

ADaM – Analysis Dataset Model

Uses for Analysis Datasets:

- Provide clear communication of the scientific results to regulatory reviewers
- Replicate or verify the sponsor's analyses, results, and conclusions
- Test the validity and robustness of the sponsor's analyses and assumptions (what if…)
- Audit the data for inconsistencies and errors
- Status: Analysis Dataset Models Completed
  - Change from baseline
  - Time to event
  - Categorical analysis
- Working on Additional Dataset Models
  - Linear model
  - Safety Analysis
- Ensuring compatibility with SDS Version 3.1 (SDTM)

Lab – Clinical Laboratory Data Model

- Core model designed to handle “simple lab data”: one test, one result structure
- 10 levels of content includes support of administrative information for transfer of samples, reporting of results
- Production Version 1.0.1 - on CDISC web site
  - Specification, data fields, reference ranges
  - Includes Microbiology extension
- Currently standard approaches are included for
  - Bar delimited ASCII (default representation)
  - SAS
  - XML
  - HL7 RIM message
- More complex tests - handled by extensions
  - Work on pharmacogenomics beginning

Case Report Tabulation Data Definition Specification (CRTDDS aka define.xml)

- Machine readable replacement for define.pdf currently used in submission process
- Organizes and describes submission content
- Extends ODM metadata for submission content
  - Enhances general column descriptive information
  - Adds item-level metadata support
  - Supports linkage to external folders and files

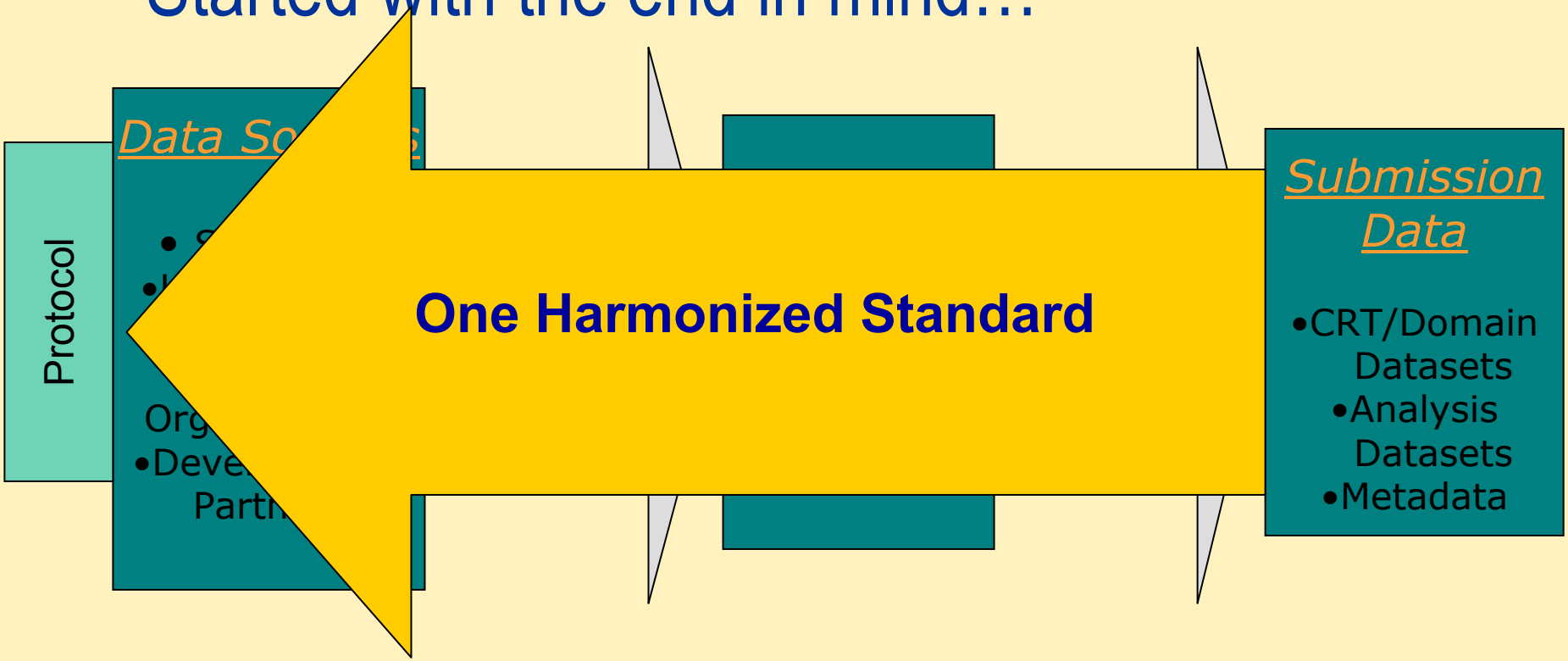
Protocol Representation Standard

- Initiated as an HL7 project to develop standard representation of clinical trial protocol elements
- CDISC team formed to provide domain expertise
- Spreadsheet of elements, with glossary definitions open for public review and comment
- Initial Clinical Document Architecture (CDA) model developed and balloted through HL7

CDISC Biomedical Research Integration Domain Group (BRIDG)

- Follows the HL7 Development Framework
- Initiated in January 2004 by CDISC Board
- Developed through numerous modeling sessions with domain experts and reviewed by CDISC, industry, FDA, NCI/NIH groups; led by HL7 RIM expert
- Purposes and Anticipated Benefits:
  - To help ensure harmonization among CDISC models (present and future)
  - To provide the industry with a standard model to represent the clinical research domain
  - To enable an HL7 implementation of the CDISC ODM
  - To help harmonize the CDISC and HL7 standards
  - To help enable interoperability between clinical research and healthcare systems

Evolution of CDISC Standards: Started with the end in mind…



ODM = Operational Data Model/Std
LAB = Laboratory Data Model/Std
SDS = Submission Domain Standards
ADaM = Analysis Data Models
SEND = Standards for the Exchange of Non-Clinical Data

How SAS Supports CDISC

"At first glance, SAS might appear to be the loser in any standards shift. After all, it owns the format in which clinical data are analyzed….

... But [SAS] declares: *Standards do not scare us. We embrace them.*

... The company is both acutely sensitive to its large user base and attuned to the shifting winds of industry, where the Clinical Data Interchange Standards Consortium (CDISC) has been gaining traction."

- Mark Uehling, Senior Science Editor, Bio-IT World | eCliniqua
Thursday, Dec 9, 2004

Support for the CDISC Organization

- SAS is a corporate sponsor
- Ed Helton, of SAS, recently elected Chairman of the Board for CDISC
- Dave Handelsman is SAS' representative on the Industry Advisory Board
- SAS has hosted the Industry Advisory Board meeting in the past, and periodically hosts Board of Directors' meetings
- SAS participates in several of the modelling teams

SAS Software Developed for CDISC

- PROC CDISC
  - ODM (v1.2.1): Data conversion between SAS and XML
  - SDTM (v3.1): Data structure verification
- XML Engine ODM Native mode (v1.2.1)
- XML Engine and XMLMap Extensions
- New base SAS formats/informats for ISO-8601
- SAS CDISC Viewer (ODM 1.2.1)

See Tony Friebel's talk at 16:05 today for more details: SAS Dataset Content Conversion to CDISC Data Standards

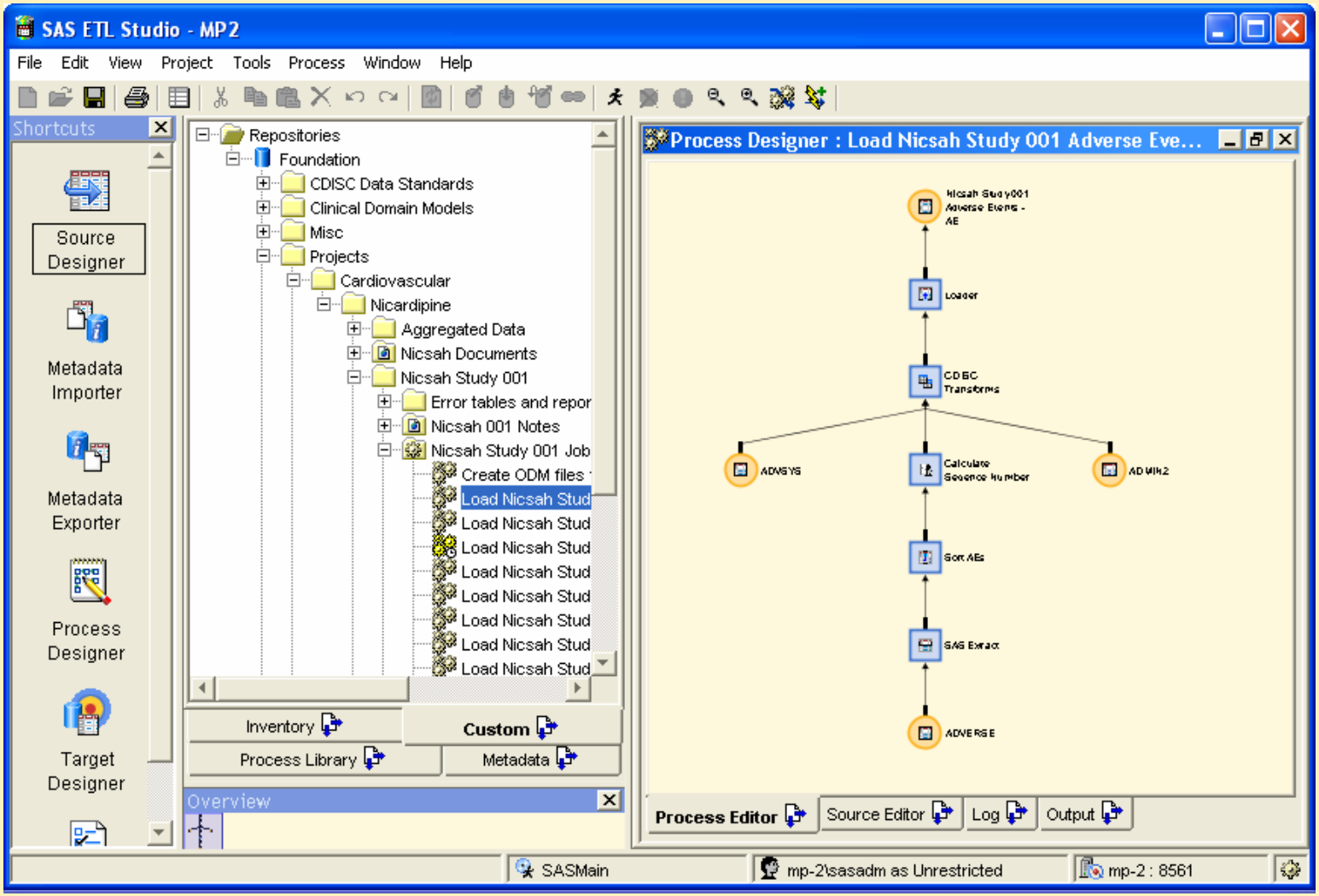
PROC CDISC Example

```
libname results  'SASEnvironment\SASCode\CDISC Demo\data' ;
FILENAME  XMLINP  '\CDISC Demo\xml\ae.xml';

PROC CDISC
    MODEL=ODM              READ=XMLINP
    formatActive=YES       formatNoReplace=NO;

    ODM                    ODMVersion = "1.2"
                           ODMminimumKeyset=NO;

    CLINICALDATA           OUT = results.AE
                           SASDATASETNAME = "AE" ;
RUN;
```

SAS Integration Based on CDISC ODM

- ODM v1.2.1 used to bridge DataTrak EDC with SAS Drug Development
- Incremental data is transferred from EDC server to SAS Drug Development
  - Scheduled, or
  - Ad hoc
- Data is then:
  - Extracted from XML (ODM) into normalized SAS data sets
  - Compared to master files
  - Updated according to ODM transaction types
- Once loaded, data sets are:
  - Versioned
  - Audit trailed
  - Available for further transformation and analysis

SAS ETL Studio



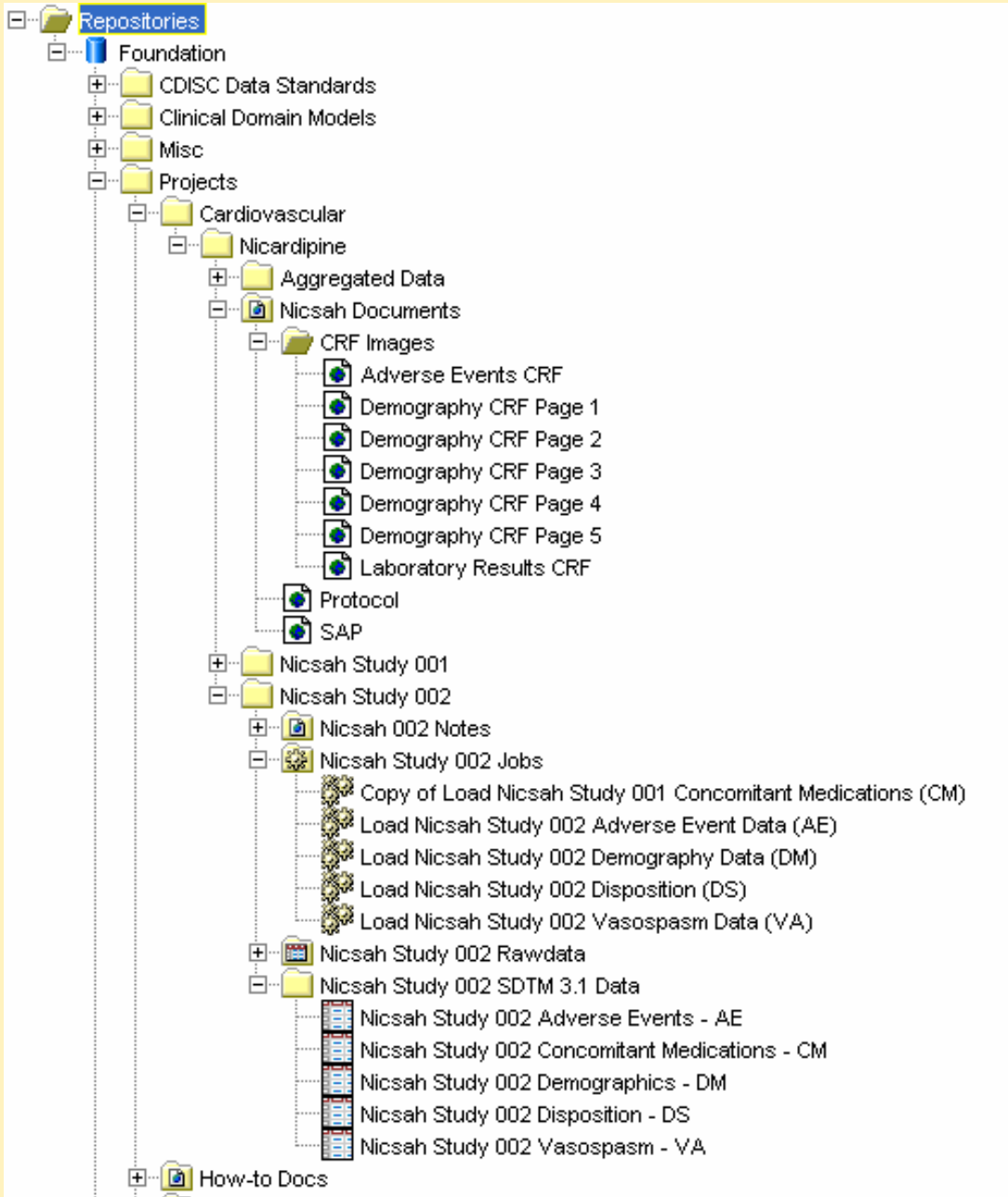
ETL Studio

- Source Designer
- Target Designer
- Process Designer

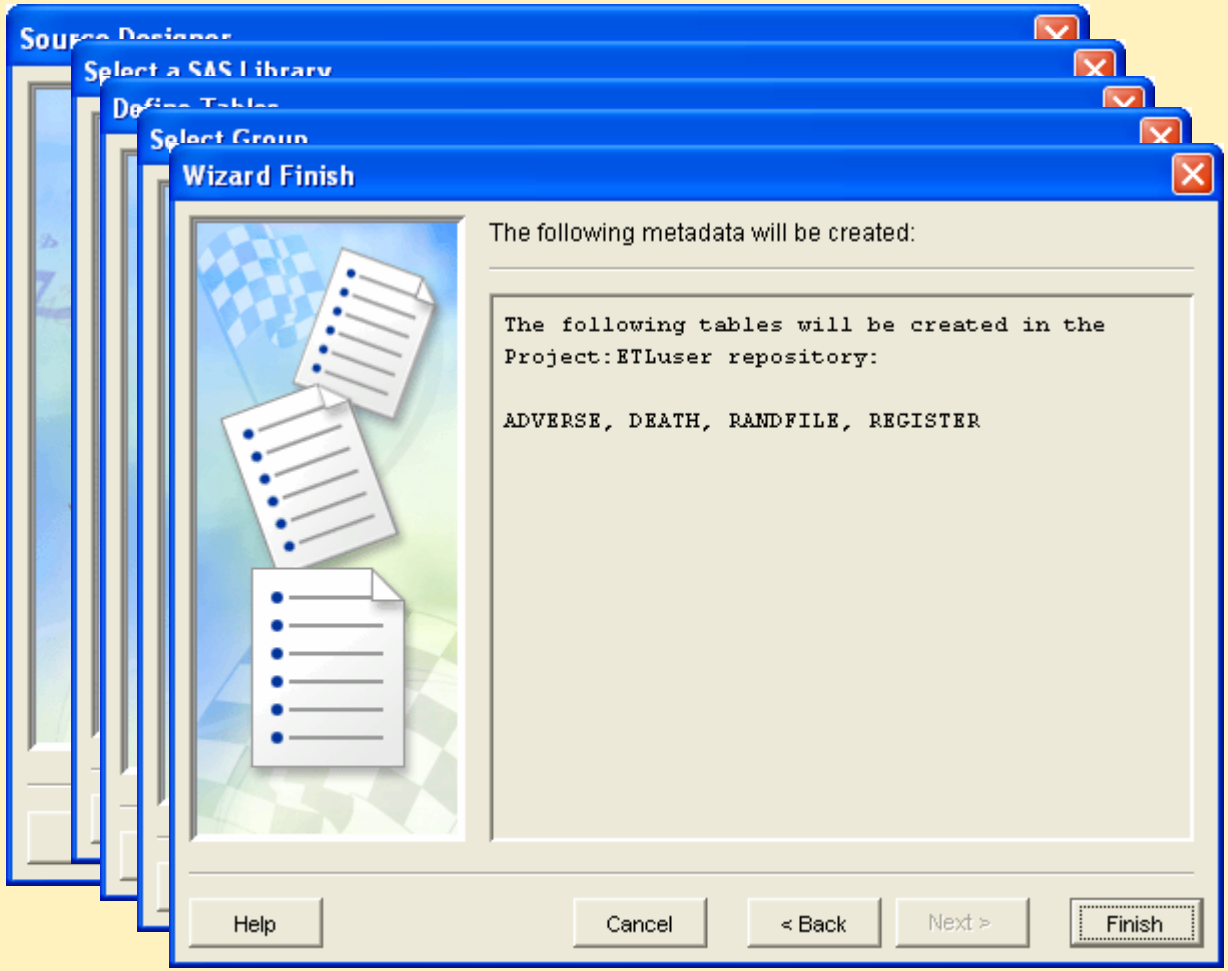
ETL Studio Desktop

- Customizable Trees
- Many Object types
  - Document
  - Source Table
  - Target Table
  - Job
  - External Files
  - Groups
  - Libraries
  - Notes

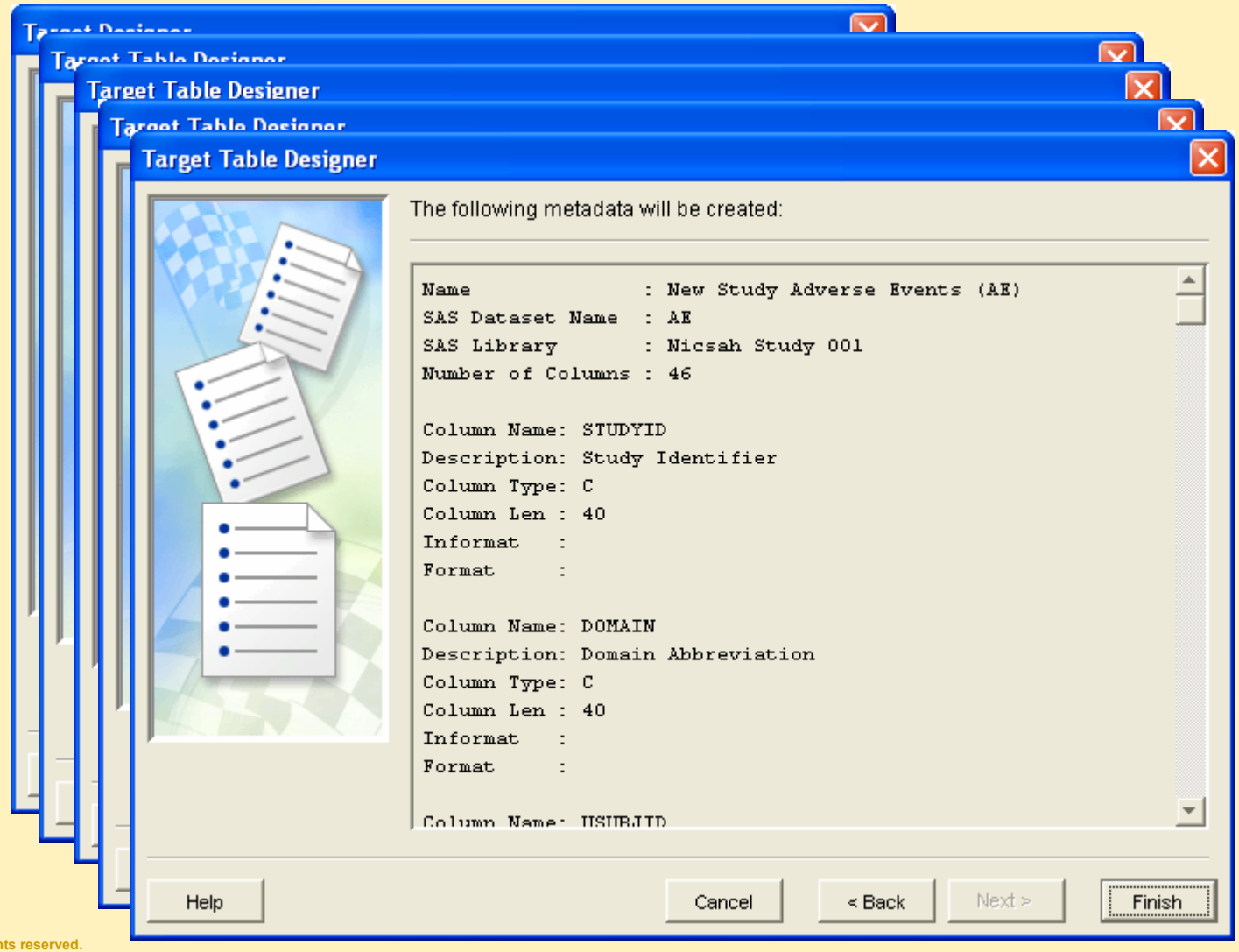
  etc



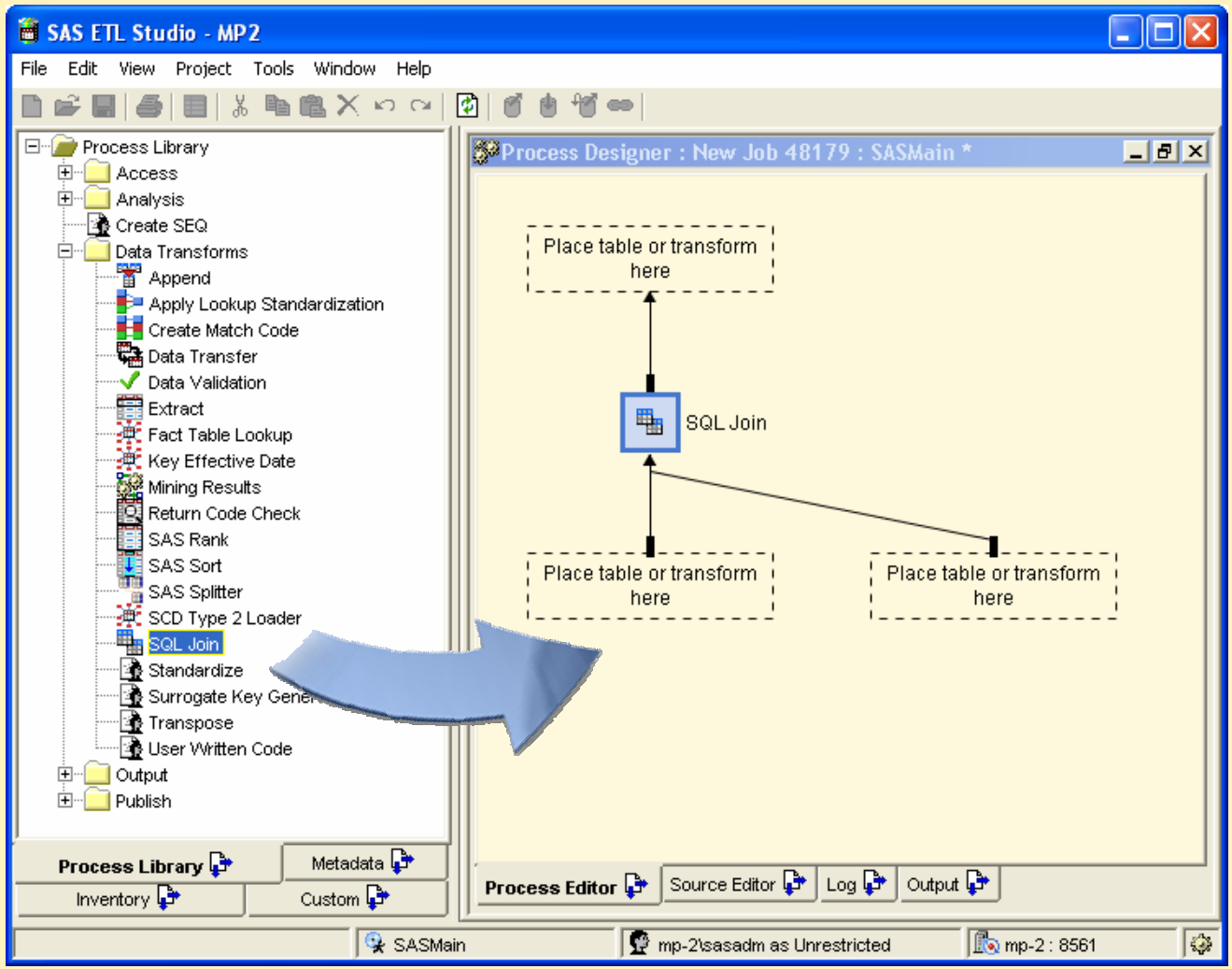
Source Designer



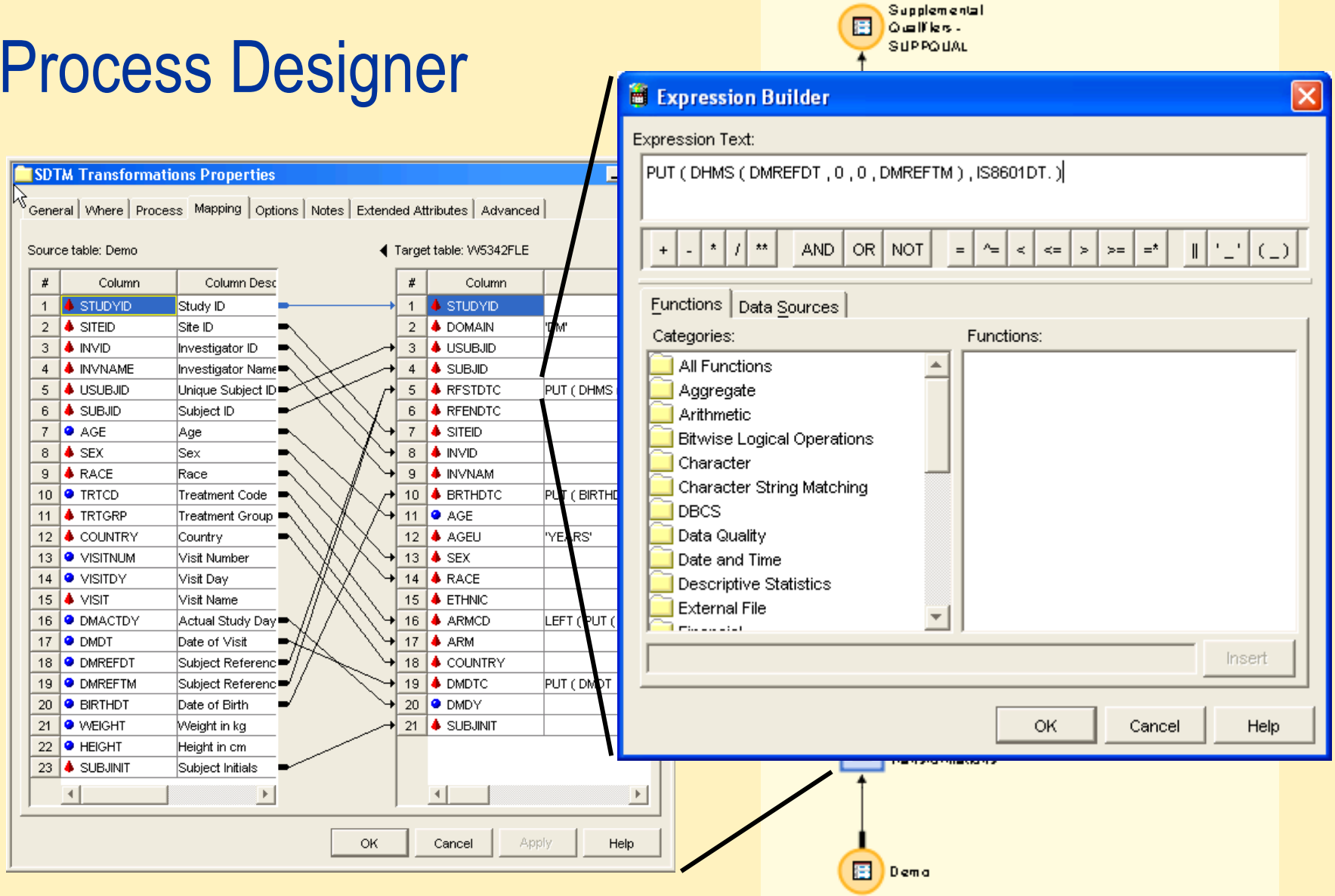
Target Designer



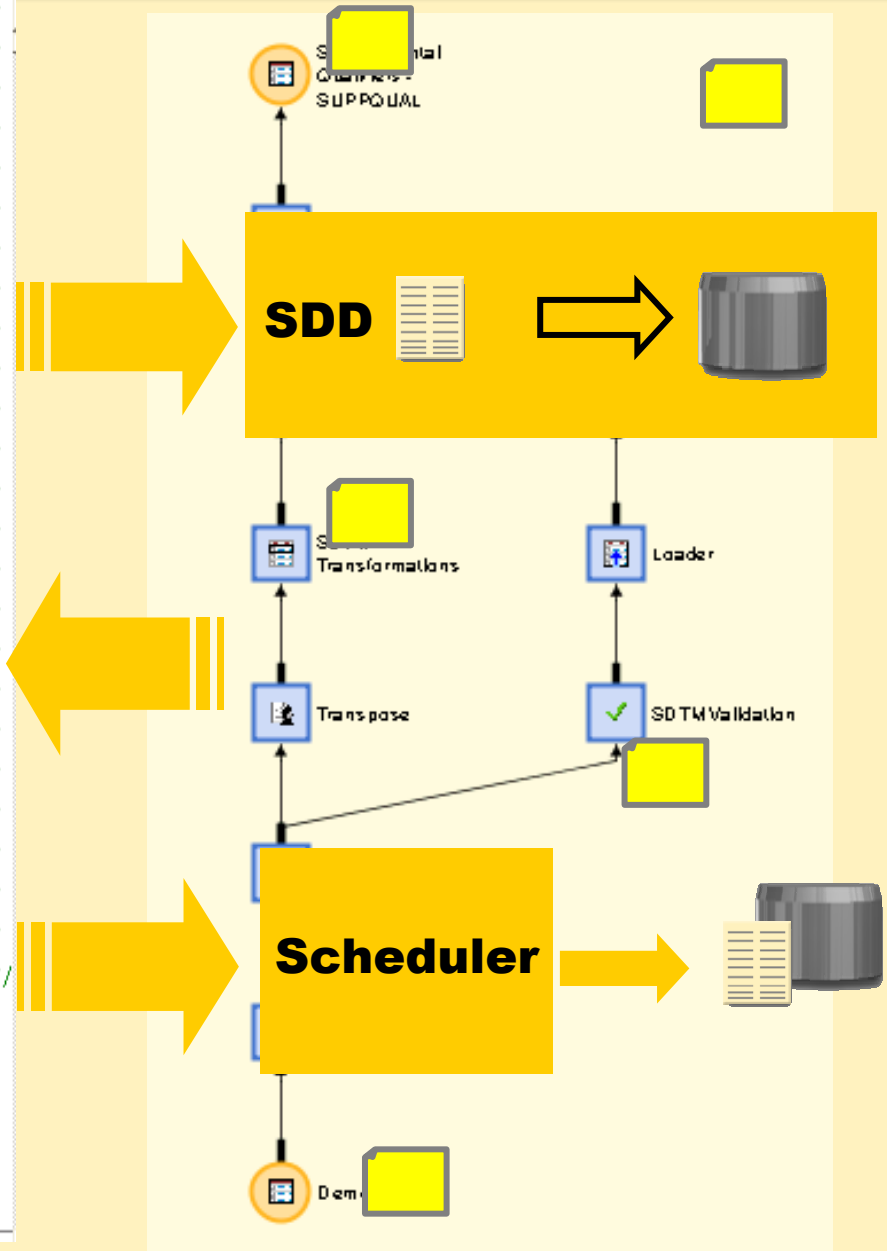
Process Designer



Process Designer

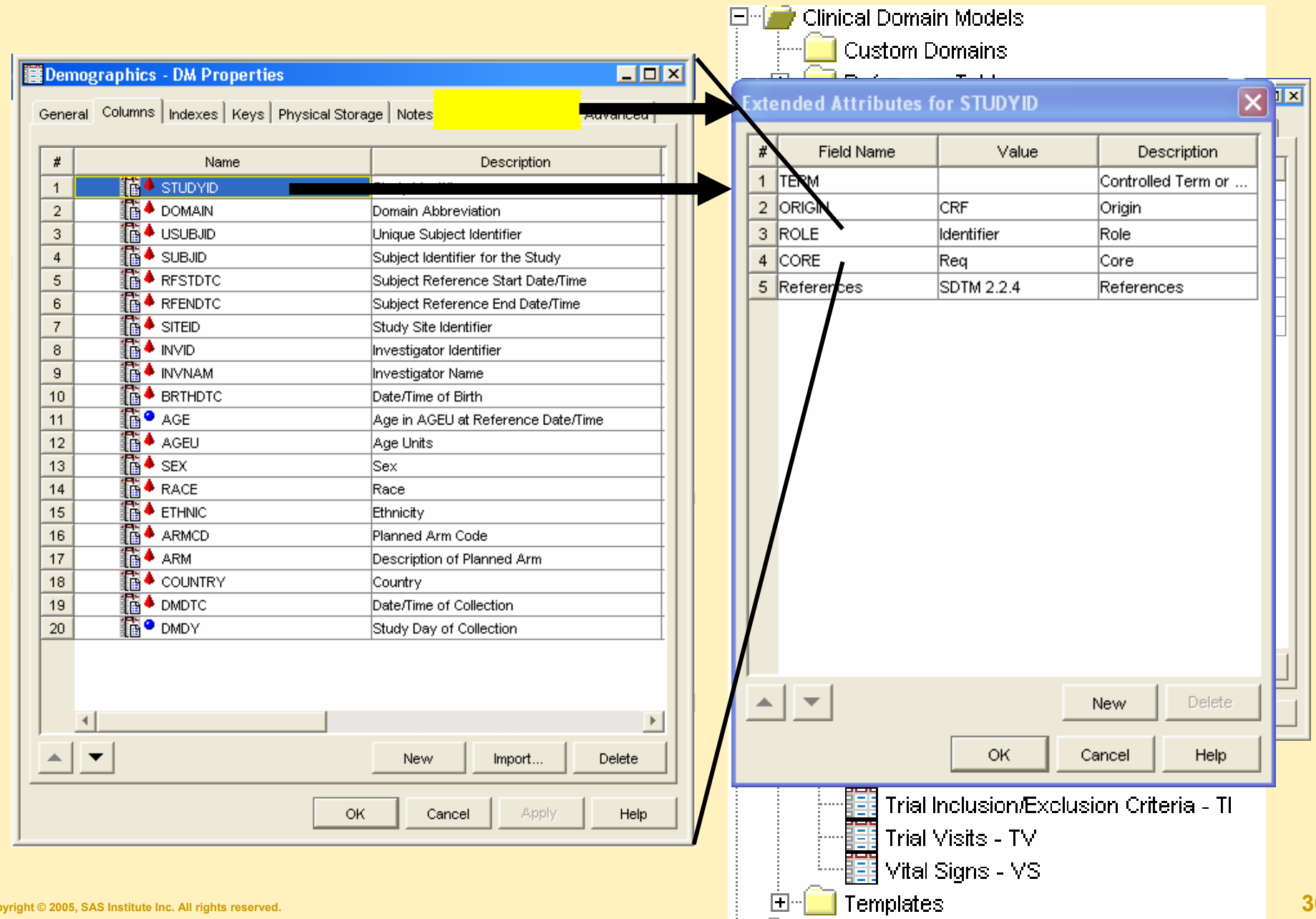


```
/*************************************************************************
 * Job:           Load Demography                          A5853KYA.AN000002 *
 * Description:                                                              *
 *                                                                           *
 * Repository:    Sandbox                                  A0000001.A5853KYA *
 * Server:        SASMain                                  A500IHYN.AR000001 *
 *                                                                           *
 * Source Table:  Demo - s_pr.Demo                         A5853KYA.AG0000RV *
 * Target Tables: Demographics - DM - std_pr.DM            A5853KYA.AG0000RT *
 *                Supplemental Qualifiers - SUPPQUAL -     A5853KYA.AG0000RZ *
 *                std_pr.SUPPQUAL                                            *
 *                                                                           *
 * Generated on:  Tue Mar 08 13:38:05 EST 2005                               *
 * Generated by:  vmxp-1\sasadm                                              *
 * Version:       9.1.20041201.4014                                          *
 *************************************************************************
                                                                           *
                                                                           *
                                                                           *
                                                                           *
                                                                           *
                                                                           *
                                                                           *
                                                                           *
 *************************************************************************/


/* Setup to capture return codes  */
%let job_rc = 0;
%let trans_rc = 0;
%let sqlrc = 0;
%global syserr;
```

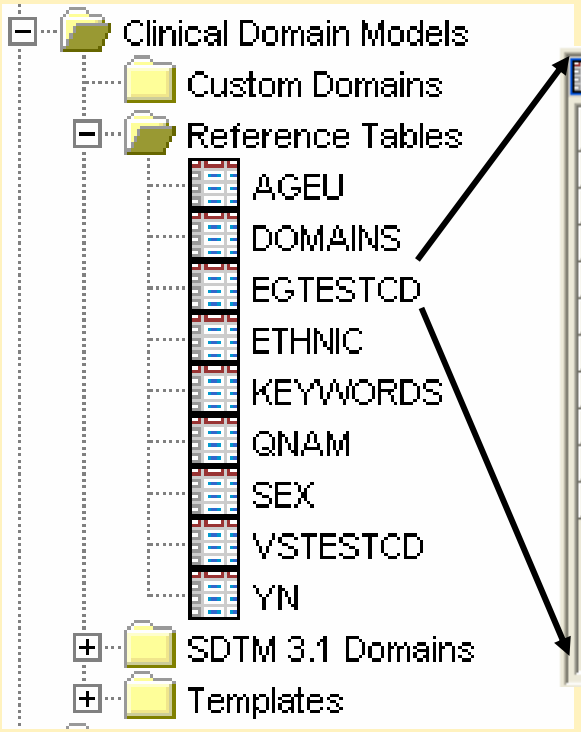


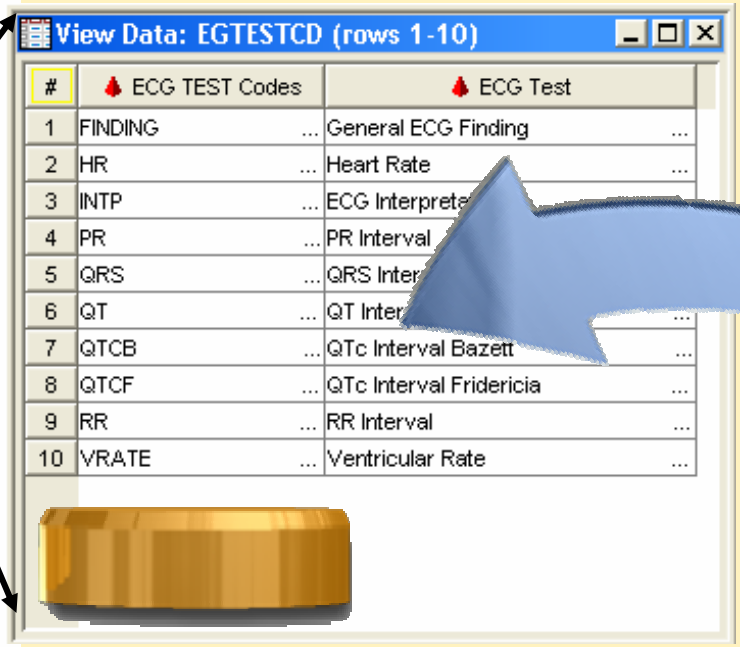
CDISC SDTM Data Model

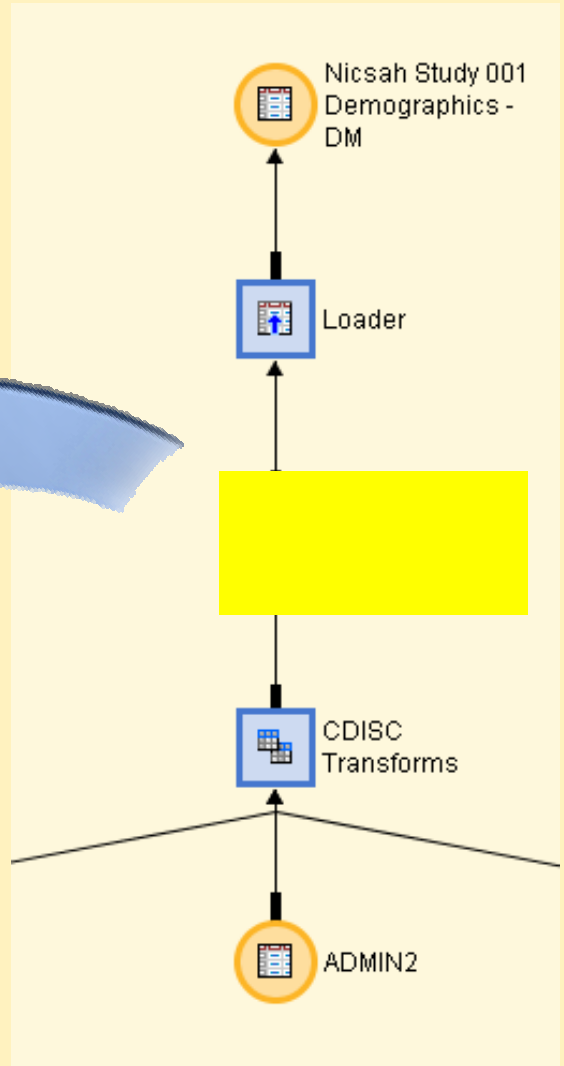
- Implemented in the metadata
- Implements all currently defined models
- Contains table definitions and model metadata
- Facilitates a workflow to define new models
- Provides supplemental tables for validation steps



Reference Tables (controlled terminology)







SAS and SDTM as the Emerging Standard

OCTAGON RESEARCH SOLUTIONS IDENTIFIED AS A PRIMARY TRAINER FOR CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM (CDISC)

Corporate Sponsor to Provide Training Curriculum on Emerging Data Standards

April 4, 2005

OCTAGON RESEARCH SOLUTIONS IMPLEMENTS SAS TECHNOLOGY [SAS® Enterprise ETL Server] **TO REVOLUTIONIZE CDISC SDTM LEGACY CONVERSION OFFERINGS**

April 11, 2005

On the SAS Radar….

- define.xml
- Lab, SEND, ADaM
- Other emerging standards

The Move to Standards…

"Faced with rapid changes, the nation's healthcare system has **fallen short of its ability to translate information into knowledge** that can be used in practice, and to apply new technology safely and appropriately.

The results are exactly what you would expect. Everyone who uses the current system **constantly confronts large information gaps**, whether it's at the doctor's office, on the hospital ward or at government agencies charged with protecting the public health. That goes for the FDA -- we're no exception."

Dr. Mark McClellan, former FDA Commissioner
CDISC Interchange, October 2003

"Innovation depends upon standardization."

Dr. Bob O'Neill, Director, Office of Biostatistics, CDER, FDA

Benefits of Standards – Regulatory View

"The importance of a standard for the exchange of clinical trial data cannot be overstated. FDA reviewers spend far too much valuable time simply reorganizing large amounts of data submitted in varying formats. Having the data presented in a standard structure will improve FDA's ability to evaluate the data and help speed new discoveries to the public." *-Lester Crawford, Former Commissioner, FDA*

"... But [SAS] declares: *Standards do not scare us. We embrace them.*"

- Mark Uehling, Senior Science Editor, Bio-IT World | eCliniqua
Thursday, Dec 9, 2004

The Power to Know®