Statistical Operations: The Other Half of Good Statistical Practice

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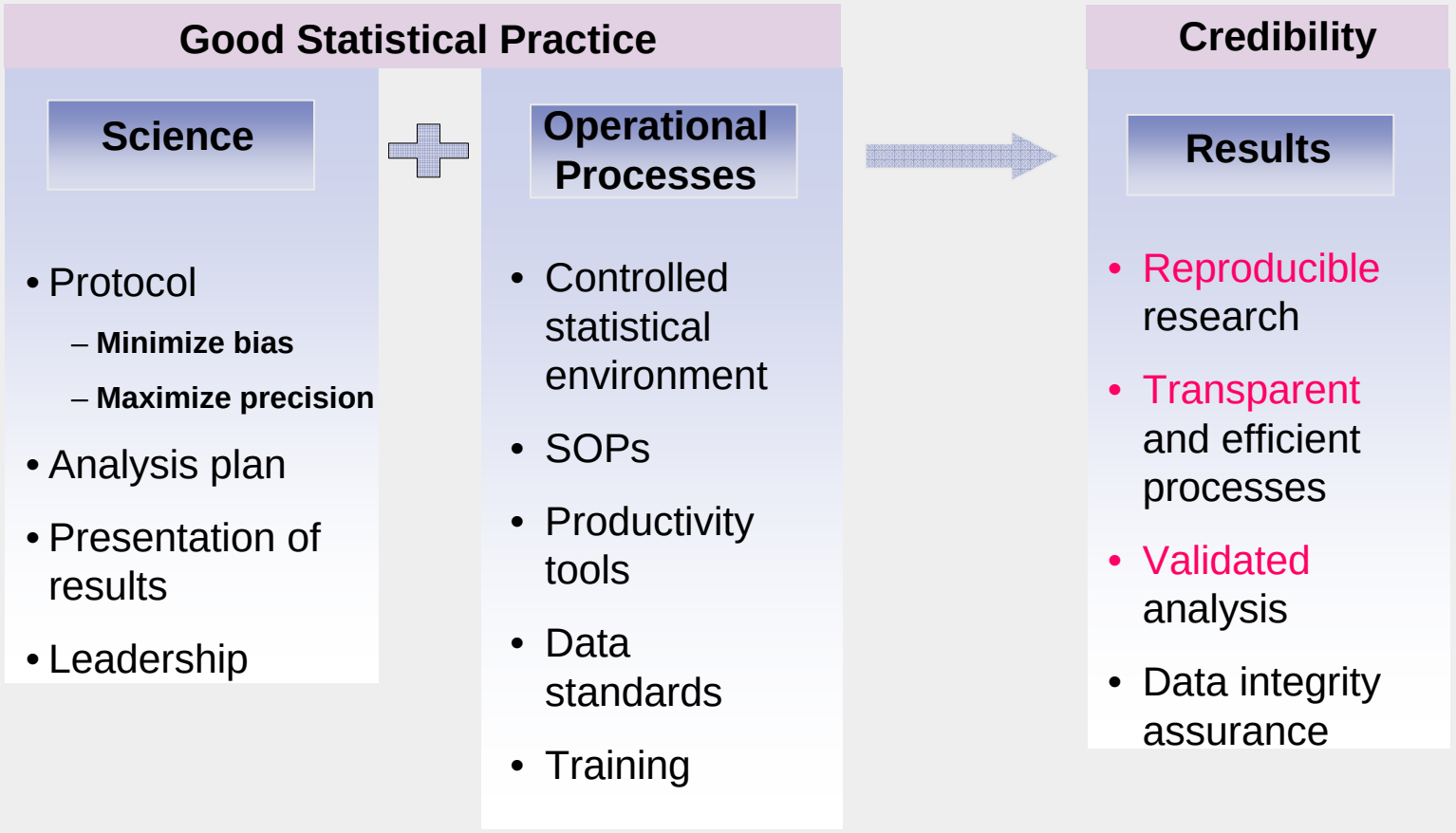
September 16, 2005

Washington, DC

Abstract

The *FDA Critical Path Initiative* calls for new *tools* to accelerate the drug development process. Nowhere is the need for new tools and standards more evident than in the statistical processing of clinical trials data. We shall discuss multiple drivers for a new approach to statistical practice that emphasizes documented reproducible research. Statistical leadership from both industry and government will be required to make a transition to new and more efficient and transparent statistical practice.

Good Statistical Practice leads to credibility of results: reproducible, transparent and validated analyses



Later Clinical Trials: Design & Analysis

- Analytical issues
  - Noninferiority
  - Multiple EP
  - Imputation of missing data
- Design: Use of Bayesian Designs

  Use of randomized withdrawal and enrichment designs
- Design: Specific design projects – including modeling and simulation

Ref: J. Woodcock. "The Critical Path Initiative: One Year Later", May 5, 2005

Statistical Science Meets Regulation: Guidances

Concept Paper on Flexible Designs
Confirmatory clinical trials with flexible designs and analysis

CPMP Choice of Noninferiority Margin
Choice of Non-inferiority margin (final July 2005)

CPMP PtC on Covariate Adjustment
(adopted May 2003)

CPMP PtC on Meta Analysis and One Pivotal Study
Points to Consider on Application with 1.) Meta-analyses and 2.) One Pivotal study (adopted by CPMP May 2001)

CPMP PtC on Missing Data
Points to Consider on Missing Data (Adopted November 2001)

CPMP PtC on Multiplicity
Points to consider on Multiplicity Issues in Clinical Trials (Adopted September 2002)

CPMP PtC on Non-Inferiority
Points to Consider on Switching between Superiority and Non-inferiority (Adopted July 2000)

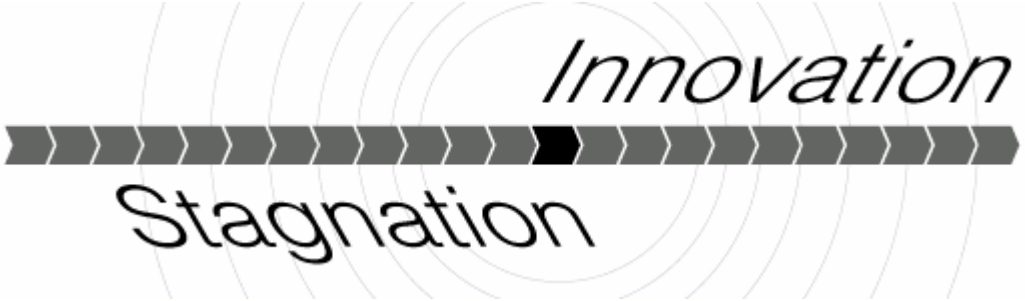
CPMP PtC on QT Interval Prologation
Points to Consider in the Assessment of the Potential for QT Interval Prolongation by Non-cardiovascular Medicinal Products(of 17 December 1997)

CHMP guideline on data monitoring committees
(final Jul 2005)

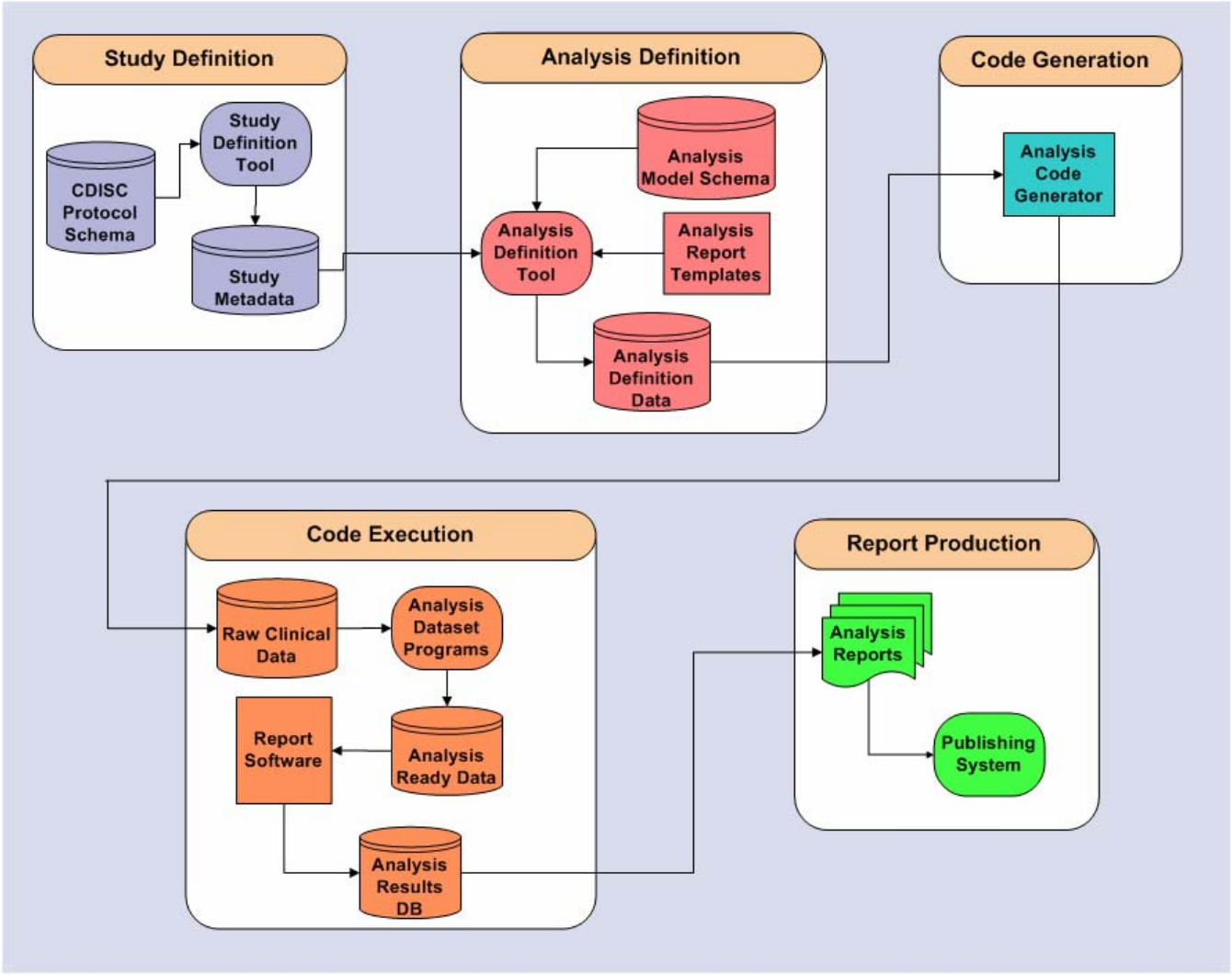
Biostatistics in the pharma industry has made few operational breakthroughs in the last 20 years compared to other disciplines

Current Situation

- Productivity systems are largely missing from statistical operations
- There is little interprocess communication between tasks; much done by hand
- Lack of industry standards and tools – documents, statistical tables and programs
- Lack of efficient systems take away time from the high value work of science



Statistical operations activities

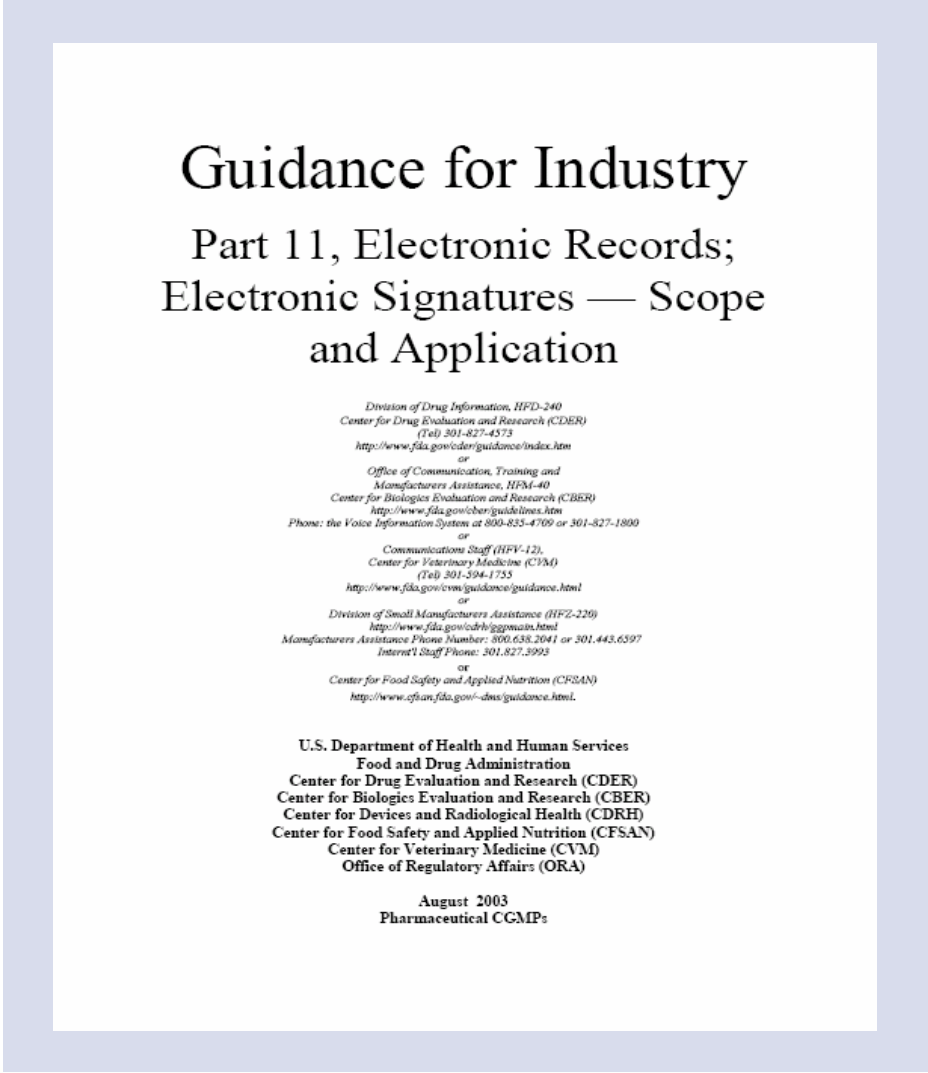


Multiple drivers for creation of controlled statistical environments

Because the clinical trials data have broad public health significance, the data are expected to be of the highest quality and integrity

- FDA Regulations/Guidelines
  - ICH E9: Statistical Principles for Clinical Trials
  - 21 CFR Part 11 & Scope and Application Guidance
  - "Computerized Systems Used in Clinical Trials" (April 1999; new draft Sept 2004)
  - eCTD specification
- Standards
  - CDISC: ODM, SDTM, ADaM, CDISC/HL7 Protocol Representation
  - Statistical analysis plans (ICH E3, CDISC/HL7 subcommittee)
- Increasing Complexity
  - Technologies: e.g. XML, Internet
  - Outsourcing and data sharing (CROs, Labs, DMCs, Partners, FDA, …)
- Cost of validation – what can be done to minimize cost?
- New tools – natural response to the FDA Critical Path Initiative of 2004

Management of Electronic Records and Signatures Applies Directly to Statistical Operations



Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

Division of Drug Information, HFD-240
Center for Drug Evaluation and Research (CDER)
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research (CBER)
http://www.fda.gov/cber/guidelines.htm
Phone: the Voice Information System at 800-835-4709 or 301-827-1800
or
Communications Staff (HFV-12),
Center for Veterinary Medicine (CVM)
(Tel) 301-594-1755
http://www.fda.gov/cvm/guidance/guidance.html
or
Division of Small Manufacturers Assistance (HFZ-220)
http://www.fda.gov/cdrh/ggpmain.html
Manufacturers Assistance Phone Number: 800.638.2041 or 301.443.6597
Internt'l Staff Phone: 301.827.3993
or
Center for Food Safety and Applied Nutrition (CFSAN)
http://www.cfsan.fda.gov/~dms/guidance.html.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2003
Pharmaceutical CGMPs

Applies to records in electronic form that are *created, modified, maintained, archived, retrieved, or transmitted,* under any records requirements set forth in agency regulations. *It's good science and business!*

There is no FDA guidance specifically directed toward e-record keeping for statistical analyses

What is an e-record for statistical analyses?

- Is each execution of the program an e-record?
- Is the final analysis in the submission to FDA the e-record?
- Is the statisticians report the only e-record?
- Are tests of the assumptions e-records?
- Are preliminary analyses in model building e-records?
- Are interim analyses e-records?
- Reference: J. McCormack (2002) Statistical Software Validation: Regulatory Perspective, Society for Clinical Trials Annual Meeting.

A solution: Manage all e-records in an environment that tracks these objects seamlessly as part of the ordinary production work environment.

Data and software transfers add complexity. Example: independent data monitoring committees

Guidance for Clinical Trial Sponsors

On the Establishment and Operation of Clinical Trial Data Monitoring Committees

DRAFT GUIDANCE

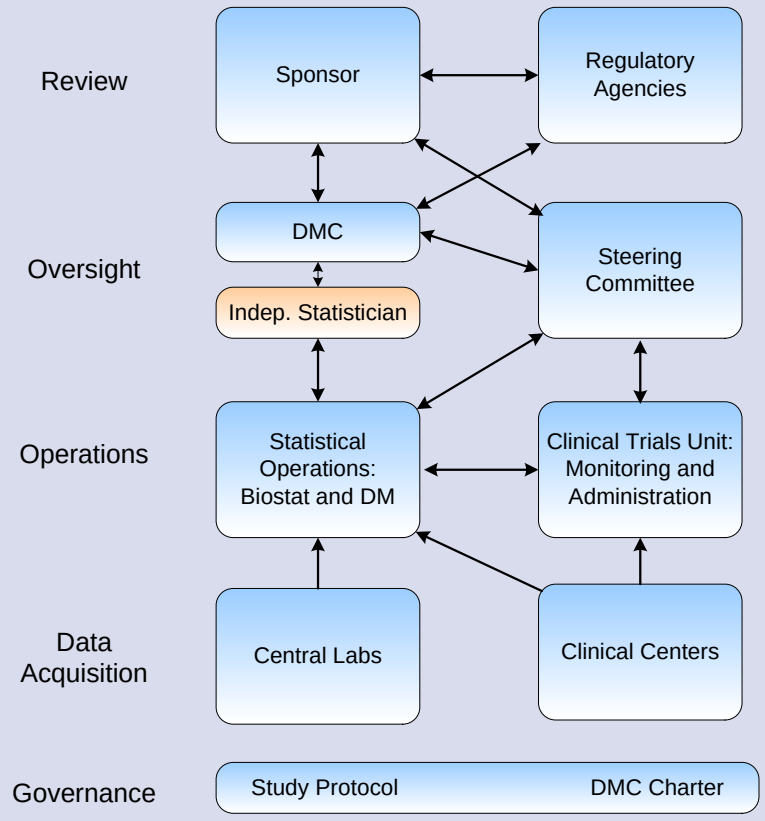
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Docket Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that published in the *Federal Register*.

For questions on the content of this draft document contact Mary Foulkes (CBER), 301-827-3034, Robert Temple (CDER), 301-594-6758, or Joanne Less (CDRH), 301-594-1190.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
November 2001

Typical Phase 3 Trial Organization



A Controlled Environment Presupposes Operational Maturity

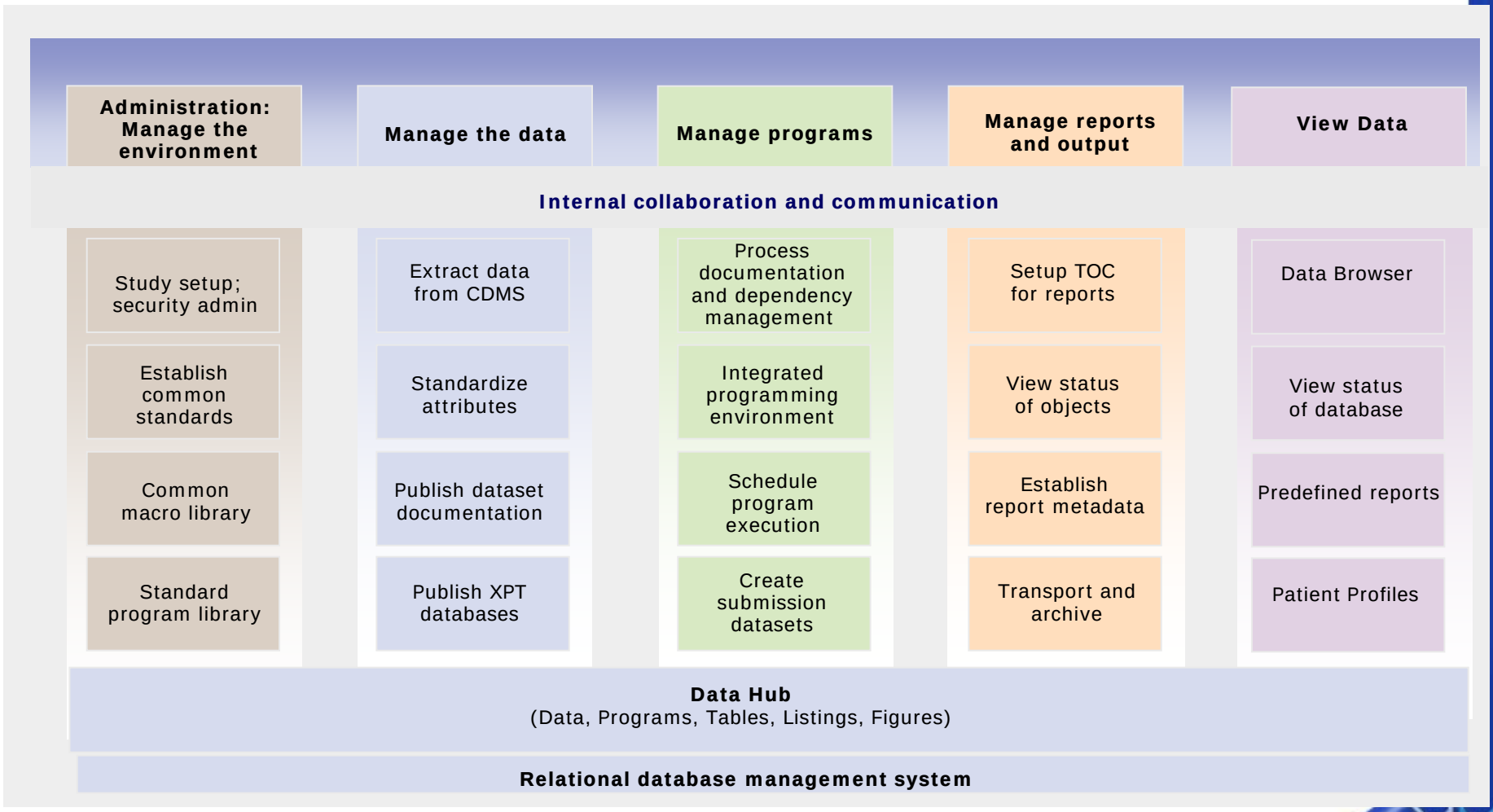
- Have a goal and a plan what you do
- Actively control how tasks get done
- Control access and changes to records and documents
- Maintain audit trails for records and documents
- Exercise discipline in the development and use of software
- Exercise appropriate security for systems and data
- Make sure everyone is trained and qualified for their tasks

Characteristics of a controlled statistical environment

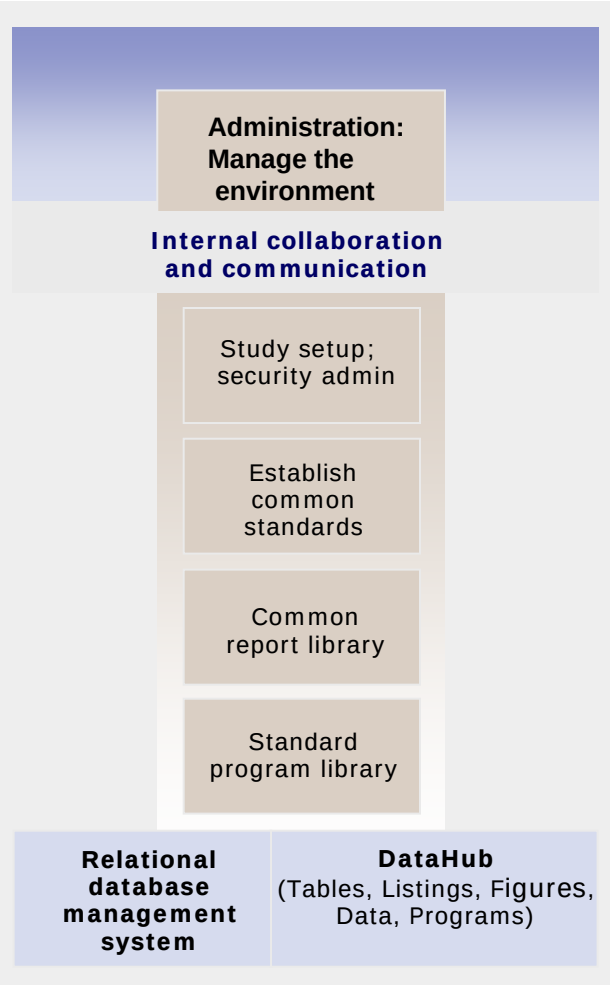
Goal: provide a foundation for documenting rigor in the analysis and reporting of clinical trial results while increasing productivity and quality.

- Tools are targeted directly to the deliverables (clinical study reports, analysis files, eCTD, etc) necessary for regulatory submissions.
- It organizes the various activities, breaking down the whole process into smaller, simpler tasks.
- The processes becomes transparent. It is easier to train new workers and to track progress on large projects.
- A shared platform usable by both programmers and statisticians facilitates communication and productivity of all concerned.
- Creates a process that makes Part 11 compliance a by-product of work not an object of work.
- Open architecture, portable or internet accessible

The Controlled Statistical Environment: Conceptual Components

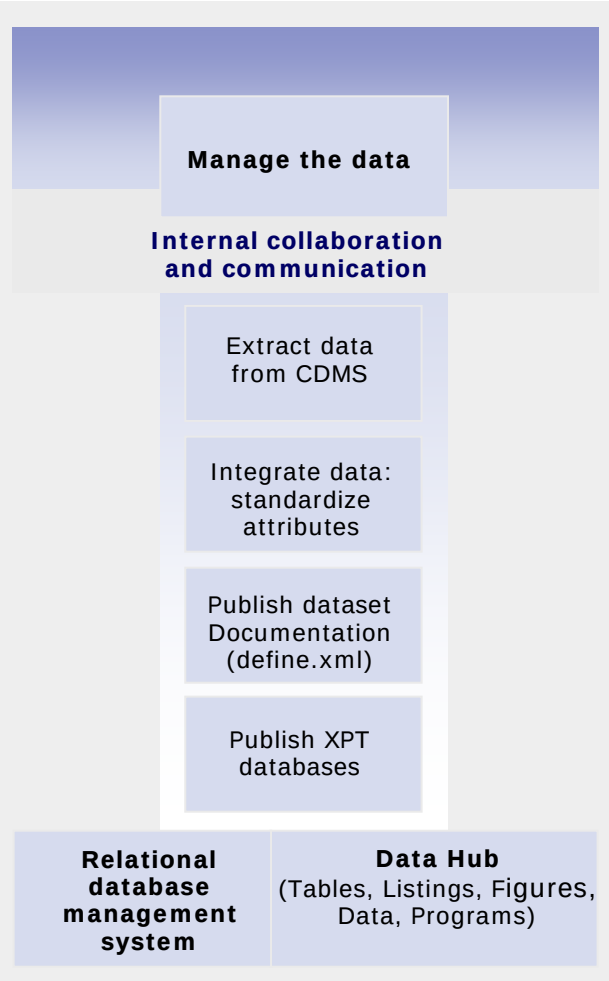


Manage the Statistical Environment



- Add users, define user roles
- Define directory structures and permissions
- Store templates
- Management of standardized reporting software e.g. SAS and S-Plus programs
- Implement business rules
- View/report project status based on metadata
  - Catalog of programs and their status
- Export or archive data, programs, results

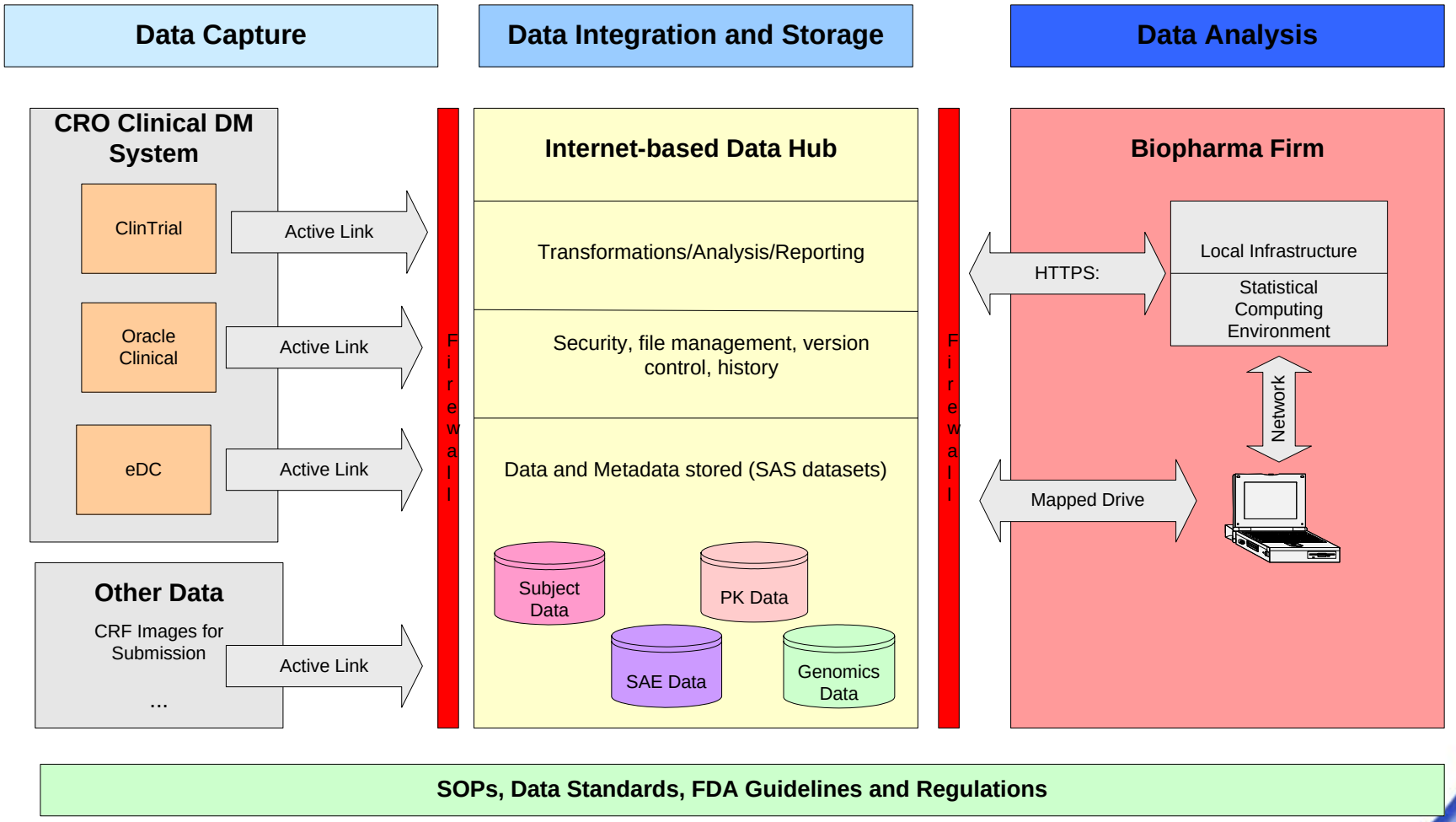
Manage the data



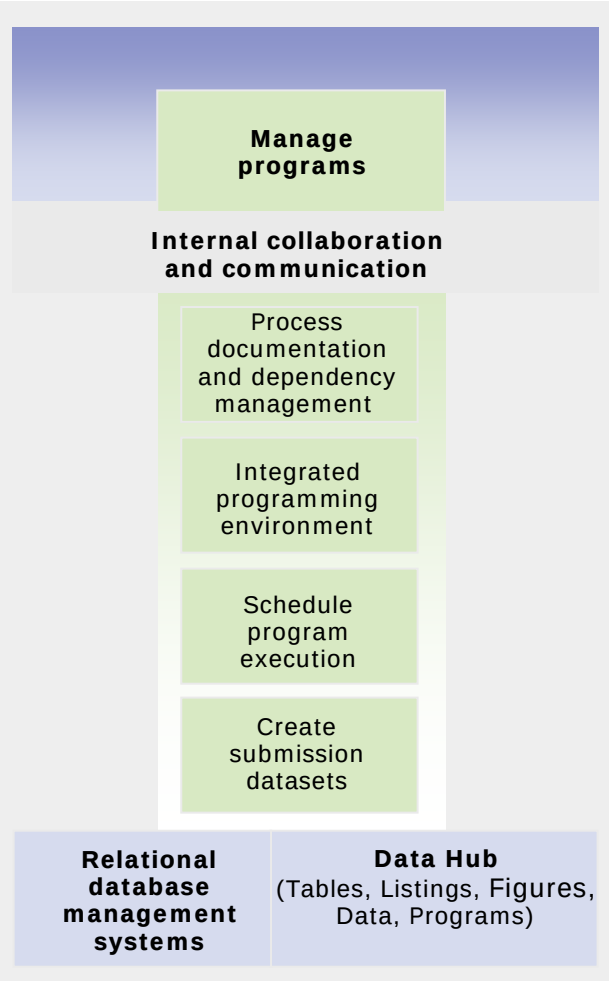
The DataHub is a single place for storing documents, data, programs, and output

- Support for import of SDTM data from clinical data management or vendor
- Provide data security and audit trails for the data warehouse
- Store data, logs, programs and output in a RDBMS. Handle these components as related objects.
- Store statistical analysis files

The data hub should have active links to the systems that are capturing data. DM systems should deliver data as SAS datasets for immediate analysis and reporting.

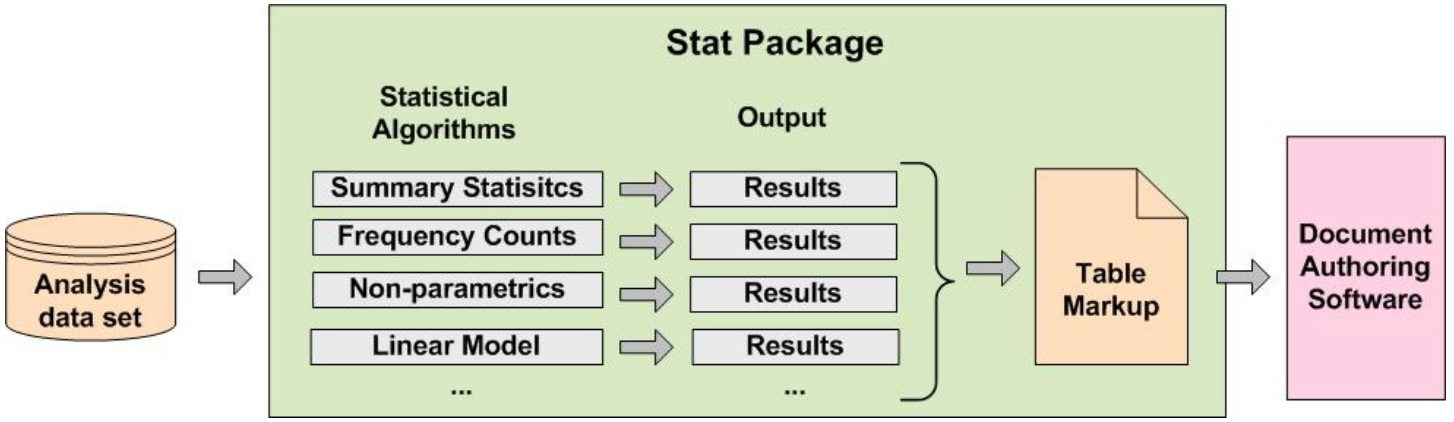


Manage analysis programs



- Code management: Check-in / check-out
- Audit trails
- Batch processing
- Dependency management
- Extensible: supports multiple tools
- Flexible: allows program execution outside the environment for early phases of program development

Statistical programming can be a “bottleneck” without efficient programming tools



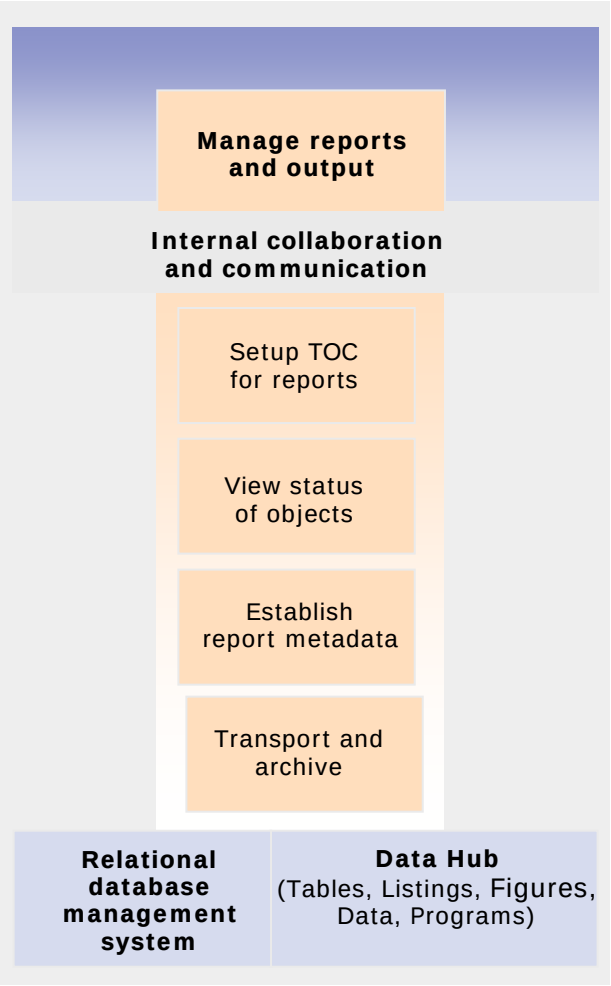
Today

- Substantial programming often required; proprietary macros, etc.
- Common code library provides building blocks for statistical tables
  - Code is easier to maintain
  - Validated building blocks save time
  - Facilitates training

What’s Needed

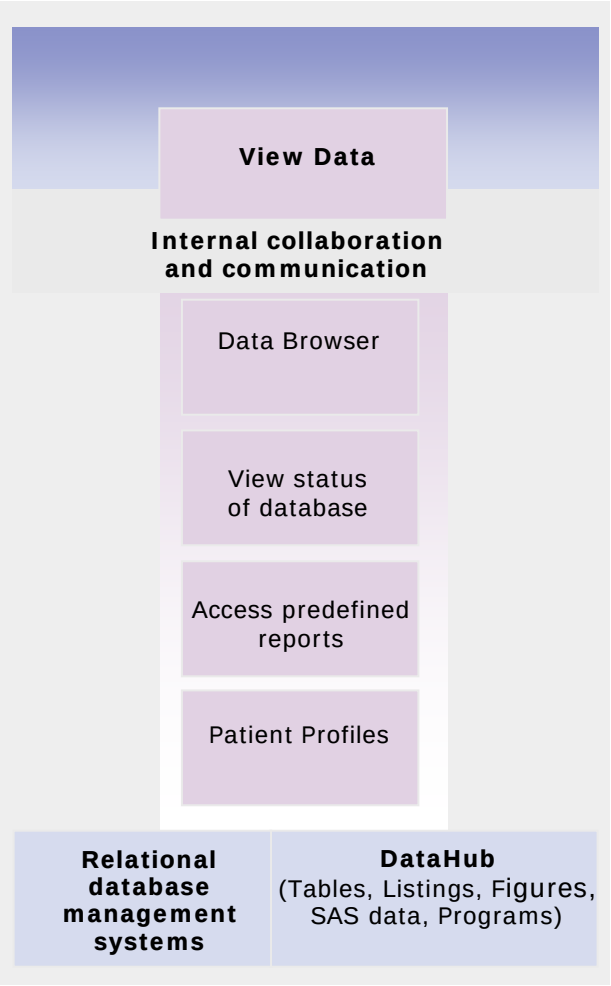
- Less programming
- Direct table specification & creation
  - Less chance for error
  - Reduced validation costs

Manage reports and output



- Manage output through a table of contents associated with the final report
- Life cycle management for tables and graphs
  - eg. draft --> validated --> final
- Export/Transport: data, programs
- Archival

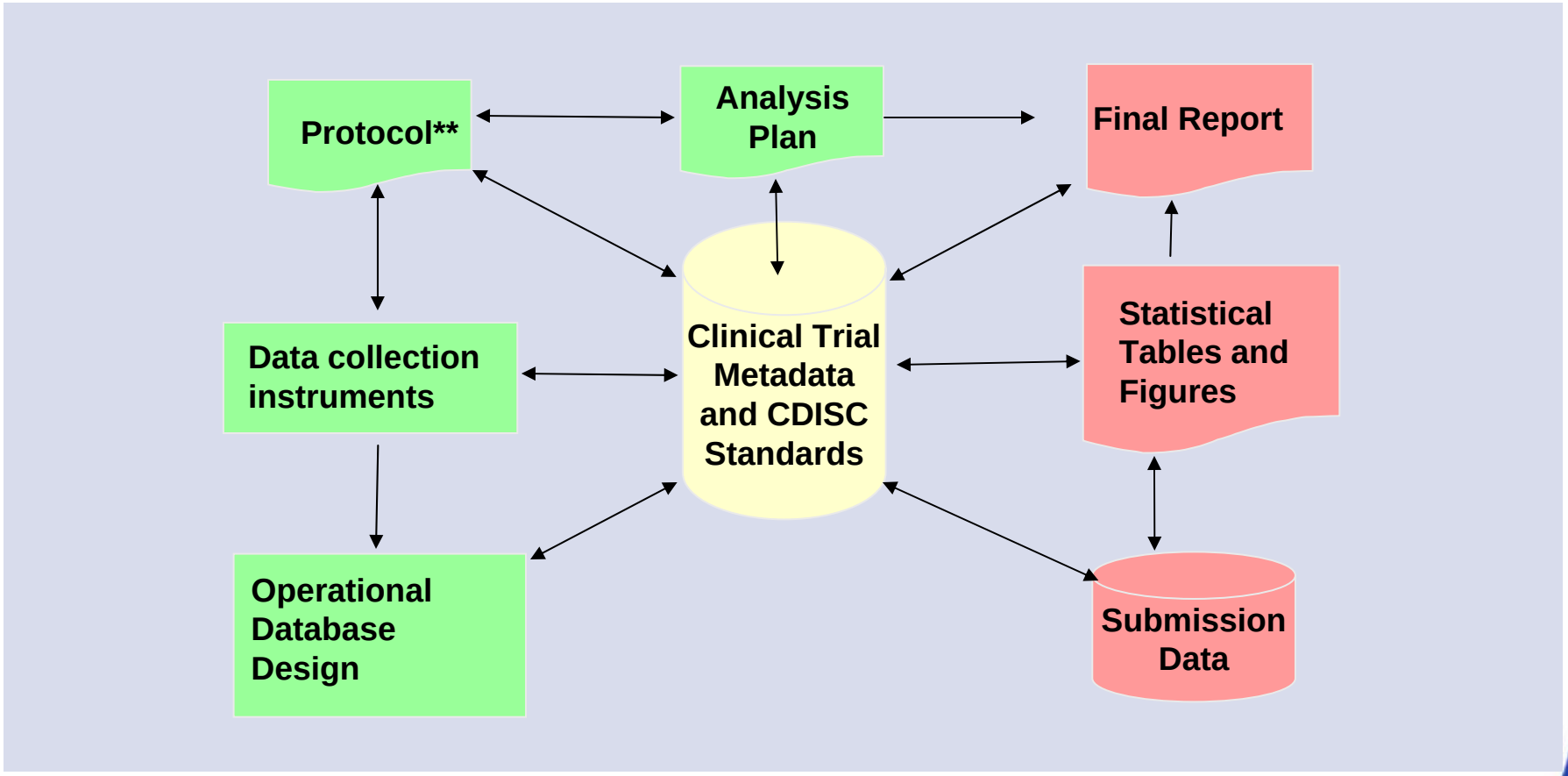
Tools to View Data



SDTM data is not readily usable in statistical software nor for viewing in context of other data

- A tool is necessary to view SDTM data in the controlled statistical environment
- Data stored in a relational database
- View study metadata
- Create domain listings
- View patient profiles
- Create graphs
- Data restructuring and export

New opportunities: metadata and data standards can drive clinical trial processes



****Publication of a standard, machine-readable model for protocol representation that will facilitate interchange of metadata among systems and stakeholders**

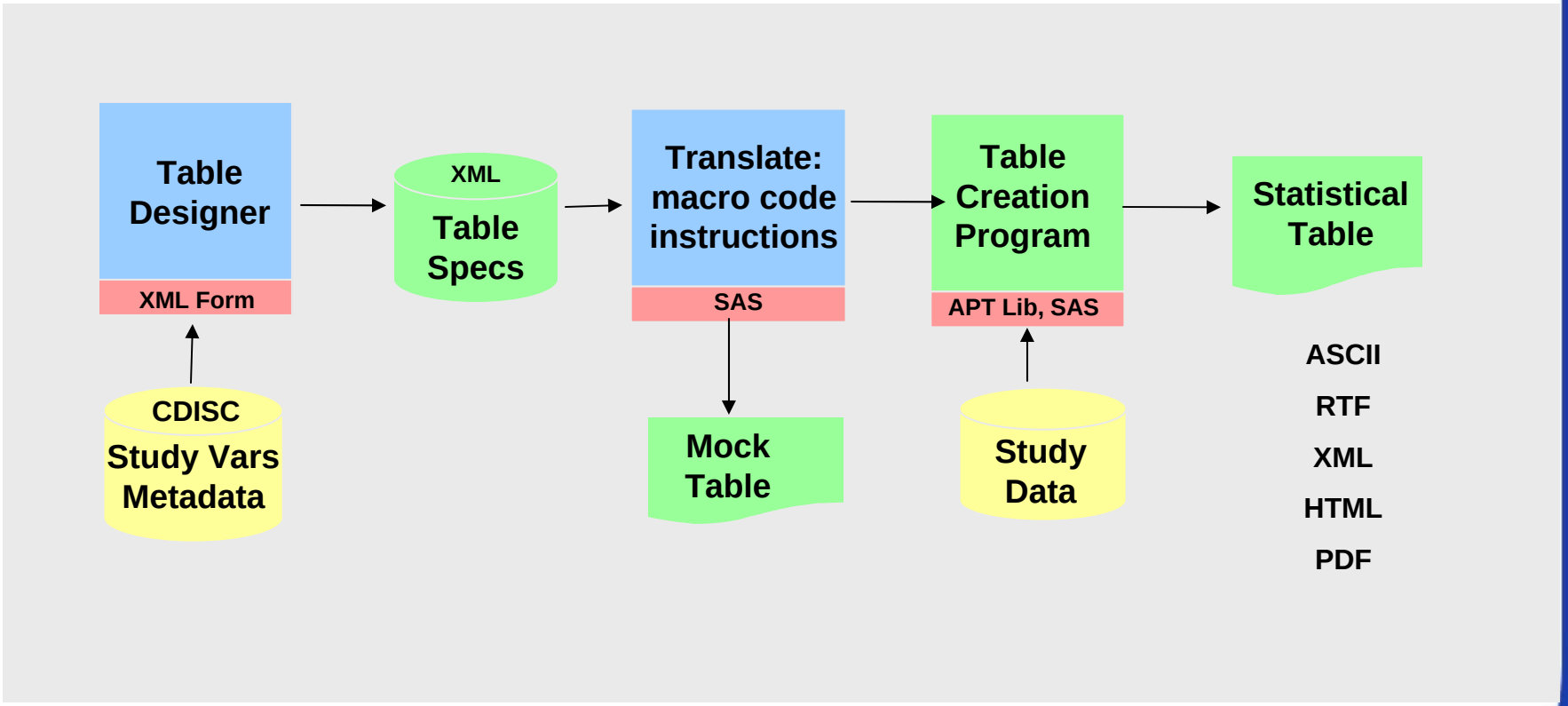
Figure adapted from W. Qubeck (2005), personal communication.

Data-based protocol representation enables automation tools for down-stream statistical processes

Consider the possibilities:

- A basis for developing an electronic statistical analysis plan
- Description of the appropriate analysis files
- Definition of tables of study results in final reports
- Automatic generation of programs for study reporting
- Final study report: integration of protocol elements, analysis plan and statistical reports

Process Flow Automation for Creation of Statistical Tables



Reference: Hopkins & Collins (2005) "Statistical Table Specification and Automatic Code Generation Using XML". PharmaSUG 2005 Proceedings, http://www.pharmasug.org/2005/papers/ad16.pdf.

Electronic Regulatory Submissions

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions

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For questions regarding this draft document contact (CDER) Randy Levin 301-594-5411, or (CBER) Robert Yetter at 301-827-0373.

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Food and Drug Administration
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August 2003
Electronic Submissions

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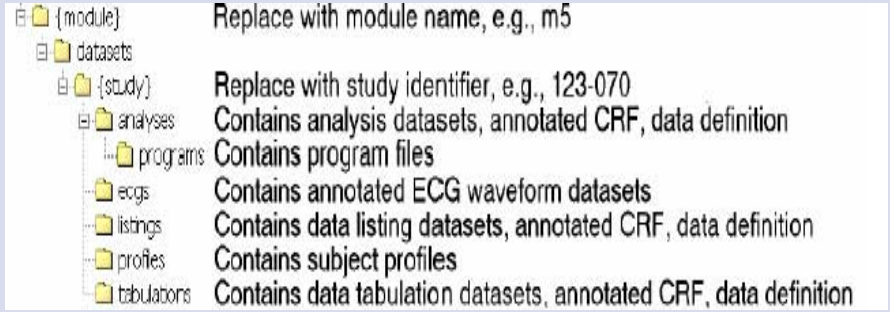
08/18/03



FDA expects to receive multiple types of data files, documentation, and programs – the whole statistical environment

Summary: Tools for the new processes

New standards provide an opportunity to structure traditional statistical processes for better communications within drug development teams and regulatory agencies. New tools are needed to create the future possibilities.

- A structured statistical environment provides a foundation for documenting rigor in the analysis and reporting of clinical trial results while increasing productivity and quality.
  - Tools to manage workflow are key to realizing full efficiency
- An active data hub can facilitate communication with a variety of external collaborators in the development process.
- Process automation is possible if standards are available. Well-defined processes can communicate through XML to create workflows.

Let's not stagnate!

Innovation requires:

- Cooperative efforts among statisticians in
  - Industry
  - Academia
  - Government
  - Vendors
- Leadership – ASA Biopharm subsection can be a forum for discussion of statistical issues related to the critical path initiative