Society for Clinical Trials 31st Annual Meeting

Workshop P9
The Essentials of Clinical Data Management

Sunday, May 16, 2010
1:00 PM - 5:00 PM
Laurel AB

Society for Clinical Trials

Pre-Conference Workshop Evaluation
Baltimore, Maryland
May 16, 2010

WORKSHOP 9 – The Essentials of Clinical Data Management

1. Overall, did the subject context of this workshop meet your expectations and needs?

   Yes ( ) No ( )

   If yes, in what way? If no, why not? _____

   _____

2. Was the content of this workshop of value to you personally or on the Job?

   Yes ( ) No ( )

3. Was the content of the workshop: New ( ) New/Review ( ) Review ( )

4. The level and complexity of this workshop was:

   Too elementary ( ) Correct ( ) Too advanced ( )

Please complete the following questions by circling the appropriate description using the rating scale listed below.

1 = excellent   2 = very good   3 = good   4 = fair   5 = poor

---

5. Rate the extent to which this workshop:

   a. Presented content clearly   1   2   3   4   5

   b. Allowed sufficient time for discussion
      and audience participation   1   2   3   4   5

   c. Provided useful information   1   2   3   4   5

   d. Utilized appropriate teaching methods,
      i.e., audiovisual, handouts, lectures   1   2   3   4   5

6. Please rate each workshop faculty member:

Name	Knowledge of Subject	Organization/Delivery
Devin J. Hunt	1 2 3 4 5	1 2 3 4 5
Hector Robertson	1 2 3 4 5	1 2 3 4 5

1.	Are you currently working in a clinical trial? (Yes) (No)

2.	What is your job title? _____

3.	Do you have any suggested topics for workshops at future meetings? If so, please list below:

_____

_____

4.	What aspect of the workshop did you like best?

_____

_____

5.	 What aspect of the workshop would you change if this workshop were offered again?

_____

_____

6.	Additional Comments: _____

_____

2010 SCT Pre-conference Workshop

Essentials of Clinical Data Management

Devin J. Hunt
EmpiriStat, Inc.

Hector Robertson
Clinical Research Management, Inc.

Workshop Purpose

This workshop has been designed to:

- Familiarize participants with the specific tasks involved in "traditional" clinical data management process
- Provide participants insight from the perspective of a clinical data manager
- Enable participants to examine the processes, regulatory requirements and best practices

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Workshop Objectives

Define the roles involved in clinical data management

Identify reciprocal tasks at critical points before, during and post-study

Practice using and becoming familiar with the required documentation

Describe the consequences of poor clinical data management and the benefits of well-executed clinical data management

List best practices in good clinical data management to avoid common mistakes

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Agenda

Introductions

Understanding clinical research

CDM Role

Planning and Preparation

   Processes and Documents

Trial Conduct and Management

Study Close out

Data Analysis and Reporting

Promoting Efficiency in Data Management

Hands on Workshop

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Your Presenters

Devin J. Hunt

  Manager, Statistical Programming for EmpiriStat, Inc.

  6 years of experience in Data Management, Protocol Monitoring, Statistical/SAS programming, and Database Development and Testing

Hector Robertson

  Lead Data Manager for Clinical Research Management

  12 years Data Management experience working in diverse therapeutic areas as well as studies in phase I – IV in the Pharmaceutical, Biotechnology and the CRO industries.

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Understanding Clinical Research

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Understanding Clinical Research Phases of Drug Trials

Phase I

The initial introduction of an investigational new drug into humans.

Phase II

Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug.

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Understanding Clinical Research Phases of Drug Trials

Phase III

Expanded controlled and uncontrolled trials that are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.

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Understanding Clinical Research Phases of Drug Trials

Phase IV

Certain post marketing studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time

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Understanding Clinical Research Types of Trials

Treatment

New treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

Prevention

Prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

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Understanding Clinical Research Types of Trials

Diagnostic

To find better tests or procedures for diagnosing a particular disease or condition. Diagnostic trials usually include people who have signs or symptoms of the disease or condition being studied.

Screening

Test the best way to detect certain diseases or health conditions.

Quality of Life

Explore ways to improve comfort and quality of life for individuals with a chronic illness.

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Data Management Roles and Responsibilities

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Clinical Data Manager's Roles

Manager
Data tracking
Data coding
Data entry
Data validation
Training
Quality Control
Quality Assurance

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Clinical Data Manager's Roles

Manager
  Protocol review
  CRF development
  Authorization and database access
  Data validation document
  Approval of processes and procedures
  Oversight of all aspects of CDM

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Clinical Data Manager's Roles

Data Tracking
  Logging of paper CRFs
  Tracking data through CDM process, e.g.
    Completeness of CRFs
    CRFs through data entry process
    Data discrepancy forms
  Data Coding
    Adverse event coding
    Medication coding
    Review of CRF for accuracy

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Clinical Data Manager's Roles

Data Entry
- Entering data
- Updating data

Data Validation
- Developing CRF instructions
- Generating computerized or manual checks on a database to check for missing, inconsistent, or illogical data
- Implementing the data discrepancy management process

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Clinical Data Manager's Roles

Data Training
- Author CDM procedures
- Train personnel on procedures
- Create and maintain training documentation

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Clinical Data Manager's Roles

Quality Control
- Accuracy of data entry
- Implementing CDM processes and procedures including documentation

Quality Assurance
- Conducts data audits
- Verifies that processes and procedures have been followed including documentation

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Relevant Documents

Each element of CDM requires:

Documented process

Documented training or review and approval

Standard Operating Procedure (SOP)

Work Instructions (WIN)

Project Documentation

Quality Control (QC)

Quality Assurance (QA)

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Relevant Documents

Documents used by many data managers include

Data Management Plan (DMP)

Case Report Forms (CRFs)

Case Report Form Instructions (CRFi)

Data Entry Guidelines

Database Design and Testing Specifications

Edit Checks and Query Resolution

Formats, Code lists, Data Dictionary

Data Validation Plan (DVP)

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Team Collaboration

Each functional representative on a team brings a unique set of experiences, skills, and knowledge

Medical/Clinical Director & personnel

CRA

IT

Statistics

Data Management

Programmers

Data Entry

The benefits & payoffs for the proper level of team involvement and inclusion are phenomenal!

The project benefits

The team members benefit

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Establish Effective Communication

Within the CDM team
Between the CDM team and:
  Project Management
  Data Management
  Clinicians
  Statisticians
  IT
  Third parties, when applicable

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Develop Research Plan

Overview
  Introduction
  Background
  Goals
Clinical Plan
Data Management Plan
Statistical Analysis Plan
Regulatory Considerations (if any)
Human Subjects Protection

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Develop Research Plan

Things to Remember:
  On-going communications
  On-going clinical/data/analysis decisions
  Written instructions for clinical process, data
  management, randomization, …
  On-going documentation
  Goal is to preplan as much as possible
  No matter how well you plan …

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Research Goal

Ultimately, the desire is for others to believe the results of clinical research -- whether it be the general public or for the government entity

So, how do we achieve this goal?

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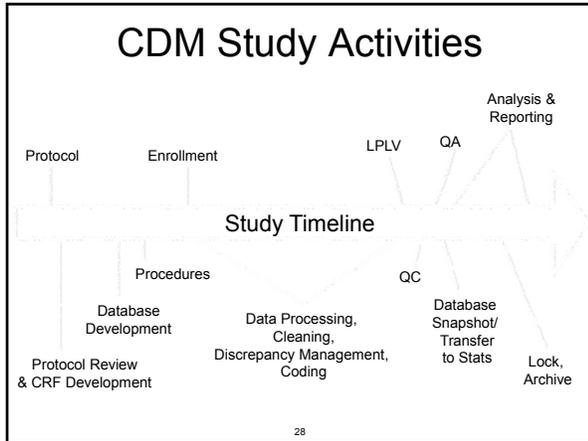
Promote Integrity in Clinical Research

Clinical trial data must possess integrity to ensure confidence in analytical results. This requires:

- Research plan
- Quality standards and processes
- Validated systems
- Trained staff
- Multidisciplinary team
- Collaboration

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Planning and Preparation

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CDM Study Activities

Analysis & Reporting

Protocol   Enrollment   LPLV   QA

Study Timeline

Procedures   QC

Database Development

Data Processing, Cleaning, Discrepancy Management, Coding

Database Snapshot/ Transfer to Stats

Protocol Review & CRF Development

Lock, Archive

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CDM Tasks – Study Start-up

Protocol Review
Case Report Forms (CRFs)
Review CRF Completion instructions
CRF Annotations
Data Management Plan (DMP)
Data Validation Plan (DVP)
Procedure (edit check) Requirements
Lab Transfer Requirements (if receiving electronic data)

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Protocol Review - CDM

Overall consistency & clarity (all team members)
Compliance with standards (all team members)
CRF design perspective
Database development perspective
Data cleaning processes
Coding considerations
Considerations for electronic data transfers
Randomization date and time specified
It is NOT CDM's responsibility to review for specific scientific content
Details should be outlined in SOP(s)

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Case Report Forms (CRFs)

CRF development is the first step in translating the protocol into data

"Ideally" , CRF development occurs concurrently with protocol development

Collect the precise data required by the protocol

> Avoid collecting extraneous data

> Avoid collecting redundant data

> Avoid collecting derived data

Easy to use (site personnel & data entry)

Address the needs of those who have to work with the data

> Data Management & dB Development

> Statistics

> Clinical

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Case Report Forms (CRFs)

Use draft protocol to design CRFs:

> Standard CRF modules

> Project- and/or protocol-specific modules

Draft CRFs to study team for review/input

> CRF review meeting

> Repeat draft reviews until no further changes

Circulate final version for approval

Coordinate CRF printing

RDC studies provide user document

Present CRFs & completion instructions at Investigator's Meeting (may be done by CRA)

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CRF Design Tips

Data captured in only one place

Fields clearly identified

Consistent categorical fields

Specify decimal point and number of places

No calculated fields

Appropriate review

Pilot

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Common Design Challenges

Evolving protocol development

Lack of communication

Electronic data sources

Non-protocol related data

Protocol amendments

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Collect Precise Data

Patient visits: scheduled and unscheduled

Medical windows

Data collected at each visit

Endpoints: primary, secondary, safety

Randomization date and time

Labs, imaging, …

Physical exam

Eligibility criteria

Study withdrawal

No extra data

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Contents of Fields

Dates, times: specify format include 24 hr clock if applicable

Numeric data responses

Few, if any, text fields

Consistent coding (e.g., yes/no)

Measurement units (e.g., in/cm, lb/kg, lab units, dosing units)

Option of 'unknown'

Collect 'raw' data

Clearly labeled categorical fields

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Concise, User-Friendly CRF

Not enough can be said about this! Why?

Remember those filling out the forms don't know the data as well as you do

Easy for the researcher to record the data

Long term benefit (e.g., quicker turn-around, fewer data discrepancies)

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CRF Completion Instructions

Document which provides clear instructions to site for accurate completion of the study CRFs

Written by the CRA

Start with "Standard Template"

Study CDM reviews & provides input

Keep in mind the:

CDM Manual Review Checklist

Data Management Plan (DMP)

Electronic Procedures/edit checks

These documents are not mutually exclusive (may be some overlap – but try to avoid unnecessary redundancies)

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CRF Completion Instructions

Easily accessed

Less is better

Key critical instructions to clarify fields

Appropriate review

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CRF Annotations (dB Specs)

CRF annotation (dB Specs) is the first step in translating the CRFs into a database application

Annotations may include:

- Field names & attributes (length, data type, dictionary, etc.)
- Module/form names
- Data Extract view names

Standard, existing modules annotated by study CDM

Reviewed by CDM and Statistician

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Sample Annotated CRF

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Elements of a DMP

Protocol

Roles and responsibilities matrix including contact information

Data flow diagram (DFD)

Case Report Form (CRF)

Annotated CRF

Data validation plan (DVP)

Scope of work for CDM

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Elements of a DMP

Deliverables

Data transfer specifications

   Don't forget HIPAA

Data closeout requirements

Archiving process

Project documentation including documentation of deviations from the DMP

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Elements of a DMP

Quality and regulatory standards to be met and how they will be achieved

Communication plan

Applicable processes and SOPs/IOPs, including project specific processes and procedures

Assignment of responsibilities for processes and procedures

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Data Validation Plan

A user-defined comprehensive list of the edit checks and field calculations for the study

Written by the CDM

Start with "Standard" document/spreadsheet

CRA reviews & provides input

"Living" document throughout the study conduct

   Finalized at study closeout – for archiving

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Lab Transfer Requirements

Scope of Work document

Define communication channels

Define timing/frequency for file transfers

File format

Specifications for file transfers:

    Test names

    Visit names

    Date formats

    Must meet the requirements of any Lab Pre-Processor program
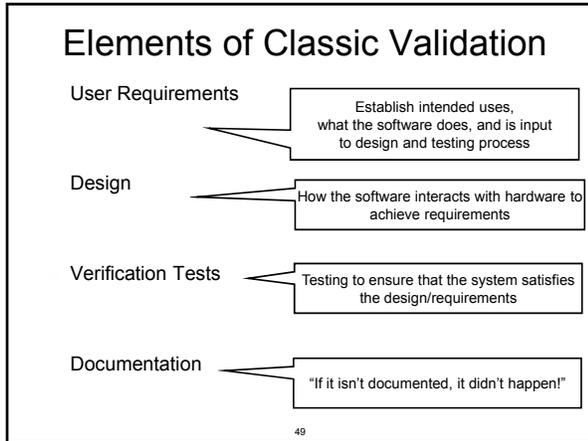
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Design and Validate Database

What is a Clinical Data Management System (CDMS)?

    A flexible relational database system for Capturing, Storing, and Processing clinical trial data

    Electronic Data Capture (EDC) vs Paper-based data capture

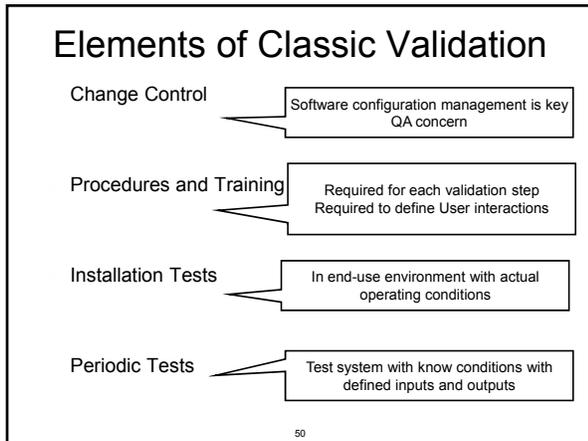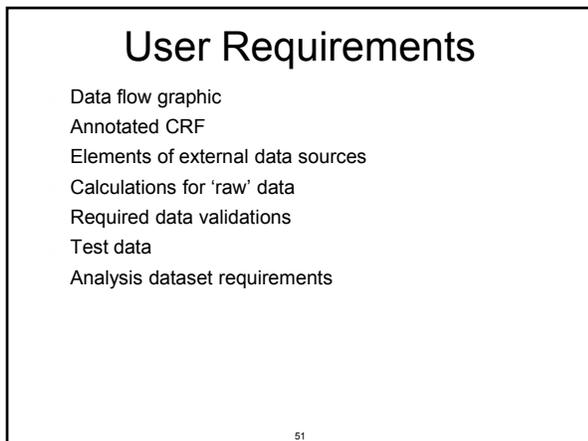   Off the shelf software solutions vs Customized software solutions

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Elements of Classic Validation

Requirements

Design

Verification Tests

Procedures

Training

Installation Tests

Periodic Tests

Change Control

Documentation

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Elements of Classic Validation

User Requirements — Establish intended uses, what the software does, and is input to design and testing process

Design — How the software interacts with hardware to achieve requirements

Verification Tests — Testing to ensure that the system satisfies the design/requirements

Documentation — "If it isn't documented, it didn't happen!"

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Elements of Classic Validation

Change Control — Software configuration management is key QA concern

Procedures and Training — Required for each validation step. Required to define User interactions

Installation Tests — In end-use environment with actual operating conditions

Periodic Tests — Test system with know conditions with defined inputs and outputs

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User Requirements

Data flow graphic
Annotated CRF
Elements of external data sources
Calculations for 'raw' data
Required data validations
Test data
Analysis dataset requirements

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User Requirements

Deliverables
- Data transfers
- Analysis dataset requirements
- Reports
- Tracking system

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User Requirements

Timeline
- Safety monitoring
- Site monitoring
- DSMB schedule (if any)
- Interim analysis, if applicable
- Final analysis

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Database Design

Platform specifications
Data transfer mechanisms
Database architecture
- CRF
- External data sources
Report(s) design
Tracking system specifications

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Database Design

Security
  Physical
  System access
  Database access
  Data access
  Data transfers

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Verification Tests

Define tests for:
  Database
  Data elements
  Tracking system
  Reports
Implement tests for each

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Procedures

Standard operating procedures (SOPs)
Work Instructions
Project specific procedures
Training

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Installation Tests

Database in system environment

Tracking database in system environment

Periodic Tests

Periodically test the database, … to ensure that no changes have occurred

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Training

User

Testing

Data transfers

Job responsibility

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Change Control

Define modification

Conduct impact analysis

Determine if change will be implemented

Implement change

Repeat testing when necessary

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The Validation Flow

Validation Process Flow

Change Control

User Requirements → Design → Test Criteria

User Documentation → Verification Test

Procedures → Installation Test

Training → Periodic Test

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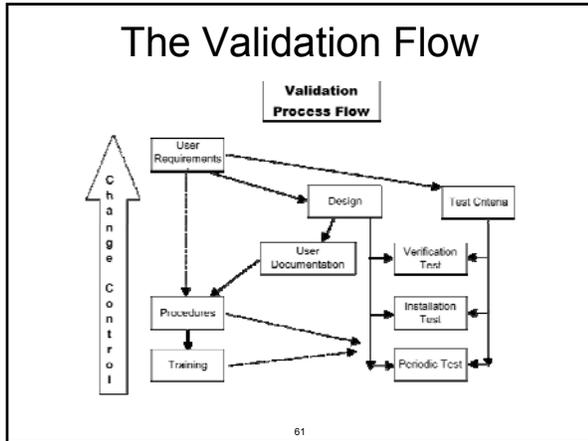
Documentation

User requirement
Design
All tests and test results
User instructions
Training
Procedures
Validation report
System validation

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Validation Requirements

Validation Process is Required:
    At the Operating Systems level
    At the Software level
    At the Applications level
    For human interactions at all levels
    Multi-disciplinary validation team

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Why is this approach used?

Repeatability and reproducibility

Best practice for quality systems

Regulations

    21 CFR Part 11

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Validation

Validation is …

… processes which ensure that software conforms to its specification and meets the need of the user.

"Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records."

… always required by Part 11.

… use a graded approach

Validation should reflect a safety-based approach to risk management.

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Validation

Application of Regulation

"Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records."

WAIT!! What does this mean?

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Safety Monitoring Plan

On-going clinical review of adverse events and serious adverse events.

Monitor recruitment

    Overall

    Site

Evaluate site compliance

Pre-planned data reports

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Safety Monitoring Plan

Potentially Reviewed by:

Steering committee

Site IRB

Individual clinical review

DSMB

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Trial Conduct and Management
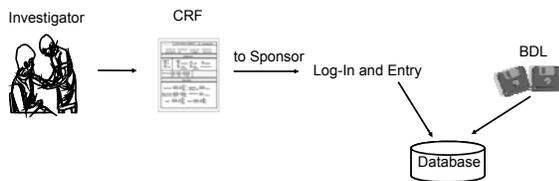
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Conducting and Managing a Clinical Trial

CRF Flow
  CRF Tracking
  Manual Review
Data Entry
Batch Data Load (BDL)
Discrepancy Management
  Data Validation
  CDM Discrepancy Resolution – conventions, etc.
  Query Flow
Coding (adverse events, medications)
SAE Reconciliation
Lab Data Review

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CDM Process Flow (Paper-based study)

Investigator   CRF   BDL

                              to Sponsor
                                          Log-In and Entry

                                              Database

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CRF Flow-Paper-based study

3-Part NCR [e.g., white, yellow, pink]
CRA sends the white and yellow copies to CDM
  Pink copy stays at site
CRF Tracking
  CRF pages logged within 24 hours of receipt
  All CRF pages stamped with the date received in house
  Forwarded to CDM

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CRF Flow-Paper-based study

Verify the CRFs are logged in correctly

Identify and retrieve missing CRFs

Forward white copies of the CRFs for archiving/scanning

Forward yellow copies ("working copy") to Data Entry with necessary notations and/or clarifications

- Verify patient initials and ID are the same for each page
- Check the spelling and legibility on text fields

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Data Entry-Paper-based study

Data Entry Guidelines – General and study-specific guidelines to enter data from CRFs into the database

Double Data Entry Performed

- All data entered twice
- Second pass is verification/reconciliation
- Same Data Entry Operator cannot perform first and second pass entry on the same data

CDM monitors ongoing data entry process

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Transition to e-CRF

Requires a paradigm shift in thinking

Requires careful planning

- Multi-disciplinary team
- Expert in paper CRF process
- Open mindedness
- Extra user training

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Use of e-CRF

Impacts
    Sites and site start-up
    DMP
    Data validation
    CRAs and monitors
Benefits
    Built-in tracking of CRFs and data discrepancies
    Data entry at site

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Benefits

Quicker startup
Reduced redundancy
Improve data quality
Reduced cost
Enhances implementation

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Efficient Methods

Establish data flow
Standardization
Pilot
Training
Quality control implemented
Quality assurance monitoring

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Batch Data Load (BDL)

The process of inputting data from an electronic file, rather than through online data entry

Multiple types of data possible (e.g., EKG, lab, patient diary)

Receives cumulative or incremental files

Data loaded into CDMS

Derivation procedures are run to populate derived fields

Develop and run edit checks

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CDM Process Flow-Paper-based study

Investigator   CRF   To Sponsor   Data Validation   BDL
Log-In and Entry
Database
Query Generation
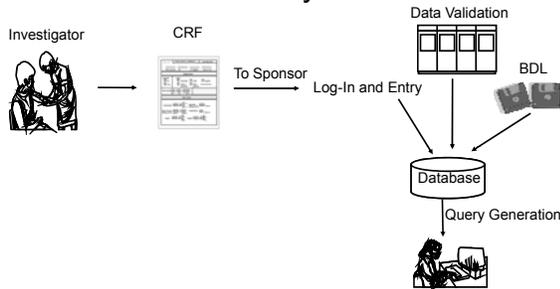
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Discrepancy Management

Note: this process may differ significantly for EDC studies

Define data handling conventions

Resolve discrepancies that arise during data entry

Data validation executed to produce electronic edit check results on the data

CDM also generates manual queries, generally on text fields; e.g.:

- Medications administered after baseline should have corresponding indications on Adverse Event
- If primary etiology is Diabetes, then Diabetes should be present on Medical History
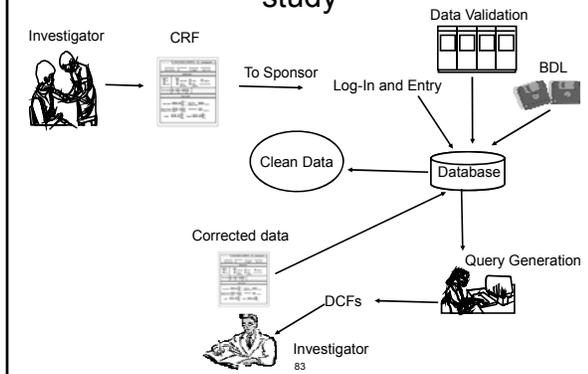
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Discrepancy Management

CDM performs discrepancy management

- Every discrepancy is reviewed to determine if it needs to be sent to the site or can be resolved in-house
- Discrepancies that do not require a query to be issued are closed
- Status in tracking system set to indicate that query will be generated
- Queries/DCFs are generated
- Status in tracking system set to indicate that query has been generated

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CDM Process Flow-Paper-based study

Investigator   CRF   Data Validation

To Sponsor   Log-In and Entry   BDL

Clean Data   Database

Corrected data

Query Generation

DCFs

Investigator

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Query Flow

Note: this process may differ significantly for EDC studies

Write clear, concise queries

Data Clarification Form (DCF) Generation

- Documents queries that are sent
- Queries electronically/manually tracked
  - internally
- Photocopy of query may be maintained internally

Sending DCFs

- Status in tracking system set to indicate that query has been sent
- Send DCFs to site (via CRA or traceable mail)

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Query Flow

Returning DCFs
- Queries can be resolved by telephone, fax, email, or by site visit
- Completed signed queries sent back to sponsor
- DCFs stamped with the date received within 24 hours of receipt
- DCFs forwarded to the CDM

Tracking DCFs
- Photocopy (yellow working copy) the resolved DCF
- Forward white copies of the DCFs for archiving/scanning
- Update query tracking spreadsheet
- Identify and retrieve missing DCFs
- Status in tracking system set to indicate that query has been received
- Review for completeness and validity

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Returned DCF

Page ID: D2002

Study of R451A
Data Clarification Form

Patient#:M5
Reviewer:

Form Name	Page # Date	Questions/Comments	Resolution
Demographic information VISIT1 Disc ID: 19302 Type: UNIVARIATE	1 20020601 Closed: N	Value of XXXXX for Date of Birth is not a valid DATE	These discrepancies are resolved DOB=12-Sep-1945 See attached for corrected copy of CRF

Investigator Signature: DR G Rose Date: 21-Apr-2006

Page 1 of 1   DCF ID: 4182   Revision #: 0

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Query Flow

Resolving Discrepancies
- Amend the database and the working CRF to correspond with resolutions on the DCF
- Status in tracking system set to indicate that query has been resolved\closed

What if the query is not answered?
- A re-query will be issued
- Will follow the same query flow

?

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Medical Coding

Understand medical terminology and the structure of electronic dictionaries

Adverse Events and Medications are coded using a system that provides a means to code verbatim terms to standard industry terms

Ensure all adverse events and medications have been appropriately coded

Coding reports are generated

At the end of the study, verify all terms are coded

Coding reports are reviewed/approved by the Medical Director (or designee)

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Medical Coding

The Right Coding Classification is Crucial

Incorrect classification can mask drug affects or make drug affects appear when none are present

The wrong classification of Adverse Events could have serious consequences for patients who later take the drug

Failure to classify and report Adverse Events correctly to the FDA can cause a drug to be taken off the market or a company to be shut down

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Why Classify Coding Terms?

Assume a study enrolling 300 patients 50% on treatment and 50% not			
Before Classification	Verbatim Term	Treatment Group Percent	Placebo Group Percent	Value of X2 Test
	Headache	2	22	1.32 not significant
	Severe Headache	71	70	0.01 not significant
	Migraine Headache	32	29	0.09 not significant
	Throbbing Headache	45	19	13.4 significant p less than .001
After Classification	Verbatim Term	Treatment Group Percent	Placebo Group Percent	Value of X2 Test
	Headache NOS	150	150	0 not significant

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Understanding Coding

Explanation of hierarchy of coding

MedDRA: LLT → PT → HLT → HLGT → SOC

WHO Drug: MP → PRG\PRT → ATC

Adverse Events vs. medications

Examples of coding process

SOC	Cardiac disorders
HLGT	Coronary artery disorders
HLT	Ischaemic coronary artery disorders
PT	Myocardial reperfusion injury
LLT	No-reflow phenomenon

SUN	A01AD - OTHER AGENTS FOR LOCAL ORAL TREATMENT B01AC - PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN C01BC - ANTIARRHYTHMICS, CLASS IC N02BA - SALICYLIC ACID AND DERIVATIVES R05FB - OTHER COUGH SUPPRESSANTS AND EXPECTORANTS
PRT	Medicinal product
PRG	<Empty>
MP	Bayer children's aspirin

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SAE Reconciliation

Data on the Adverse Event CRF is compared to data from independent SAE database

Carried out during the manual review of the CRF

If any discrepancies, a query is generated

If query results in a change to the SAE database, safety manager makes the change

If query results in a change to study database, CDM makes the change

Once all discrepancies are resolved the SAE database is final

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Lab Data Review

Reports generated to ensure lab data is accurate

Expected lab tests are present, lab unit conversions are correct

New reports generated when new data is received

Queries sent on discrepant data

Lab Outliers

Determine whether or not discrepancies for BDL lab outliers will be queried

Outlier reports sent to the Medical Director for safety monitoring perspective which are reviewed/approved

May be necessary to contact the provider (e.g. central lab) to confirm results or rerun samples

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CDM Tasks – Other

Write department WINs and SOPs

Standards 'police' (CRFs, dB modules, processes, templates, etc.)

Provide internal training/coaching for DM team

Interact with CRO for contracted DM tasks

Understand roles and responsibilities of CRO vs sponsor

Provide oversight and QC of CRO activities

Recognize, communicate, and document changes in Scope of Work

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CDM Tasks – Other

Systems

Understand architecture and functionality of clinical software applications

Provide troubleshooting for system-specific problems

Perform system-specific validation of new applications / releases

Develop, approve, and/or execute user acceptance tests

Requires understanding of regulatory guidelines

21 CFR Part 11

International Conference on Harmonization (ICH)

Good Clinical Practices (GCP)

Good Documentation Practices (GDP)

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CDM Tasks – Other

Develop & validate custom reports, utilities, etc.

Batch Data Load (BDL)

Process data transmissions from electronic sources

Participate in the identification of & request for new

CDMS features / enhancements / 'bug' fixes

System support for clinical systems

Active participation in professional organizations (e.g., OCUG, SCDM, SCT)

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Study Close Out Tasks

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Study Close-Out

Pre-QC Checklist

Database QC

Data Extracts to Statistics

QA Audit

Database Lock

Archiving (Data, Docs)

98

Database QC (paper study)

Pre-QC checklist

Ensure all steps completed before QC is performed

QC Audit

Final Data Validation to ensure no further discrepancies

Manually compare critical items from data listings to CRFs and DCFs

% of all data points to be reviewed depends on the no. of patients & volume of data

100% QC done on Safety and Efficacy data

QC should only be done on patients with no outstanding queries

QC may be performed depending upon the number and significance of outstanding queries

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Data Extracts

Create a 'snapshot' of the database (SAS format)

    This can be considered a 'soft lock'

SAS database sent to Statistics

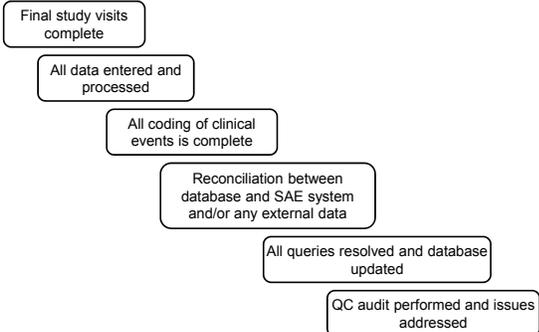Statistics creates data listings for QA audit

100

QA Audit

QA performs audit on all data

If discrepancies found, database is updated, (another) final Data Validation is run

CDM creates a new snapshot

New datasets (final database) sent to statistics

If no discrepancies, first QA snapshot is final database

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Pre-Lock Activities

Final study visits complete

All data entered and processed

All coding of clinical events is complete

Reconciliation between database and SAE system and/or any external data

All queries resolved and database updated

QC audit performed and issues addressed

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Definition

Lock: When all clinical trial data has been reviewed, queries resolved and issues addressed, the database is closed or locked.

The database cannot be changed in any manner after locking – unless an unlock has been performed (not optimum situation).

Often, the amount of time it takes from the last subject visit to database lock can be a measurement of the study team's efficiency.

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Logistics

The database lock checklist is the main tool used by the clinical data manager to carry out database lock procedures.

Exact checklist of procedures to follow before lock comes from the data management SOP, SSP or data management plan (DMP)

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Processes

Review and assure all coding of clinical events have been completed.

Determine that SAE reconciliation has been completed.

Ensure that there is agreement between the study medical monitor, biostatistician, and clinical data manager for data lock.

Determine date following last subject visit for lock and manage this timeline effectively.

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Processes

Quality Control (QC) should:

Audit the database for accuracy and completeness

Provide the clinical data manager with any questions or comments.

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Processes

Clinical Data Manager should:

Resolve QC concerns.

Provide QC with resolutions and/or changes made to the database.

QC audits changes and reports back to the clinical data manager on audit results.

Clinical data manager obtains signatures on lock memo and informs programmer that the clinical research database is ready to be extracted for analysis.

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Processes

Programmer extracts data from clinical study database:

Lock the clinical research database by request from clinical data manager and restricts all write-access to the clinical research data.

Notify members of the clinical study team the date of the database lock.

Create data exports or extracts of the clinical research trial data to support the analysis reporting by the biostatistician.

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Processes

Study Biostatistician performs preliminary analysis on the data:

- Conduct analysis and reporting according to the methodology described in the study's Statistical Analysis Plan,
- Perform analysis using tested programs,
- Review output for data accuracy and layout of the tables, listings and figures,
- Report and coordinate with clinical study team members (as appropriate) on any data issues identified during analysis and reporting,
- If any additional analyses are required, the SAP is updated and new programs are developed and implemented, and
- Communication of analysis results to Clinical Study Team for reporting.

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Database Lock Summary

Team collaboration is important for locking data appropriately and efficiently.

Use of a checklist and proper documentation is essential.

Ensure review time is understood and adhered to

Measuring your trial efficiencies leading to and including locking the database can yield useful information for future study management.

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Locking & Archiving

Ensure all pre-lock steps are accomplished
- All CRFs and DCFs received
- All discrepancies resolved
- All external data loaded
- All coding completed

QA certificate submitted
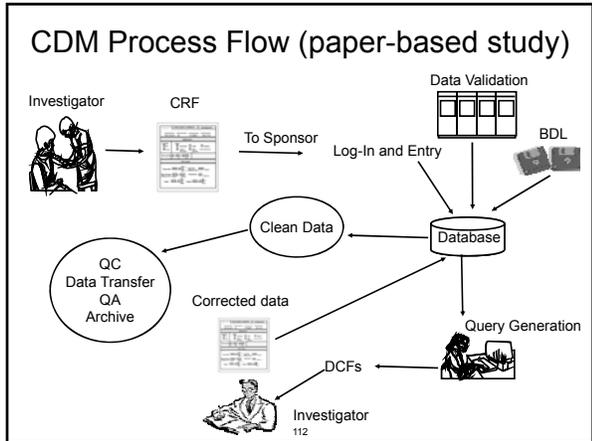- States that QA audit is satisfactorily completed

Ensure no data has been changed after the last snapshot before the database is locked
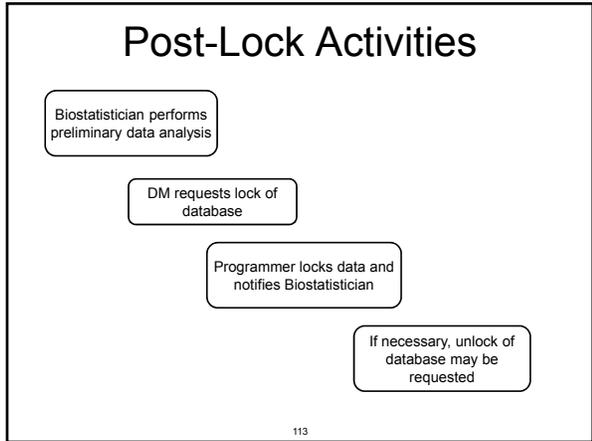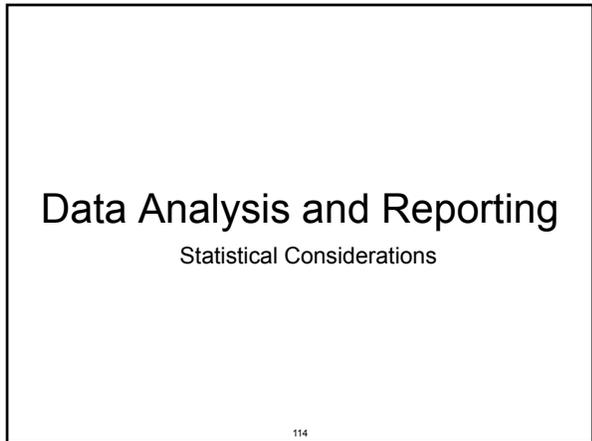
Database is locked and access limited to privileged users

Create database lock memo

Archive all study documentation

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CDM Process Flow (paper-based study)

Investigator

CRF

To Sponsor

Log-In and Entry

Data Validation

BDL

Clean Data

Database

QC
Data Transfer
QA
Archive

Corrected data

Query Generation

DCFs

Investigator

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Post-Lock Activities

Biostatistician performs preliminary data analysis

DM requests lock of database

Programmer locks data and notifies Biostatistician

If necessary, unlock of database may be requested

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Data Analysis and Reporting

Statistical Considerations

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Database Reports and Statistical Analysis

Collaboration and early planning are necessary between CDM and statistics!

Format and contents of reports typically require compromise to best optimize efforts for the two groups

Many of the standard statistical reports could be done more efficiently by CDM

Statisticians rely on CDM to 'track down' inconsistencies in the data

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Prepare Data for Use in Clinical Reports

First step for preparing data for use in clinical reports is incorporating discussion when the research plan is developed!

Pre-planning for the needs of technical, safety, and DSMB reports as well as manuscripts is critical!

Requires collaboration of CDM, statistics and clinical, and regulatory

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Prepare Data for Use in Clinical Reports

Requires pre-planning by each team member before coming together as a group

Team needs to know, ahead of time, what templates are available for reports and any applicable requirements

Team needs to decide what CDM platform will be used as well as define exporting requirements (e.g., Views, ASCII, SAS)

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Prepare Data for Use in Clinical Reports

Statisticians need to communicate their data structure needs clearly to CDM

Team needs to know the DVP thoroughly (hopefully, members of the team helped develop the DVP)

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Unblinding

Definition of unblinding

Why studies are protected from unblinding during the study

Reasons for unblinding during the study and at the conclusion of the study

Documentation for unblinding

Importance of unblinding at the end of the study

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Blinding Treatment Assignments

Blinding a study's randomized treatment assignments is vital in controlling the potential treatment biases of study participants and study personnel.

During the development and conduct of the study there are many ways that the treatment assignments may purposely or incidentally become unblinded.

Unblinding during the trial may jeopardize the scientific integrity of the study.

To minimize this risk there are a variety of procedural steps that can be taken to ensure that the likelihood of incidental unblinding is minimized.

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Unblinding Treatment Assignments

Unblinding SOP will be in place, fully written and approved by the study sponsor and appropriate committees, prior to entry of the first participant.

Procedures describe unblinding of:

individual participants for safety purposes,

entire study for interim analysis and reporting,

entire study at completion and final analyses, and

informing participants of their group assignment.

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Unblinding Study at Completion and Final Analyses

Individuals involved in endpoint assessment should not be informed of the treatment assignments prior to the lock of the data sets.

No changes should be made to the data after the dissemination of the treatment assignments.

122

Unblinding

Should occur in a consistent and controlled manner

SOP describes processes for breaking the statistical blind in a work flow process.

Roles and responsibilities should be clear.

Properly document the break (signatures and dates).

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Unblinding Summary

Three Key Elements:

Descriptions of when and when not to unblind, and authorized personnel

Established processes

Proper documentation

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Clinical Study Report (CSR)

A CSR can be described as:

A written report that integrates information from the clinical protocol, statistical methods and analyses, and the results of the human clinical trial.

Developed in accordance with ICH Guidances.

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Important Guidance Documents

ICH E6 Good Clinical Practice: Consolidated Guidance: A written description of a trial/study of any therapeutic, prophylactic, of diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

ICH Topic E3: Structure and Content of Clinical Study Reports

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Purpose of the CSR

Describes and interprets the clinical study for the regulatory reviewer.

Synthesizes the study objectives, methods and endpoints, interprets the results and includes the conclusions that justifies the choices made in the protocol and significance of the findings.

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Important Requirements

A complete report enables someone who is not familiar with the study to review and understand the details.

CSRs therefore must be:

Concise and consistent

Well organized

Easy to follow and read (cross linked appropriately and formatted)

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General Overview of Clinical Study Report

Key Elements of the CSR:

Title Page

Synopsis

Table of Contents

List of Abbreviations and Definitions of Terms

Ethics

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General Overview of Clinical Study Report

Key Elements of the CSR:
- Investigators and Study Administrative Structure
- Introduction
- Study Objectives
- Investigational Plan (Methods)
- Study Subjects and Treatment Information

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General Overview of Clinical Study Report

Key Elements of the CSR:
- Results (Efficacy Evaluation and Safety Evaluation)
- Summary and Discussion
- Overall Conclusions
- References
- Supporting Data
- Appendices

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General Overview of Clinical Study Report

Appendices
- Batch numbers by subject
- Discontinuation of subjects
- Key demographics and baseline characteristics
- Key efficacy/PK/PD by subject
- Adverse Events
- Deaths
- Non-fatal SAEs
- Discontinued study due to AEs
- Medical Labs/Vital Signs/ECG Abnormalities
- Other pertinent attributes

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General Overview of Clinical Study Report

Paper vs. Electronic

- Most organizations have an electronic CSR template
- Business rules (organization style guide) are applied for formatting, displays and headings
- Electronic publishing is an important component of "e" study reports and is a function of a document management system (future)

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General Overview of Clinical Study Report

Development of CSR

- Medical writer uses an approved template
- Meets with clinician and biostatistician at a minimum in advance of the data outputs
- Develops many sections in advance
- Standardizes across a program
- Agreement on list of tables, listings and figures

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Clinical Data Management CSR Responsibility

- Clinical data management and QC reviews the entire report
- Comments regarding findings are reviewed with the medical writer
- Verifies any changes in the conduct of the study or planned analyses
- Reviews efficacy results and tabulations of individual subject data
- Reviews appendices

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Summary

Team collaboration is key!

Content must be consistent, concise and well organized

Complete document

Efficacy results and tabulations of individual subject data

Tables, figures and graphs referred to but not included in the text

Appendices

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Promoting Efficiency
in
Clinical Data Management

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Continual Process Improvement

Promote efficiency

Reporting and Metrics

Avoid common mistakes

Trained and motivated staff

Commitment to best practices/standards

CDISC

Standardize database and CRFs when possible

Promote team communication

Commitment to Quality Assurance

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Promote Efficiency

Reporting and Metrics

Essential component of Clinical Data Management

Develop ad-hoc reports for clinical team as requested

Identify and follow up inconsistent data points

Statistics on performance

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Promoting Efficiency

Reporting and Metrics (cont.)

Analyzing measures of efficiency can provide process improvements that increase data quality for future studies. This includes:

Total number of discrepancies

Percentage of discrepancies resolved "in house"

Percentage of discrepancies resolved via site data modifications

Top 5 or 10 discrepancies

Average time to resolve queries

Time from last query resolved to study lock

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Promoting Efficiency

Prevent Common Mistakes

Poor database design

Poor CRF design

Missing items—times, dates, etc.

Poor coding

Generic and brand name drugs coded differently

Unnecessary queries

Insufficient data checks

Expensive to resolve

Untrained staff

Statistical analysis of "dirty data"

Inadequate company standards

Naming conventions, documentation, etc

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Promoting Efficiency

Trained and Motivated Staff

Review training programs on a regular basis.

Ask trainees for input on how to make training program better.

Give staff the opportunity to present relevant data management topics at meetings.

Reward staff for above average performance.

Give your staff the training resources they need to perform their job effectively.

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Commitment to Best Practice

CDISC

CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

CORE PRINCIPLE:

Lead the development of standards that improve process efficiency while supporting the scientific nature of clinical research.

MISSION:

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

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Commitment to Best Practice

CDISC

What is the SDTM?
STUDY DATA TABULATION MODEL

SDTM is an example of the promotion of the gold standard for study data naming conventions

CDISC Study Data Tabulation Model (SDTM) and implementation guide available at www.cdisc.org

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Promote company standards

Standard naming conventions

Standard CRFs

Templates-DMPs, SAPs, etc

Standard databases

Increase reproducibility

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Consequences of Good vs Poor Data Management

Good CDM   Poor CDM

Loss of data integrity

Invalid study

Frustrated team

Angry sponsor

Wasted time & $$$

Unemployed team

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Promote team communication

Each functional representative on a team brings a unique set of experiences, skills, and knowledge

Medical/Clinical Director & personnel

CRA

Statistics

Data Management

Programmers

Data Entry

Ensure that the team is communicating on a regular basis via meetings, teleconferences, emails, reports, etc.

The benefits & payoffs for the proper level of team involvement and inclusion are phenomenal!

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Summary

Clinical Trial: a complicated process, made possible via:

- Teamwork / Team reviews
- Communication
- Standards
- Continual process improvements
- Participation

Involve CDM early & throughout

Keys:

- Quality … Quality … Quality!
- Standards … standards … standards!
- Team work … team work … team work!

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Questions?

References

Annex 11 to the EU Guide to Good Manufacturing Practice – Computerized Systems, European Commission, Directorate General III – Industry Pharmaceuticals and Cosmetics, Final Practice1998 Edition

BioPharm Systems Inc, Glossary of Terms

Clinical Data Management Practices, Society for Clinical Data Management Version 2 January 2002

Clinical Research Dictionaries, Michigan Institute for Clinical and Health Research

General Principles of Software Validation; Final Guidance for Industry and FDA Staff, U.S. Department of Health and Human Services Food and Drug Administration, January 11, 2002

Glossary of Clinical Trials Terminology, Applied Clinical Trials

Glossary of Clinical Trials Terms, ClinicalTrials.gov

Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, U.S. Department of Health and Human Services, Food and Drug Administration, April 1999

ICH Topic E3: Structure and Content of Clinical Study Reports

http://en.wikipedia.org

www.cdisc.com

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