Workshop P9
The Essentials of Clinical Data Management

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Knowledge of Subject</th>
<th>Organization/Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devin J. Hunt</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Hector Robertson</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>
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

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
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

Your Presenters

Devin J. Hunt
   Manager, Statistical Programming for EmpirStat, 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.

Understanding Clinical Research
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.

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.

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.
## 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.

## 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.

## Data Management Roles and Responsibilities
Clinical Data Manager’s Roles

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

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

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
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

Clinical Data Manager’s Roles

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

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
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)

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)

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
Establish Effective Communication

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

Develop Research Plan

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

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 …
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?

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

Planning and Preparation
CDM Study Activities

Protocol
Enrollment
LPLV
QA

Analysis & Reporting

Study Timeline

Procedures
Database Development
Data Processing, Cleaning, Discrepancy Management, Coding
Database Snapshot/ Transfer to Stats
Lock, Archive

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)

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)
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

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)

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
Common Design Challenges

- Evolving protocol development
- Lack of communication
- Electronic data sources
- Non-protocol related data
- Protocol amendments

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

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
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)

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)

Easily accessed
Less is better
Key critical instructions to clarify fields
Appropriate review
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

Sample Annotated CRF

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
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

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

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
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

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

Elements of Classic Validation
  Requirements
  Design
  Verification Tests
  Procedures
  Training
  Installation Tests
  Periodic Tests
  Change Control
  Documentation
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!"

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 known conditions with defined inputs and outputs

User Requirements

- Data flow graphic
- Annotated CRF
- Elements of external data sources
- Calculations for 'raw' data
- Required data validations
- Test data
- Analysis dataset requirements
User Requirements
Deliverables
- Data transfers
- Analysis dataset requirements
- Reports
- Tracking system

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

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

- Security
- Physical
- System access
- Database access
- Data access
- Data transfers

Verification Tests

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

Procedures

- Standard operating procedures (SOPs)
- Work Instructions
- Project specific procedures
- Training
Installation Tests
Database in system environment
Tracking database in system environment

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

Training
User
Testing
Data transfers
Job responsibility

Change Control
Define modification
Conduct impact analysis
Determine if change will be implemented
Implement change
Repeat testing when necessary
The Validation Flow

Validation Process Flow

Documentation

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

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
Why is this approach used?
- Repeatability and reproducibility
- Best practice for quality systems
- Regulations
  - 21 CFR Part 11

Validation
- Validation is ...
  - processes which ensure that software conforms to its specification and meets the need of the user.
- ... always required by Part 11.
- ... use a graded approach

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?
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

Safety Monitoring Plan

Potentially Reviewed by:
Steering committee
Site IRB
Individual clinical review
DSMB

Trial Conduct and Management
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

CDM Process Flow (Paper-based study)

Investigator to Sponsor Log-In and Entry

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
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

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

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
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

Benefits

- Quicker startup
- Reduced redundancy
- Improve data quality
- Reduced cost
- Enhances implementation

Efficient Methods

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

CDM Process Flow-Paper-based study

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
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

CDM Process Flow-Paper-based study

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)
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

Returned DCF

DR G Rose 21-Apr-2006
DOB=12-Sep-1945

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
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)

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

Why Classify Coding Terms?

<table>
<thead>
<tr>
<th>Verbatim Terms</th>
<th>Treatment Group Percent</th>
<th>Placebo Group Percent</th>
<th>Value of X2 Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>20</td>
<td>20</td>
<td>1.32 not significant</td>
</tr>
<tr>
<td>Severe Headache</td>
<td>11</td>
<td>70</td>
<td>0.011 not significant</td>
</tr>
<tr>
<td>Migraine Headache</td>
<td>32</td>
<td>39</td>
<td>0.09 not significant</td>
</tr>
<tr>
<td>Throbbing Headache</td>
<td>80</td>
<td>89</td>
<td>13.4 significant less than .001</td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>Headache NOS</td>
<td>190</td>
<td>150</td>
<td>0 not significant</td>
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</tbody>
</table>
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

<table>
<thead>
<tr>
<th>SOC</th>
<th>Cardiac disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLT</td>
<td>Coronary artery disorders</td>
</tr>
<tr>
<td>HLGT</td>
<td>Ischaemic coronary artery disorders</td>
</tr>
<tr>
<td>PT</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>LLT</td>
<td>No-reflow phenomenon</td>
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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

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
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

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)

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)
Study Close Out Tasks

Study Close-Out
Pre-QC Checklist
Database QC
Data Extracts to Statistics
QA Audit
Database Lock
Archiving (Data, Docs)

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
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

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

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
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.

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).

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.
Processes

Quality Control (QC) should:
Audit the database for accuracy and completeness
Provide the clinical data manager with any questions or comments.

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.

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.
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.

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.

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
CDM Process Flow (paper-based study)

Post-Lock Activities

Data Analysis and Reporting

Statistical Considerations
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.

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.

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).
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).

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

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.
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.

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.

Unblinding

Should occur in a consistent and controlled manner. SOP describes processes for breaking the statistical blind in a workflow process. Roles and responsibilities should be clear. Properly document the break (signatures and dates).
Unblinding Summary

Three Key Elements:
- Descriptions of when and when not to unblind, and authorized personnel
- Established processes
- Proper documentation

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.

Important Guidance Documents

ICH E6 Good Clinical Practice: Consolidated Guidance:
A written description of a trial/study of any therapeutic, prophylactic, or 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
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.

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)

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
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

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

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
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)

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

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
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

Promoting Efficiency in Clinical Data Management

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
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

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

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
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.

Commitment to Best Practice

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.

Commitment to Best Practice

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
Promote company standards

Standard naming conventions
Standard CRFs
Templates-DMPs, SAPs, etc
Standard databases
Increase reproducibility

Consequences of Good vs Poor Data Management

Good CDM
Loss of data integrity
Invalid study
Frustrated team
Angry sponsor
Wasted time & $$$
Unemployed team

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!
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!

Questions?

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