Clinical Data Management

Sponsored by
Center for Cancer Research
National Cancer Institute

Introduction

- Clinical data management (CDM) consists of various activities involving the handling of data or information that is outlined in the protocol to be collected/analyzed. CDM is a multidisciplinary activity.

- This module will provide an overview of clinical data management and introduce the CCR's clinical research database. By the end of this module, the participant will be able to:
  - Discuss what constitutes data management activities in clinical research.
  - Describe regulations and guidelines related to data management practices.
  - Describe what a case report form is and how it is developed.
  - Discuss the traditional data capture process.
  - Describe how protocols are developed in Cancer Central Clinical Database (C3D).

Clinical Data Management

- A multi-disciplinary activity that includes:
    - Research nurses
    - Clinical data managers
    - Investigators
    - Support personnel
    - Biostatisticians
    - Database programmers

- Various activities involving the handling of information outlined in protocol

Clinical Data Management Activities

- Data acquisition/collection
- Data abstraction/extraction
- Data processing/coding
- Data analysis
- Data transmission
- Data storage
- Data privacy
- Data QA

Guidelines and Regulations…

- Good Clinical Practice (GCP):
  - Trial management; data handling, record keeping (2.10, 5.5.3 a-d)
  - Subject and data confidentiality (2.11; 5.5.3 g)
  - Safety reporting (4.11)
  - Quality control (4.9.1; 4.9.3; 5.1.3)
  - Records and reporting (5.21; 5.22)
  - Monitoring (5.5.4)

…Guidelines and Regulations

- 21 CFR Part 11
  - Applies to all data (residing at the institutional site and the sponsor's site) created in an electronic record that will be submitted to the FDA
  - Scope includes:
    - validation of databases
    - audit trail for corrections in database
    - accounting for legacy systems/databases
    - copies of records
    - record retention

Case Report Forms

Patient X1 Page 13 (Pharmacoki for Course 1) Page 1 of 1.

Visit Date 12-Dec-2006   Blank ☐   Comment _____

Phkm1 Phkm2 COM

Type PK1   Blank ☐ ☐

PHARMACOKINETICS - 1

Course # ☐   Day in Course ☐

Study Agent _____   Specimen Sampled _____

Start Date ____   Start Time ____   Stop Date ____   Stop Time ____

Sample ID #	Planned Interval	Sample Collected?	Actual Start Date	Time	Time Interval (min)	Parent Study Agent Assay 1	Assay 2	Mean	UOM	Metabolite Assay 1	Assay 2	Mean	UOM
	PRE-DOSE												
	0												
	0.5												
	1												
	2												
	4												
	8												
	12												

CONCOMITANT MEASURES/MEDICATION
NCI/DCTD/CTMS CASE REPORT FORM
(Include all supportive measures instituted while on study)

Date Completed: (dy/mth/yr)	Protocol #:	Institution:	Sheet #:	Patient ID:
Start Date (dy/mth/yr) ---------- Stop Date (dy/mth/yr)	Agent Or Procedure	Total Daily Dose --------------- Units		Schedule --------------- Reason
1. ----------		---------------		---------------
2. ----------		---------------		---------------
3. ----------		---------------		---------------

PharmaForm - E-Form

File

New Patient Screening

Protocol: MP_914_98_5

Subject ID: talbert-1

Visit ID: Screening

Date of Birth: Month 12   Day 31   Year 98

Sex: ☐ Female   ☉ Male

Ethnicity: ☉ Caucasian   ☐ Hispanic   ☐ African American   ☐ Other _____

Height (in cms): 100

Weight (in kgs): 100

Body surface area: 40.39

Ideal Body Weight: 2.551

Save   Submit to   Exit

What is a Case Report Form (CRF)?...

- Data-reporting document used in a clinical study

- Collects study data in a standardized format:

  - According to the protocol
  - Complying with regulatory requirements
  - Allowing for efficient analysis

…What is a Case Report Form (CRF)?

- Allows for efficient and complete data collection, processing, analysis and reporting

- Facilitates the exchange of data across projects and organizations especially through standardization

- Types: Paper, electronic/web interface

- Accompanied by a completion/instruction manual

CRF Relationship to Protocol

- Protocol determines what data *should* be collected on the CRF

- All data *must* be collected on the CRF if specified in the protocol

- Data that will not be analyzed *should not* appear on the CRF

General Considerations for CRF Development…

- Collect data with all users in mind

- Collect data required by the regulatory agencies

- Collect data outlined in the protocol

- Be clear and concise with your data questions

…General Considerations for CRF Development

- Avoid duplication

- Request minimal free text responses

- Collect data in a fashion that:
  - allows for the most efficient computerization
  - similar data to be collected across studies

Elements of a CRF

- The term CRF indicates a single page

- A series of CRF pages makes up a CRF Book

- One CRF book is completed for each subject enrolled in a study

- Three major parts:
  - Header
  - Safety related modules
  - Efficacy related modules

Header Information

- Key identifying Information

- ***MUST HAVES***
  - Study Number
  - Site/Center Number
  - Subject identification number

Safety Modules

- Keep safety analysis requirements of the protocol in mind

- Follow the general guidelines for CRF development

- Safety Modules include:
  - Demographic information
  - Adverse Events
  - Medical History/Cancer history (e.g., diagnosis, staging)
  - Physical Exam, including Vital Signs
  - Concomitant/Concurrent Medications/Measures
  - Deaths
  - Drop outs/off-study reasons
  - Eligibility confirmation

Efficacy Modules

- Considered to be "unique" modules and can be more difficult to develop
- Protocol dictates the elements required in efficacy modules
- Define
  - Key efficacy endpoints of trial (primary and secondary_
  - Additional test to measure efficacy (e.g.: QOL)
  - How lesions will be measured (longest diameter, bi-dimensional, volumetric)
  - CR, PR, SD, PD
  - Required diagnostics
- Include appropriate baseline measurements
- Repeat same battery of tests

Standard CRFs

- Allows rapid data exchange
- Removes the need for mapping during data exchange
- Allows for consistent reporting across protocols, across projects
- Promotes monitoring and investigator staff efficiency
- Allows merging of data between studies
- Provides increased efficiency in processing and analysis of clinical data

CRF Development Process…

- Begins as soon in the study development process as possible

- Responsibility for CRF design can vary between clinical research organizations (e.g.: CRA, data manager, Research Nurse, Database Development, Dictionary Coding, Standards)

- Include all efficacy and safety parameters specified in the protocol using standard libraries

…CRF Development Process

- Collect ONLY data required by the protocol

- Work with protocol visit schedule

- Interdisciplinary review is necessary
    - Note:
        - each organization has its own process for review/sign-off
        - Should include relevant members of the project team involved in conduct, analysis and reporting of the trial

Properly Designed CRF

- Allows components or ALL of the CRF pages to be reused across studies
- Saves time
- Saves money

Poorly Designed CRF

- Poorly designed CRFs will result in data deficiencies including:
  - Data not collected as per protocol
  - Collecting unnecessary data (i.e.: data not required to be collected per protocol)
  - Impeding data entry process
  - Database requiring modifications throughout study

Electronic CRFs

- The use of Remote Data Capture (RDC) is increasing
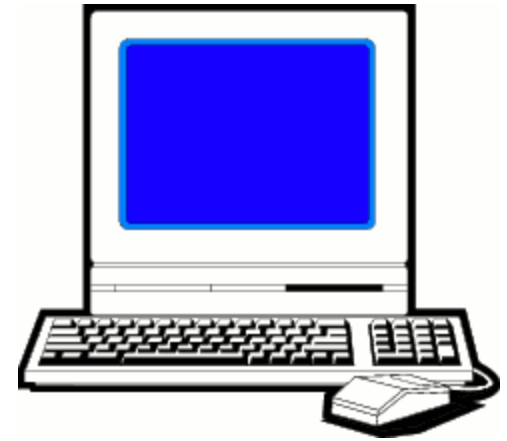
- In general, the concepts for the design of electronic CRFs/RDC screens are the same as covered for paper

- No need to print and distribute paper

CRF Completion

CRF Completion…

- According to GCP Section 4.9.1, the investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported on the CRFs and in all required reports. This includes ensuring:
  - all sections have been completed, including the header with identifying items
  - all alterations have been properly made
  - all adverse events are fully recorded and that for all serious adverse events, any specific documentation has been completed

…CRF Completion

- Data is taken from the source documents (e.g.: medical record) and entered onto the CRFs by study personnel. This is referred to as data abstraction.

- Only designated members of the research staff should be allowed to record and/or correct data in the CRFs

  - Typically this responsibility resides with the Data Manager/ Research Nurse

Tips: CRF Completion…

1. CRF completion/instruction manual should be observed to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor

2. Make sure appropriate protocol, investigator and subject identifying information is included in the Header (for RDC, may be pre-populated)

3. Ensure data is entered in the correct location or data field

…Tips: CRF Completion…

4. Use the appropriate units of measurement (UOM), and be consistent

5. Check to see that data is consistent across data fields and across CRFs
   - E.g.:
     - Make sure visit dates match dates on the laboratory or other procedure reports;
     - Make sure the birth date matches the subject's age;

6. Use only the abbreviations authorized per completion/instruction manual

7. Double check your spelling

…Tips: CRF Completion

8. Watch for transcription errors
   - E.g.: sodium level should be "135" and entered as "153"

9. Do not allow entries to run outside the indicated data field; this important data might be missed during data processing

10. Use "comments" section to elaborate on any information, ***but keep to a minimum***

Timeliness of CRF Completion

- Ideally CRFs should be completed as soon after the subject's visit as possible

- Ensures that information can be retrieved or followed-up on while the visit is still fresh in the healthcare provider's mind, and while the subject and/or the information is still easily accessible

REMEMBER....

- Data cannot be entered onto a CRF if it is not in the medical record or for some documents, in the research record

- If the individual completing the CRF, finds missing or discrepant source data he/she should:
  - Notify the research nurse or health care provider who then will provide the data
  - If applicable, contact outside source (i.e.: outside lab or doctor's office)

Common Errors …

- Logical
  - date of the second visit is earlier than the first visit
- Inaccurate information
  - source document says one thing, the CRF says another
- Omissions
  - AE is recorded on the CRF but not on the source document
- Transcription errors
  - date errors, 11-2-59 instead of 2-11-59

...Common Errors

- Abbreviations
  - unless an approved list of abbreviations is distributed and utilized, data entry personnel often misinterpret abbreviations
- Spelling errors
- Illegible entries/"write-overs"
- Writing in margins

Correcting Paper CRF Entries…

- If corrections are necessary, make the change as follows:
    - Draw one horizontal line through the error;
    - Insert the correct data;
    - Initial and date the change;
    - **DO NOT ERASE, SCRIBBLE OUT, OR USE CORRECTION FLUID OR ANY OTHER MEANS WHICH COULD OBSCURE THE ORIGINAL ENTRY**

- These procedures ensure a complete "audit trail" exists for all entries.

…Correcting Paper CRF Entries

ENROLLMENT

NCI/DCTD/CTMS CASE REPORT FORM

Date Completed (dy/mth/yr)	Protocol #	Institution	Patient ID
01/JAN/2005	05C1234	NCI EN ~~NIC~~ 9/8/05	12345678

Sex (circle): M (F)	Date of Birth (dy/mth/yr): 03/JAN/1925	Age: **80**

Race: *check one* or *more*   [ ] 01 White   [X] 06 American Indian or Alaska Native   [ ] 03 Black or African American   [ ] 99 Unknown   [ ] 04 Native Hawaiian or Other Pacific Islander   [ ] 05 Asian

Ethnicity: [ ] 9 Unknown   [ ] 1 Hispanic or Latino   [X] 2 non-Hispanic

1. Complete each form in black or blue pen to ensure good photocopies.

2. All dates are to be expressed in day/month/year (dy/mth/yr) format. To avoid ambiguity, months are to be recorded using a three letter abbreviation (i.e., Jan, Feb, Mar., etc.). Years are to be recorded as four digits (i.e. 1998).

Electronic Data Collection Process

- Web-based interface
  - Sponsor or site dependent

- Ensures data integrity:
  - Controls the ability to delete or alter previously entered data
  - Provides an audit trail for data changes
  - Protects the database from being tampered with
  - Ensures data preservation (e.g. automatic back ups)

Process of Data Transfer to Sponsor

Traditional (Paper)
Electronic

Traditional Data Transfer…

- CRF Books developed by sponsor and supplied to the site for completion along with completion/instruction manual

- Paper CRFs are either 2 or 3 part NCR (No Carbon Required paper)
  - Use a black or blue ballpoint pen for permanency – and PRESS HARD

- At the time of a monitoring visit, CRFs are reviewed for adherence to completion guidelines and verified against source documents by the Monitor

…**Traditional Data Transfer** …

- During the monitoring visit, site staff make required corrections to CRFs

- Verified/corrected CRFs are submitted to the sponsor, leaving a legible copy of the CRF at the site
  - e.g.: CRA may hand carry completed CRFs to the sponsor;

- If data is not retrieved at the time of the monitoring visit, sponsor may want the CRFs submitted via mail or facsimile

…Traditional Data Transfer

- Sponsor enters the CRF data into a centralized database (generally done by 2 separate individuals, called double data entry) and reviews the data for errors

- If inconsistencies are found, the sponsor generates data queries (forms may vary slightly from sponsor to sponsor) and sends to the site

- Site staff investigates these queries and responds to them either directly on the data query form or on the CRF. The data correction is then re-submitted to the sponsor for entry into their database.

Data Transfer:
Electronic CRF (eCRF)

- Site records data from source documents to the electronic database or the web interface
- Data periodically electronically transmitted to Sponsor/CRO or automatically resides in Sponsor database
- Real-time review of data performed by in house CRAs
  - Less frequent CRA visits
- Electronic queries generated and sent to site
- Database lock

Cancer Central Clinical Database (C3D)…

- C3D is an integrated clinical trial information system for the CCR

- System is secure, compliant with regulatory requirements (21 CRF Part 11)

- System is friendly and flexible for user

…Cancer Central Clinical Database (C3D)

- Designed to allow integration with the NCI extramural divisions and the NIH Clinical Center CRIS (Clinical Research Information System).
  - Currently this is being done with labs drawn at the Clinical Center.

- Oversight is done by the Control and Configuration Management Group (CCMG) whose membership has clinical and IT expertise

C3D Overview…

- Based on commercial software produced by the Oracle Corporation called Oracle Clinical (OC)

- Allows for Remote Data Capture (RDC) so that local and remote personnel enter and manage clinical data over a LAN, intranet, telephone line, or the Internet

- Data can be electronically transferred to Sponsors (responsibility of DM IT team)

…C3D Overview

- A template set of master CRFs have been created to collect the data required by CCR protocols

- Templates are reused and each study will only use the eCRFs that are appropriate and required for that study

- Confidentiality statement signed at time of training

J-Review

- J-Review is a software product that allows us to get data out of C3D into a variety of reports

- Numerous template reports have been developed including:
  - Adverse event summary
  - Demographics
  - Drug administration

- Also allows for customized reports

C3D eCRFs Resources

- [C3D Data Entry](#)

- [Manual for the Completion](#) of the NCI/CCR/C3D Case Report Forms

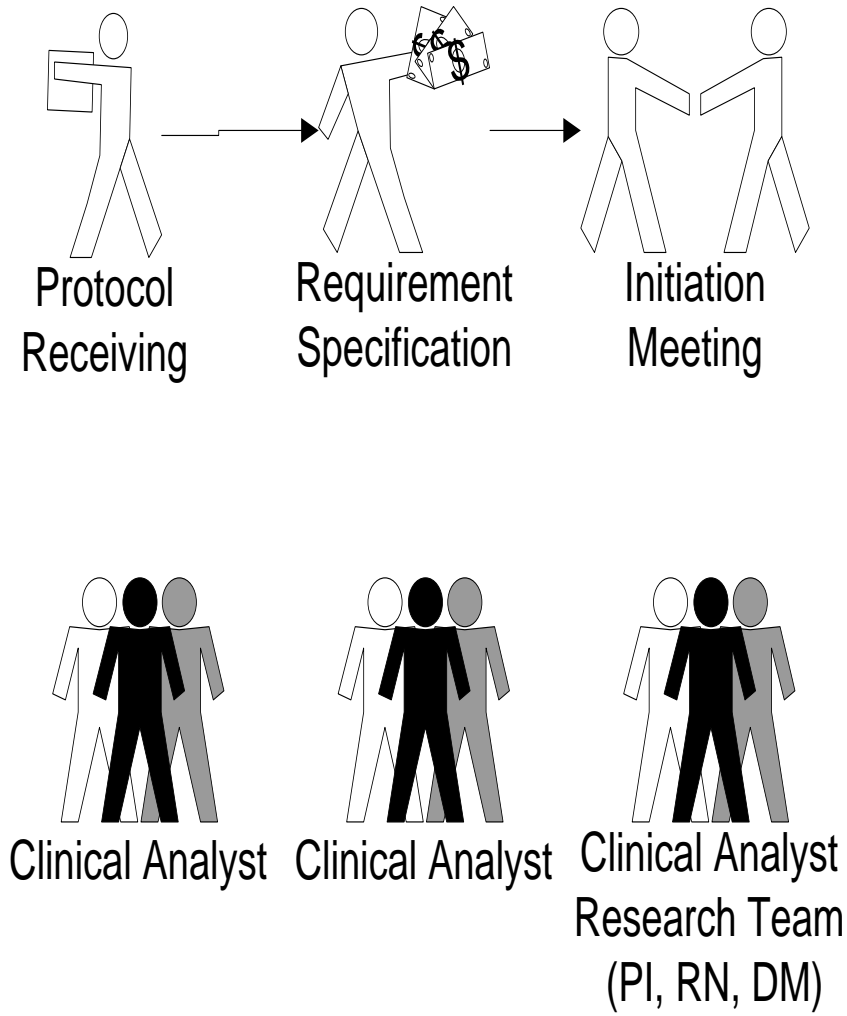- Access to [J-review](#) is granted once training occurs.

C3D Protocol Build Process…

- OCD determines if a protocol will be built in C3D

- Currently the following are built:
  - All CTEP-sponsored, non-cooperative group trials
  - All industry-sponsored trials with company agreement (if not, sponsor will then provided paper crfs)
  - All internal/non-sponsored interventional trials

… C3D Protocol Build Process…

…

- Clinical Analyst (CA) receives protocol from IRB
- CA identifies standard eCRFs to be used
- CA develops the eCRF book and identifies if new eCRFs are needed
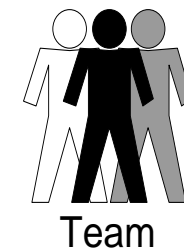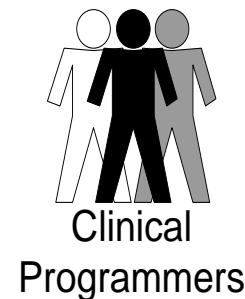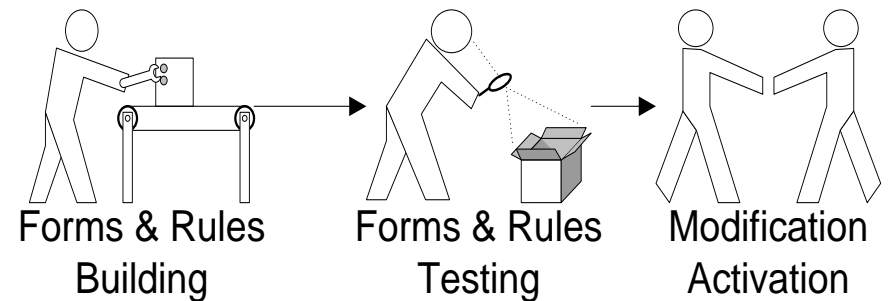- CA meets with research team to confirm eCRF book

Protocol Receiving

Requirement Specification

Initiation Meeting

Clinical Analyst

Clinical Analyst

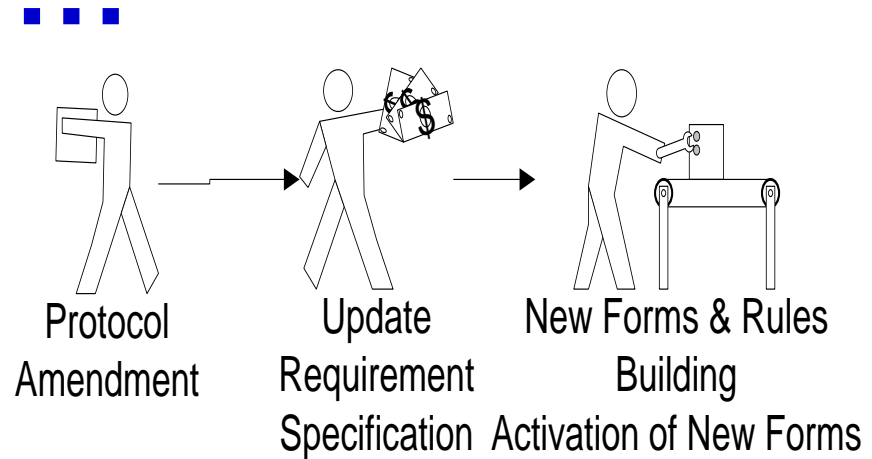Clinical Analyst Research Team (PI, RN, DM)

… C3D Protocol Build Process…
…

- Clinical Programmers (CP) build protocol (eCRFs) in C3D
- Research team tests the build/enters data
- Modifications made as needed
- Protocol activated in C3D by CA/CP
- eCRFS available for data entry

Forms & Rules Building

Forms & Rules Testing

Modification Activation

Clinical Programmers

Team

Clinical Analyst Clinical Programmers Team

… C3D Protocol Build Process…

…

- If a protocol amendment requires changes in C3D (e.g. eligibility criteria), CA/CP will develop new eCRF
- Team will review, sign-off
- CA/CP will activate new eCRF Book

Protocol Amendment

Update Requirement Specification

New Forms & Rules Building Activation of New Forms

Clinical Analyst   Clinical Analyst   Clinical Programmers

Training

- There is specific training required for use of C3D and I-review.
  - See <u>Training Sessions</u> for date, time and location.

Industry Sponsored Queries

- Sponsor generates questions/queries:
  - During/end of a monitoring visit
  - After data sent to sponsor and reviewed/entered in sponsor's database

- Site corrects CRF:
  - During/between monitoring visit
  - May need to also sign-off on query form itself

CTEP Sponsored CTMS Clarification

- These are paper queries generated for CTEP-sponsored, CTMS-monitored trials
- Sent every Monday by Theradex (contractor for CTEP)

CTEP Sponsored CDS Rejection/Notification

- These are electronic data queries for CTEP-sponsored, CDS-monitored clinical trials
- CDS submitter receives notice
  - For studies in C3D, the notification will be sent to the CCR IT Programmer who transfers the data to CDU
- CCR staff corrects data in the database and resubmits
- Process occurs until data is loaded correctly in CDS

Missing Data at Time of Transfer

- Missing data elements
    - Source Document (SD) not supporting CRF
    - CRF not supporting SD
- Referred to as:
    - Discrepancies
    - Queries
    - Clarifications
- Identified by:
    - Sponsor
    - Database

Sponsor Queries

- Sponsor generates:
  - During/End of a monitoring visit
  - After data sent to sponsor and reviewed/entered in database
- Site corrects CRF:
  - During/between monitoring visit
  - May need to sign-off on query

Database Discrepancies

- Failure of entered data to pass a validation check as applied by a database

- Univariate discrepancy – single data element errors (e.g., not using provided pick-list, missing data in a field)

- Multivariate discrepancy – multiple data element errors (e.g., male patient with + beta HCG)

Quality Control

According to GCP Section 5.1.3 quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Assessing the QC/QA Process

- Are staff checking their own work?

- Are staff relying on others to check their work?

- Does the organization have a QA plan for monitoring protocol adherence and data collection?

- Are there SOPs related to data management?

- How soon after a visit is a CRF completed?

- Is all data, as defined in the protocol, captured from the source document to the CRF?

Terminology

- Quality Control

- Quality Assurance

- Quality Improvement

Quality Control (QC)

- Ongoing and concurrent review of subject data
  - Typically 100%
  - Checking your own work and work of others

- Verify that data collected and abstracted:
  - Correctly entered onto CRF
  - Able to be found in source document
  - Follows regulations and guidelines

- Individual team member level

Quality Assurance (QA)

- Planned, systematic check done at the branch or organizational level

- Verifies:
  - Trial is performed as per the approved plan
  - Data generated is accurate

- Identifies problems and trends:
  - Retrospective and involves sampling of subjects and data
  - Pulls all the pieces together to gain a picture (measurement) of compliance
  - Ensures staff is compliant with internal and external regulations/guidelines

QA Activities

- Internal monitoring/audits
  - Compile all data components and gain a measurement of compliance
- Clarification monitoring
  - Assess for trends
  - Review clarifications responses before they are submitted to sponsor
- Measure data inconsistencies and trends using a sampling of the data prior to audits/monitoring visits
- Summarize QA findings and report to management
- Identify learning needs

QA Activities for CCR

- The following are examples of QA activities for the CCR:
  - Office of the Clinical Director (OCD)
    - Internal monitoring/audits
    - Conduct audits per upon request, for PI sponsored studies
    - Clarification monitoring

  - Data Management Contractor
    - Develop QA tools
    - Summarize QA findings and report to management, education and training
    - Identify needs

Quality Improvement (QI)

- Result of QC and QA
- Developing a plan includes:
  - Identifying root causes of problems
  - Intervening to reduce or eliminate these problems
  - Taking steps to correct the process(es)
  - Identifying trends and areas for improvement
  - Identifying solutions:
    - Assess work flow and time management activities
    - Develop tools for source documentation
    - Assess training needs
    - Involve appropriate staff in resolution
  - Implementing new/updated solution

QI Activities for CCR

- ## Team Level:
  - Based on QC activities: identifying trends
  - Based on audit/monitoring visit results

- ## OCD CCR Level:
  - Based on audit/monitoring visit results
  - Guide in implementing processes for making corrective changes

Responsibilities

- Research Team responsibilities

- Research Nurse responsibilities

- Data Manager responsibilities

Research Team

- Ensure that all source data is documented in the Medical Record/Research Chart with accuracy, completeness, and consistency

- Ensure the overall quality of the research data is verifiable and acceptable for sponsor submissions, publications, etc.

- Review data discrepancy/clarification resolutions for accuracy, consistency and timely response

Research Nurse….

- Provide accurate and complete source documentation

- Develop, implement, and maintain a team QC plan:
  - Establish a schedule of QC activities
  - Quality check source documentation, data abstraction, CRFs completion
  - Quality check of database
    - Verify function in database

- Develop team quality improvement plan, as needed

….Research Nurse

- Lead Team QC meeting:
    - Provide administrative updates
    - Provide patient updates
    - Perform QC on data/resolve issues

- Review query/clarification:
    - Assign to Data Manager(s), if appropriate, to investigate and resolve or resolve yourself
    - Review and sign off:
        - Follow sponsor SOP

Data Manager….

- Abstract data onto CRFs according to what is found in the source documents (Medical Record or Research Chart) and CRF Instruction Manual

- Abstract data in a timely fashion, this includes entry into database

- Code Adverse Events accurately utilizing the appropriate version of CTCAE, as per protocol

....Data Manager

- Apply quality control checks at each stage of data handling
  - Ensure that data elements abstracted are complete and accurate
    - Contact Research Nurse for missing source data
  - Resolve discrepant data – ongoing
  - Utilize database report tools to assist with QC activities

Guiding Principles

- Source documents need to be accurate and complete
- Data abstraction should occur in real time
- QC/QI is the responsibility of every research team member
- QC/QI should be completed on all protocol data for all protocols
- QC/QI should be proactive and ongoing
- Each team member should know and understand the roles and responsibility of each team member

Resources

- Guidelines for Good Clinical Practice. International Conference on Harmonisation (ICH).
  - http://www.ich.org

- FDA, Title 21 CFR Part 11
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11

Evaluation

Please complete the [evaluation form](#) and fax to Elizabeth Ness at 301-496-9020.

For questions, please contact Elizabeth Ness
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nesse@mail.nih.gov