Data Management in Clinical Trials

Introduction to the Principles and Practice of Clinical Research

February 19, 2013
Diane St. Germain, RN, MS
Nurse Consultant
Division of Cancer Prevention
National Cancer Institute
Objectives

Discuss the importance of proper data collection.
Identify the types of data collected for clinical trials.
List potential source documents used for data collection.
Describe adverse event reporting.
Describe the regulatory requirements for data collection.
Why is Data Management so Important?
Drives the outcome of a clinical trial
Analyzed to determine the results of a trial
Determines toxicities
Data needs to be
Accurate
Scrupulous
Verifiable
Timely
Graphic:
garbage in = garbage out
The Research Team

Principal investigator
Clinical research nurse/CRA
Data manager
Database administrator
Statistician
Graphic: Following the Protocol Road Map...
Considerations During Protocol Design & Development

The data elements to be collected
The Design of the data collection instruments
The design of the computer database
Data Elements Captured
Study Entry
Demographic data
Eligibility criteria
Family history
Patient history
Prior cancer treatment
Concomitant medications
Lab data/test results
Review of current symptoms
Data Elements Captured
Treatment
Assessments
Concomitant meds
Adverse events
Patient diaries
QOL questionnaires
Follow-up
Common Data Elements
Data elements that have been determined to be identical between projects or contexts
Facilitates understanding and sharing of cancer research information
Methods of Data Collection

Graphics showing different ways to collect data
Choosing an Electronic Database System

Considerations

Scope
Scalability
Interoperability
Security
Underlying structure of the system
User friendly with training available

(Reeves, 2007, Manual for Clinical Trial Nursing)
CFR 21-11 Electronic Records & Signatures
Ensure data is accurate, reliable and has not been altered
Create accurate and complete copies of the records for inspection and review
Protect the records and retrieve when necessary
Limit access to authorized individuals
CFR 21-11 Electronic Records & Signatures
Readily identify who has entered data and to clearly see when data has been modified
Hold individuals accountable and responsible for the data under their electric signature
Provide appropriate training
Electronic Database SOP
Coding system
Relational database
Computer support
Periodic password change
Identify person entering data
Back-up tapes/storage
Maintain confidentiality

(Tompkins, 2007, Principles and Practice of Clinical Research)
Quality of Data Entry
Data entry procedures
Certification of data entry personnel
Edit checks
Ongoing quality checks
QA plan
Correction of errors
Data lock
Source Documents
Any document where data is first recorded
Confirms protocol adherence
Serves to substantiate the integrity of the data
Confirms observations that are recorded
Confirms the existence of study participants
Source Documents
Hospital records
Clinic and office charts
   Lab reports
   Pathology reports
   Surgical reports
   Radiology reports
   Physician progress notes
   Nurses notes
Source Documents (cont’d)
Letters from referring physicians
Original radiological films
Tumor measurements
Participant diaries, medication logs
Participant interviews
Pharmacy dispensing records
Photographs
Source Documents

“If it isn’t documented, it didn’t happen”.

Auditors should be able to reconstruct a patient’s on study course by piecing together all of the data obtained from the original source documents.
Graphic: man looking at two piles of paper
Problems Encountered
Lack of source documentation
Errors in protocol adherence
Missing data
Transcription errors
Lag in data entry
Poor patient recall of adverse events
Poor patient compliance
Graphic: Form
Data Safety Monitoring
Monitors and reviews
  accrual rates
  adverse events
  Data reports/interim analyses
May generate protocol amendments
May recommend trial closure
Audits
Federal (NCI)
FDA
OHRP
Sponsor
Cooperative groups
Internal investigational site audits
Purpose of an Audit

To determine that the rights, safety and welfare of the study participants were upheld
To evaluate the conduct of the trial and protocol compliance
Evaluate the site’s standard operating procedures
To verify the integrity & reliability of the data
To determine that all regulatory procedures are being followed
For-Cause FDA Audits
Data is surprisingly favorable
Unexpected high enrollment at the site
Investigator is conducting a large number of trials outside of his/her area of expertise
Unexpected death
Components of an Audit
Regulatory documents
IRB documents and correspondence
Informed consent
CRF data compared to source documents
Drug accountability records
Study site facilities (lab, pharmacy etc)
Informed Consent
Are all required elements in the consent form
Was the appropriate version of the consent form used
Was the consent obtained prior to study tests/assessments
Was the consent obtained before study medication given
Eligibility
Did the participant meet eligibility criteria?
Is the eligibility documented in Medical Record
Assessments according to Protocol

Physical examination
Performance status
Laboratory tests
Diagnostic tests
  X-ray, CT scan, MRI
Tumor measurements
QOL questionnaires, patient diaries

Treatment According to Protocol
Drug/dose administered
Diary/pill count
Pharmacy log
Timing of administration
Dose modification/treatment delays and rationale documented
Were contraindicated drugs given?
Concomitant Medications
Date started
Generic name of medication
Indication
Dose/frequency
End date
Drug Accountability
Was the investigational agent properly stored?
Was the investigational properly disposed of?
Was the blind kept properly?
Were the patients properly randomized?
- **Adverse Events**
  
  Any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, and which may or may not have a casual relationship with the treatment. (21 CFR, part 312)
Toxicity
An adverse event that has a causal relationship to the investigational treatment
Example: EGFR agents and skin rash

Graphic of a face with its tongue stuck out.
Adverse Event Reporting
Common Terminology Criteria for Adverse Events (CTCAE)

- Identify and grade the severity of the event
- Is the event expected or unexpected
- Is it related to the study intervention

Expedited or routine reporting
AdEERS
IRB, sponsor, FDA
Serious Adverse Event (SAE)
Results in death
A life-threatening event
Requires hospitalization or prolongs hospitalization
Causes persistent or significant disability/ incapacity
Results in congenital anomaly/birth defect
Common Terminology Criteria for Adverse Events v. 4.0

Chart
Adverse Event Attribution Categories

Chart
Example of AE Reporting

Chart
Legal & Regulatory Issues

Regulatory Agencies
- The Office for Human Research Protections (OHRP)
- The U.S. Food and Drug Administration (FDA)

Regulatory Documents
- The Belmont Report
- Code of Federal Regulations (CFR)
- International Conference on Harmonization (ICH): Good Clinical Practice (GCP) Guidelines
Legal & Regulatory Issues

Regulatory Agencies
- The Office for Human Research Protections (OHRP)
- The U.S. Food and Drug Administration (FDA)

Regulatory Documents
- The Belmont Report
- Code of Federal Regulations (CFR)
- International Conference on Harmonization (ICH): Good Clinical Practice (GCP) Guidelines
CFRs Applicable to Data Management

21 CFR: Food and Drugs

Part 11: electronic records & signature
Part 50: informed consent
Part 56: IRBs
Part 312: investigational new drug application
CFRs Applicable to Data Management

45 CFR: Public Welfare & Human Services

Part 46: protection of human subjects

HIPAA
Regulatory Documents
Signed study protocol and amendments
Investigational Drug Brochure
FDA form 1572
CVs for all personnel listed on FDA 1572
IRB approval letter and all correspondence
All IND safety reports and letters of receipt by the IRB
Site safety reports to the IRB
Regulatory Documents (cont’d)
IRB approved consent form
IRB approved advertisements
IRB membership list
Investigational drug inventories & shipping logs
Telephone logs
Copies of lab certification, lab normals and reference ranges
Logs documenting CRA visits
Signature logs
Study closeout letter
NIH Regulatory Documents
Human Subjects Protection
Training
Conflict of Interest
Financial Disclosure
Data Safety Monitoring Board & Plan
Data Sharing Policy
Adequate plan to include minorities, women and children
Record Retention
Duration to be determined by sponsor
Minimum: 2 yrs following the date the marketing application is approved for an investigational new drug (IND)

If application is disapproved, 2 years after shipment & delivery of the drug for investigational use is discontinued & the FDA notified
IRB records: at least 3 years after study completion
Follow-up and Analysis
No further participant enrollment
Minimal data collected during this phase
Data queries in preparation for final analysis. Once complete, data is frozen for final analysis
Study closeout visit by sponsor
Study Close-out
Review of regulatory documents, outstanding CRF queries and drug inventory
Verification that all AEs and SAEs have been reported to IRB and sponsor
Remaining study drug returned
Arrangements made for record storage
Guiding Principles of Data Management
Stay organized
Do not get behind
Thorough and complete documentation
Design CRFs in accordance with protocol requirements
Standardize data entry procedures
Resources

FDA website:
http://www.fda.gov

Good Clinical Practices in FDA-regulated clinical trials:
http://www.fda.gov/oc/gcp/

Comparison of FDA and HHS Human Subject Protections:
http://www.fda.gov/oc/gcp/comparison.html

Guidance for Industry. E6 Good Clinical Practice: Consolidated Guidance:

Office for Human Research Protections:
http://www.hhs.gov/ohrp/

Cancer Therapy Evaluation home Page:
http://ctep.cancer.gov/

HIPAA:
http://privacyruleandresearch.nih.gov/

Cancer Data Standards Repository:
http://ncicb.nci.nih.gov/NCICB/infrastructure/cacore_overview/cadsr/
Resources (cont’d)

Office of Research Integrity
   http://ori.hhs.gov

National Cancer Institute
   www.cancer.gov

Office of Civil Rights Privacy Protection
   http://hhs.gov/ocr/hipaa/assist.html

Association of Clinical Research Professionals
   www.acrpnet.org

Society of Clinical Research Associates
   www.socra.org

Regulatory Affairs Professionals Society
   http://raps.org
Graphic: National Cancer Institute brochure