Data Management in Clinical Trials

Introduction to the Principles and Practice of Clinical Research

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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
- Reviewed by regulatory agencies
Data

- scrupulous
- accurate
- verifiable
- timely
The Research Team

- Principal Investigator
- Clinical Research Nurse/CRA
- Data Manager
- Database Administrator
- Statistician
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
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.
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
<table>
<thead>
<tr>
<th>Screening Trial</th>
<th>Number of patients screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFU-07-02-03 (Cancer Control in CLL)</td>
<td>84</td>
</tr>
<tr>
<td>Tailor Rx (Adj Breast Ca)</td>
<td>24</td>
</tr>
<tr>
<td>NSABP B-42 (Breast ca)</td>
<td>157</td>
</tr>
<tr>
<td>ECOG 1505 (Adj NSCL Ca)</td>
<td>29</td>
</tr>
<tr>
<td><strong>CALGB 80405 (Met Colon Ca)</strong></td>
<td>36</td>
</tr>
<tr>
<td><strong>Total Screened</strong></td>
<td>330</td>
</tr>
<tr>
<td><strong>Total Accrued</strong></td>
<td>75</td>
</tr>
<tr>
<td>Ethnicity captured</td>
<td>251/330</td>
</tr>
<tr>
<td>Race captured</td>
<td>300/330</td>
</tr>
<tr>
<td>Gender captured</td>
<td>321/330</td>
</tr>
<tr>
<td>Patient navigators that assisted with screening patients</td>
<td>16/330</td>
</tr>
</tbody>
</table>
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

- Stage III or Stage IV epithelial ovarian cancer?
- Baseline CA-125 > 70 units/ml (drawn within 14 days)
- No prior chemotherapy or pelvic radiation
- ECOG Performance Status of 0-2
- Platelets >100,000
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 causal 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
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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1-2 episodes</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(separated by</td>
<td>2</td>
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<td></td>
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<tr>
<td>5 minutes) in</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hrs</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6 episodes</td>
<td>5</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>(separated by</td>
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<td>5 minutes) in</td>
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<tr>
<td>24 hrs</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
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</tr>
</tbody>
</table>
## Adverse Event Attribution Categories

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unrelated</td>
<td>The AE is clearly NOT related to the intervention</td>
</tr>
<tr>
<td>2</td>
<td>Unlikely</td>
<td>The AE is doubtfully related to the intervention</td>
</tr>
<tr>
<td>3</td>
<td>Possible</td>
<td>The AE may be related to the intervention</td>
</tr>
<tr>
<td>4</td>
<td>Probable</td>
<td>The AE is likely related to the intervention</td>
</tr>
<tr>
<td>5</td>
<td>Definite</td>
<td>The AE is clearly related to the intervention</td>
</tr>
</tbody>
</table>
**Example of AE Reporting**

<table>
<thead>
<tr>
<th>C</th>
<th>D</th>
<th>Onset</th>
<th>Adverse event</th>
<th>Gr</th>
<th>Rel</th>
<th>Act</th>
<th>Ther</th>
<th>Out</th>
<th>Date Resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1/5/2012</td>
<td>Nausea</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1/5/2012</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1/6/2012</td>
<td>Pain: Headache</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1/6/2012</td>
</tr>
</tbody>
</table>

John Smith, MD

1/26/2012
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

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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
- Comparison of FDA and HHS Human Subject Protections: http://www.fda.gov/oc/gcp/comparison.html
- Office for Human Research Protections: http://www.hhs.gov/ohrp/
- 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