# 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.  
- Describe the legal requirements for data collection for a clinical trial.  
- Identify the types of data collected for clinical trials.  
- List potential source documents used for data collection.  
- Describe adverse event reporting.

## 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
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 Harmonisation (ICH): Good Clinical Practice Guidelines (GCP)
  - FDA: GCP
GCPs 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

GCPs 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

## 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
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
How are the Data Collected

- Case Report Forms (CRF)
- Electronic Data Capture (EDC)

Case Report Forms

- Standardize
- Captures all needed data to determine the study’s endpoints
- Includes all assessments
- Limit text entries
- Version the CRFs
Electronic Database

- Coding system
- Relational database
- Computer support
- Periodic password change
- Identify person entering data
- Back-up tapes/storage
- Maintain confidentiality

Quality of Data Entry

- Data entry procedures
- Certification of data entry personell
- Edit checks
- Ongoing quality checks
- QA plan
- Correction of errors
- Data lock
Who Collects the Data

- Investigators
- Research Nurses
- Clinical Research Associate (CRA)
- Pharmacists
- Participants
- Participant's family

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>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total Screened</td>
</tr>
<tr>
<td></td>
<td>Total Accrued</td>
</tr>
<tr>
<td></td>
<td>Ethnicity captured</td>
</tr>
<tr>
<td></td>
<td>Race captured</td>
</tr>
<tr>
<td></td>
<td>Gender captured</td>
</tr>
<tr>
<td></td>
<td>Patient navigators that assisted with screening patients</td>
</tr>
<tr>
<td>Total Screened</td>
<td>330</td>
</tr>
<tr>
<td>Total Accrued</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</td>
<td>16/330</td>
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</tbody>
</table>
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

Components of an Audit

- Regulatory documents
- IRB documents and correspondence
- Informed consent
- Drug accountability records
- CRF data compared to source documents
- Study site facilities (lab, pharmacy etc)
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

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 ≤2?
- Platelets >100,000?
### 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?

### Study Drug Administration

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Admin Date</th>
<th>Unit</th>
<th>Dose</th>
<th>Route</th>
<th>Course</th>
<th>Start Date</th>
<th>End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure-All</td>
<td>1/5/2004</td>
<td>250</td>
<td>mg</td>
<td>IV</td>
<td>1</td>
<td>1/5/2004</td>
<td>1/5/2004</td>
</tr>
</tbody>
</table>

John Smith, MD 1/26/2004

### Drug Accountability

- Was the investigational agent properly stored?
- Was the investigational properly disposed of?
- Was the blind kept properly?
- Were the patients properly randomized?
Assessments according to Protocol

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

Adverse Events

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).
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

Adverse Event Attribution Categories

<table>
<thead>
<tr>
<th></th>
<th>Unrelated</th>
<th>The AE is clearly NOT related to the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></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>
Common Terminology Criteria for Adverse Events v 3.0

<table>
<thead>
<tr>
<th>Grade</th>
<th>Adverse Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nausea</td>
<td>1 episode in 24 hrs</td>
</tr>
<tr>
<td>2</td>
<td>Pain: Headache</td>
<td>2-5 episodes in 24 hrs or IV fluids indicated in &lt;24 hrs</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>6 or more episodes/24 hrs or IV fluids or TPN indicated for 24 hrs or longer</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

Serious Adverse Event (SAE)

- Death
- A life-threatening event
- Requires hospitalization or prolongs hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Example of AE Reporting

<table>
<thead>
<tr>
<th>Date</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>1/5/2004</td>
<td>Nausea</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1/5/2004</td>
</tr>
<tr>
<td>2</td>
<td>1/6/2004</td>
<td>Pain: Headache</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1/6/2004</td>
</tr>
</tbody>
</table>

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Concomitant Medications

- Date started
- Generic name of medication
- Indication
- Dose/frequency
- End date

Record Retention

- 2 years following the date the marketing application is approved for investigational new drug (IND)
- OR
- 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

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.htm
- Office for Human Research Protections: http://www.hhs.gov/ohrp/
- HIPAA: http://www.hhs.gov/ohrp/hipaa.html

Resources (cont’d)

- Office of Research Integrity – http://ori.hhs.gov
- Regulatory Affairs Professionals Society – http://raps.org