Development of Case Report Forms

Introduction to the Principles and Practice of Clinical Research

February 12, 2013
Diane St. Germain, RN, MS
Nurse Consultant
Division of Cancer Prevention
National Cancer Institute
Objectives

• Name 3 key factors to consider during case report form development
• Describe the typical data elements captured on case report forms
• Describe how data is submitted electronically
• Discuss what constitutes a poorly designed case report form
Use of Data

- Data analysis and reporting
- Subject tracking
- FDA safety reporting
- New Drug Application submissions
- Support of labeling claims
- Reviewed by Data Safety Monitoring Boards
- Publication in medical journals
Data Management Reporting

- Outcomes of a clinical trial dependent on data that is collecting accurately and is verifiable
- Data must reflect the aims of the clinical trial
- Collection must comply with regulatory agencies
- Adequately designed case report forms is essential
Investigator Recordkeeping and Record Retention

21 CFR Sec. 312.62

“An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data…”.
Case Report Form

- A pre-printed form developed by the sponsor or PI to document the data elements outlined in the protocol
  - Gathers all necessary information to test the hypothesis
  - Ensures standardization and consistency of data collected
Case Report Form

- Design impacts the quality of data collected
- Properly designed CRFs = streamlined audits, data analysis and reporting
Users of the Case Report Form

- **Investigator**: to recall tests/evaluations to be performed according to the protocol
- **CRA**: to verify protocol requirements and required source documentation
- **Statistician**: to ensure data requested will answer the aims of the study
- **IT**: to develop database
Protocol Analysis Plan

Describes Study Conduct
- purpose
- objectives
- operational aspects

Describes Analysis
- data presentations
- key endpoints
- statistical methods

Collects data to support the above

D. Mailhot

National Cancer Institute
Methods of Data Collection
Developing Case Report Forms

- When will data be available?
- Where will the data be collected?
- Who will be completing the forms?

(McFadden, 2007)
Considerations During CRF Development

- Involve members of the research team
  - Research nurse
  - Data manager
  - Statistician
- Review the analysis plan
- Determine if there are suitable, existing forms
- Develop standardized forms
Considerations During CRF Development

- Data to be collected and forms to be used should be clearly outlined in the protocol
- Data requested should be unambiguous
- Data requested should correlate with statistical software
<table>
<thead>
<tr>
<th>Study Requirements</th>
<th>Screening/Baseline Visit</th>
<th>Clinic Visit Day 14 ± 3 days</th>
<th>Clinic Visit Day 28 ± 3 days</th>
<th>Phone Contact Days 35, ± 3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signed Informed Consent/Assent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility Form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics Form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Sample Collection</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SHS Questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medical History Form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-Up Visit Log</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Off Study</td>
<td>X&lt;sup&gt;1a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;1b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
The following forms need to be completed online at time points specified

<table>
<thead>
<tr>
<th>Type of Form</th>
<th>Time of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Register Participant Form</td>
<td>Prior to screening</td>
</tr>
<tr>
<td>Eligibility Form</td>
<td>Prior to screening</td>
</tr>
<tr>
<td>Participant Demographic</td>
<td>Prior to randomization</td>
</tr>
<tr>
<td>Urine Test Strip Results Form</td>
<td>Prior to randomization</td>
</tr>
<tr>
<td>SHS Exposure Questionnaire</td>
<td>Baseline, Day 14, and Day 28</td>
</tr>
<tr>
<td>Medical History</td>
<td>Baseline</td>
</tr>
<tr>
<td>Follow-up Visit Form</td>
<td>Day 14 and Day 28</td>
</tr>
<tr>
<td>Off-Study Form</td>
<td>At end of study</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>As needed</td>
</tr>
</tbody>
</table>
Considerations During CRF Development

• Generate user friendly forms
• Avoid lengthy text
• Collect essential data only
• Number data elements for easy reference
• Number each version generated
**SIGNIFICANT MEDICAL/SURGICAL HISTORY:**

- [ ] (1) NOT DONE
- [ ] (1) No Significant History

<table>
<thead>
<tr>
<th>Specify:</th>
<th>Past (1)</th>
<th>Present (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specify:

<table>
<thead>
<tr>
<th></th>
<th>Past (1)</th>
<th>Present (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specify:

<table>
<thead>
<tr>
<th></th>
<th>Past (1)</th>
<th>Present (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specify:

<table>
<thead>
<tr>
<th></th>
<th>Past (1)</th>
<th>Present (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Considerations During CRF Development

• Consider use of common data elements
• Consider piloting forms
• Complete CRF development prior to study activation
Common Data Elements

- Standardized, unique terms and phrases that delineate discrete pieces of information used to collect data on a cancer clinical trial
- Uniform representation of demographics and data points to consistently track trends
- Elements define study parameters and endpoints

B. Meadows
Format of Questions

• Consider the following:
  – Recording data in a paper form
  – Data entry into the computer
  – Data retrieval for analysis

McFadden (2007)
Consistency!

Layout, design and coding

D. Mailhot

*National Cancer Institute*
Considerations During CRF Development

• Request data consistently!
  – Dates
  – Decimal points
  – Units of measurement
  – Unknown/not applicable/not available/not done
  – Other
<table>
<thead>
<tr>
<th>VITALS NOT DONE:</th>
<th>□ (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ (1) lb</td>
</tr>
<tr>
<td></td>
<td>□ (2) kg</td>
</tr>
<tr>
<td><strong>Height:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ (1) in</td>
</tr>
<tr>
<td></td>
<td>□ (2) cm</td>
</tr>
<tr>
<td><strong>Blood Pressure, (1) Sitting:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ □ □ / □ □ □ mmHg</td>
</tr>
<tr>
<td><strong>Heart Rate, (1) Sitting:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ □ □ beats/minute</td>
</tr>
</tbody>
</table>
Header

- Standardize!
- Identifies the patient
  - Unique patient identifier (do not use initials, DOB)
- Identifies the trial
  - Study number
  - Name of institution
Protocol ID:

Visit: Screening

Please print all details, and INITIAL and DATE all corrections. Indicate ☑ where applicable.
Typical Data Elements Captured on CRF: On Study Forms

- Demographic data
- Eligibility criteria
- Family history
- Patient history, physical exam
- including PS
- Surgical history
- Prior treatment
- Concomitant medications
- Laboratory and radiology results
- Pathology
- Review of current symptoms
Typical Data Elements Captured on CRF

**During the Study**
- Study treatment
- Laboratory & radiology results
- Concomitant medications
- Adverse events
- Toxicities
- Hospitalizations
- Treatment response

**Follow-up**
- Disease status
- Non-protocol treatment
- Long term adverse events
- Date of death
- Cause of death
- Autopsy results in performed
CRF Development Process

- CRF Designer

CRF Development Process:
- Drafts CRF from protocol
- CRF Review Meeting
- Comments back to designer
- Updates CRF to include comments
- Review and Sign off/approval
- Coordinate printing and distribution

Site

J. Mailhot

National Cancer Institute
Basic Rules for CRF Completion

• Always use ink
• Avoid extraneous writing in the margins/ outside of the text boxes
• Data added in response to a query is initialed and dated
Basic Rules for CRF Completion

• Correction of an error
  – Never obliterate an entry: do not erase, use whiteout
  – Cross out with a single horizontal line and initial and date
  – Should be performed by person who entered the data initially
Electronic Data Capture
Advantages: Electronic Data Capture

- Shortened time from subject visit to data entry
- Rules/edit checks will decrease queries
- Errors in input can be identified in real-time
- No need to decipher handwriting
- Decreases transcription error
- Real-time data collection

Ryan, J (2008)
Advantages: Electronic Data Capture

- Rapid and timely data transmission from multiple sites simultaneously
- Generate reports more rapidly
- Manageable audit trail
- May be able to download data from other sources (labs)

J. Ryan (2008)
Designing Electronic CRF

- The method of data collection will impact the design of the data entry screens
- Same considerations for designing electronic forms as for paper forms
- Consider volume and frequency of data submission
- Avoid excessively detailed screens
- Thoroughly test data capture screens
- Develop detailed user instructions

McFadden (2007)
How is Data Submitted Electronically

- Paper version of CRF, then entered electronically
- Entered directly into an electronic device
- On-line entry
  - Virtual private network (VPN)
  - Via a web application
  - Electronic gathering at the site

Razvillas (2008)
EDC – Electronic Data Capture

Source Document(s)

Case Report Forms

Audit

Sponsor’s Database

Sponsor’s Data Report

EDC – Electronic Data Capture

Patient’s Medical Record (Source Document)

T. Budd

Sponsor’s Database

Site’s Database

National Cancer Institute

T. Budd

Source Document(s)

Case Report Forms

Audit

Sponsor’s Database

Sponsor’s Data Report
 Poorly Designed CRF

- Necessary data not collected
- Database may require modification
- Data Entry process impeded
- Need to review/clean data increases
- Target dates are missed
- Collected too much data – Wasted resources in collection and processing
- *Delay in getting study results and ability to adequately test the protocol objectives*

D. Mailhot
Additional Methods to Capture Data

- Patient Diaries
- Calendars
- Questionnaires
- Phone logs
- Mail surveys
Data Submission

- Data submitted according to the protocol
- Data corrected and resubmitted
- Data Center generates queries
- Internal quality control checks/audit
“Data must be treated with a scrupulousness that exceeds the care with which we treat most information in daily life”.

(Whitebeck, 2006)