Data Management & Case Report Form Development 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.
- Name 3 key factors to consider during case report form development

Objectives (cont'd)

- Discuss things to consider when developing CRFs
- Discuss what constitutes a poorly designed case report form
- Review audit process
- Describe adverse event reporting
- Describe regulatory requirements for data collection

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
- Informs development of future trials

Data Management Reporting

- Outcomes of a clinical trial dependent on data that is collected accurately, in a timely manner 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

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 and content of the data collection instruments
- The selection of a computer database

Common Data Elements

- Data elements that have been determined to be identical between projects or contexts
  - e.g., name, age, gender, etc.
- Facilitates understanding and sharing of cancer research information

Data Elements Captured: Study Entry

Each Category may contain multiple data elements

- Demographic data
- Eligibility criteria
- Family history
- Patient history
- Prior cancer treatment
- Concomitant medications
- Lab data/test results
- Review of current symptoms

Data Elements Captured: On Study

Each Category may contain multiple data elements

- Treatment
- Assessments (labs/radiology)
- Concomitant meds
- Adverse events
- Hospitalizations
- Treatment Response
- Patient diaries
- QOL questionnaires
- Follow-up (disease status, long term adverse events, date & cause of death)

Source Documents

- Any document where data is first recorded
- Confirms protocol adherence
- Confirms/validates data submitted/reported
- Serves as audit trail allowing for recreation of trial
- Confirms the existence of study participants

Source Documents
Examples

- Hospital records
- Clinic and office charts
  - Lab reports
  - Pathology reports
  - Surgical reports
  - Radiology reports
  - Physician progress notes
  - Nurses notes

Source Documents
Examples

- Letters from referring physicians
- Original radiological films
- Tumor measurements
- Participant diaries, medication logs
- Participant interviews
- Pharmacy dispensing records
- Photographs

Data Abstraction

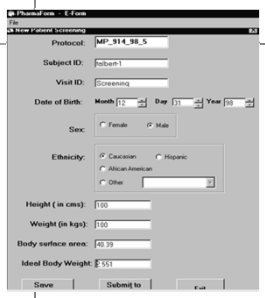
- Anything recorded on CRF should be in a source document
  - If not written, did not happen!!
- Any change or correction should be dated, initialed, and explained (if necessary) & should not obscure the original entry
  - Applies to source document as well as CRF
- Only provide the requested data
  - Avoid unnecessary comments
- Use standard medical terminology

Data Abstraction

- Auditors should be able to reconstruct a patient's study course by piecing together all of the data obtained from the original source documents

Methods of Data Collection

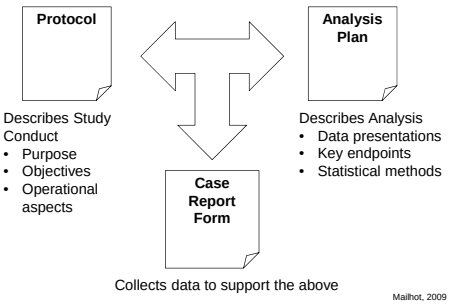
Case Report Form (CRF)



Case Report Form

- A pre-printed form developed by the sponsor or PI to document the data elements outlined in the protocol
  - Translates protocol-specific activities into data
- Ensures standardization and consistency of data collected across participating research sites
- Design impacts the quality of data collected
  - Properly designed CRFs = streamlined audits, data analysis and reporting

Case Report Form Relationship to Protocol



Mailhot, 2009

Considerations During CRF Development

- Protocol determines what data *should* be collected on the CRFs
- All data *must* be collected on the CRF if specified in the protocol
- Data that will not be analyzed *should* not be requested on the CRF

Mailhot, 2009

Considerations During CRF Development

- Involve members of the research team
  - Clinician/Investigator
  - Research nurse
  - Data manager/CRA
  - Statistician
  - Programmer
- Review the analysis plan
- Determine if there are suitable, existing forms

Considerations During CRF Development

- What data is needed in relation to when the data will be available?
- Where will the data be collected?
- Who will be completing the forms?

(McFadden, 2007)

Considerations During CRF Development

- Data to be collected and forms to be used should be clearly outlined in the protocol
- Data requested should be clearly stated and self explanatory
- Data requested should correlate with statistical software

Considerations During CRF Development

- Generate user friendly forms
- Avoid lengthy text
- Collect essential data only
- Number each version generated

Considerations During CRF Development

- Use consistent formats, font style and font sizes throughout the protocol-specific CRFs
- Use clear and concise questions, prompts, and instructions
- Using the option of "circling of answers" should be limited as it's hard to interpret; instead check boxes would be appropriate

Bellary, et al (2014)

Considerations During CRF Development

- Provide boxes or separate lines to hold the answers. This indirectly informs the data recorder where to write/enter the response and helps to differentiate it visually from the entry fields for other questions
- Separate the columns with thick lines
- Provide bold and italicized instructions
- Minimize free text responses
- Avoid collection of derived data to decrease calculation errors

Bellary, et al (2014)

Considerations During CRF Development

- Avoid using "check all that apply" as it forces assumptions about the clinical data
- Specify the unit of measurement
- Indicate the number of decimal places to be recorded
- Use standard data format (e.g., dd/mm/yyyy) throughout the CRF
- Use pre-coded answer sets wherever possible:
  - yes/no,
  - male/female,
  - severity of adverse event (AE) (mild/moderate/severe)

Bellary, et al (2014)

Considerations During CRF Development

- Consider use of common data elements
  - NCI caDSR CDE Curation Tool: https://cdecurate.nci.nih.gov/cdecurate/NCICurationServlet?reqType=homePage
- Consider piloting forms
- Complete CRF development prior to study activation

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 getting study results and ability to adequately test the protocol objectives***

Mailhot, 2009

Poorly-Designed Vs. Well-Designed Data Fields

Poorly designed

- Date of visit: _____
- Blood Pressure: _____
- Pulse: _____
- Temperature: _____
- Respiration: _____

Well designed

- Date of visit: □□/□□/□□□□ (DD/MM/YYYY)
- Blood pressure: □□□/□□□ (mmHg)
- Pulse: □□□ (beats/min)
- Temperature: □□. □ (°C)
- Respiration: □□ (/min)

Bellary, et al (2014)

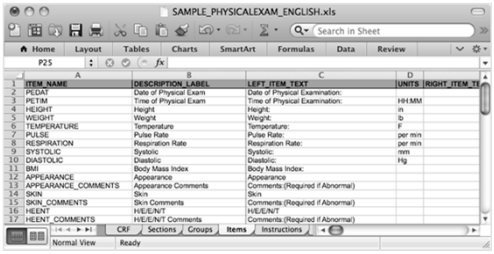
Electronic CRFs (eCRFs)

- Use of remote data capture (RDC) is increasing
  - Oracle Clinical, Clintrial, Macro, Rave, eClinical Suite
- Advantages:
  - Faster data collection
  - Cleaner data collection due to system built "checks"
  - Easier monitoring
  - Central database for storage of all trial data
  - Near real-time data access to authorized personnel
- Drawbacks:
  - Lack of onsite technology
  - High investment cost
  - Complexity of installation & maintenance of software
  - Investigator lack of motivation/training

CRF Web View

https://docs.openclinica.com/3.1/study-setup/build-study/create-case-report-forms-crfs

CRF Excel File



https://docs.openclinica.com/3.1/study-setup/build-study/create-case-report-forms-crfs

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

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 Trials Nursing)

CFR 21-11 Electronic Records & Signatures

Persons using electronic records are required to employ mechanisms to:

- 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 (cont)

- 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

Data Transfer

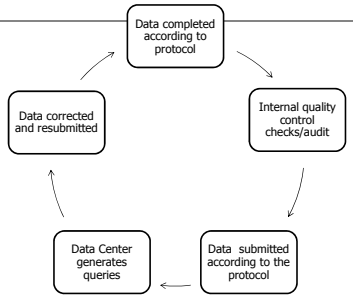
- Paper
  - Paper CRFs are completed, submitted to sponsor and entered into electronic system by sponsor
- Electronic
  - Investigator or designee log into Clinical Data Management System (CDMS) and enter data directly at the site.
  - Real time data review, correction and resolution

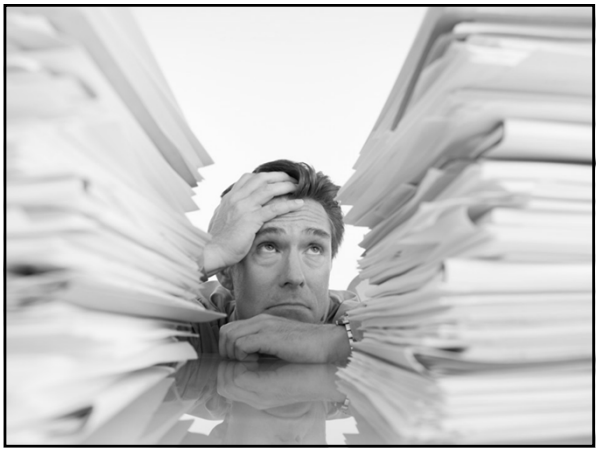
Additional Methods to Capture Data

- Patient Diaries
- Calendars
- Questionnaires
- Phone logs
- Data supporting source documents

Managing the Data

Data Submission





Investigator Responsibility: CRF Completion

- Per GCP Guidelines (4.9.1), investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported on the CRFs. Including:
  - all sections have been completed
  - 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

Timeliness of CRF Completion

- Ideally CRFs should be completed as soon after the subject's visit as possible
  - Protocol document defines study-specific timelines
- 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

CRF Completion:
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

Query Resolution

- Critical activity within clinical data management process
- Helps in cleaning the data
- Assesses and resolves inconsistent data, missing data, range discrepancies, deviations from protocol
- Sponsor generates Data Clarification Forms (DCFs) sent to investigator for resolution

Internal Quality Management

- Waiting for external audit does not result in process improvement
- Proactive, self-identification of errors; cause analysis and implementation of corrective action plan (CAP) is essential
  - CAP may include site staff education, changes in processes/SOPs
  - Key to prevention of non-compliance is well-trained and experienced research nurses/CRAs who have been provided devoted research-related time

Data Safety Monitoring Board

- Monitors and reviews
  - accrual rates
  - adverse events
  - Data reports/interim analyses
- May generate protocol amendments
- May recommend trial closure

Sponsor Monitoring & Auditing

- **Monitoring** – Act of overseeing the progress of a clinical trial
  - Purpose: ensure trial is conducted, recorded, and reported in accordance with protocol, SOPs, GCP & applicable regulatory requirements (i.e., optimizing systems and processes in such a way that mistakes are prevented)
- **Auditing** – Systematic and independent examination of trial-related activities & documents
  - Purpose: document accuracy of data submitted

Audits

- Federal (NCI)
- FDA
- OHRP
- Sponsor
- 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 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

What do auditors look for

Knowing will help you prepare for an audit and improve data quality.

Elements of an Audit

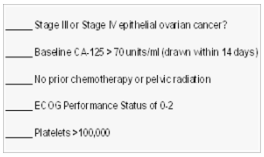
- **Regulatory/IRB review**
  - Documentation of full initial IRB approval/annual re-approval and review of amendments
  - Consent documents
- **Pharmacy/drug accountability**
  - Verification of receipt, storage/security, inventory control
- **Patient Case Review**
  - Consent form signature, eligibility, correct treatment, disease outcome/tumor response, AEs, general data quality

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?
- Does the information in the source document support the data reported?



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?

Drug Accountability

- Investigational agents properly stored?
  - In secure area (Investigational Pharmacy)
  - Stored by protocol/study
  - Temperature monitored frig/freezer
- DARFs completed correctly/completely
- Investigational agent properly disposed of?
- Study blind maintained properly?
- Commercial agent not used
- Drug inventory completed regularly

Common Audit Deficiencies

- Failure to follow the investigational plan
- Protocol deviations (and failure to properly document and report deviations)
- Failure to ensure that informed consent was obtained in accordance with 21 CFR 50
- Failure to maintain accurate, complete, and current records
- Lack of appropriate accountability for investigational agent
- Failure to obtain IRB approval

NCI Audit Determinations

- Deficiency Categories
  - Lesser/Minor deficiencies
  - Major deficiencies
- Final Audit Determinations
  - Acceptable
  - Acceptable needs Follow Up
  - Unacceptable

FDA Inspection

- FDA Form 483
  - List of observations found during FDA inspection
  - Investigator responds
- Reviewed at FDA
  - Determines final classification
  - Issues response letter

FDA Response Letters

1. A letter indicating FDA observed basic compliance with pertinent regulations
2. An *Informational or Untitled Letter that identifies deviations from statutes and regulations* that do not meet the threshold of regulatory significance for a Warning Letter
3. Warning Letter *that identifies serious deviations from applicable statutes and* regulations.
4. *Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)*

Adverse Event Monitoring and Reporting

Adverse Events (AE)

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

Serious Adverse Event (SAE)

- Any medical occurrence that at any dose results in death, is life-threatening, requires hospitalization, results in disability/incapacity or congenital anomaly/birth defect.
  - All SAEs should be reported immediately to sponsor unless protocol or other document indicates otherwise
  - Should also comply with regulatory requirements, e.g., report to regulatory authorities & IRB

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
  - Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS)
  - IRB, sponsor, FDA

Common Terminology Criteria for Adverse Events v. 4.0

Blood and lymphatic system disorders

	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <-25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					

CTCAE 4.03 - June 14, 2010
5

Adverse Event Attribution Categories

1	**Unrelated**	**The AE is clearly NOT related to the intervention**
2	**Unlikely**	**The AE is doubtfully related to the intervention**
3	**Possible**	**The AE may be related to the intervention**
4	**Probable**	**The AE is likely related to the intervention**
5	**Definite**	**The AE is clearly related to the intervention**

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
- 45 CFR: Public Welfare & Human Services
  - Part 46: protection of human subjects
  - HIPAA

ICH GCP Guidelines

- Guideline for Good Clinical Practice (GCP)
  - E6(R1)
  - http://www.ich.org/products/guidelines.html
  - Principles of ICH GCP (2.0)
  - Trial management; data handling, record keeping (5.5)
  - Safety reporting (4.11)
  - Quality Assurance & Quality Control (5.1)
  - Records and reports (4.9)
  - Monitoring (5.18)

Regulatory Documents/ Study Binder

- 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

- Design CRFs in accordance with protocol requirements
- Standardize data entry procedures
- Stay organized
- Do not get behind
- Thorough and complete documentation

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: http://www.fda.gov/cder/guidance/959fnl.pdf
- 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

Additional References

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Questions