Data Management & Case Report Form Development in Clinical Trials

Introduction to the Principles and Practice of Clinical Research

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Marge Good, RN, MPH, OCN

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.

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

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

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

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

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

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?

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

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

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)

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

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)

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

CRF Excel File

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

Choosing an Electronic Database System

Considerations

Scope

Scalability

Interoperability

Security

Underlying structure of the system

User friendly with training available

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

A letter indicating FDA observed basic compliance with pertinent regulations

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

Warning Letter that identifies serious deviations from applicable statutes and regulations.

Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)

Adverse Event Monitoring and Reporting

Adverse Events (AE)

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

Adverse Event Attribution Categories

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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Mailhot D. (Previous IPPCR Presentation) https://ippcr.nihtraining.com/handouts/2009/Mailhot.pdf

NCI Clinical Trials Monitoring Branch (CTMB) Audit Guidelines:
http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring.htm

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Questions