OREGON CLINICAL & TRANSLATIONAL RESEARCH INSTITUTE

Case Report Form Development

Investigator Initiated Trials

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Case Report Forms

- CRF Jargon
- CRF Purpose and Standards
- CRF Content
- CRF Development Considerations
- CRF Instructions and Documentation

CRF Fundamentals

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Jargon

- Case Report Form (CRF)
  - A set of standardized documents in which the study team records data collected in a clinical trial (may be electronic (EDC) or paper forms)
- Electronic Data Capture (EDC)
  - Computer hardware/software that create, modify, maintain, archive, retrieve, or transmit study data in digital form
- Source Data/ Documents
  - Original documents (or certified copies) of relevant clinical findings, observations, or other activities collected during the study
  - The first place information is documented

Purpose of CRFs

- "Adequate Case Histories" must include records of clinical findings, observations, and other activities that occurred during a clinical trial necessary for the reconstruction and evaluation of the data
  - Source documents
  - Case Report Forms (CRFs)
  - Consent forms
- Standardize data collection
- Preserving and maintaining quality and integrity of data
- Enable study (with source docs) to be reconstructable
- Demonstrate compliance with the study protocol

GCP Quality Standards

A	Attributable
L	Legible
C	Contemporaneous
O	Original
A	Accurate
C	Complete
C	Consistent
E	Enduring
A	Available when needed

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When to Develop CRFs?

- BEST!
  - In parallel with protocol development and report specifications
  - Prevents protocol modifications
- BAD – after you have started study enrollment

CRF Content

- Review protocol to determine:
  - What data is needed to meet study objectives
  - Statistical Plan
  - Eligibility Criteria
  - Relevant patient groups/arms
  - Schedule of events
  - Collaborators/multicenter?
  - Do you need Surveys/Diaries
    - Standardized surveys or create your own

Map out your CRFs

- **Use the protocol visit schedule to help**
- **Common forms for many studies:**
  - Demographics
  - Medical History
    - Make it detailed so you document baseline
  - Medications, AEs and Protocol Deviations forms
  - Serious Adverse Event form
- **Study Specific forms:**
  - Screening procedures
    - Verify inclusion/exclusion criteria
  - Visits (are they the same or different?)
  - Final visit/early termination visit?
  - Other repeating research events

What to include in CRFs

- Collect all data outlined in the protocol
  - Don't forget screen failures and controls
- Collect data to fulfill funder requirements
  - Sex, Race, Ethnicity (NIH Patient Level Data Reporting)
- Is the data going into a repository?
  - Is there a standard data format?
- Only collect what you have IRB approval to collect
  - Do the CRFs match the protocol?
  - Is identifiable information recorded on the CRF consistent with the Consent/HIPAA Waiver of Authorization?

What not to include in CRFs

- Don’t record extraneous information on the CFR
  - Just more to monitor
  - More to clean
  - More to enter (if paper)
  - May be little to no benefit for the effort

Example Pacemaker study:

NYHC (select one)

I	II	III	IV

Paper vs EDC

12

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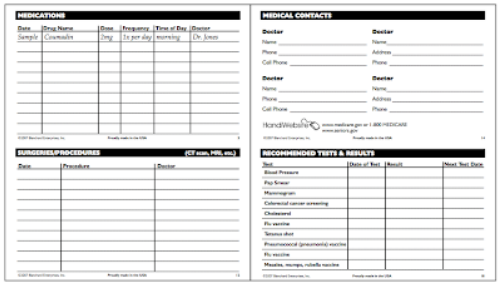
Paper Case Report Forms Process

Protocol Visit 2

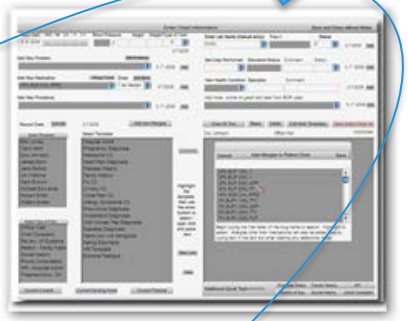
Chest X-Ray

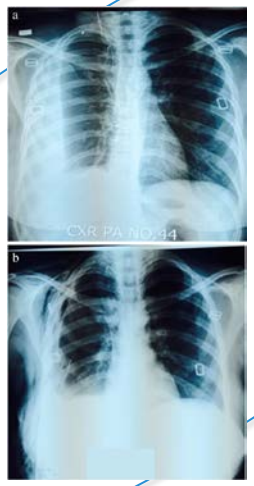
Patient QOL Survey

CRFs



Source Docs





Database

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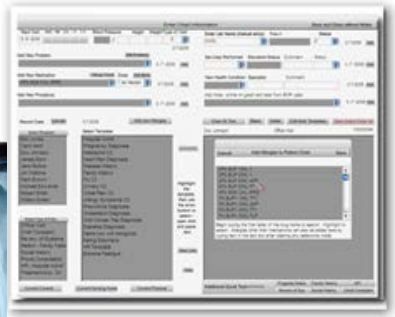
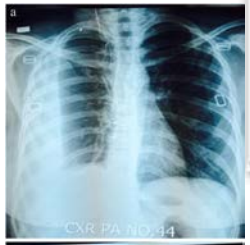
Electronic Case Report Forms Process

Protocol Visit 2

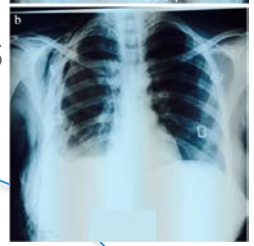
Chest X-Ray

Patient QOL Survey





Source Docs



EDC/Database

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When CRF is the Source Document

- Protocol should specify when CRF is the source
- Should be able to verify who completed the form
  - unless anonymous
- If other source docs are available they are still subject to inspection by FDA

Paper or Electronic

Data Activities	Paper	Electronic
Data Entry	Slower	Faster
Chances of Errors	More	Less
Query Resolution	Slower	Faster
Time to analyze data	Slower	Faster
Access to data	Worse	Better

Other considerations :

- Size of study
- Phase of study (feasibility vs pivotal trial)
- Regulations (21 CFR Part 11)
- Language

CRF Design Considerations

Always

Always

Always

Consider the

Source

and the User

CRF Design Fundamentals

- Make CRFs easy to understand and user friendly
  - Facilitate transcription from source docs
    - Consider workflow (group all lab questions together)
  - Designed for all users
    - Investigators, coordinator, monitor, coder, statistician
- Unambiguous instructions
  - Should be next to the CRF field when possible
  - Good instructions reduce queries
- Visually uncluttered
- Avoid duplication
- Avoid open text fields when possible
- Don’t collect what you don’t need

Defining CRF/EDC fields

BAD

Date_____

Time_____

Weight _____

TIPS:
Pick a format/unit of measure and use the same one on all forms

Use checkboxes instead of circling answers

Specify the # of decimals

GOOD

Date _ _/_ _/_ _ _ _
MM/DD/Y Y Y Y

Time _ _: _ _
(24 hour clock)

Weight _ _ _._ (Kg)

Missing Data

- CRFs should be designed to anticipate missing data
  - Include directions for missing data
- Paper CRFs
  - Indicate ND (not done), --, checkbox for missing
- EDC
  - Don't make fields required without providing a way for the user to indicate it wasn't done
- Missed visits
  - Do you want CRFs for missed/out of window visits?
- FDA Covid-19 Guidance
  - Large numbers of protocol deviations are expected
  - Need to be able to distinguish those related to Covid and which were not

Multi-Center Trial CRFs

- When designing multicenter trial CRFs you need to account for site differences
  - SOC – Timing of procedures
  - Local labs – reference ranges and units of measure
  - Individual Investigator differences in assessments
  - Language

Concomitant Medications

- Visit CRF should include a prompt

  Did any changes in medication occur? Yes ☐ No ☐

  If yes, complete Con Med Form

- Provide pre-coded information units/route of administration/frequency (checkboxes)
- Drug names (generic or trade name)
- Prompt user to use the same indication as medical history/adverse event form
- Start/stop dates –same format as rest of CRF
  - Consider flagging medication started pre-study and on ongoing at end of study
  - Instructions for unknown dates

Adverse Event CRFs

- Collect preferred terms for analysis
  - Review the expected reporting format(s) FDA, IRB, then:
  - Select a medical dictionary (WHOART, MedDRA, etc.)
  - Select a severity grading criteria based on your disease/area of study
    - CTCAE, DAIDS, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers
  - Select a causality rating scale
- Provide clear instructions

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Serious Adverse Events

- Additional information is required and CRFs should be designed to aid collection
  - Is it a common event in the population under study?
  - Was it “treatment-emergent”?
  - Did it respond to de-challenge?
  - Did it recur on re-challenge?
  - Were there concomitant medications?
  - Were pertinent labs/other tests done?
  - Was there an obvious alternative cause?
  - Is it a study endpoint?
- Collect enough relevant information on CRF to allow for good quality narratives
- Use FDA form 3500/3500A as a guide

Who will you report to?

Look at the content of reporting requirements

- FDA (look at clinical report requirements and guidance for your drug class/device)
- DSMB (look at charter)
- IRB (consider RNI reporting)
- NIH (Participant Level Data Template)
  - Don’t reinvent the wheel – use standardized forms/questions when available/appropriate
  - Develop your report parameters along with your CRFs

Test CRFs Before Use

- Do the questions mean what you think they mean?
- Are instructions clear?
- Ask:
  - Investigator
  - Coordinator/data entry staff
  - Statistician
  - Multi-center staff
  - Anyone who agrees to look at them
- EDC -Database testing and validation

Example

Investigator	

Site Name	

Lack of instructions led to:

- Undetected protocol deviation
- FDA 483
  - Failure to adequately train (sponsor and investigators)
  - Failure to secure compliance
  - Failure to control the investigational product (device)

IRB Review

- IRB needs to review and approve Source/CRFS that are participant facing
  - Surveys, Questionnaires, Diaries
  - Any changes need to be IRB approved
  - All versions need approval (paper/electronic) in their final format
- The IRB doesn't need to see forms the study team completes

OHSU Resources

- EDC
  - OCTRI
    - REDCap/REDCap Survey
    - 21 CFR Part 11 compliant systems
    - Twilio
    - octri@ohsu.edu
  - OHSU
    - Qualtrics https://o2.ohsu.edu/information-technology-group/software/qualtrics.cfm
- Biostatistics, Epidemiology & Research Design (BERD)
  - bdp@ohsu.edu
- Regulatory Consultation
  - adamsb@ohsu.edu or octri@ohsu.edu

Thank You!

Next OCTRI Research Forum
3/10/2021 12:00
Clinicaltrials.gov Common Challenges and Solutions

Register in Compass