Case Report Form Development
Investigator Initiated Trials

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PRESENTED BY: Bridget Adams, MSHS, CCRA, Manager OCTRI Regulatory Knowledge and Support
Case Report Forms

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

GCP & GMP

Regulations

Compliance
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

Source Documents + Case Report Forms = Adequate Case Histories

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

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
</tbody>
</table>
Paper vs EDC
Paper Case Report Forms Process

Protocol Visit 2
- Chest X-Ray
- Patient QOL Survey

Source Docs

CRFs

Database
Electronic Case Report Forms Process

Protocol Visit 2
- Chest X-Ray
- Patient QOL Survey

Source Docs → EDC/Database
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

<table>
<thead>
<tr>
<th>Data Activities</th>
<th>Paper</th>
<th>Electronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Entry</td>
<td>Slower</td>
<td>Faster</td>
</tr>
<tr>
<td>Chances of Errors</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>Query Resolution</td>
<td>Slower</td>
<td>Faster</td>
</tr>
<tr>
<td>Time to analyze data</td>
<td>Slower</td>
<td>Faster</td>
</tr>
<tr>
<td>Access to data</td>
<td>Worse</td>
<td>Better</td>
</tr>
</tbody>
</table>

**Other considerations:**

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

Always
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__________________

GOOD
Date ___/__/__/__
MM/DD/YYYY

Time __:__
(24 hour clock)

Weight ____.__ (Kg)

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
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
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

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
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