Source Documents and Case Report Forms: Forms and Function

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Office of Clinical Research Policy and Regulatory Operations (OCRPRO)
Regulatory Compliance and Human Subjects Protection Program (RCHSPP)
Clinical Trials Management Team (CTM)
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Purpose

- To review definitions of Source Documents and Case Report Forms
- Provide information regarding the function of each document
- To clarify when each document is to be used
Source Documents
Source Documents

“Source documentation is the beginning of a clean, verifiable audit trail.”

Source Documents

- Source Documents:
  - Original documents, data and records or certified copies of original records of clinical findings, and observations.

- Examples:
  - Signed informed consent forms
  - Hospital records
  - Clinical charts
  - Laboratory reports
Source Documents

- Source documents are:
  - Records on which clinical observations are **first** recorded
  - Legally valid
  - Raw data
  - Support the study’s findings
  - **Signed** and dated by person completing

- Together with CRFs, comprise “case histories”

Source Documents

- **Electronic Source Documents/Data**
  - Any combination of text, graphics, data, audio, pictorial, or other information represented in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system [21 CFR 11.3(b)(6)].

  - Initially recorded in electronic format.
Source Documents

- Electronic Source Documents/Data
  - eSource documents and eSource data can come from a variety of activities and places.
  - A list of all authorized data originators should be developed and maintained by the sponsor and site.
    - Data originators entering source data can be:
      - Persons
      - Systems
      - Devices
      - Instruments

_FDA Guidance for Industry: Electronic Source Data in Clinical Investigations, September 2013_
Source Documents

• Maintain Adequate and Accurate Records
  • GCP Expectations:
    • Record observations and all pertinent study related data.
    • At a minimum, capture as part of a subject’s record:
      • Demographic information
      • Study selection criteria
      • Information to support data
      • Exposure to study drug
Source Documents

Apply the ALCOA standard to achieve data quality:

• Attributable
• Legible
• Contemporaneous
• Original
• Accurate
Source Documents

- Standardized forms—same across multiple studies.
  - Examples: demographics, history, and physical examination.

- Study specific forms—designed to meet data needs for a specific protocol, diseases entities or time points.
  - Examples: laboratory data, inclusion/exclusion criteria, participant symptom assessments, specific tumor disease/typing, etc.
# Source Documents

## Corrections/Changes to Source Documents

<table>
<thead>
<tr>
<th>Error Noted</th>
<th>Do’s</th>
<th>Don’ts</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Correction needed on original source document</td>
<td>• Make a single line through original entry and initial/date correction (with current date)</td>
<td>• Scribble over mistake</td>
</tr>
<tr>
<td></td>
<td>• Keep original information clearly visible</td>
<td>• Use White Out/Tape</td>
</tr>
<tr>
<td>• Missing data located at a later date</td>
<td>• Incorporate into research record with current date</td>
<td>• Re-write over top of entry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Destroy originals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alter past-dated notes (by writing alongside or adding to prior entries)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ignore</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Backdate information</td>
</tr>
</tbody>
</table>
Source Documents

• Common Issues Noted
  • Source Document/Data is unavailable
  • Source Documentation is incomplete or missing.
  • Results of study related procedures not documented.
  • Investigator/designee did not sign/date form as required.
  • Adverse Events recorded in progress notes were not reported in the study data.
  • Discrepancies between source documentation and CRFs/eCRFs.
Case Report Forms

• What is a Case Report Form (CRF)?
  • A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.
  • Provided by the sponsor.
  • Must be checked against the source document.

• Information applies to both paper and electronic CRFs

ICH GCP E6 1.11
Case Report Forms

- Examples:
  - MiForm
  - ClinPlus
  - 3-part NCR paper
  - Single-sheet Paper
Case Report Forms

• Purpose of CRFs
  • Capturing all protocol-required information.
  • Facilitates data collection and entry.
  • Benefits data management and statistical analysis.
  • Promote data sharing between the study team and other institutions.

ICH GCP E6 5.23.2
<table>
<thead>
<tr>
<th>Test Name</th>
<th>Abnormal</th>
<th>Normal</th>
<th>Units</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chem-SCREEN Panel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glucose</td>
<td>87.0</td>
<td>55.0-125</td>
<td>g/dL</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>140.0</td>
<td>136-144</td>
<td>mEq/L</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>4.8</td>
<td>3.60-5.10</td>
<td>mEq/L</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>106.0</td>
<td>95.0-108</td>
<td>mEq/L</td>
<td></td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>20.0</td>
<td>21.7-30.7</td>
<td>mEq/L</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>0.20</td>
<td>0.80-26.0</td>
<td>mg/dL</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.30</td>
<td>0.70-1.30</td>
<td>mg/dL</td>
<td></td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein, Total</td>
<td>7.0</td>
<td>6.50-6.60</td>
<td>g/dL</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>4.10</td>
<td>4.00-5.00</td>
<td>mg/dL</td>
<td></td>
</tr>
<tr>
<td>Bilirubin, Total</td>
<td>0.41</td>
<td>0.20-1.50</td>
<td>mg/dL</td>
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<tr>
<td>Bilirubin Direct</td>
<td>0.05</td>
<td>0.00-0.20</td>
<td>mg/dL</td>
<td></td>
</tr>
<tr>
<td>ALP Phosphatase</td>
<td>92.0</td>
<td>50.0-320</td>
<td>Units/L</td>
<td></td>
</tr>
<tr>
<td><strong>AST (SGOT)</strong></td>
<td>44.0</td>
<td>5.00-40.0</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td><strong>ALT (SGPT)</strong></td>
<td>25.0</td>
<td>5.00-50.0</td>
<td>IU/L</td>
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<tr>
<td><strong>Aspartate Transaminase</strong></td>
<td>33.0</td>
<td>0.00-100</td>
<td>IU/L</td>
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</tr>
<tr>
<td><strong>Complete Blood Count (CBC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red Blood Cell (RBC) Count</td>
<td>5.10</td>
<td>4.00-11.0</td>
<td>/µL</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (HGB)</td>
<td>14.0</td>
<td>12.0-16.0</td>
<td>g/dL</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (HCT)</td>
<td>42.3</td>
<td>37.0-47.0</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>White Blood Cell (WBC)</td>
<td>3.88</td>
<td>4.00-10.0</td>
<td>x10^3/µL</td>
<td></td>
</tr>
<tr>
<td>Platelet Count</td>
<td>215.0</td>
<td>150-410</td>
<td>x10^3/µL</td>
<td></td>
</tr>
<tr>
<td><strong>T-Lymphocyte subsets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ Helper (35.0 PCT)</td>
<td>661</td>
<td>500-1500</td>
<td>/µL</td>
<td></td>
</tr>
<tr>
<td>CD4+ Suppressor (44.0 PCT)</td>
<td>795</td>
<td>150-1000</td>
<td>/µL</td>
<td></td>
</tr>
<tr>
<td><strong>CD4/CD8 Ratio</strong></td>
<td>0.81</td>
<td>0.90-6.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Differential</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly</td>
<td>52.2</td>
<td>1650-4800</td>
<td>/µL</td>
<td></td>
</tr>
<tr>
<td>Lymph</td>
<td>35.5</td>
<td>1000-3500</td>
<td>/µL</td>
<td></td>
</tr>
<tr>
<td>Mononuclear</td>
<td>5.0</td>
<td>45.0-500</td>
<td>/µL</td>
<td></td>
</tr>
<tr>
<td>EOS</td>
<td>2.5</td>
<td>50.0-500</td>
<td>/µL</td>
<td></td>
</tr>
<tr>
<td>BASO</td>
<td>3.5</td>
<td>0.00-325</td>
<td>/µL</td>
<td></td>
</tr>
</tbody>
</table>

*These reference ranges are for females. The ranges for males are: RBC = 4.7-6.1, HGB = 140-160, HCT = 42.0-56.0.
Case Report Forms

• CRF Completion
  • Ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs.
  • Data reported on the CRF should be consistent with the source documents.
  • Initial and date the completed form.
  • Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry.

ICH 8.3.14 & ICH GCP E6 4.9
Case Report Forms

• Study Status Change/End-of-Study/Final Status CRF
  • The PI must sign this form after all the CRFs for the subject are complete and reviewed by the PI.
XXI-XXXX Protocol Short Name

BARCODE SPACE

Subject ID #  Site ID #

END OF STUDY

1. Did the participant complete all screening and study follow up per protocol?  □ Yes  □ No

1.1 If yes, date participant completed the study:  OR  If no, date of last visit:

<table>
<thead>
<tr>
<th>dd</th>
<th>MMM</th>
<th>yyyy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>201</td>
</tr>
</tbody>
</table>

1.2 If no, Please determine the reason for the participant not completing the study:

□ Screen failure
□ Found to be ineligible during study
□ Reported / known to be deceased

Date of Death:

<table>
<thead>
<tr>
<th>dd</th>
<th>MMM</th>
<th>yyyy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>201</td>
</tr>
</tbody>
</table>

Cause of Death: _______________________________________

□ Research terminated by Sponsor or Investigator
□ Withdrawal of consent
□ Noncompliant with protocol
□ Developed an AE
□ Other: ______________________________________________

I certify that:

1. I have reviewed all entries on the Case Report Forms.

2. All information entered onto the Case Report Forms by my associates or me for this subject is, to the best of my knowledge, correct.

Principal Investigator Signature: __________________________ Date: __________________

CONFIDENTIAL: This material will not be disclosed or used except as authorized by the Investigator or Sponsor. Version XX 00MON 2012
Case Report Forms

• Design
  • Data are collected as outlined in the protocol.
  • User-friendly and uncluttered.
  • Clear instructions for completion.
  • Avoid duplication of data.
Case Report Forms as Source Documents
Source Documents and CRFs

- Tying everything together
  - Source Document
  - CRF
- What about when the documents overlap?
Per ICH GCP, CRFs or portions of CRFs may serve as source documents.

Therefore, the CRF now has 2 functions:
1. Part of medical record (first point of entry)
2. Data collection tool
Case Report Forms as Source Documents

• When CRFs or portions of CRFs serve as source documents:
  • The protocol should prospectively define which data may be treated in this way.
  • Sections of the CRF also functioning as source documents should be:
    • Signed and dated by the person collecting that information.

ICH GCP E6 6.4.9
1. Vaccination
1.1. Was participant eligible for vaccination? Yes ☐ No ☐
1.1.1. If No, indicate reason:
☐ Oral temperature > 37.5°C
☐ Any other condition that in the opinion of the Investigator poses a threat to the individual immunized or that may complicate interpretation of the safety of vaccine following immunization
☐ Other, specify: ____________________________
1.2. Signature/date of study staff member confirming eligibility: ____________________________ / __________________
1.3. Time first vaccination given: _____:______

hh  mm
1.4. First vaccine location: ☐ Right deltoid ☐ Left deltoid ☐ Other
1.5. Signature/date of study staff member performing first vaccination: ____________________________ / __________________
1.6. Time second vaccination given: _____:______

hh  mm
☐ NA → Skip to 1.6
1.4. Second vaccine location: ☐ Right deltoid ☐ Left deltoid ☐ Other
1.5. Signature/date of study staff member performing second vaccination: ____________________________ / __________________
1.6. Were any adverse reactions noted after vaccination? Yes ☐ No ☐
If Yes, complete AE CRF.
1.7. Were any medications given after vaccination? Yes ☐ No ☐
If Yes, complete ConMed CRF.

Investigator/Designee Signature: ____________________________ Date: ____________________________

CONFIDENTIAL: This material will not be disclosed or used except as authorized by the Investigator or Sponsor. Version #, X Date XXMON2012
Case Report Forms as Source Documents

• Remember!

• When using CRFs as source (paper OR electronic)
  • Any regulatory agency can request more information for evidence of testing or diagnosis

• “When pertinent supportive information is available, FDA could request other documents during an inspection to corroborate a direct entry of source data elements into the eCRF by an authorized data originator.”

  FDA Guidance for Industry: Electronic Source Data in Clinical Investigations, September 2013
## Quick Reference Guide

<table>
<thead>
<tr>
<th>Document</th>
<th>Signature or Initials?</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source Document</td>
<td>Signature and Date</td>
<td>Data is attributable to person completing procedure; also part of a medical record; hospital documentation/accreditation requirement</td>
</tr>
<tr>
<td>CRF</td>
<td>Initials and Date</td>
<td>Data is attributable to authorized study member</td>
</tr>
<tr>
<td>Entire CRF is also Source Document</td>
<td>Signature and Date</td>
<td>Both CRF and Source Document requirements apply</td>
</tr>
<tr>
<td>Part of CRF is Source Document, Part is CRF</td>
<td>Signature and Date on Source section; Initial/date CRF portion</td>
<td>Both CRF and Source Document requirements apply</td>
</tr>
</tbody>
</table>
Case Report Forms as Source Documents

- **Worksheets**
  - Act in a similar manner to source documents.
  - Not original source – secondary source.
  - Not CRF (*even though it may look like one*).
  - Used to facilitate data entry.
Conclusion

Source Documents (Site)

Case Report Forms (Site)

Source Document Verification (Monitor)

Database Locked & Clean-Up (DCC)

Analysis, Auditing, and Reporting (Statisticians)

Final Study Report (Site & Sponsor)

Regulatory Agencies (DHHS, FDA, IRB, DSMB)
Any questions or comments?
References

- ICH GCP E6

- Good Clinical Practice: A Question & Answer Reference Guide, May 2010

- FDA Guidance for Industry: Electronic Source Data in Clinical Investigations, September 2013

- www.fda.gov