Essential Regulatory and Source Documents

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Topics To Be Covered

- Subject Research Records
  - Source Documents
  - Case Report Forms
- Regulatory Files
  - Essential Documents
- Financial Files

Subject Research Records

- If documented it was not; done it was not.

Why do we need Source Documents?

- Federal Requirement to maintain "Adequate Case Histories" for FDA studies
  - 21 CFR 312.62 Investigator recordkeeping and record retention (Drug studies)
  - 21 CFR 812.140 (G) Records (a) Investigator Records (Device Studies)
  - FDA cites ICH guidance as their current thinking on Good Clinical Practices (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm)

Source Documents

- 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
- Records must be present for all individuals who participate in a research study (including screen failures and control subjects)

Source Documents

- Source Documents
  - First place subject data is recorded
    - Certified Copies of original records are also acceptable
  - International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidance
    - any data recorded that will not have a source must be outlined in the protocol (e.g. direct data entry)
    - case report forms and the source docs must match, data point to data point
    - where the terms "source data" and "source documents" are defined for clinical trials

Source Documents

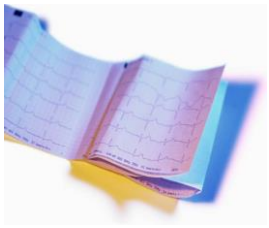
- Examples
  - Patient history documents
  - Medical charts with progress notes
  - Laboratory/Pathology reports
  - Investigator interpretation of results
  - Other Ancillary reports (ECG, Scans, chest x-ray)
  - Informed Consent Form (ICF) and HIPAA authorization signed and dated by subject
  - Diaries, questionnaires (paper or electronic)

Source Documentation

- Why is it so hard to have good source documentation?
  - Not always clear what records need to be maintained
  - Not always clear how records are to be completed
    - Who is responsible for recording data?
    - Study may not have written standards for quality source data

Example: Which is the Source?

ECG



MD Interpretation

Source Documentation Cont'd

- How to make it easier?
  - Make sure you know what information needs to be recorded (e.g. What does medical history mean?)
    - Investigator initiated trials – review standard with PI
    - Sponsor initiated trials – review with your monitor
  - Use existing record-keeping as much as possible
    - redundant systems lead to errors
    - minimize the need for transcription

Source Documents

Quality Source Documentation must be:

- A Attributable
- L Legible
- C Contemporaneous
- O Original
- A Accurate

Source Documents

- L – Logical!!
- Your source documents need to tell a story
- Remember your audience
  - PI
  - Other MDs participating in the patient's care
  - FDA!
  - IRB and other auditors
- If it wasn't documented (or doesn't make sense)… it wasn't done (or it might be misconstrued)

Writing Progress Notes

- Record what you observe
  - Vital signs
  - Compliance (with medication, diaries, etc)
  - Your observations of subject
    - Within your scope of practice
  - Don't use unacceptable abbreviations (see OHSU unacceptable and dangerous abbreviations list: http://ozone.ohsu.edu/healthsystem/HealthSystems/pharmacy/unacceptable%20abbreviations1-06.htm)
  - Just the facts not your impression
    - Don't editorialize

Writing progress notes

- When documenting AEs record what the subject says
  - Have you been sick/ill since your last visit?
- Prompt the subject for information but don't lead the subject in their response
  - Ask onset date
  - Duration/ongoing
  - Severity and characteristics
  - Did they take any medication?
    - Name of medication and indication
    - When (start and stop dates)
    - Dosage and frequency

Writing progress notes

- Report your findings/observations to PI/co-I
  - You can send via email and file their email response in the research records
    - Separate emails for separate studies/subjects
  - If you discuss with the PI on the phone or in person it is best to follow-up in writing
    - Ask the PI to confirm your understanding by co-signing a note or by responding to an email.

Writing Progress Notes

- Record the plan for the subject
  - When will the subject return
  - Changes to medications/ study regimen
  - Repeat testing/ procedures planned
  - Reason for withdrawal (if applicable)
  - Referrals (to PCP or other MD)

Creating your own Data Collection Worksheets

- Data collection forms should only capture data specified in the protocol
- Organize data collection forms to match your workflow
- Be clear and concise with your questions
  - Collect Date Of Birth vs. Age

If you have to create your own Data Collection Forms

- Avoid duplication
- Request minimal free text responses
- Provide units to ensure comparable values
  - Lbs vs Kg
- Check with the statistician to see if you are collecting the data in a way they can easily analyze

Data Collection Forms

- Inclusion/Exclusion Criteria
- You need to document the actual criteria/values not "yes/no"
- For example, if inclusion criteria states Hgb $\geq$ 10.0
  - Record the actual result
- Why is this important?
  - Need proof that subjects met the inclusion/exclusion criteria
  - May need the actual values for data analysis later

Research Procedures in Medical Records

- What research data need to be filed in the medical records?
  - The Signed consent if subjects are receiving clinical services at OHSU
  - Documentation of all Clinical Services provided at OHSU and the results (https://ohsu.ellucid.com/documents/view/264)
  - Anything that will be billed to insurance
  - Point of Care testing
    - Pregnancy tests
    - Hgb/Hct

Research Procedures in Medical Records

- What data should not be filed in medical records
  - Lab results that are not from a CLIA approved lab
  - Genetic test results that aren't validated
  - Results collected by an individual that has not completed the appropriate training/competencies (see OHSU Clinical Research Coordinator Required Training Checklist http://www.ohsu.edu/xd/research/centers-institutes/octri/education-training/for-study-coordinators.cfm)

Case Report Form Completion

- Looks easy…

  But it is very easy to make mistakes!!!!

Completing Paper Case Report Forms

- Make sure you are listed as study personnel in the eIRB
- Make sure your name is on the delegation log stating you can complete CRFs (if applicable)
- Use only black ballpoint pen
- Note: if using carbonless copies ensure that the entry has gone through to the other pages
- Print!
- Only write in the data fields – don't make extraneous marks on the CRF pages

Completing Paper Case Report Forms Cont.

- Be sure to use the correct date and time format
- Record the data in the correct measurement
  - (Kg vs. Lbs)
- Ensure you use the CRF completion guidelines provided by the sponsor (if applicable)
- Only have the PI sign off on a CRF when it is complete (never before)
- Don't backdate signatures

Completing Paper Case Report Forms Cont.

- Don't use abbreviations unless they are agreed upon by the sponsor
  - BA can mean Barium, Backache, Blood Alcohol, Bone Age, or Boric Acid to name just a few
- Don't use nursing/medical shorthand
- NEVER leave blank fields
  - Use leading zeros, dashes, or not done (ND) per the sponsor instructions
- Never write in data that doesn't have a source or that was not collected.

Completing Electronic Case Report Forms

- Only complete electronic CRFs under your own log in
- Never share your log-in
- Be brief in your responses to free text fields
- Save work frequently
- PI sign off is the same as a paper signature

Examples of CRFs Questions

- What would you record on the CRF?
- Lab report lists estradiol <20.0 pg/mL
  Estradiol ___.__
- PI progress note lists NYHC as 3-4
  Class I ◯ Class II ◯ Class III ◯ Class IV ◯

Correcting Source Docs and CRFs

- Four elements that must be visible each time data is changed
  - Old value
  - New value
  - Date of change
  - Identification (e.g. initials) of person making change
- Only authorized study staff can make changes
- Don't use whiteout

Corrections to Source Documents and CRFs

Patient was seen on 11/01/07 PE 11/12/07 ~~10/31/07~~ for shortness of breath.

BACK in 10 minutes

Practicum

Regulatory Files

Regulatory Files

- Regulatory documents must be completed and filed at the clinical site, the sponsor, and/or IRB
- Documents demonstrate compliance of site, sponsor, IRB with Good Clinical Practice Guidance and regulatory requirements

Investigator Regulatory Files

- Essential Documentation
  - **Protocol Personnel**
  - **IRB Documents**
  - **Correspondence**
  - Protocol and Amendments
  - Informed Consent/HIPAA
  - FDA Forms
  - Screening/Enrollment
  - Investigational Product
  - Laboratory
  - **Monitoring**

Investigator Regulatory Files

- Clinical Trial Regulatory File Checklist on OCTRI website http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/forms.cfm

Investigator Regulatory Files
Protocol Personnel

- **Delegation of authority documentation**
- **Documentation (e.g. training logs) of training on the following:**
  - Study Protocol and amendments
  - Investigator Drug Brochure/Device Manual
  - Study procedures outside of the investigators/study staff's practice (e.g. new surgical procedure)
  - Equipment
  - Case Report Form Completion
  - Database entry and audit procedure

Investigator Regulatory Files
IRB Documents

- IRB membership list
- **IRB Initial Review Questionnaire (IRQ)**
- IRB initial review/approval memo(s)
- **Continuing Review Questionnaires (CRQs) and approval memos**
- Modification forms/PRAFs and approval memos
- **Cover memos and correspondence with IRB including Analyst and PI comments in eIRB**
- Unanticipated Problem and Protocol Deviation Reports

Investigator Regulatory Files
Correspondence/Communications

- Relevant study communications/ telephone calls/ emails
- Including correspondence between:
  - **the PI and co-investigators, study coordinators**
  - the PI/study staff and the manufacturer
  - the PI/study staff and monitor
  - the PI/study staff and the research pharmacy
  - the PI/study staff and laboratory
  - other study related correspondence
- **Follow-up on telephone calls with an email or write it up in a log**

Investigator Regulatory Files Monitoring

- Monitoring Log
- Monitoring Reports
- Audit Reports
- **Documentation of any activities completed to fulfill your data and safety monitoring plan.**

Regulatory Files

- Print your submissions, correspondence, and approved eIRB documents for your Regulatory Binder
- IRQ information may change over time so it is good practice to print
- Documents in the eIRB may be inadvertently deleted or archived
  - Check after modifications/CRQs are approved to make sure all of your documents are in the approved documents bin
  - If you don't print it you may loose it
  - Check the dates on your approval memo, IRB approval date in the eIRB and status, and the consent form dates

Financial Documents

- Contract and Financial documents should be stored in a central but separate location from the study records
  - Contract
  - Budget
  - Invoices
  - Monthly reports from Oracle
  - Financial Correspondence
    - With Sponsor
    - With SPA

Financial Documents

- Track when activities occur on a study that need to be invoiced
  - Additional study procedure
  - Start-up fees
- Communicate billing to Department personnel invoicing if not doing it yourself

Notes to File

- **What is a note to file?**
- A memo written to explain a documentation deficiency or a deviation
- Notes to file are
- They do not co em
- If used incorre provide a trail for an auditor to find all of your problems

Notes to File

- **Essential elements of the note(s):**
  - Date(s)
  - Document the problem(s) (# of occurrences)
  - Document the root cause (if known)
  - Document how you will prevent the problem in the future (if applicable)
    - Procedural change
    - Staff re-education
    - Protocol/Consent form changes
  - Training occurred on the new procedure/corrective action
  - Date new procedure was implemented
  - If applicable, steps to monitor that the procedural change is working
  - PI Sign-off

What is wrong with this NTF?

Date: 12/28/2008

PI: Dr. Jones

Protocol: ABC123

Re: Informed Consent Version 1 date 11/23/2008 approved by the OHSU IRB 12/02/2008

Dr. X is listed as a co-investigator on the ICF but he is not listed on the 1572 form therefore he will not be able to work on this study.

Subjects will be informed of the discrepancy during the consent process and this will be documented. The consent will be revised on the next updated consent that is submitted to the IRB.

Study Document Retention

- Documents must be retained after study termination
  - (see OHSU Summary of Regulatory Retention Requirements for Records Associated with Research http://www.ohsu.edu/xd/research/centers-institutes/octri/resources/policies-forms/upload/Regulatory-Retention-Requirements.pdf)
  - Per FDA 2 years after investigational product has been approved or IND/IDE withdrawal (Sponsor may require you to keep longer)
  - Protected Health Information must be retained for 6 years
    - Do not keep PHI longer than outlined on the HIPAA authorization form
  - Keep Financial Records for 3 years from the date of submission of the final expenditure report

Quality Assurance

- Whether you are monitored for an Industry sponsored study or you have an investigator- initiated trial it is good practice to review your study records periodically
  - Allows you to catch errors
  - Change study activities in a timely manner to ensure quality data
  - Ensure you are reporting appropriately to the IRB and or sponsor
  - Make sure you are billing appropriately

Quality Assurance

- QA recommendations
  - Review records early in the trial to make sure things get off to a good start
  - Review consents/HIPAA authorizations for all subjects enrolled
  - At least 10% of records - more if errors are found
  - Share results of your review with the study team
  - Document corrective actions, if necessary
  - Take corrective actions, if necessary

Evaluation Form

- If you want to receive continuing education credits for the class today, you need to complete the evaluation form

"May the Source be with you"

STAN WOOLLEN, FORMER DEPUTY DIRECTOR FDA