Notes to File: An Auditor's Perspective

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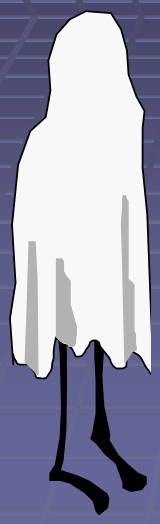
Objectives

- The Paper Tells (or Doesn't Tell) the Story
  - Critical role of documentation in the conduct of clinical trials
- Whose Documentation Is It, Anyway?
  - Sites, Sponsors or the FDA?
- How to Keep Your Nightmare from Becoming an Auditor's Dream Come True!
  - Corrective and Preventive Actions

The Paper Tells the Story



- If it isn't documented…
- ***How*** it's documented matters too!

The Paper Tells the Story

- **Source documentation is a regulatory responsibility of clinical investigators**
  - **21 CFR 312.62,** Investigator recordkeeping and record retention
    - "…adequate and accurate case histories that record all observations and other data pertinent to the investigation…" including documentation of informed consent
    - Disposition of drug(s)
    - Progress reports and Safety reports
    - Financial disclosure

The Paper Tells the Story

- **21 CFR 812.140(a)** – "…accurate, complete, and current records…" including:
  - Correspondence (IRB, FDA, other investigators, sponsor, monitors)
  - Receipt, use or disposition of device
  - "…each subject's case history and exposure to the device…" including adverse device effects, documentation of informed consent
  - Required reports (unanticipated adverse effects, progress, deviations, final report)

Paper that Doesn't Tell the Story

- Documentation is frequently cited as inadequate during FDA inspections
  - For the past 10 years, the second most common observation cited by CDER FDA inspectors
  - **Others include**:
    - Failure to follow the protocol/investigational plan
    - Failure to account for disposition of study drugs
    - Failure to report Adverse Events
    - Inadequate subject protection – including informed consent issues

Paper that Doesn't Tell the Story

- "For the Month 6 visit, the subject apparently visited the office on two different days, 10/6/03 and 10/7/03. A ***note to file*** dated 6/8/04 states that page 2 of the source document for the visit done on 10/7/03 is missing and indicates that the physical exam was not done because you were not in the office….By contrast, a note written on 10/6/03 by a different study coordinator states that all appropriate procedures were done except for a biopsy because the physician had to leave the office."

[Source: Jan 21, 2009; Stewart]

The Paper Tells the Story

- **How** the paper tells the story is equally important
  - Inaccurate or incomplete records
  - Late entries
  - Improper corrections
  - Inappropriate personnel completing
- Electronic records
  - 21 CFR Part 11
  - FDA Guidance: Computerized Systems Used In Clinical Investigations, May 2007
    - Draft guidance on Electronic Source Data in Clinical Investigations, November 2012

ALCOA principles for GDP

- ***Attributable:*** Appropriately signed, initialed, dated, (who wrote it when)
- ***Legible:*** No hieroglyphics; properly corrected
  - One line through, add new information, initial and date
- ***Contemporaneous:*** Documented in proximity to occurrence, not 6 months later
- ***Original:*** If not, why not? → Certified copies
- ***Accurate:*** Correct subject; sensible dates; modifications clearly explained if not self-evident

Whose Documentation Is It?

- Investigator responsibilities
- Regulatory requirements
- Sponsor / Monitor expectations

Whose Documentation Is It?

- Source documentation is a regulatory responsibility of **clinical investigators**
  - Can delegate authority but not responsibility
  - Delegation of authority log with printed name, signature, initials, roles, date(s) involved
  - Appropriately trained, qualified and ***supervised***
  - **No** appearance of falsification or fraud

Whose Documentation Is It?

- "Our investigation indicates that you permitted individuals to conduct *study tasks which they had not been delegated the authority to execute*, and that your *supervision of personnel to whom you delegated study tasks was not adequate* to ensure that the clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and *in a manner that protected the rights, safety, and welfare of human subjects*."

[Source: Feb. 17, 2009; Chappel]

Whose Documentation Is It?

Just one example:

- "There were entries made on subject source documents long after those documents were created that provided information concerning the results of adverse events, concomitant medication assessments, alcohol and smoking habits, and/or study drug dosing. However, there is no documentation concerning from where or when this information was obtained."

[Source: Feb. 17, 2009; Chappel]

Whose Documentation Is It?

- Sponsors' expectations regarding source documentation
  - FDA Guideline for the Monitoring of Clinical Investigations, January 1988
    - "A sponsor is responsible for assuring that data submitted to FDA in support of safety and effectiveness of a test article are accurate and complete. The most effective way to assure the accuracy of data submitted to FDA is to review individual subject records and other supporting documents and compare those records with the reports prepared by the investigator for submission to the sponsor."

Whose Documentation Is It?

- Source data verification
  - "All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial." [ICH E6, 1.51]
    - Note the new draft guidance definition is identical, adding, "Source data are contained in source documents (original records or certified copies)."
- Site's normal record-keeping practices
- Study-specific source worksheets

Source Documentation

- Normal record-keeping versus source worksheets
  - What are the investigator's / site's routine records?
  - Source worksheets should supplement, **not** substitute for **or** duplicate, source data
    - Normal clinical documentation ≠ clinical research record-keeping **but** if normal documentation is adequate, using different documentation is risky
    - *An Auditor's Perspective:* What if there are **only** source worksheets?

Source Documentation

An Auditor's Perspective:

- "In addition to the standard office chart, [sponsor's] monitors required the completion of study specific source templates that were bound separately from [PI's] office chart. Some data may be recorded in either chart or both depending on the visit and the testing required. This complicates the data verification process and may increase the probability of transcription errors."

Source Documentation

- Monitors are individuals (so are auditors)
  - Some things are clear regulatory requirements
    - Other elements are subject to interpretation
  - Past experiences may impact current thinking
  - Impact of Monitor personnel changes
    - Consider keeping monitoring visit notes
    - Please speak up! – it is ***your*** source documentation

An Auditor's Perspective

- *The same note to file appeared in a number of study subjects' records as a copy*
  - It contained information that conflicted with what the clinical investigator stated during an interview
  - The site staff indicated that they were instructed by a monitor to write the note to file to address a protocol requirement
  - They completed the note to file, the PI signed it, and it was copied for placement in several subjects' records ***even though they knew the information was not entirely accurate***

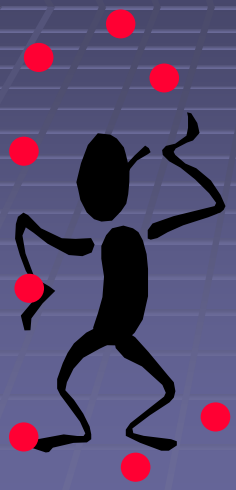
The Paper Tells the Story

- Documentation is how auditors and inspectors determine how the study was conducted
  - Help them just turn the pages….
- Accurate, complete documentation of all aspects of the study **illustrates** regulatory and protocol compliance
  - Subject records
  - IRB records
  - Drug or device accountability
  - Informed consent
  - AE / SAE reporting
  - Correspondence

An Auditor's Perspective

- *Notes to file documenting*
  - The ongoing AE of bilateral conjunctivitis
  - The ongoing AE of headaches
  - "Adverse event follow-up was done"
  - The treating physician was not present when the study medication was dispensed (this was a protocol-requirement) [x 8]
  - The CA Bill of Rights was not signed until Visit 3 [x 4]
- *"All the memos to file generated and collected at this visit have the incorrect site number. Please resolve this discrepancy"*

Nightmares and Dreams



- The controversies
- Mistakes are human
- The solutions?

NTF Nightmares and Dreams

- From *'Note to Self: No More Notes to File'* by Carl Anderson, Applied Clinical Trials, March 2008
  - "A common document at many clinical sites is the memo or note to file (NTF). **When used properly, an NTF can be a positive practice.** Some in the clinical trials community, however, seem to think an NTF is a panacea for all things that have gone wrong. Make a mistake? Then write an NTF…"

'Note to Self: No More Notes to File'

- "The practice has become so ubiquitous that new CRAs and study coordinators sometimes think that they are a regulatory requirement…. During my own auditing experience, I have noticed that NTFs are frequently a contentious issue between monitors and study staff…. **[some] have developed a habit of writing NTFs instead of developing good record-keeping practices.** All [such an] NTF accomplishes is documenting poor performance. And ineffective work seldom impresses the FDA." [Carl Anderson]

Bad Documentation Practices

An Auditor's perspective

- How poor practices often lead to the need for retrospective notes to file
  - "Late entries are sometimes made without adequate documentation by the person making the entry including the time and date the entry was made. In addition, the actual source of the late entry is not always evident."
  - "Progress notes occasionally had multiple date stamps, or were undated, making it difficult to determine the date the exam was actually performed. Some changes are not dated or initialed by the person(s) making the change."

Nightmares …

- Retrospective "documentation" is a ***very*** risky practice
  - Warning letter issued to Sanofi-Aventis in October, 2007
  - "Our investigation found that Aventis failed to take any action to secure compliance while the study was ongoing except to generate numerous memos to file ***after*** all subjects had completed the study."

Sanofi-Aventis, October, 2007

- "According to an FDA interview with an Aventis manager involved with study 3014, these memos to file served as a mechanism to train the investigator. However, this same Aventis manager conceded that because the majority of these memos to file were generated after all subjects had completed the study, there wasn't much value in training the clinical investigator. **We note that generation of numerous memos to file after all subjects have completed the study does not adequately secure compliance of an investigator**."

Nightmares …

- From a Warning Letter issued to a clinical investigator
  - "We note that there were no medical histories in these subjects' research files. For subjects [-] you created Memos to File stating that medical records were not obtained due to subjects' primary care physicians being located in Mexico. **These memos do not sufficiently address the issue of the missing medical histories.** Without the medical histories…it is not possible to verify if the subjects met inclusion criteria for the study."

[Source: June 30, 2008; Hsueh]

Nightmares …

- Just documenting errors without
  - Examining the cause of the problem
  - Explaining the remediation
  - Being necessary
- Notes to file that are
  - Poorly and/or inaccurately written
  - Frequent and repetitive

… and Dreams

- Notes to file written to correct, clarify, or add to the existing source documentation can be effective if they are
  - **Well-written** – clear and accurate
  - **Relevant** – appropriate level of detail
  - **Infrequent** – and not repetitive
  - **Timely** – not written the day before an audit or inspection

Nightmares **and** Dreams

- Notes to file are ***"flags"*** for auditors and inspectors
  - Prompt us to look at processes and procedures related to the issue documented
  - Prompt us to ask more specific questions
  - Tell us a "story" about the conduct of the study, including about the monitoring

Nightmares …

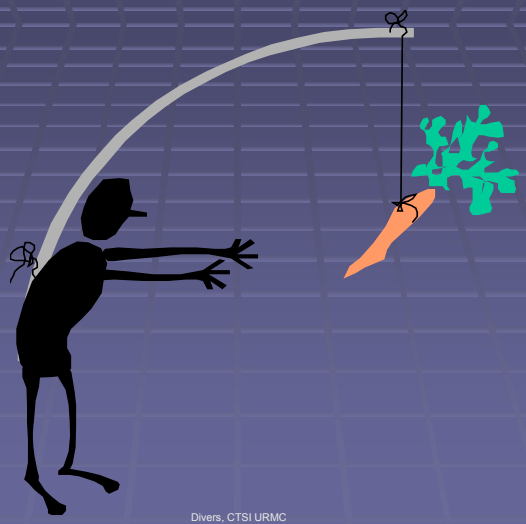
An Auditor's Perspective:

- "A deviation was noted for this subject. Prednisone (steroid) and Ketek (antibiotic) [disallowed medications] were prescribed to the subject by an outside doctor during the study. Dr. [PI] did not know the subject was taking these medications until Visit 3."
- *What procedures do you think this NTF would prompt an auditor to explore?*

… and Dreams

- There is no expectation of perfection
  - Clinical trials are conducted, monitored and audited by human beings
- ***Effective*** use of Notes to File
  - Demonstrate GCP compliance and GDP by documenting corrective and preventive actions (CAPA)

Corrective and Preventive Actions



Nightmares …

- "Documenting a mistake means absolutely nothing during an FDA inspection. What requires documentation is the corrective action taken and whether the action worked."
  - From *'Note to Self: No More Notes to File'* by Carl Anderson, Applied Clinical Trials, March 2008

… and Dreams

- **Correct** the source of problem / error / non-compliance **and prevent** future problems
  - Start with ***root cause analysis***
    - The 5 why's of a problem
  - Then ***develop effective resolutions***
    - SOPs
    - Checklists
    - Remedial training
    - Internal audits

CAPA – Root Cause

- When a mistake or an error or an incident of non-compliance occurs, evaluate ***why***
  - What was the actual mistake?
    - *Hint:* It may not be what it appears to be
  - Under what circumstances did it occur?
  - Who was involved?
  - When was the error detected and how?
  - What were the consequences?
    - Were subjects' safety, rights or welfare impacted?

An Auditor's Perspective - The Problem

- *"A significant number of signed Consent Forms have date and signature anomalies made both by subjects and study personnel."*
  - Date(s) changed – with or without time changing
    - In several instances, changed by several days, weeks, or in one case, by more than a month
  - Two instances of subject signing on "Person obtaining consent line."
    - One instance was lined through, one remained uncorrected
  - Often not dated by subject and/or PI themselves but obviously by someone else

An Auditor's Perspective - The Reason(s)

- What is really happening here? Was this just random human error?
  - From visit to visit, monitoring needs to connect the dots – *"Haven't I seen this mistake before?"*
- Root cause analysis
  - Correct the real problem: *Realistically,* do people get the date wrong by several days or a month, or does the signature date change but not the time?
- Informed Consent **process** issues illustrated by the ***pattern of errors***

How to Develop CAPA

- Once you have defined the problem, how can you develop corrective and preventive actions?
  - Be **SMART**
    - **S**pecific, **M**easurable, **A**ttainable, **R**elevant, **T**ime-bound/**T**rackable
  - Be clear and precise
    - Avoid extraneous information, obfuscation, defensive remarks
    - Describe ***how*** the action will be ***implemented***

An Auditor's Perspective - The Problems

- First 8 subjects enrolled
  - 3 mis-randomizations
  - 4 improperly signed ICFs
- Next 10 subjects enrolled
  - 3 mis-randomizations
  - All 10 ICFs/assents incorrectly signed
- Next 21 subjects enrolled
  - Two adults signed child assent forms
  - 2 mis-randomizations
  - Multiple instances of disallowed concomitant meds and/or improper use of study drug

An Auditor's Perspective - The Non-Solutions

- *"[The PI] was asked to closely follow the protocol instructions regarding obtaining and documenting the informed consent process with future subjects. [The PI] was asked to submit all protocol deviations to the IRB."*
- *"The PI and SC were advised of these protocol deviations and verbalized their understanding."*
- *"A note to file will be written to explain the discrepancies."*

CAPA

- Don't just take the PI / study staff / or the monitor's word for it
  - ***Investigate*** the root cause
    - In a manual system, occasional / rare randomization errors may be possible but 6 of the first 18 subjects is not rare
- **Correct** the cause of the error, don't just document it
  - Lack of ***controlled process***: Poorly organized supplies and improper use of the accountability log

Notes to File – Tips and Techniques

Notes to File – Tips and Techniques

- For a retrospective Note to File:
  - **Define the problem**
    - What is the *root cause*?
  - **Evaluate the impact of it**
    - Subject safety? Data integrity? Administrative?
  - **How can it be corrected?**
    - What actions does the investigator need to take?
    - Documentation and follow-up
  - **What needs to occur to prevent it from happening again?**
    - Does investigator/site staff training or behavior need to be addressed?

Example of an Effective NTF

- "As noted during the site initiation visit 1/15/08, the site does not use the Sponsor provided temperature log found in the Regulatory Binder. **The site's standard temperature log maintained on the side of the refrigerator where culture medium is stored contained the necessary information.** At the first monitoring visit 2/29/08, it was noted that the temperatures were not logged on Saturdays and Sundays. **SC and Monitor confirmed with ACM 2/29/08 that culture medium remains acceptable for use up to 48 hours at room temperature and a closed refrigerator is not likely to reach room temperature for at least several hours. The site staff will check and document refrigerator temperatures first thing Monday AM and last thing Friday PM. Culture medium will be discarded and re-ordered if any temperature anomalies are suspected. This plan was discussed with and approved by ACM and Sponsor Project Management."**

What Notes to File Cannot Do

- A note to file, in and of itself, does **not**
  - Correct
  - Prevent
  - Secure compliance
  - Appropriately escalate non-compliance
- Correction / compliance is an ***action / behavior***
  - Training
  - Monitoring
  - Auditing

What You Can Do

- Practice good documentation practices from the start of the study
  - **ALCOA**
- Document errors and their correction in a timely manner
  - Recognize patterns and consider the story they tell
  - Make CAPA a habit, including assessing effectiveness
- Understand the protocol and GCP requirements and investigator responsibilities
  - Ask questions of the monitor, sponsor, PI, IRB, auditors
  - Checkout the FDA website

We're all in this together!

Questions

Contact Information

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"Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives."

- Willa A. Foster