Demystifying Audits

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Audits and Audit Preparation

What is an Audit

- A systematic and independent examination of trial related activities and documents to determine whether
  - the evaluated trial related activities were conducted,
  - the data were recorded, analyzed and accurately reported,
  - according to the protocol, sponsor's SOPs, GCP and the applicable regulatory requirements

-ICH Guideline for GCP

Types of Audits

- Institutional Audits: Performed by institution or Departmental units per institutional policy
  - Knight Institute
    - Routine: At least annually
    - For cause
  - ORIO:
    - For cause
    - Future: Routine
  - VA:
    - For cause
    - Routine: Every 3 years, includes all consent forms

Types of Audits (cont.)

- Sponsor Audits
  - Sponsor Monitoring visit:
    - Timing: Regular intervals throughout study
    - Purpose: Assure quality of the data collected
  - Sponsor QA audit:
    - Routine
      - Timing: Just after submission of product to FDA
      - Purpose: To prepare for FDA audit
    - For cause
- Cooperative Group/NIH Audits
  - Routine audit: every 2-3 years to assure data quality
  - "For cause" audit: To follow-up on problem detected in a routine audit

Types of Audits (cont.)

- FDA audits (inspections)
  - Routine
    - What:
      - Those studies that are crucial to a product's evaluation and approval
      - The sites with the highest enrollment
    - Timing: Retrospective audits after a product has been submitted for marketing approval
    - Purpose:
      - To assure the integrity of scientific testing and the reliability of test data submitted to FDA to permit sound judgments regarding the safety and efficacy of regulated articles
      - To assure the protection of human rights and the welfare of human research subjects
  - For Cause
    - Patient complaint
    - Other "suspicious" activity
  - Whenever they want to
    - Spring '00 audit of all gene therapy clinical trials

What Would Make the FDA Suspicious

- Complaints (subjects, employees, sponsor)
- Too many study subjects
- Results “too perfect”
- Attempts to delay the inspection
- Attempts to limit access to documents
- Investigator conducted the study without staff
- Similarities in signatures on consent forms

Would Make the FDA Suspicious? (cont.)

- The “dog ate my homework” excuse
- White out or obliteration of data
- Notes not in chronological order or squeezed between lines
- Photocopied source documents

Advance Audit Preparation

- Perform internal “self” audits periodically during study
- Request a peer audit
- Obtain a copy of applicable audit requirements to become familiar with what they will be looking for

FDA and NIH Site Inspections

Notification of Inspection

- Clinical sites will usually receive prior notification of an impending inspection, unless for cause
  - Auditor will usually schedule with site
  - Principal investigator should be available
  - Usually only a few days notice, otherwise seen as stalling
    - PI not available: Tell the auditor. Leave it to them.
    - You weren't the study coordinator on the study: Doesn't matter. You are there now.
  - Notify:
    - IRB
    - Pharmacy if drug study and drug on site
    - Sponsor if industry sponsored
    - All study personnel
    - Sola Whitehead if VA study

Notification of Inspection (cont.)

- NIH differences
  - Auditor will contact the PI and Study Coordinator to arrange a mutually satisfactory time and place
  - Normally at least 30 days advance notice

Selection of Cases

- A select number of cases will be reviewed based upon a percentage
- Cases will be randomly selected
  - NIH:
    - Informs study team of cases prior ~2 weeks prior to audit
    - Flag medical records of selected cases as instructed
  - FDA: Often does not inform study team of selected cases

Audit Preparation

- Once the audit is scheduled:
  - Reserve a room with a large table and access to a copier
  - Make sure the auditors will have privacy and quiet, not located near any other patient or study information
  - Have clinical records printed from EPIC if not yet available
    - Auditors will only audit from originals or certified copies
    - HIM Audit Record Request: http://ozone.ohsu.edu/healthsystem/HIS/medrectrx/CRC_HISaudit.pdf
  - Make sure all source documents, regulatory documents, and CRFs are available and preferably in room reserved

Subject Case Records Needed

- Clinical records (must be hardcopy)
  - Inpatient and outpatient charts
  - Diagnostic reports (x-rays, scans, ECGs, etc.)
  - Outside records
  - Laboratory reports
  - Subject diaries/calendars
  - Radiologic images & other source diagnostic information

Subject Case Records Needed (cont.)

- Research records, as applicable
  - Original signed consent forms for each patient
  - Eligibility checklist
  - Subject tracking log
  - SAEs reported for each subject
  - Research shadow chart
  - Case Report Forms
  - Completed Data Correction Forms/Queries

Regulatory Records Needed

- IRB Documentation
  - Approvals: Initial, modifications, revised consent forms, Annual review, advertisements
  - All correspondence to IRB and from IRB
  - Documentation of IRB review and approval of all Unanticipated Problems
  - IRB committee membership list
  - All IRB Correspondence should list: item name, number, issue date, type of approval, version date

Regulatory Records Needed (cont.)

- File all versions in chronological order, most recent on top, as applicable:
  - Informed consent used at the site
  - Protocol used at the site
  - Investigator drug/device brochure
  - FDA Form 1572
  - Lab certifications and normal ranges
  - CVs and licenses

Drug Accountability Records Needed

- Records
  - Drug receipt documentation
  - Drug order forms
  - Drug accountability records
  - Drug dispensing records
  - Records regarding disposal of investigational drugs
- If drug still on site, have auditor go to Pharmacy

Documentation

- Review medical record
- Use a checklist
- Assure documentation to support:
  - Each eligibility criterion
  - All data in data collection forms/Case Report Forms
- Document reasons for any missed visits
- Document all efforts to contact patient for follow-up

Documentation (cont.)

- If you find deficiencies, can they be addressed prior to the audit? - Yes
  - Late entry annotations:
    - Real-time with explanation
    - Never backdate signatures
  - Directly on consent form
  - Notes to file
    - 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

Conclusion

- If data is lost or missing, don't try to hide it!
- Auditors REALLY like to see that problems were identified, addressed and resolved PRIOR to the audit

Inspection

- FDA inspector should present
  - a badge/credentials
  - form FDA 482 - Notice of Inspection
  - Resources for FDA Regulated Businesses (optional)
- VA: Bring auditor to R&D Office to sign in

Inspection (cont.)

- Interaction with inspectors:
  - Do:
    - Remember FDA inspectors and NIH auditors are representatives of the Federal Government
    - Limit conversation to study and auditor's questions
    - Stay on topic
    - Politely point out inaccuracies
    - Reference protocol, policy or procedure references when possible
  - Don't:
    - Be defensive
    - Withhold information
    - Argue
    - Complain (sponsor, PI, IRB, etc.)
  - If you don't know the answer to a question:
    - Don't guess
    - Answer honestly
    - Find out answer if possible
  - Make yourself available but don't hover
  - Cannot offer refreshments or lunch

Inspection (cont.)

- FDA Inspector reviews:
  - Selected subjects from a list provided by the FDA Central Office
  - Regulatory files
  - Documentation of receipt, distribution, and return of test drug
- Not subject to inspection (access should be limited):
  - Contracts
  - Budgets
  - Studies not involved in the inspection
  - Subjects/patients not enrolled in the study

Inspection (cont.)

- What the inspector is looking for
  - Protocol and consent form
    - Approved by IRB
      - Prior to first patient in study
      - Annually
    - All amendments
      - Documented, dated and with protocol?
      - Reported to the sponsor?
      - Reported to the IRB?
    - Was the protocol followed?
  - What was the source of patients for the study?
    - In-house
    - Outside: advertisements approved by IRB?

Inspection (cont.)

- What the inspector is looking for (cont.)
  - Was the investigational article represented as safe and/or effective for the proposed indication?
  - Study subject records
    - All subjects sign and date consent forms prior to treatment with the study article?
    - Did/do the subjects exist?
    - Were subjects available during the course of the study and keep their appointments?
    - Did the subjects have the condition being studied?
    - Did the subject meet the enrollment criteria and, if not, was the exception approved by the sponsor?

Inspection (cont.)

- What the inspector is looking for (cont.)
  - Study subject records (cont.)
    - Do the CRFs and the source documents agree?
    - Were adverse reactions reported on the CRF and to the sponsor and was the association with the test article documented?
    - Were concomitant therapies reported on the CRF?
    - Were all dropouts with reasons reported to the sponsor?
    - Who recorded information in the records and what records were maintained?
  - Sponsor communication
    - Were periodic reports submitted to the sponsor and how?
    - How and when were CRFs submitted?

Inspection (cont.)

- What the inspector is looking for (cont.)
  - Test article accountability
    - Was the test article administered and dispensed by qualified and authorized personnel?
    - Is there documentation of
      - Receipt dates and quantity?
      - Dates and quantity dispensed and identity of subjects?
    - Was the distribution of the test article limited to persons under the investigator's supervision?
    - Does the date, quantity, frequency, duration, and route of administration match the source documents?
    - Date and quantity of final distribution of test article documented and accurate?
    - Was the test article stored under appropriate conditions?

Inspection (cont.)

- What the inspector is looking for (cont.)
  - Test article accountability (cont.)
    - Does blinding, identity, lot number, and package labeling agree with each other and all study records?
  - Study record maintenance
    - Who maintains custody of the study records?
    - If not maintained by the investigator, has the sponsor been notified?
    - Have study records been maintained per regulations
  - Are electronic data systems involved in gathering, storing, or transmitting data to the sponsor?

Inspection (cont.)

- Conclusion of FDA inspection
  - Inspector conducts exit interview
    - With investigator
    - May include study staff (ask)
  - The inspector will discuss the findings with the investigator, Investigator may (and should if possible) respond to the findings
  - PI is presented with Form FDA 483, Inspectional observations
  - Investigator should not sign anything in the exit interview
  - Can request presence of general counsel
  - Note what copies, if any, the inspector takes with them and remove PHI from any subject source documents
  - VA
    - Call Sola Whitehead at end of audit
    - Complete & FAX Monitoring Visit Report Form

Post-Inspection

- Copy IRB(s) and sponsor (if industry sponsored) on all inspection findings
- Response to 483
  - Written response to 483 not required, but may be warranted
  - Need for response to 483 determined by Research Integrity
  - If response:
    - Involve all areas noted in findings
    - Copy IRB and sponsor, if industry sponsored, on response (sponsor should be allowed to review response before submitted to FDA)

FDA Inspection Outcome

- Inspector writes an EIR, Establishment Inspection Report
- Report is sent to the FDA Central Office for review and final disposition

FDA Inspection Outcome (cont.)

- The FDA issues a letter to the investigator with one of the following classifications:
  - NAI - No Action Indicated
    - Notice no deviations were observed
    - No response necessary from investigator
  - VAI - Voluntary Action Indicated
    - Identifies deviations
    - May or may not require a response
  - OAI - Official Action Indicated
    - Called a “warning letter”
    - Serious deviations from regulations requiring prompt correction and response
- Inform IRB(s) and sponsor, if applicable, of all inspection outcomes
- If VAI or OAI, coordinate response with Research Integrity and copy IRB(s) and sponsor, if applicable, on response

Potential Additional FDA Actions

- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain Letter (NIDPOE letter)
  - When evidence of repeat or deliberate violation of regulations
  - To determine if further action necessary
  - Written response necessary
  - If investigator fails to respond or response unsatisfactory an informal hearing is offered to the investigator

Potential Additional FDA Actions (cont.)

- Disqualification from receiving investigational products or restricted
  - If the investigator has repeatedly or deliberately failed to comply with regulations or has falsified data
  - Disqualified: Cannot receive investigational drugs for a specified period of time
  - Restricted: Agreement with the FDA to conduct trials with certain restrictions

Potential Additional FDA Actions (cont.)

- Disbarment
  - If investigator convicted of a felony under federal law for conduct relating to the development or approval of a drug application
  - Investigator cannot provide services in any capacity to a person with an approved or pending drug product application for the term specified (often permanent)

NIH Inspection Outcomes

- PI provided with audit findings
- NIH findings include:
  - Acceptable
  - Acceptable, needs follow-up
  - Unacceptable
- The audit team conducts an exit interview with the investigator and research staff to go over preliminary findings and recommendations
- A written report is sent to PI
- Copy IRB on report

NIH Inspection Outcomes (cont.)

- If any finding requires follow-up a response from the PI must be sent within 30 days of receiving the audit findings
- If either component is deemed **Unacceptable**, a re-audit may be required as well as a written response and/or corrective action plan
- If PI response is considered adequate, NIH sends a final letter to the PI