

# Monitoring & Auditing of Clinical Trials

*Slides from: Elizabeth Ness, RN, MS  
Nurse Consultant (Education)  
Center for Cancer, NCI*



# Overview

- Monitoring and auditing of clinical trials is necessary to assure that the:
  - rights and safety of patients (i.e., human subjects) are protected
  - reported trial data are accurate, complete, and verifiable from source documents
  - conduct of trial is in compliance with protocol, good clinical practice (GCP) and applicable regulatory requirements.
- When conducting an IND trial, the regulations require the sponsor to monitor the study.

<b>Monitoring</b>	<b>Auditing</b>
Act of overseeing the progress of a clinical trial	Systematic and independent examination of the trial related activities and documents
100% source document verification of all participants	Snapshot in time of a subset of participants
<p>Ensuring that the study is conducted, recorded and reported in accordance with:</p> <ul style="list-style-type: none"> <li>• Protocol,</li> <li>• SOPs,</li> <li>• GCPs,</li> <li>• All applicable regulatory requirements</li> </ul>	<p>Determine whether the trial related activities were conducted and data recorded accurately, analyzed and appropriately reported according to:</p> <ul style="list-style-type: none"> <li>• Protocol</li> <li>• Sponsor's SOPs</li> <li>• GCP</li> <li>• All applicable regulatory requirements</li> </ul>
Each protocol will outline a data safety and monitoring process and plan	
Some studies may require a data safety monitoring board/committee (DSMB/DSMC)	

# Types of Monitoring Plans

- PI/research team plan
- Independent Monitor
- Data and Safety Monitoring Board/Committee (DSMB/DSMC)
- IC QA Plan/Program
- Sponsor (IND/IDE) plan

# **Data Safety Monitoring Plan (DSMP): SOP #17**

- All protocols submitted to an NIH IRB must include a Data Safety Monitoring Plan (DSMP)
- Method and degree of monitoring
  - risk involved in participation
  - size
  - complexity of trial

# Elements of the DSMP

- Monitoring mechanism
- Frequency of the monitoring
- Stop or change rules
- Advanced plans for any interim analyses and/or futility analyses
- Information to be monitored
- Communication

# PI Responsibilities

- Establishing a DSMP
- Implementing the IRB-approved DSMP
- Implementing monitor recommendations
- Assure that all FDA-required data and safety monitoring requirements are met

# Monitor and Institution Responsibilities

- Monitors
  - provide oversight of the study consistent with IRB-approved DSMPs
- Institution
  - establish monitoring groups
  - implement monitor recommendations

# IRB Responsibilities

- Review and approve DSMP
- Review of monitor reports
- Review of monitor recommendations

# PI/AI/Research Team...

- Criteria per SOP #17
  - No more than minimal risk
  - Minor increase over minimal risk
  - Conducted at a single site

# ...PI/AI/Research Team

- Example:
  - PI will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities
  - Team will meet on a regular basis
    - Decisions about enrollment
    - Review adverse event and response data
  - All data collected in a timely manner and reviewed by the PI
  - Adverse events and protocol deviations will be reported

# Independent Monitor

- Criteria per SOP #17
  - More than minimal risk
  - Multi-site protocols
  - Investigator has a potential conflict of interest
  - FDA-regulated research

# Data Safety Monitoring Board (DSMB)

- An independent and external group
- Monitor data for safety and emerging efficacy
  - the progress of a clinical trial
  - safety data
  - critical efficacy variables
- Make recommendation to the sponsor
  - Continue, modify or terminate a trial

# **DSMB Criteria per SOP #17**

- Phase III blinded randomized clinical trials
- High risk multicenter protocols
- Protocols using gene transfer or gene therapy methodology
- FDA-regulated research

# IC QA Program

- Risk based
- Identify aspects of GCP that need to have quality review
- Develop matrices
  - Pre-post SOP development
  - Prior deficiencies
  - Include frequency
- Use for quality improvement

# Sponsored Trials

Several types of site visits conducted by the sponsor

- Pre-study qualification visit
- Initiation visit
- Monitoring visit
- Close-out visit

# Pre-study Qualification Visit

- Purpose: Determine the site's ability to conduct the clinical trial prior to commencement of the investigation. Often place new trials at sites with a good track record of success
- Goal of the pre-study qualification visit:
  - Visit the site
  - Meet with study staff
  - Inspect the facilities
- Sponsor contacts PI
- Need to determine who the sponsor wants to meet with and what they want to see at the site
- Allow 2-3 hours for the visit

# Purposes of Initiation Visit

- Assure PI and site staff understand:
  - Roles/responsibilities/regulatory obligations
  - Protocol procedures
  - CRF completion instruction review
  - Requirements for records management/retention
  - Drug handling requirements
  - Enrollment and consent procedures
  - Expedited adverse event reporting procedure
  - Patient recruitment resources
- Identify potential problems and concerns

# Timing and Scheduling of an Initiation Visit

- Timing of visit:
  - Prior to patient enrollment
  - After all essential documents in place
  - After supplies received
  - After IRB approval
- Sponsor/CRO contacts PI/RN
  - Mutually agreed upon date/time
  - Letter sent to confirm date/time, location, number of attendees
  - Agenda developed and sent by sponsor

# Attendees

- Sponsor/CRO:
  - Clinical Research Associate (CRA)/Monitor
  - Medical Monitor
  - Project Manager
- Site:
  - PI/AIs
  - Research Nurse/Study Coordinator
  - Data Manager
  - Pharmacist
- Tip:
  - RN/SC and Data Manager should plan to attend entire meeting
  - PI and pharmacist will need to attend, at a minimum, at time designated by the agenda
  - Others may attend as appropriate

# Preparing for an Initiation Visit...

- Review protocol and any other documents received by sponsor/CRO (i.e.: CRFs, Investigator Brochure)
- Become familiar with the study's procedures
- Confirm supplies received (i.e.: drug, binders, test tubes, regulatory binder, etc.)

# ...Preparing for an Initiation Visit

- Write down questions for sponsor/CRO when reviewing documents
- Secure room
- Ensure staff availability for the visit
  - Research nurse to remind staff involved a few days in advance

# During the Initiation Visit...

- Introductions
- Develop CRO & Site Contact List
- Review protocol
  - Focus on eligibility criteria, drug, and study procedures
- Review AE and expedited AE reporting requirements
- Review regulatory obligations
  - Sponsor and PI responsibilities

# ...During the Initiation Visit

- Review study documentation
  - Drug accountability forms
  - CRFs
  - Logs (enter this visit on the site visit log)
- Review Regulatory Binder
- Obtain signatures for Monitoring Log
- Start delegation of accountability log
- Review sponsor/CRO Monitoring Plan
- Pharmacy/site tour

# After an Initiation Visit

- Site to follow-up with sponsor/CRO on outstanding issues (i.e.: missing CV, CLIA, missing supplies, etc)
- Monitor sends final site initiation visit report
  - File in the Regulatory Binder

# Purposes of the Routine Monitoring Visit

- Review progress of a clinical study
- Ensure protocol adherence
- Assure accuracy of data
- Assure safety of subjects
- Regulatory Compliance (CFR & GCP)

# Timing of Routine Monitoring Visits

- Timing/Frequency Depends on:
  - Complexity of the protocol
  - Disease being studied
  - Rate of recruitment
  - PI/staff experience
  - Site performance
  - Sponsor's SOPs
    - Frequency not dictated by FDA regulations, but FDA will hold Sponsor accountable for their SOPs.

# Scheduling of Routine Monitoring Visits

- Monitor contacts PI/RN requesting the first monitoring visit (email, phone call)
  - Date and time negotiated
  - Monitor confirms via letter to PI
    - Date and time
    - Expectations of visit
    - Which record/patients will be reviewed

# Attendees

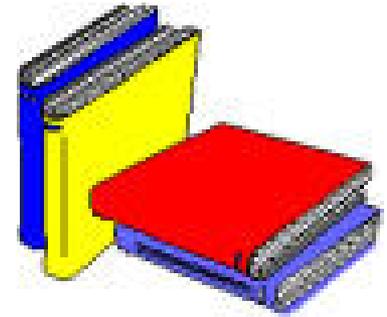
- Sponsor/CRO
  - Clinical Research Associate (CRA)/Monitor
- Site
  - PI, AIs
  - RN/SC
  - Data Manager
  - Pharmacist

# **Preparing for a successful monitoring visit**

# Securing Room/Record and Availability of Staff

- Review NIH procedure
  - [Regulatory Audit Guide](#)
  - [Regulatory Audit Scheduling Form](#)
- Inform pharmacy of visit and schedule appointment
- Make sure PI and AIs will be available for monitoring date.
- If multiple monitoring visits occur simultaneously, make sure each sponsor has a separate room to ensure privacy and confidentiality

# Regulatory Review...



- Make sure Regulatory Binder is complete and up to date:
  - **All** protocol versions and approvals
  - **All** Investigator Brochure versions
  - Lab certifications and normal ranges
  - **All** versions of Form 1572
  - CVs, licenses and Financial Disclosures for all Investigators – signed and dated
  - All IRB correspondence
  - All Sponsor correspondence
  - SAEs
  - Update Delegation of Responsibility/Signature Log as needed

# ...Regulatory Review

- Assure IRB receipt of
  - Amendments
  - SAEs
  - Continuing Reviews
- Assure all participant original consents are in the medical record, signed & dated

# Source Document Review...

- Assure medical records contain
  - All laboratory reports
  - X-ray, scan reports
  - Physician notes, nursing notes
  - Drug compliance/administration notes
  - Procedures documenting study parameters reported in CRF's
  - Informed consent **process** documentation
- Obtain missing information **or** document why unobtainable

# ...Source Document Review

- Flag the medical record to assist monitor's retrieval of information in a time efficient manner
- Make sure laboratory reports and procedure reports are reviewed and signed by PI (if required per sponsor SOP)

# Review CRF's

- Assure CRF's are complete, accurate, up to date
- Review adverse events
  - Assure attribution of events is documented
- Review concomitant medications
  - Assure stop & start dates are recorded
- Review study medications
  - Assure stop & start dates are recorded

# Review Pharmacy Records

- Pharmacy should review drug dispensing records prior to visit
  - Drug Accountability Record Forms (DARFs)
- Assure drug count is accurate
  - Disposal of returned meds
- Assure “notes to file” are written for any discrepancies
- Inform PI of discrepancies

# Steps to Make the Monitoring Visit Go Smoothly...

1. Ensure monitor's current CV is in Medical Records
2. Arrange all charts, CRFs and regulatory files in monitor room
3. Provide only charts and files for studies listed in letter
4. Greet monitor and escort to the designated room
5. Review format of medical record with monitor
6. Orient monitor to appropriate areas on unit such as bathroom, phone
7. Confirm appointment times with PI and Pharmacy

# ...Steps to Make the Monitoring Visit Go Smoothly

8. Check in on monitor in short intervals to ensure all questions are answered
9. Escort monitor to pharmacy and PI office at appointed times
10. Allow time for corrections of CRFs
11. For monitoring visits that are over multiple days, ensure that medical record and files are kept in a locked room
12. Set up next visit at the end of the current visit

# Site's Expectations of the Monitor

- Monitor will come prepared
  - Be knowledgeable about the protocol
- Communicate honestly about findings
- Show cooperation, respect, and courtesy
- Appreciate the effort that went into the preparation

# Monitor's Expectations of the Site

- Site will have prepared for the visit
- Records will be organized so they can work efficiently and finish on time
- Communicate honestly about findings
- Show cooperation, respect, and courtesy
- Appreciate the effort that went into the preparation

# After the Monitoring Visit...

- Monitor meets with PI/RN/SC to:
  - Share findings
  - Identify needed corrections, if applicable
  - Identify remedial training needs, if applicable
  - Answer questions
  - Set up next visit
- Monitor will sign Visit Log, if not done already, and site staff will need to initial
- Return all medical records to Medical/Legal

# ...After the Monitoring Visit

- Site answers queries/clarifications
  - May be done during the monitoring visit
  - Corrected CRFs may be sent to monitor or picked up at next visit
- Monitor sends monitoring visit report
  - Placed in the Regulatory Binder
- Monitor sends follow-up letter of thanks and confirmation of next visit

# Common Deficiencies

- Failure to follow the protocol
- Failure to keep adequate and accurate records
- Problems with the informed consent form
- Failure to report adverse events
- Failure to account for the disposition of study drugs

# Purpose of a Close-Out Visit

To review:

- All regulatory documents
- All drug accountability record forms (DARFs)
- Review record retention guidelines



# Timing and Scheduling of Close-out Visit

- Timing:
  - Study is complete
  - Investigator obligations fulfilled
  - All data has been retrieved, entered and database locked
  - Sponsor decision:
    - Inadequate enrollment
    - Protocol deviations, regulatory violations
    - Safety
  - At PI request
- Monitor contacts PI/RN/SC
  - Mutually agreed upon date/time
  - Letter sent to confirm date/time, location, number of attendees

# Attendees

- Sponsor/CRO:
  - Clinical Research Associate (CRA)/Monitor
- Site:
  - PI, AIs
  - RN/SC
  - Data Manager
  - Pharmacist

# How to Prepare for a Close-Out Visit.....

- Secure room (doesn't have to be in medical/legal since no medical records are needed)
- Ensure site staff are available
- Retrieve all CRF binders and Regulatory Binder

# During a Close-Out Visit.....

- Monitor will:
  - Confirm that all case report forms are retrieved and queries completed
  - Destroy or return all extra CRFs
  - Review site's regulatory binder to ensure consistency with sponsor's master file

# ..... During a Close-Out Visit

- Monitor will:
  - Ensure that all study supplies have been returned or destroyed
  - Ensure that all biologic samples have been shipped or back-up samples destroyed
  - Ensure PI has provided IRB with final report

# At the Conclusion of the Close-Out Visit

- Monitor meets with PI/RN/SC to:
  - Share findings
  - Review record retention requirements

# After the Monitor Leaves

- Monitor sends final report, which is to be placed in the Regulatory Binder
- If FDA decides to audit the site after the study has been closed, the sponsor/CRO will contact the PI and discuss

# Reminders

- **Do:**
  - Think about monitoring visit preparation the day the patient goes on study
  - Report to PI/supervisor major areas of concerns noted while preparing for monitoring visit
  - Report to PI/supervisor any Medical Records or original consent forms which cannot be found
  - Use this information to develop QA/audit procedures within your team for all case records in real time
  - Establish a team system of securing required source documents as they occur
  - Take monitoring visit seriously

## .... Reminders

### **DO NOT:**

- Erase or change dates
- Falsify information
- Use white out
- Use pencil
- Get too *stressed-out*

**Ask for help!**

# FDA Inspections/Audits...

- Bioresearch Monitoring Program or “BIMO”:
  - Program of on-site inspections (i.e., audits) for GCP and Good Laboratory Practice (GLP)
- The purpose of the program is to:
  - Verify the quality and integrity of bioresearch data
  - Protect the rights and welfare of human research subjects

# ...FDA Inspections/Audits...

- BIMO includes inspections of:
  - [Clinical Investigators](#)
  - [Sponsors, monitors, CROs](#)
  - [Institutional Review Boards](#)
  - [Bioequivalence Laboratories and Facilities](#)
  - [GLP Facilities \(nonclinical studies\)](#)

*(Note: links are to the FDA's Compliance Program Guidance Manual)*
- Information Sheet  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf>

# Goals of FDA Inspection

- Ensure quality and integrity of data and information submitted to the FDA
  - Is the data valid
  - Was data collected under proper conditions
- To protect human research subjects
  - Was the study conducted to ensure the rights, safety, and welfare of subjects
  - Did Sponsor, CRO and PI/Site adhere to all regulations, guidelines, GCPs and approved protocol

# Types of FDA Audits/Inspections

- Study-related Audit or Routine
  - primary efficacy studies
  - studies submitted to FDA for NDA, BLA
- Investigator-related Audit or For Cause
  - interest or concern regarding a specific investigator
- Bioequivalence Audits
  - when 1 study is the sole basis for approval

# Study-Related/Routine

- Sites are randomly selected or are sites that:
  - have particularly high or rapid enrollment
  - conduct multiple studies or large pivotal trials for which the majority of the investigational product's claims are based
  - conduct studies to support a switch to OTC status
- Sponsors can usually predict which sites will be selected

# Investigator-Related/For Cause

- Most common reasons PI selected:
  - Conducts many studies or study outside their specialty
  - Conducts a pivotal study for NDA, license
  - Submits safety & efficacy data that is inconsistent with other studies under the IND/IDE
  - Sponsor or IRB notifies FDA of problems or Subject complaint
  - Highly publicized in media
  - Enrollment more rapid than expected or in comparison with other participating sites
  - Unexpected number of subjects w/specific diagnosis for area

# FDA Notification and Authority...

- Sponsor/Investigator will be notified directly using FDA Form 482 *Notice of Inspection*
- FDA representative will arrange a reasonable time that is mutually convenient
  - generally from a few days to a few weeks notice
  - be accommodating; requests to delay audit more than 10 days without valid reason raises suspicion

# ...FDA Notification and Authority

- FDA audit lasts 3 – 5 days on average
- FDA may request an audit anytime during an investigation, and up to years after the study has been completed
- Sponsor or Investigator cannot refuse FDA access to requested files for review

# Site's Responsibilities

- Notify your sponsor as soon as you are notified
- Notify IRB as soon as you are notified
  - FDA may inspect the IRB if not previously inspected, or has not been inspected within past 5 years
- Prepare for the audit

# Audit Preparation

Always be **“Audit-Ready”!!**

- **Know your study inside and out**
  - what does your approved protocol state?
  - what do your SOPs state?
  - what does your IND/IDE application state?
- **Listen to your monitor**
- **Prepare as for a routine monitoring visit**

# During the FDA Audit

- Reserve a separate area or room with adequate space, and bring documents to the FDA inspector as requested
- Ensure Sponsor, Investigator and pertinent staff are available for the duration of the FDA audit
- Ensure FDA inspector will be accompanied at all times
- Ensure inspector has access to photocopier

# During the FDA Audit

- Upon arrival, FDA Inspector presents credentials and FDA Form 482.
  - *Note: for NIH inspections, no CV needs to be on file.*
- FDA Inspector may ask to interview any staff
  - Staff should honestly answer the question asked, but do not offer more information.
- FDA Inspector will meet with pertinent staff at the end of each day to address any issues that can be resolved before the end of audit
- Exit Interview at end of audit to discuss and clarify findings

# After the FDA Audit

- FDA Form 483
  - documents all inspection findings and deficiencies
- Response to FDA Form 483
  - sponsor/investigator's response to deficiencies submitted to FDA inspector
- Establishment Inspection Report (EIR)
  - FDA Form 483 and responses compiled into final report submitted to FDA headquarters
  - If sponsor/investigator responses are deemed adequate, the corresponding finding(s) may be removed from the Form 483, in effect, not noted in the EIR

# FDA Inspection Findings

- **NAI: No Action Indicated**
  - Site is in compliance
  - Acknowledgment letter sent to site and no response required
- **VAI: Voluntary Action Indicated**
  - Objectionable practice having minimal effect on study integrity (data or/or subject protections) noted
  - Formal letter sent to site and response is required
- **OAI: Official Action Indicated**
  - Objectionable conditions identified requiring sanctions
  - Site response/action required and re-inspection likely

# Warning Letters

- Inadequate response to EIR
- Significant deficiencies requiring corrective action to avoid further regulatory action
- Investigator/Sponsor must submit written response within 15 days, outlining corrective actions
- Investigator/Sponsor non-response or continued non-compliance will result in disqualification, disbarment or prosecution

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>

# Sponsor's Audits...

- Sponsor's QA department may chose to audit a site:
  - as preparation to filing the NDA/BLA. Serves as a pre-audit before the FDA inspection
  - result of monitoring findings
- Ensures source documentation is complete and that the site is well-organized and prepared for the inspection

# ...Sponsor's Audits

- Auditor will discuss good clinical research conduct for the potential FDA inspection
- Also may be done:
  - for review of monitoring practices (ie, QA of the monitor)
  - aid in identifying and correcting problem areas
  - provide suggestions to improve site performance

# OHRP Compliance Oversight Investigation

- OHRP's Division of Compliance Oversight (DCO) reviews institutional compliance with the federal regulations governing the protection of human subjects in HHS-sponsored research 45 CFR 46.
  - [OHRP's Compliance Oversight Procedures for Evaluating Institutions](#)
- 2 types of inspections/visits:
  - For cause
  - Not for cause
- A formal written inquiry sent to appropriate institutional officials

# OHRP: For-Cause ...

- Based upon:
  - Nature and severity of the allegations
  - Evidence of systemic problems
  - Appropriateness of any corrective actions taken
  - Perceived need for more in-depth discussions with institution staff

# ...OHRP: For-Cause ...

- Interview:
  - Institutional administrator(s)
  - IRB Chairperson(s)
  - IRB members
  - IRB staff
  - Investigators who conduct human subjects research
  - Others as appropriate

# ...OHRP: For-Cause ...

- Review IRB Records:
  - Select 50-75 active protocols for review of entire IRB record on-site
    - Last 25 protocols approved by the IRB under an expedited review procedures
    - Last 25 amendments approved by the IRB under an expedited review procedure
  - Protocols determined to be exempt during the past 6 months
  - Minutes for all IRB meetings for last 4 years

# OHRP: Not-for Cause

- Assess institutional compliance with Title 45 CFR Part 46
- In absence of specific allegations
- Somewhat proactive
- Some evaluations are partially “for cause” – previous compliance problems

# OHRP Compliance Oversight Determinations/Outcomes...

- Protections under an institution's Assurance are
  - in compliance
  - in compliance, but recommended improvements have been identified
- Noncompliance identified, and
  - corrective actions required
  - Assurance restricted pending required corrective actions
  - OHRP approval of Assurance withdrawn

# ...OHRP Compliance Oversight Determinations/Outcomes

- OHRP may recommend that HHS Officials
  - Suspend
  - Terminate
- OHRP may recommend:
  - Debarment (ineligible for HHS research support)
    - Institutions
    - Investigations

# Summary and Questions

- Monitoring vs. Auditing
- Data and safety monitoring plans
- Sponsor visits
- FDA Inspections
- OHRP Inspections