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Presents: Audit Prep 101

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Always Audit Ready:

The Busy Clinical Researcher's Guide To Audit Preparation and
CAPA Plans

July 23, 2019

Disclosure Statement

The presenter for today's educational program is:

Lisa Haney

Nura Research Institute/Nura PA

- ▶ I have relevant financial relationship(s) with respect to this educational activity with the following organization(s):
Becton Dickinson - Shareholder
Nura PA - Employee

Lisa Haney, BS, CCRC

- ▶ Over 14 years of experience in clinical research; CCRC
- ▶ Research Assistant and Clinical Research Coordinator at Clinical Research Advantage, Inc.
- ▶ CRC, Clinical Operations Coordinator and Clinical Research Manager at Scottsdale Medical Imaging, Ltd.
- ▶ Senior Consultant and Associate at Booz Allen Hamilton supporting projects for the DoD and NIH
- ▶ Project manager at ACRP
- ▶ DSMC Manager at the University of Colorado Cancer Center
- ▶ Clinical Operations Manager at Becton Dickinson (formerly C.R. Bard/Lutonix)
- ▶ Director of Research at Nura Research Institute



Learning Objectives

Upon completion of this presentation, participants should be able to:

- ▶ ***Distinguish*** between monitoring and auditing activities
- ▶ ***Evaluate*** previous audit findings
- ▶ ***Formulate*** a plan for conducting clinical research that is always “audit ready”
- ▶ ***Develop*** a simple CAPA Plan Process
- ▶ ***Implement*** audit readiness and CAPA Plan

A Note About Terminology

Disclaimer

- ▶ FDA = Inspection
- ▶ Rest of the industry/worldwide = Audit
- ▶ Today I will use the term audit, but I may use the term inspection
- ▶ Please forgive me



Audit Preparation

Most audit preparation presentations focus on preparation in the short-term

- ▶ FDA (or sponsor) calls and then audit preparation starts
- ▶ Provide tips on how to effectively scramble to get ready, what to provide, and how to behave
- ▶ Recommendations on how to answer questions, what to say and not say (and hope for the best)
- ▶ Damage control after the audit



This Presentation

- ▶ Not that kind of presentation
- ▶ In addition to the learning objectives, my goal is to get you to change the way you think (and act):
 - ▶ About audit preparation
 - ▶ About clinical trial conduct
 - ▶ About responding to audit findings and (more importantly) potential audit findings



Auditing and You!

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Pop Quiz!

1. What is auditing?
2. What is the difference between auditing and monitoring?



Auditing is Quality Assurance (QA)

- ▶ **Systematic** and **independent** examination of all trial related activities and documents
 - ▶ **Systematic**: Occur at predetermined intervals, or in cases where a predetermined threshold has been met triggering the audit, such as a 'for cause' audit when non-compliance has been detected
 - ▶ **Independent**: Only persons unaffiliated with the management of the trial may conduct the audit
- ▶ Determine if pre-established standards and procedures are being followed
- ▶ Determine if evaluated activities were appropriately conducted and the data were generated, recorded and analyzed, and accurately reported per the protocol, SOPs, Good Clinical Practice (GCP), and the Code of Federal Regulations (CFR)
- ▶ **ICH GCP E6 Section 5.19 - Audit**

Monitoring is Quality Control (QC)

- ▶ On-going process of evaluating a clinical trial to identify and remedy areas of non-compliance
- ▶ Overseeing the progress of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the CFR
- ▶ Conducted by parties directly involved in the trial
 - ▶ Site: Quality control procedures as set forth in site SOPs, and through self-monitoring of trial data collection and entry against protocol procedures
 - ▶ Sponsor: Based on the predetermined trial monitoring plan through the constant review of data received centrally via the electronic Case Report Form (eCRF) and routine on-site monitoring visits verifying the source data against data recorded in the eCRF
- ▶ **ICH GCP E6 Section 5.18.3 - Extent and Nature of Monitoring**

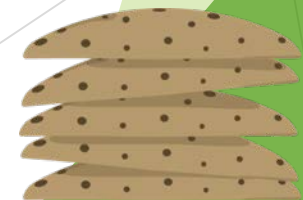
What?!

▶ **Quality Control**

- ▶ Accountant does your taxes; Ensures you pay your bills/taxes per tax code
- ▶ Cookie factory puts steps in place so when making batches of cookies the same amount of ingredients are added every time per the recipe, yielding uniform (and delicious) cookies
- ▶ Monitor looks at data in real-time to make sure it is collected in a timely manner and accurate

▶ **Quality Assurance**

- ▶ IRS auditor audits you; Checks to see if you followed government regulations by paying the taxes you said you paid
- ▶ Cookie inspector inspects the cookies baked to ensure they were baked per the standards of cookie manufacturing and the recipe, thus resulting in uniform (and delicious) cookies
- ▶ Auditor looks at data to ensure processes and procedures were followed per protocol and the regulations



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Common Audit Findings and Their Sources

Top FDA Inspection Findings in 2017

#	Regulation	Short Description	Long Description
140	21CFR312.60	FD-1572, protocol compliance	An investigation was not conducted in accordance with the [signed statement of investigator] [investigational plan]. Specifically, ***
76	21 CFR 312.62(b)	Case history records- inadequate or inadequate	Failure to prepare or maintain [adequate] [accurate] case histories with respect to [observations and data pertinent to the investigation] [informed consent]. Specifically, ***
18	21 CFR 312.62(a)	Accountability records	Investigational drug disposition records are not adequate with respect to [dates] [quantity] [use by subjects]. Specifically, ***

Protocol Deviation Example

- ▶ **Finding:** An investigation was not conducted in accordance with the investigational plan, as participant weights were not obtained at every visit per protocol.

Case History/Records Example

- ▶ **Finding:** Failure to maintain case histories with respect to data pertinent to the investigation. 3 of 10 the subjects reviewed were missing complete source records.

Finding the Source of the Finding

- ▶ Root cause analysis
 - ▶ Multiple tools are available to conduct this
- ▶ Systemic problem
 - ▶ Usually a trend (unless it is caught early)
 - ▶ The source of the problem comes from a specific procedure and may be throughout the system
 - ▶ Could be a protocol
 - ▶ Could be the site
 - ▶ Could be EDC!
- ▶ One-off issue
 - ▶ Cannot link issue to a set procedure
 - ▶ Often one person, one time

Protocol Deviation Example

- ▶ **Finding:** An investigation was not conducted in accordance with the investigational plan, as participant weights were not obtained at every visit per protocol.
- ▶ **Cause:** Standard of care practice does not require obtaining a weight during follow up visits.

Case History/Records Example

- ▶ **Finding:** Failure to maintain case histories with respect to data pertinent to the investigation. 3 of 10 the subjects reviewed were missing complete source records.
- ▶ **Cause:** Shadow source charts extracted data from the medical records maintained by the clinic practice. If a patient does not return to the practice in two years, medical records are sent to long-term storage per SOPs. Upon requesting medical records for the inspection, 3 medical records could not be retrieved from long-term storage as they were not found.

Responding to Potential or Actual Audit Findings

If you see something, say something!

- ▶ **Good:** Note to File
 - ▶ Better than nothing, but may not address the root of the problem if systemic
- ▶ **Better:** Deviation Log
 - ▶ One location for all deviations
 - ▶ Assist with spotting trends or systemic issues
 - ▶ Depending on the log, may not address systemic issue
 - ▶ Does not prevent future deviations
- ▶ **BEST:** Corrective And Preventive Action (CAPA) Plan
 - ▶ Identifies the root cause
 - ▶ Corrects the issue
 - ▶ Prevents the issue from occurring again
 - ▶ Plan for reassessing the prevention plan



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Back to Basic Clinical Research (Audit Planning and Preparation)

Long-Term Audit Preparation (aka Clinical Trial Conduct)

- ▶ General trial conduct preparation
 - ▶ Standard Operating Procedures (SOPs)
- ▶ Protocol specific preparation
 - ▶ Protocol conduct best practices
- ▶ Other considerations and resources

General Audit Preparation: Standard Operating Procedures (SOPs)

- ▶ **Good News!**
 - ▶ Excellent way to standardize procedures for all protocols
 - ▶ Excellent training tool
 - ▶ Holds team members accountable
- ▶ **Bad News!**
 - ▶ If SOPs are not updated, you probably are not following them
 - ▶ If you are not following them, then procedures are no longer standardized
 - ▶ Auditor can hold team accountable and it is a finding if procedures not conducted per SOP
- ▶ **Be smart about your SOPs!**
 - ▶ Review and update regularly
 - ▶ Train on SOPs regularly

General Audit Preparation: Staff Training

▶ New Staff

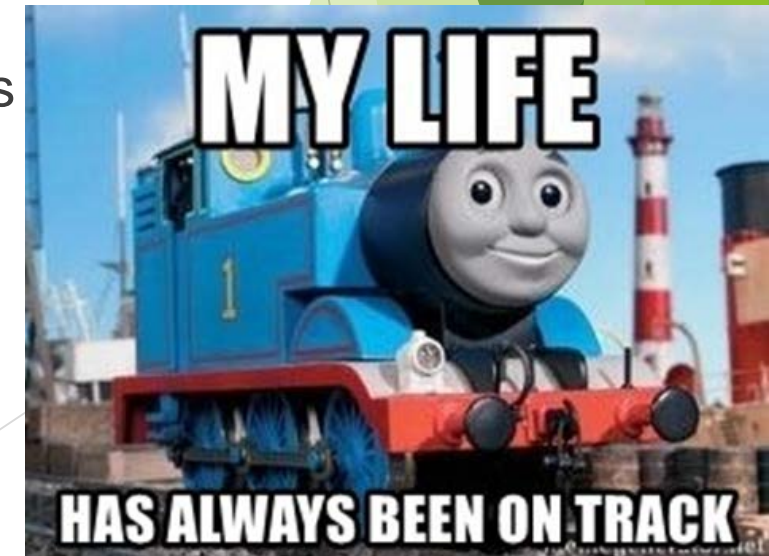
- ▶ Provide proper orientation
- ▶ Initial SOP training
- ▶ Other required training in anticipation of delegated trial responsibilities

▶ Current Staff

- ▶ Refresher training on SOPs
- ▶ Train the trainer
- ▶ Refresher on delegated trial responsibilities
- ▶ New training for new duties delegated

▶ All Staff

- ▶ Document all training in real time
- ▶ Complement training with mentoring
 - ▶ Ensure manageable workload
- ▶ Less turnover = less errors



Protocol Specific Audit Preparation

- ▶ Break down the protocol training and clinical trial conduct procedures in the same way the trial master file is broken down in ICH GCP
 - ▶ Before the trial starts
 - ▶ During the trial
 - ▶ After the trial
- ▶ Plan to conduct the trial like it will be audited next week
 - ▶ “Always be audit ready!”
- ▶ Develop systematic internal checks (QC) to see if the trial is being conducted like it will be audited next week
 - ▶ Peer reviews
 - ▶ Guide lists
 - ▶ Worksheets/Checklists (Careful with these!)

Before the Trial Starts

- ▶ Train all personnel that will be touching the protocol on the protocol
- ▶ Train those delegated duties by the PI on their specific duties
 - ▶ Make sure those delegated are qualified and have qualifying documentation
 - ▶ Develop a training plan that ends in training and DOA log sign off
- ▶ Document all training on a training log
- ▶ Document all delegation on a Delegation of Authority (DOA) log
- ▶ Organize regulatory binder and file documents in a timely manner (within 1 week)
- ▶ Standardize subject chart organization

During the Trial

- ▶ Perform all protocol required procedures, per protocol
 - ▶ Report deviations as soon as they are discovered
 - ▶ Document ALL retraining to include staff and study participants
- ▶ Complete all protocol required source documentation, as well as data entry
- ▶ Use an Informed Consent Form (ICF) Process checklist
- ▶ Standardize Adverse Event (AE) collection and assessment
 - ▶ Collect AEs on an ongoing log and cross reference with medical record, diaries, etc.
 - ▶ Investigator must assess AEs in a timely manner
- ▶ Standardize method of determining clinical significance of Labs and/or EKGs; Ensure done in a timely manner
- ▶ File all study related documentation within subject charts and regulatory binder within a timely manner (within 1 week)
 - ▶ ***Filing Friday!!!***

After the Trial

- ▶ Follow up and resolve all queries from final monitoring visits within a timely manner (within 1 week of notification)
- ▶ File final study documents in a timely manner upon their receipt (within 1 week)
- ▶ Upon notification that study records may be stored in long-term storage, review and follow storage procedures per the regulations, sponsor's request and site's SOPs as applicable
- ▶ Document where study records are filed long-term
 - ▶ Audits can happen after study closes
 - ▶ Records must be made available in the event of an audit
 - ▶ Electronic records must also be made available; Plan to provide access

Bonus Survival tips

- ▶ Pre-plan your audit plan
 - ▶ Develop an audit/inspection SOP
 - ▶ Identify locations of activities; front room, back room, copier, etc.
- ▶ Determine who the audit participants will be before the end of the study
 - ▶ Make them aware
 - ▶ Have an “Audit Seating Chart”
- ▶ Develop a call list to have on hand in the event of an audit
 - ▶ Don't forget your sponsor!
 - ▶ Don't forget your institution!

Make (Some) Time Before Site Initiation

- ▶ Start thinking about audits from the beginning
- ▶ Set aside time to plan before the study starts
 - ▶ Plan will be different based on the site's strengths and weaknesses
 - ▶ Plan will be different for each protocol based on its level of difficulty
 - ▶ Any amount of time spent planning will be a return on investment



Develop Processes

- ▶ General audit preparation processes
 - ▶ SOPs: Annual review, revision, and development
 - ▶ Training Annually: SOPs, other annual or routine trainings
 - ▶ Review of CVs for updates and license expiration
 - ▶ Update of CVs
- ▶ Study specific
 - ▶ Activities to complete prior to SIV
 - ▶ Activities to complete on a routine basis throughout the study
 - ▶ Activities to complete after closeout

Develop Tools

- ▶ Develop processes and include job aids or checklists
- ▶ Ensure checklists are completed
 - ▶ May require review and sign off
- ▶ Review checklists completed for process improvement
- ▶ Example portion of Annual Audit Preparation Process Checklist

Check Box	Item Description	Target Date For Completion	Date Actually Completed
	Annual Review of SOPs		
	Annual Revision of SOPs		
	Annual Training of SOPs		
	Annual Staff Training and Certification Review		
	Annual Staff Training Notification		
	Follow up on staff training until completion		

Bring It Back to the Basics

- ▶ Training
 - ▶ Make the investment, there will be a return on it
- ▶ *“If it wasn’t documented, it didn’t happen!”*
 - ▶ Most findings could have been avoided with just a little more documentation
 - ▶ Document it in real-time
 - ▶ File that documentation!
- ▶ Just do good research



Other Considerations - Investigator Initiated/Investigator Sponsored

- ▶ You are the Investigator AND the Sponsor, so you will be audited as both
 - ▶ Both FDA regulations and GCP considerations, PLUS whatever is stated in the protocol
- ▶ Develop a QC strategy
 - ▶ Obtain monitors or develop monitoring strategy
 - ▶ Have a monitoring plan (in addition to SOPs)
 - ▶ Document monitoring conducted and follow up of action items generated from monitoring
- ▶ Develop a QA strategy
 - ▶ Obtain audit team
 - ▶ Develop audit plan (in addition to SOPs)
 - ▶ Document the audit in the form of an internal report and a certificate
- ▶ Clearly define boundaries between conducting the study, monitoring the study and auditing the study

Corrective and Preventative Action (CAPA) Plans and Audit Prep

What is a CAPA Plan?

- ▶ CAPA Plan = Corrective Action and Preventative Action Plan
- ▶ Per FDA: *“The purpose of the corrective and preventive action subsystem is to collect information, analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive action to prevent their recurrence.”*

<https://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm170612.htm>

What is the difference between a CAPA and CAP?

- ▶ CAP = Corrective Action Plan
- ▶ CAPA is technically 'better'
- ▶ If you do not include a preventive action, you are missing out!
- ▶ If you do not follow up you are REALLY missing out!

Steps of a CAPA Plan

1. Identify an issue
2. Define the root cause of the issue
3. Correct the issue
4. Develop a plan to prevent the issue from reoccurring
5. Implement the plan to prevent the issue
6. Follow up on and evaluate the plan implemented
7. Repeat as necessary
8. Document closure

Common Scenario

- ▶ Monitor finds repeated issue with BP not being obtained after administering IP and before subject leaves
- ▶ Monitor retrains SC and investigator on protocol
- ▶ Oops....At the next visit the monitor still continues to see missed BPs after administering IP

What is the root cause of this issue?

1. **Why** is BP consistently not done after IP administration?

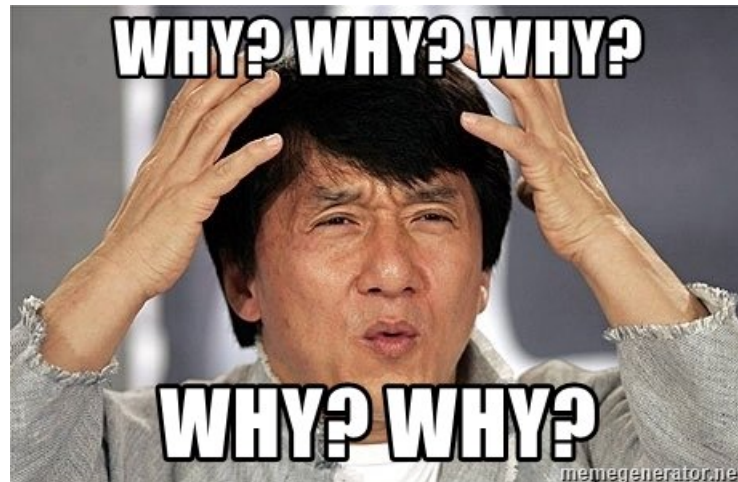
2. **Why** does the SC forget to take BP?

3. **Why** are SCs assuming the investigator is obtaining BP after IP administration?

- SC forgets to take BP after IP administered.

- SCs are seeing multiple subjects, and not always with the subject when investigator administers IP. SC makes assumption investigator is obtaining after administering IP.

- Obtaining BP is the next step on the visit checklist after administering IP and could be done by investigator prior to providing follow up education to subject.



Root Cause - Identified

4. **Why** is obtaining BP after IP administration on the visit checklist missed?

5. **Why** is the investigator or SC still not checking to see if obtaining BP after IP administration has been completed?

- Obtaining BP is listed on the checklist after IP administration, but before providing follow up education which is required to be completed by investigator.

- Investigator routinely checks off all three items on the checklist (IP administration, obtaining BP post administration and subject education), therefore it appears BP was obtained per the checklist.



Corrective Action

- ▶ **What:** BP is missed after IP is administered
- ▶ **Why:** Investigator routinely checks off all three items on the checklist (IP administration, obtaining BP post administration and subject education); Appears BP was obtained per the checklist
- ▶ **How:** Review subject source and data entry for all subjects previously seen and administered IP and complete/report protocol deviations for missing BP post IP administration as they are identified
- ▶ **When:** PDs written up and reported as found, lumped all PDs within one IRB submission
- ▶ **Who:** SCs conduct review and Investigators assess and sign off on PD documentation and reports; PI signs off on IRB submission
- ▶ **Document:** PDs documented to completion and reports completed, acknowledged and filed in appropriate locations

Preventive Action

- ▶ **What:** Plan: 1.) revise checklist so that the two 'investigator only' activities are listed together and other delegated activities are immediately after and 2.) educate the investigator and SC to properly use the checklists
- ▶ **When and How:** Plan will be implemented as soon as reasonably possible after the checklist has been revised and final version available with all SCs and Investigators trained
- ▶ **Who:** SCs and Investigators will be trained on new checklist and will be required to use it
- ▶ **When and How:** Actions will be evaluated after the next 5 subjects have completed study visits where IP was administered and BP post administration was required
- ▶ **Document:** New revised visit worksheet, training and those who attended training, study visit checklist completion along with source, assessment of 5 study subjects' visit checklists, and closure if resolved after assessment OR new plan should issue not be resolved

Outcome

- ▶ Successfully submitted and reported all PDs
- ▶ Identified 2 more missed BPs than the monitor
- ▶ Updated checklist
- ▶ Even came up with a standardized checklist for all studies by listing tasks in order and clearly identifying who may complete the tasks and batching by role(s) if possible
- ▶ Educated all users of the checklist
- ▶ Assessed 5 subjects' source and checklists post IP administration
- ▶ No further issues identified
- ▶ Monitor no longer saw the issue at the next visit



Review and Summary

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What Auditors “Like”

- ▶ Adequate documentation
- ▶ Sites that learn from mistakes
- ▶ Sites that show improvement



Recap

- ▶ Auditing and You!
 - ▶ The difference between auditing and monitoring
 - ▶ Your role in a clinical trial audit
- ▶ Common Audit Findings and Their Sources
 - ▶ Common audit findings
 - ▶ Focus on finding the source of the findings
 - ▶ Example audit findings and their sources
- ▶ Back to Basic Clinical Research (Audit Planning and Preparation)
 - ▶ Tools and plans for audit preparation
 - ▶ Basic clinical research conduct to prevent audit findings
 - ▶ Considerations for audit preparation
- ▶ Developing and Completing CAPA Plans
 - ▶ Steps for creating and executing a CAPA Plan
 - ▶ Implementing CAPA plans

You Should Now Be Thinking About...

- ▶ Preparing for an audit well before you have been selected
- ▶ Conducting clinical trials in such a way that they are always “audit ready”
- ▶ Responding to potential or actual audit findings in ways that address the finding, prevent future findings and above all survive the audit

You Should Now Be Able To...

- ▶ ***Distinguish*** between monitoring and auditing activities
- ▶ ***Evaluate*** previous audit findings
- ▶ ***Formulate*** a plan for conducting clinical research that is always “audit ready”
- ▶ ***Develop*** a simple CAPA Plan Process
- ▶ ***Implement*** audit readiness and CAPA Plan

References and Resources

- ▶ ICH Guideline for Good Clinical Practice E6 R2

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2/Addendum_Step2.pdf

- ▶ FDA FY 2017 Inspectional Observation Summaries

<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fy-2017-inspectional-observation-summaries>

- ▶ American Society of Quality: ASQ.org - FISHBONE (ISHIKAWA) DIAGRAM - Fishbone Diagram

<http://asq.org/learn-about-quality/cause-analysis-tools/overview/fishbone.html>

- ▶ “Five Whys and Five How's” By Ron Bialek, Grace L. Duffy, and John W. Moran - Five Whys

<http://asq.org/healthcare-use/why-quality/five-whys.html>

- ▶ “Get to the Root of It” by David M. Rucker - Is/Is Not Diagram

<http://asq.org/quality-progress/2010/03/back-to-basics/get-to-the-root-of-it.html>

- ▶ PLAN-DO-CHECK-ACT (PDCA) CYCLE

<http://asq.org/learn-about-quality/project-planning-tools/overview/pdca-cycle.html>

References and Resources

- ▶ WHAT IS A PROCESS FLOWCHART? - Process Flow Diagram

<http://asq.org/learn-about-quality/process-analysis-tools/overview/flowchart.html>

- ▶ Memes - Clinical Research Memes

<https://www.facebook.com/groups/1664725823783443/>

- ▶ Meme Generator

<https://memegenerator.net/>

- ▶ US Food and Drug Administration: FDA.gov - Corrective and Preventive Actions (CAPA)

<https://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm170612.htm>

Audit Resources

- ▶ Compliance Program 7348.811
Bioresearch Monitoring: Clinical Investigators and Sponsor Investigators
<http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm>
- ▶ Compliance Program 7348.810
Bioresearch Monitoring: Sponsors, Contract Research Organizations and Monitors
<http://www.fda.gov/iceci/enforcementactions/bioresearchmonitoring/ucm133777.htm>
- ▶ Compliance Program 7348.809
Bioresearch Monitoring: Institutional Review Boards
<http://www.fda.gov/downloads/iceci/enforcementactions/bioresearchmonitoring/ucm133768.pdf>
- ▶ Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors
FDA Inspections of Clinical Investigators
<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126553.pdf>

Questions

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Thank you!

WHAT DO YOU CALL AN
ALLIGATOR IN A VEST?



AN INVESTIGATOR.