Internal and External Audits
or
Being Audit Ready, All the Time!

Presented by:

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Objectives

- Identify common pitfalls pertaining to study regulatory binders
- Identify three common audit findings
- Identify three methods to prevent these findings
- Learn preliminary steps in preparing for an FDA inspection

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Auditors get a bad rap!

Why audit?

- Ensure compliance with research standards
- Take advantage of “teachable moments” for staff training
  - Encourage best practices among research team members

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What is audited?

Compliance with:

- Applicable federal & state regulations
- International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines
- Organizational Policies & Procedures
- Study protocol

How are studies selected?

- Routine "Quality Assurance" Audits:
  - Investigator-initiated interventional studies
  - Non-commercially sponsored study
  - New or inexperienced investigators/research team
  - High enrolling commercial study
  - Can be performed upon request
- At-cause
  - Concerns raised by IRB

Audit-Ready, All the Time

- Start preparing by organizing your regulatory files at the time of initial IRB submission.
- Maintain meticulous source documentation.
  - Checklists are your friend!
  - Clean data -> Happy Monitor ->Less CRC time spent on paperwork
- Don’t wait to complete Clinical Research Forms (CRFs)!

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Maintaining Regulatory Files

- Section 8, “Essential Documents” of the ICH GCP Guidelines is an excellent reference
- Common pitfalls:
  - No Delegation of Responsibility Logs, or inappropriate delegation;
  - Surveys and any subject literature need to be approved by IRB
  - No SOPs for investigator-initiated studies

Common Audit Pitfalls

- Typically fall into 3 categories:
  - Informed Consent Documentation
  - Inconsistent Adverse Event Documentation
  - Poor or Missing Source Documentation

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Common Pitfalls
Adverse Event Documentation

- Adverse event: “untoward medical occurrence” that occurs after consent.
- An AE does not need to be related at all to study device, drug, procedure..
- However, all AEs need to be assessed by PI.
- If PI thinks the AE does not need to be reported, then justification needs to be given why the event is an expected clinical occurrence.

Common Pitfalls
Adverse Event Documentation

Solution? Utilize an AE assessment report in REAL-TIME

Protocol 2006-XYZ, Silly Putty for Laughteritis. Patient is Course 1, Day 6 of his treatment with Silly Putty. Medication compliance and toxicities were reviewed with patient. Medication diary and pill count indicate 87% compliance with study regimen. The following toxicities were noted:

Adverse Event	CTC Grade	Start Date	End Date	Relationship to Study Medication	Comments
Flushing	2	10/27/06	continuing	Possible	Unexpected Event
Bruising R. arm	1	10/20/06	10/22/06	Not Related	Result of venipuncture

Patient instructed on return appointment and given a thirty day supply of study medication.

Research Nurse/date | Physician Signature/date

Common Pitfalls
Adverse Event Reporting

- AEs not properly reported to IRB or sponsor.

SOLUTION:

Intimately know the study protocol!

Read your IRB's adverse event reporting policy!

Internal Audits: Acceptable-Y or N?

- Only one physician listed on 1572 for study-i.e., no co-investigators.
- Subject consented with wrong version of ICF. Subject re-consented with new version. Study team throws away previous version of signed ICF.
- Protocol includes digital photography of wound with study camera during follow-up visit. Instead, PI uses cell phone to take pictures.
- Subjected re-consented with new ICF form. New HIPAA authorization form not signed.
- Protocol requires physical exam on Day 7, but not Day 14. Physical exam performed on Day 14 by Co-Investigator.
- PI assesses abnormal lab value as “CS” and does not add abnormality to AE Log.

Acceptable-Y/N?

- Study drug stored at room temperature in locked cabinet. Thermometer breaks and not monitored for three days. Study drug dispensed during this time.
- PI assesses an AE as serious, related and expected. Research team does not report SAE to IRB.
- IRB approval lapses, but CRC conducts telephone follow-up visit.

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FDA Inspection Preparation

(Also called a BIMO Inspection—Bioresearch Monitoring)

Good News: FDA Inspection

- Relatively small number: FDA performed 415 inspections of PIs in 2016 (68% in U.S.)
- 84% of overall inspections were routine (surveillance), usually within 6 months of marketing application.
- What they're going to inspect isn't a surprise.
  - http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133569.htm

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FDA Audit-Bad News

- Inspectors don't have to give much heads-up
- Can choose to audit a study at any time—usually inspect studies that are completed, some many years after the fact.

If the FDA comes knockin'….

- "Field investigator" from field office will call the PI
- Average advance notification is five days
- Who should you notify?
  - Sponsor; IRB; Institution compliance officer
- Prepare like a super-duper monitoring visit
- Mock Q&A with PI/CRC
- Obtain all medical records
- Decide who will be the institutional "debriefer"

Logistical Considerations

- Reserve quiet room away from office gossip & other study documentation
- Decide who is going to be present for the inspection
  - The fewer the better
- Assignments:
  - Copy maker (noting which documents are requested)
  - “Note taker” for the end of the day wrap-up session with the Inspector

FDA Inspection-Day 1

- Auditor will present 482 “Notice of Inspection” and credentials
- Opening meetings with all team members
  - Will ask questions relating to recruitment, consent, training, delegation of responsibilities
- DO NOT provide:
  - Internal audit reports
  - Financial records

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During Inspection

DO:

- Answer questions concisely.
- Provide copies of documentation if requested.
- Maintain a log of what is copied for Inspector.

DON'T:

- Guess or volunteer information.
- Be defensive.

Completion of Inspection…

- The FDA investigator will usually hold an exit interview with team.
- After audit, FDA will issue 483:
  - Lists significant inspection observations
  - Written response by PI should be completed in 15 working days
  - PI's response should be reviewed by institutional officers.

Potential Inspection Outcomes

- NAI: "No Action Indicated"-483 is not issued
- VAI: "Voluntary Action Indicated"
  - Objectionable conditions or practices were found that represent departures from regs
- OAI: "Official Action Indicated"
  - Objectionable conditions or practices found represent SIGNIFICANT departures from regs & may require the imposition of administrative/regulatory sanctions

And in the end….

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Resources

- 1996 ICH GCP Guidelines, especially Section 8
- MHRI Policies & Procedures (found on Starport)
  - Government Inspection
  - Adverse Event Reporting Policy
  - Source Documentation Procedure
- FDA responses to GCP questions (Easiest way to find website is to google).

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Questions?

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