Developing Monitoring and Auditing Programs for Clinical Research

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Agenda and Learning Objectives

- Outline and explain the key relevant regulatory requirements for clinical research activities in a health care setting
- Identify processes, tips and tools for developing auditing and monitoring programs for clinical research
- Provide proactive strategies for minimizing compliance risks
- Discuss specific examples of clinical research audits and monitoring activities

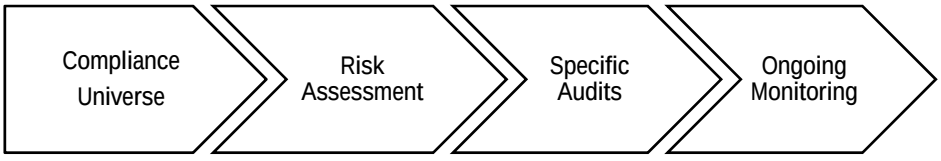
2

Key Acronyms

- FWA: Federalwide Assurance
- FDA: Food and Drug Administration
- FDAMA: Food and Drug Administration Modernization Act
- FDAAA: Food and Drug Administration Amendments Act of 2007
- GCP: International Council on Harmonization (ICH) Good Clinical Practice Guidelines
- IDE: Investigational Device Exemptions
- IND: Investigational New Drug Application
- IRB: Institutional Review Board
- NIH: National Institutes of Health
- OHRP: Office for Human Research Protections
- PI: Principal Investigator

3

General Auditing/Monitoring Process



4

Compliance Universe

5

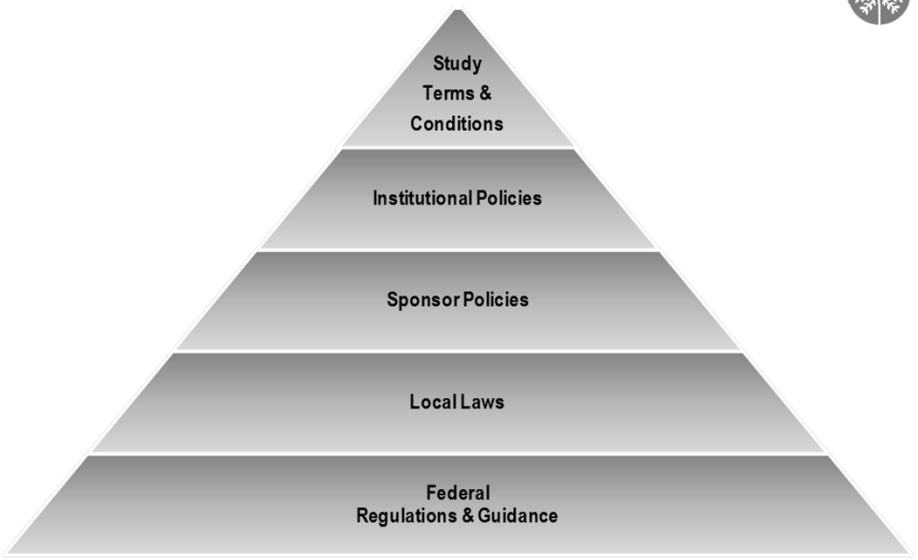
Identify Compliance Universe

Does your organization:

- Accept federal research funding?
- Engage in research involving human research participants?
- Conduct clinical trials?
  - Involving drugs?
  - Involving devices?
- Perform human embryonic stem cell research?
- Use of any of the following in research: biohazards, chemicals, hazardous materials, radiation, lasers, or controlled substances?
- Have its own IRB?

6

Understand Compliance Universe



Understand Compliance Universe

Key Federal Requirements		
Agency	Regulatory References	Applicability
OHRP	• 45 CFR Part 46 • OHRP Guidance Documents	• Non-exempt human research • Federally-funded research ▪ May expand to more than federally-funded research depending on institution's FWA

8

Understand Compliance Universe

Key Federal Requirements		
Agency	Regulatory References	Applicability
FDA	• 21 CFR part 50, Protection of Human Subjects • 21 CFR part 56, IRBs • 21 CFR part 312, INDs • 21 CFR part 812, IDEs • Food and Drug Administration Modernization Act (FDAMA) • Food and Drug Administration Amendments Act (FDAAA) of 2007	• Research involving drugs, devices and biologics • Regardless of funding source

Understand Compliance Universe

Key Federal Requirements		
Agency	Regulatory References	Applicability
GCP	ICH GCP E6	• International ethical and scientific quality standard for clinical trials • The FDA has "officially adopted" E6 GCP for FDA-regulated clinical trials

10

Understand Compliance Universe

Examples of additional specific local requirements to consider:

- Privacy
  - Additional privacy or security requirements may apply to certain types of information
    - For example, some states may have specific requirements for "sensitive information"
- Scope of practice
  - Licensing requirements for certain clinical activities may differ among states

11

Understand Compliance Universe

Examples of additional sponsor-specific policies to consider:

- NIH Grants Policy Statement
- American Heart Association Award Guides

Example of additional institutional-specific policies to consider:

- IRB policies and procedures

Examples of additional project-specific terms and conditions (e.g., protocol or agreement) to consider:

- Data safety monitoring plan
- Research data and document privacy and security standards

12

Baseline Risk Assessment

13

Complete Baseline Risk Assessment

Based on compliance universe, identify broad potential clinical research compliance risk areas, such as:

- IRB protocol adherence
- Investigational drugs
- Investigational devices
- Environmental health & safety
- Privacy & security
- Data management
- Reporting
- IRB compliance

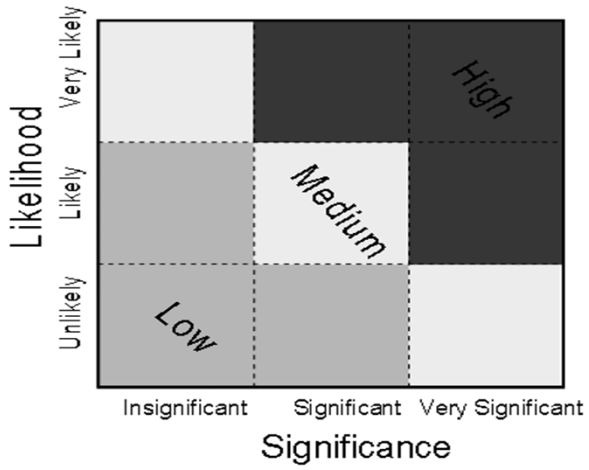
14

Then, break down further as needed
For example:

IRB Protocol Adherence
IRB approval
Informed consent
Research activity
Authorized personnel
Privacy & confidentiality
Reporting safety events

Complete Baseline Risk Assessment

Based on existing institutional policies, procedures and practices, assign baseline risk ratings to each potential risk area



15

Complete Baseline Risk Assessment

Create a baseline risk assessment matrix

Example of a portion of a baseline compliance risk assessment matrix

Clinical Research Compliance					
Compliance Area	**Likelihood**	**Significance**	**Baseline Risk**	**Relevant Requirement(s)**	**Potential Risks**
IRB protocol adherence	*Likely*	*Significant*		° 45 CFR Part 46 ° 21 CFR 50 ° 21 CFR 56 ° GCP Guidelines ° Institutional Policies	° Unapproved research activity ° Adjustments in research activity prior to IRB approval of revision ° Deviations from the IRB-approved protocol ° Failure to provide or appropriately document informed consent ° Unauthorized personnel interacting with human participants ° Unauthorized access to or sharing to confidential information ° Research data not maintained and secured in manner required ° Safety events not reported as required ° Lapse in IRB approval

Specific Audits

17

Perform Specific Audits

- Compliance area audits
  - Select a compliance area to audit
  - Select a sample population of studies or activities to audit specific compliance components of a particular compliance area
- Study-specific audits
  - Select a sample of studies to audit
  - Audit for a broad array of compliance considerations
    - Study-specific audits can be beneficial to identify problem areas to focus on more in-depth in subsequent compliance area audits

18

Perform Specific Audits

General Approach

- What should be happening (per applicable requirements)
- What is happening in practice (based on audit observations)
- What are the gaps between what should be happening and what is happening?
  - What is the root cause of each gap?
    - Isolated incident of non-compliance?
    - Broad internal control deficiency?
    - Lack of knowledge and understanding?

19

Perform Specific Audits

What documents and information are critical?

- IRB-approved protocol and associated documents
- Signed informed consent documents
- Regulatory binder documents
- Documentation of enrollment, inclusion/exclusion criteria, randomization, consent, delegation logs, etc.
- Study records for each participant
- Study data management and security practices
- IND/IDE documentation
- Drug accountability records
- Research grant/clinical trial agreement

20

Perform Specific Audits

- Clearly document and articulate any issues identified during the audit
  - Be specific: on X date, audit identified X issue
  - Identify the span of relevant dates and how many research participants (if any) the issue affected
  - Identify whether or not the issue affected the safety or confidentiality of the research participants
  - Identify whether or not the issue affected the integrity of the study data

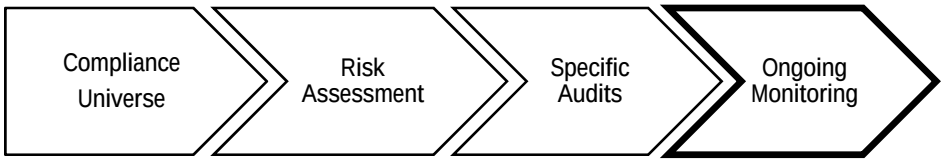
21

Perform Specific Audits

- Identify specific corrective action and identify methods that may prevent the issue from recurring
  - Corrective action plan may include the implementation of specific procedures, increased monitoring, and/or education
  - Corrective action plan should be specific relative to responsible parties and timeline for each item
- Identify required internal or external reporting, and what parties should handle reporting and follow-up
  - Internal organizational office
  - IRB
  - Sponsor
  - Federal agencies

22

Ongoing Monitoring



23

Conduct Ongoing Monitoring

- Audit follow-up
  - For non-compliance and internal control deficiencies, monitor timely completion of corrective action
  - For audits that identified major issues, schedule follow-up visits at a specific point in time (e.g., 6 months after audit)
- Routine monitoring
  - Include research-related audits on yearly audit plan

24

Proactive Strategies

- Education
  - Present and/or coordinate educational sessions
  - Create and distribute tip sheets on compliance issues
  - Make tools and resources accessible to facilitate compliance
    - Example: NIH Clinical Research Study Investigator's Toolbox
    - Example: FDA Information Sheet on FDA Inspections
- Visibility of compliance/audit function
  - Attend clinical staff and researcher lab meetings
  - Be available for and willing to answer questions – serve as a resource
- Regular audits

25

Case Study

Audit: IRB Protocol Adherence

Finding	Corrective Action
Outdated consent form used to consent participants	• PI will report incident to IRB (+ sponsor if required) immediately • PI or study team will make efforts to re-consent participants within 7 business days • PI will establish study team procedure immediately to prevent use of outdated consent forms
Human research conducted during a lapse in IRB approval	• PI will report incident to IRB (+ sponsor if required) immediately • PI will establish systematic reminders of protocol expiration dates within 7 business days • Going forward, PI will submit continuing reviews at least 40 days prior to expiration date • Going forward, PI will notify study team immediately of protocol expiration so all human research activity stops

Case Study

Audit: Investigational Drugs

Finding	Corrective Action
Study drug dosage incorrect	• PI will provide Pharmacy with updated IRB protocol immediately • PI will report incident to IRB (+ sponsor if required) immediately • Going forward, PI will notify Pharmacy and study team of all study revisions immediately upon IRB approval of revision • Going forward, study team will verify study drug labeling with IRB-approved protocol at each administration
Accountability logs for study drugs not maintained appropriately	• PI and/or Pharmacy will establish and adhere to record-keeping requirements for study drugs immediately

Case Study

Audit: Data Management

Finding	Corrective Action
Study data and documentation not maintained as required	• PI will report incident to IRB if required (+ sponsor if required) immediately • PI must establish data and document management practices and documentation in compliance with requirements within 7 business days and will communicate expected standards to study team immediately thereafter
Study data and documentation not secured as required	• PI will report incident to IRB if required (+ sponsor if required) immediately • PI must establish and adhere to data and documentation security procedures as identified in the IRB-approved protocol within 7 business days and will communicate expected standards to study team immediately thereafter

Questions

29

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30