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
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

General Auditing/Monitoring Process

- Compliance Universe
- Risk Assessment
- Specific Audits
- Ongoing Monitoring
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?
Understand Compliance Universe

Key Federal Requirements

<table>
<thead>
<tr>
<th>Agency</th>
<th>Regulatory References</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHRP</td>
<td>• 45 CFR Part 46</td>
<td>• Non-exempt human research</td>
</tr>
<tr>
<td></td>
<td>• OHRP Guidance Documents</td>
<td>• Federally-funded research</td>
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<tr>
<td></td>
<td></td>
<td>▪ May expand to more than</td>
</tr>
<tr>
<td></td>
<td></td>
<td>federally-funded research</td>
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<tr>
<td></td>
<td></td>
<td>depending on institution’s FWA</td>
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</table>
## Key Federal Requirements

<table>
<thead>
<tr>
<th>Agency</th>
<th>Regulatory References</th>
<th>Applicability</th>
</tr>
</thead>
</table>
| 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 |

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## Undergraduate and Complianc Universe

<table>
<thead>
<tr>
<th>Key Federal Requirements</th>
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</table>
| 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 |
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

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
Baseline Risk Assessment

Compliance Universe → Risk Assessment → Specific Audits → Ongoing Monitoring

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

Then, break down further as needed

For example:

<table>
<thead>
<tr>
<th>IRB Protocol Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB approval</td>
</tr>
<tr>
<td>Informed consent</td>
</tr>
<tr>
<td>Research activity</td>
</tr>
<tr>
<td>Authorized personnel</td>
</tr>
<tr>
<td>Privacy &amp; confidentiality</td>
</tr>
<tr>
<td>Reporting safety events</td>
</tr>
</tbody>
</table>
Complete Baseline Risk Assessment

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

Example of a portion of a baseline compliance risk assessment matrix:

<table>
<thead>
<tr>
<th>Compliance Area</th>
<th>Likelihood</th>
<th>Significance</th>
<th>Baseline Risk</th>
<th>Relevant Requirement(s)</th>
<th>Potential Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB protocol adherence</td>
<td>Likely</td>
<td>Significant</td>
<td></td>
<td>45 CFR Part 46</td>
<td>Unauthorized access to or sharing of confidential information</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21 CFR 50</td>
<td>Unauthorized personnel interacting with human participants</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21 CFR 56</td>
<td>Misuse of research data not maintained and secured in manner required</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>GCP Guidelines</td>
<td>Research data not maintained and secured in manner required</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Institutional Policies</td>
<td>Safety events not reported as required</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>Lapse in IRB approval</td>
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</table>
Specific Audits

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
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?
    o Isolated incident of non-compliance?
    o Broad internal control deficiency?
    o Lack of knowledge and understanding?

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
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

• 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
Ongoing Monitoring

Compliance Universe ➔ Risk Assessment ➔ Specific Audits ➔ Ongoing Monitoring

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
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

Case Study

Audit: IRB Protocol Adherence

<table>
<thead>
<tr>
<th>Finding</th>
<th>Corrective Action</th>
</tr>
</thead>
</table>
| Outdated consent form used to consent patients | • 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

<table>
<thead>
<tr>
<th>Finding</th>
<th>Corrective Action</th>
</tr>
</thead>
</table>
| 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                                                                                                       |

#### Audit: Data Management

<table>
<thead>
<tr>
<th>Finding</th>
<th>Corrective Action</th>
</tr>
</thead>
</table>
| 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

Contact Information

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