FDA Expectations in 2013: Investigator-Site
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Agenda
- Update: FDA BIMO Clinical Investigator Inspection Findings 2012
- How and Where has the FDA communicated information about a quality system for the PI-site level?
- FDA and CTTI definition for Quality
- Description of a Quality System
- Quality Systems – site level (select topics)
Program 7348.811

Chapter 48: Bioresearch Monitoring

Clinical Investigators and Sponsor-Investigators

Date of Issuance: December 8, 2008

Guidance for FDA Staff

<table>
<thead>
<tr>
<th>SUBJECT: Clinical Investigators and Sponsor Investigators</th>
<th>IMPLEMENTATION DATE</th>
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Data Reporting

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<th>PRODUCT CODES</th>
<th>PROGRAM ASSIGNMENT CODES</th>
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<tr>
<td>FACTS does not require product codes for</td>
<td>09811 Food Additives</td>
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<tr>
<td>Bioresearch Monitoring Inspections</td>
<td>41811 Biologics (Cell, Gene Transfer)</td>
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<td>42811 Biologics (Blood)</td>
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<td>45811 Biologics (Vaccines)</td>
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<td>45811 Human Drugs</td>
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Diagram:

- Human Subject Protections
- Investigator Quality Management Systems
- Site’s Data Integrity
- Regulatory Compliance
- Protocol Compliance

- Data Confidentiality & Privacy
- Study - Specific Requirements and Procedures Compliance
Clinical Investigator FDA Inspection Findings 2012

Most Common CI Deficiencies

• Failure to follow the investigational plan and/or regulations
• Protocol deviations
• Inadequate recordkeeping
• Inadequate accountability for the investigational product
• Inadequate communication with the IRB
• Inadequate subject protection – including informed consent issues
Common international deficiencies

- Similar to domestic inspectional findings
- Sponsor inspections
  - Inadequate monitoring
  - Failure to bring investigators into compliance
- CI inspections
  - Protocol deviations
  - Inadequate investigational product accountability
    - Inadequate subject protections
BIORESEARCH MONITORING PROGRAM INSPECTIONS* (CDER, FY 2012)

- Clinical Investigator: 22%
- Bioequivalence: 8%
- Good Laboratory Practice: 12%
- Institutional Review Board/Radioactive Drug Research Committee: 5%
- Sponsor/CRO/Sponsor-Investigator: 53%

*Based on inspection start date – [OSI database as of January 24, 2013]
IRB includes only CDER numbers – previously reported metrics may have used combined data across CDER, CBER and CDRH

FREQUENCY OF CLINICAL INVESTIGATOR RELATED DEFICIENCIES BASED ON POST-INVESTIGATIONAL CORRESPONDENCE ISSUED: OFFICIAL ACTION INDICATED (OAI) FINAL CLASSIFICATION* (CDER, FY 2012)

9 OAI INSPECTIONS

- Protocol: 78%
- Records: 56%
- Consent: 44%
- Drug Accountability: 33%
- IRB Supervision: 33%
- IRB Communication: 22%
- Submission of False Information: 22%

*Based on letter issue date. Inspections may have multiple deficiencies. Includes OAI untitled letters. [OSI database as of January 24, 2013]
Note that this does not denote number of inspections completed in FY 2012, but rather number of inspection reports evaluated and closed in FY 2012.
FDA Communications

Quality Systems: Site Level

Building Quality in Clinical Trials With Use of a Quality System Approach

There is no denying that a strong quality system is the number one priority in a quality system, and the importance of this cannot be overemphasized. The ability to ensure that all quality systems are effective and that they are implemented and maintained properly is critical to the success of any quality system. In order to ensure that quality systems are effective, it is important to have a clear understanding of the goals and objectives of the system. The goals and objectives of the system should be specific, measurable, achievable, relevant, and time-bound (SMART). The system should also be evaluated regularly to ensure that it is effective and that it is achieving its goals. In addition, the system should be reviewed periodically to ensure that it is up-to-date and that it meets the needs of the organization.
FDA Communications
Quality Systems: Site Level

Guidance for Industry
Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

Prepared
October 2000

Building Quality into Clinical Trials®
A Regulatory Perspective

This article highlights the consequences of noncompliance and outlines key attributes of quality-by-design and quality-risk-management approaches.

Leslie S. S. PD. Capt (CGPCH) / Ann M. O’Connell, MD

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ISO 9000 Series

– The **quality** of something can be determined by comparing a set of inherent characteristics with a set of requirements.
– If those inherent characteristics **meet all requirements**, high or excellent quality is achieved.
– If those characteristics **do not meet all requirements**, a low or poor level of quality is achieved.
– *Note: ICH Q’10 is based on ISO 9000*

Quality

Quality is characterized by the ability to:

1. **Effectively and efficiently answer the intended questions about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure, while,**
2. **Ensuring protection of human subjects**
Quality in Clinical Research

• Human Subject Protection
  – Clinical Trials
  – Post-marketing Surveillance
  – Subject’s health, safety and welfare are always paramount!

  ❖ Good Clinical Practices
  ❖ Protocol execution and adherence
  ❖ Subject’s access to medical care

Definition

• A quality management system is a set of interrelated or interacting elements that organizations use to direct and control how quality policies are implemented and quality objectives are achieved.
  – Aggregate of the organizational activities, incentives, plans, policies, procedures, processes, resources, responsibilities, and infrastructure.
  – Plan, monitor, measure, document, evaluate, improve

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Network of Interrelated Processes with each process made up of:

- People
- Training
- Experience
- Work
- Activities, Tasks
- Records, Documents, Forms
- Resources, Rules, Regulation
- Reports, Materials
- Supplies, Tools, Equipment

GCP Quality Management System
“Building Quality Into the Clinical Program”

- Protocol Design & Operational Design
- Study Planning
- Study Start Up
- Study Conduct
- Study Close-Out
- Data Analysis, CSB
- Marketing Application

Investigational Product-Device

- Management Responsibilities
- Quality Culture, Policy, Objectives
- Resources
- Quality Commitment: All Staff

- Process Performance – Systems, Processes, Documentation to “Quality Standards”

- GCP

- QMS Elements
  - Quality-Performance Monitoring System (QC/QA)
  - Corrective & Preventive Action (CAPA) System
  - Change Management System, CQI, Document Control
  - Management Review: On-Going Acceptability of the QMS

- Enabler
  - Knowledge Management

- Enabler
  - Risk Management

Adapted from ICH Q’10
Quality Standards
- Accrediting Bodies
- Regulatory Authorities
- National, State Regulations
- Clinical Research Regulations/Guidelines
- Licensing Requirements
- Other...

How you perform to the quality standards “can vary from site to site.”

Processes

Governance, Management Oversight
PI SUPERVISION

People, Organization, Knowledge Management

Risk Management

Quality Policy, Quality Manual, Quality Procedure, Standards

Procedural Documents, Document Control

Performance Dashboards

Metrics System

Issue Escalation

GCP QA Unit, Annual Audit Plan

Process Improvement

Issue Escalation

GCP QA Unit, Annual Audit Plan

Process Improvement

Education & Training: Business Operations: Role Base Training Curricula that Includes On-the-Job Training
QMS Core Elements

**Quality & Business Standards**
- Established throughout organization
- Entire process, lifecycle, functional area, activity in RBM (biostats, Ops etc.)

**Business Processes**
- Procedural documents, flow charts,
- Technology-IT systems, Facilities, Equipment

**People**
- Ensure people are informed and understand their jobs and role, responsibilities and ‘why’
- Each job function: defined, qualifications outlined, role/responsibility, education and trg for each job function

**Organization**
- Leadership involved, engaged, active and communications effective and timely
- Organizational structure meets the needs of the business
Quality Management System

- A system to direct and control an organization with regard to quality
- Helps to plan and monitor for quality
- Records the work done, justifications for deviations and action escalated/taken for improvement
- Helps to implement improvement action

F. Sweeney, Considerations for Quality Systems and Pharmacovigilance System Master Files, DIA Annual Meeting, Date unknown

Quality, compliance and ‘performance’ is ‘built within’ the organization
Begins with ...Quality Culture
CI/PI is the leader!
All of us are leaders!

An organizational value system that results in an environment that is conducive to the establishment and continual improvement of quality.

Clinical Investigator - Site
Quality Management System
Benchmark to ISO 9000
FDA FINAL GUIDANCE:

INVESTIGATOR RESPONSIBILITIES: PROTECTING THE RIGHTS, SAFETY, AND WELFARE OF STUDY SUBJECTS DRUGS, BIOLOGICS, MEDICAL DEVICES

FINAL 2009
This guidance provides an overview of the responsibilities of a person who conducts a clinical investigation of a drug, biological product, or medical device (an investigator as defined in 21 CFR 312.3(b) and 21 CFR 812.3(i)).

The goal of this guidance is to help investigators better meet their responsibilities with respect to protecting human subjects and ensuring the integrity of the data from clinical investigations.

This guidance is intended to clarify for investigators and sponsors FDA’s expectations concerning the investigator’s responsibility

(1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties and

(2) to protect the rights, safety, and welfare of study subjects.
FDA Guidance 2009: Investigator Responsibilities

*Provides the foundation for quality approach and elements of a quality system for industry—that maps to medical practice and care of subjects and healthcare system methods.*
A FEW EXCERPTS...NOT ALL INCLUSIVE
Personnel roles and responsibilities
“Resources”

• The investigator, subinvestigator, clinical trial manager, research assistant, and all others involved in the planning and implementation of a clinical trial should:
  - understand and accept their roles and responsibilities as outlined not only in the regulations, international guidances.

Delegation

• A document (e.g., a log) that describes the delegation of duties should be created before a clinical trial begins.
  - It should always be checked against any responsibilities outlined in the clinical protocol (e.g., the electrocardiogram must be read by a cardiologist).
  - As the trial progresses, the delegation-of-duties documents should be:
    • periodically reviewed
    • updated as needed.
  - There should also be a written plan for coverage of key personnel if there is need for one (i.e., sickness or resignation).
Example

• Healthcare Providers for Research Subjects: Local laws for healthcare providers *(non-research subjects)* is the foundation for caring of the research subjects- 'SCOPE OF PRACTICE'
  – Medically qualified -licensed to state requirements (country requirements)
    • Medical Doctor
    • Nurse Practitioner
    • Physician assistant
  – Clinically qualified - licensed to state requirements (country requirements)
    • Nurses
    • Pharm D/Pharmacist
  – Clinically qualified - Certified staff – to state requirements (country requirements)
    • Medical technicians
    • Radiology technicians
    • Phlebotomists
GCP and Protocol Training

- Sponsors should have policies in place that approve the robustness of the good clinical practice training offered to research staff and that require periodic updating of all such training.
- When a clinical trial involves an investigational product, all key personnel should be knowledgeable of all applicable regulations, including those that pertain to human subject protections.
- Protocol training should also be documented and, especially for complex trials, periodically repeated. To ensure the adequacy of training procedures, testing of knowledge is highly recommended.
### Example: Implementation

#### Adequate Site Staff Training

<table>
<thead>
<tr>
<th>Protocol-Specific</th>
<th>Regulatory - Ethical Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Therapeutic area</td>
<td>• 21 CFR 312</td>
</tr>
<tr>
<td>• Purpose of study</td>
<td>• 21 CFR 812</td>
</tr>
<tr>
<td>• Protocol</td>
<td>• 21 CFR 11</td>
</tr>
<tr>
<td>• Investigational product, per the delegated tasks</td>
<td>• 21 CFR 50, 56</td>
</tr>
<tr>
<td>• Provide staff training with Sponsor training materials and information, per their role on study</td>
<td>• 21 CFR 54</td>
</tr>
<tr>
<td></td>
<td>• Acceptable standards for the conduct of clinical trials</td>
</tr>
<tr>
<td></td>
<td>• Acceptable standards for human subject protection</td>
</tr>
</tbody>
</table>

Reference FDA Guidance Investigator Supervisory Responsibilities, 2009
### Adequate Site Staff Training

<table>
<thead>
<tr>
<th>Protocol-Specific</th>
<th>Training Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Competent to perform or are trained to perform their delegated tasks</td>
<td>• Competent to perform the task</td>
</tr>
<tr>
<td>• Study team/staff informed of pertinent changes during the trial</td>
<td>• <em>Staff possess</em> ‘competent performance’</td>
</tr>
<tr>
<td>• Educated or given additional training, as appropriate</td>
<td>• <em>Translated this means:</em> Having suitable or sufficient skill, knowledge, experience, etc., for some purpose; properly qualified</td>
</tr>
</tbody>
</table>

Reference FDA Guidance Investigator Supervisory Responsibilities, 2009

### Policies and Procedures

- Before a protocol is written, the investigator should be aware of his or her institution’s policies and procedures.
  - These include protocol review procedures, handling of biological samples, human subject protections, confidentiality, data management, and procedures for handling possible scientific misconduct.
  - Frequently, the record retention policy specifies a longer retention period than that required in the federal regulations.
  - Many such policies may need to be outlined in the protocol, as appropriate.
Policies and Procedures

• The importance of having written standard operating procedures (SOPs) in place for each clinical site cannot be overstated.
• Protocol-specific SOPs, often called a Manual of Operations, can outline the protocol procedures in greater detail; it is imperative that the SOPs are critically reviewed to ensure consistency with the protocol.
• All staff should have documented SOP training.
• SOPs should be reviewed on a scheduled, periodic basis for potential updates.

Example: Implementation
Site Procedures – Protocol Plan

Ensure study staff comply with the protocol, AE assessment and reporting.

Correcting problems identified at the site identified by study personnel, outside monitors or auditors, or other parties involved in study.

Handling of data queries and discrepancies.

Informed consent process.

Documenting performance of delegated tasks in a satisfactory manner, and, verify findings.

Address medical & ethical issues that arise during the trials.

Data on CRFs is 'present' in the source data.

Ensure source data: accurate, contemporaneous, original.

Routine meetings with sponsor's monitors.

Routine meetings with staff to review: trial progress, AEs, update staff on any changes - protocol, other procedures.

Details: Page 5 Guidance Document
Example

• **Location where research is conducted – your facility:** Local laws for healthcare systems/manufacturer requirements for equipment-facility are the foundation for caring of the research subjects–
  – Equipment maintenance and calibration *(especially when used in collecting/analyzing safety or endpoint data)*
    • Everything!! BP cuffs, electronic thermometers, EKG machines, IP storage, sample storage

Example

• **Healthcare institution requirements – should be adhered to for research subjects**
  – Medical care/delivery standards are established for alignment with:
    • Local laws, regulations, etc.
    • Industry standards
    • Accrediting bodies
    • Continuous quality improvement interventions
    • Managing risk
    • Patient care and safety *(our research subjects!)*
Quality Assurance

• Quality-assurance programs at the investigator site are less frequently seen:
  – Establishing such a program is not arduous and should be done promptly if none exist
  – Internal Audits

Document Management, Record Retention, and Reporting

• Archival procedures should be documented, and all staff should understand these procedures.
• Handling of documents, including conventional naming, tracking, filing, version control, and the systematic back-up of real-time data collection, should follow standardized procedures.
Document Management, Record Retention, and Reporting

- All files should be kept in a locked area with restricted access.
- All computers should be password protected. Any breach of subject confidentiality is a violation that should be reported to the institutional review board.
  - If any such violation were to occur, a swift corrective action plan should be implemented.

Corrective and Preventive Action (CAPA)

- Potential problems should be anticipated, and steps should be taken to avoid them.
- Problems will inevitably arise, and the discovery of a problem should trigger swift corrective action and the development of a plan to prevent recurrences.
  - If the same problem ‘happens again’ prepare for a query:
    - Did you know the problem happened before?
    - If yes, what did your evaluation problem reveal as the ‘cause’?
    - What did you do to correct the issue based on your evaluation?
    - Did you go back to see if this worked?
    - Did you know this happened again?
    - What did you do when it happened again?
Corrective and Preventive Action (CAPA)

- A reevaluation of the system should be performed to ascertain how the problem occurred.
- Documentation of these actions is necessary to avoid any questions from an auditor/inspector.

Additional Communications

- Indicate a clear understanding of the scope of the problem
  - Provide evidence for a structured approach to investigating the deficiencies and evaluation of root cause, commensurate with the risk
  - If appropriate, conduct or promise to conduct internal audit of other studies not inspected, to assess if similar problems occurred
Additional Communications

- Consider proposing both general and specific corrective action plans
  - Offer item-specific responses, with strategies to correct specific problem
  - Propose a general plan that addresses current and future studies
  - Consider whether SOPs need revision
  - Consider the need for improved, targeted, or periodic training

L Ball, 2011

Additional Communications

- Consider including, if appropriate:
  - Proposed timeline for corrections, including projected completion dates
  - Documents necessary to demonstrate adequate correction has been achieved

L Ball, 2011
### Example: Informed Consent

**Issue**

#### Table 2. The Plan-Do-Check-Act Cycle

<table>
<thead>
<tr>
<th>Step</th>
<th>Stage of cycle</th>
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</thead>
<tbody>
<tr>
<td>Identify the error in the process and develop solutions</td>
<td>Plan: Who is authorized to consent subjects? Is there a pattern? How is the staff trained? Are there other factors involved? Develop a retraining plan</td>
</tr>
<tr>
<td>Apply the planned changes</td>
<td>Do: Retrain the identified staff</td>
</tr>
<tr>
<td>Measure the results by monitoring and checking for any errors</td>
<td>Check: Directly observe staff performing the consent procedure; conduct an internal audit of the next 20 consent forms before the subjects leave the clinic</td>
</tr>
<tr>
<td>Implement the plan on a wider scale if all consent forms checked have been signed; if unsigned consent forms are still found, begin the cycle again</td>
<td>Act: If dates are still missing, have subjects date their consent forms, retrain staff or authorize another staff person to consent incoming subjects, correct any other factors that may be involved (e.g., overburdened staff or distracted staff member).</td>
</tr>
</tbody>
</table>

**NOTE** In the Plan-Do-Check-Act model, there is no end. In the example shown here, suppose that hopefully found through systematic auditing subjects are not dating consent forms in a clinical trial.

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### Example: Implementation
Case study: Lost or Misplaced ICF

What should the site do?
- Document the 7 CAPA Steps
- Conduct a Root Cause Analysis
- Document the CAPA implemented
  - Correct current issue
  - Steps taken to prevent it from happening in the future

CAPA: 7 Steps

- The Identification of the problem, nonconformity, or incident or the potential problem, nonconformity, or incident.
- An Evaluation of the magnitude of the problem and potential impact on the company.
- The development of an Investigation procedure with assignments of responsibility.
- Performing a thorough Analysis of the problem with appropriate documentation
- Creating an Action Plan listing all the tasks that must be completed to correct and/or prevent the problem.
- The Implementation the Action Plan.
- A thorough Follow up with verification of the completion of all tasks, and an assessment of the appropriateness and effectiveness of the actions taken
- Analyze - Evaluate
### SAMPLE: Issue Log with CAPA

<table>
<thead>
<tr>
<th>Issue</th>
<th>Solution</th>
<th>Impact (isolated or pervasive)</th>
<th>Responsible Parties</th>
<th>Corrective Action(s)</th>
<th>Preventive Action(s)</th>
<th>Training</th>
<th>Targeted Completion Date</th>
<th>Completion Date</th>
<th>F/U Assessment Date</th>
<th>Outcome</th>
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**Do not reconstruct by emails, minutes, agendas or reports**

Have all supporting documentation in the efile or TMF for the trial for inspection readiness

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**Where is the CI-PI in all of this?**
Focus on Your Organization
“How you do your business”
“Incorporate elements of the Quality System”

Sub-processes for each ..map out..
“ safety risks, risk to clinical trial quality; risk to subjects; risk to data quality/integrity”

References

• Ball, L., Defining Quality in Clinical Trials: An FDA Perspective, DIA Annual Meeting, 2012
• DeMarinis, A., A Quality System Primer for Clinical Research Operations, Research Practitioner, Vol 5, number 3, May-June, 2004

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• Kleppinger, C., Investigator Responsibilities – Regulation and Clinical Trials, FDA 2012 Clinical Investigator Training Course
• Miskin, B, Neuer, A., QA for the Investigative Site, Applied Clinical Trials, November, 2004

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References


• ICH Q’9 Quality Risk Management

• *FDA Guidance*: Investigator Responsibilities, Protecting the Rights, Safety and Welfare of Study Subjects  October 2009
Performance Monitoring of the Clinical Trial

FDA Program: Risk Based Approach to Site Inspections
Pre-Approval Inspections (PAI)
## Risk Attributes by Site

### Number of INDs per Site/Investigator
- Financial disclosures
- Site type
- Protocol deviations

### Principal Investigator complaints
- Time since last inspection
- Inspections:
  - OAI
  - VAI

### Enrollment
- Efficacy outcome
- Protocol violations
- Non-serious adverse events
- SAEs

### Percentage of subject deaths
- Enroll/screen percentage
- Subject discontinuation

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