

Meeting the FDA requirements for a clinical trial: Investigator, staff and IRB responsibilities

Mukesh Kumar, PhD, RAC

Senior Director

Regulatory Affairs & Quality Assurance

Amarex Clinical Research

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Agenda

- Differences between IND and GCP requirements
- Role of sponsor, investigator, sponsor-investigator
- IRB oversight of clinical trials
- FDA oversight of clinical trials
 - Reporting/documentation requirements
 - Audits/inspections
- Practical issues and possible solutions
 - Case studies

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Common Terms

- Investigational New Drug (IND) application
- Good Clinical Practices (GCP)
- Sponsor
- Investigator
- Study staff (co-investigators, nurses, fellows, coordinators)
- Institutional (Independent) Review Board (IRB)

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Fraud in Clinical Trials is Rare

Almost all violations:

- Are driven by ignorance or negligence instead of deliberate falsification
- Can be avoided by adequate supervision
- Happen very few times in a career
- Involve multi-party errors
- Are implicated on the most responsible party, e.g., investigators and/or IRB

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Every Aspect of Clinical Trials is Subject to Oversight

- Science and Ethics
- Subject safety
- Public Safety

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Multiple Parties Oversee Clinical Trials

- Division of Scientific Investigations, FDA
- OHRP, DHHS
- Office of Inspector General (OIG), DHHS
- Government Accountability Office (GAO)
- US Congress
- Non-Profit bodies: Institute of Medicine

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There are Penalties to Not Following the Law

- Loose credibility of data generated
 - Cannot be used to get market approval
 - Punitive actions
 - Debarment
 - Fine and prison term
 - Injury to end-users
 - Criminal litigation
 - Tort law
- Imposed by FDA, DJ, FTC and others

Inspections, Compliance, Enforcement, and Criminal Investigations

Warning Letters

Picus, Dr. Joel 9/20/10

WARNING LETTER

SEP 20, 2010

CERTIFIED MAIL RETURN RECEIPT REQUESTED

Ref: 10-WFD-45-10-02

Dear Dr. Picus:

Between October 24 and 28, 2009, Ms. Kathleen Grant, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of the following clinical investigations:

Protocol (b)(4), entitled (b)(4) of the investigational drug (b)(4), performed for (b)(4)

Protocol (b)(4), entitled (b)(4) of the investigational drug (b)(4), performed for (b)(4)

Protocol (b)(4), entitled (b)(4) of the investigational drug (b)(4), performed for (b)(4)

The inspection is a part of FDA's Research Monitoring Program, which includes expedients designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of these studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable regulatory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, we stated presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your responses dated November 13, 2009, and January 6, 2010, to Form FDA 483. We wish to emphasize the following:

1. You failed to personally conduct or supervise the clinical investigation [21 CFR

Inspections, Compliance, Enforcement, and Criminal Investigations

Warning Letters

MI Hope Inc. dba Center for Complex Infectious Diseases IRB

WARNING LETTER

SEP 20, 2010

CERTIFIED MAIL RETURN RECEIPT REQUESTED

Ref: 10-WFD-45-10-02

Dear Dr. Martin:

Between May 24 and 27, 2009, Ms. Diane Van Louscheur, Ms. Stephanie Courtenay, and Ms. Natalie Arnold, representing the Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at MI Hope Inc. dba Center for Complex Infectious Diseases. The purpose of the inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), parts 312 and 316. These regulations apply to clinical investigations of products regulated by FDA. We are aware that at the conclusion of the inspection, our investigators presented and discussed with you, a Form FDA 483, Inspectional Observations.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We wish to emphasize the following:

1. The IRB failed to make IRB records, required by the regulations, accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner [21 CFR 312.115(d)]. Our inspection revealed that the IRB records are stored at the private residence of Dr. M. John Martin. FDA investigators were not permitted access to inspect and copy IRB records at

Money & Policy

Report Assails F.D.A. Oversight of Clinical Trials

By DANIEL F. LEVINSON

Published September 20, 2010

Correction Appended

WASHINGTON, Sept. 27 — The Food and Drug Administration does very little to ensure the safety of the millions of people who participate in clinical trials, a federal investigator has found.

In a report due to be released Friday, the inspector general of the Department of Health and Human Services, Daniel F. Levinson, said federal health officials did not have enough oversight of clinical trials being conducted, audited fewer than a percent of the testing sites and, on the rare occasions when inspectors did appear, generally showed up long after the tests had been completed.

The F.D.A. has 200 inspectors, some of whom audit clinical trials part time, to police an estimated 320,000 testing sites. Even when those inspectors found serious problems in human trials, top drug officials in Washington downgraded their findings 69 percent of the time, the report found. Among the remaining cases, the agency almost never followed up with inspectors to determine whether the corrective actions that the agency demanded had occurred, the report found.

"To ensure safety, rate and allow get greater protection at research subjects in the Clinical

Several Regulations Govern Clinical Trials

- CFR Title 21:
- Part 312 - Investigational New Drug Application
 - Part 50 - Protection of Human Subjects
 - Part 54 - Financial Disclosure by Clinical Investigators
 - Part 56 - Institutional Review Boards
 - Part 11 - Electronic Records; Electronic Signatures

ICH E6: Good Clinical Practices

What is an IND?

- A formal application to the FDA asking permission to conduct a clinical trial
- Most clinical trials for new products or new indication or population for an approved product need FDA permission
- Follow 21CFR 312 for the application format and general responsibilities
 - Several other regulations apply
- FDA has the right to audit all clinical trials

What is in an IND?

- Clinical protocol: scientific rationale, procedures, statistical methods
- Informed consent documents
- Background non-clinical and clinical information
 - Investigator's brochure
 - Review of completed studies & literature
- Drug information
 - Chemical & physical properties
 - Manufacturing information
 - Storage and labeling information

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How does FDA review an IND?

- Within 30 days of receiving the initial application, FDA allows the study to proceed or put a hold on it
- During the life of the IND, FDA expects to be in the loop
 - Periodic reports
 - Incidental reports
 - Comments and discussion
- FDA delegates day-to-day oversight to IRB

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An IND is a Living Document

- Protocol/ICD Amendments
- Background info updates
- Investigator information updates
 - FDA 1572, Investigator CV(s), IRB approval letter(s)
- IND Safety Reports (Serious Adverse Events)
- IND Annual Reports (Progress report and all adverse events, cumulative)
- FDA communications (comments and feedback)
- Any other updates (papers, posters, seminars, audits, etc)

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An IRB acts as an FDA Surrogate

- Almost all FDA submissions are also sent to the IRB
- IRB approval before implementing protocol/ICD amendment is a must
- IRBs also initiate several changes
 - Protocol/ICD amendments
 - Follow-up to safety incidences
- IRBs are held-responsible when investigators are poorly supervised
- IRBs are also audited by the FDA

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What if the study is not subject to an IND (non-IND study)?

- GCP still applies
- IRB approval and constant supervision is still needed
- Serious Adverse Event reporting to FDA still applies (MedWatch)
- FDA still reserves the right to audit

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What Does FDA Expect?

- Complete transparency and documentation proof in all IND decisions
 - Rationale for protocol/ICD changes
 - Pre-approval for major changes
 - Information about all changes
- Trained and qualified personnel
- Auditable steps to ensure data quality and integrity

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e.g.: Protocol/ICD Amendment

- Reason for change: Comments from the PI, IRBs, SRCs, Site personnel, Sponsor or FDA
- Scope of change: major or minor (clarification)
- IRB review and approval before implementation
- Informing subjects: re-consent
- Re-training personnel
- Implementation of change

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e.g.: IND Safety Reports

- Only for non-expected, related events or expected, more frequent events
- Within a short time of occurrence
 - 7 calendar days for life-threatening or death
 - 15 calendar days for all others
- Chronology of events
 - Initial information
 - Steps taken to address event
 - Any supporting lab reports/autopsy report
 - IRB information and comments
 - Follow-up

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Data Quality and Data Integrity

- Data Quality: Basic Elements (ALCOA)
 - Attributable
 - Legible
 - Contemporaneous
 - Original
 - Accurate
- Data integrity: The systems and processes for data capture, correction, maintenance, transmission, and retention

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Ensuring Data Quality and Integrity

- Good Documentation Practices
 - Differentiate between source and reported data
 - Appropriate coding: Subject ID, access control
 - Well-defined processes: CRFs, database
 - Data organization and storage: binders, tabs, etc
- Monitoring and auditing
 - Independent process checks
 - Correction and prevention of errors
 - Iterative process: Plan, Do, Check and Act

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Responsibility is Split Over Defined Parties

- Principal Investigator
- Study Staff
- Sponsor
- IRB
- Monitors and Auditors

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Investigator Responsibilities

- Compliance with Protocol
 - Inclusion/exclusion criteria
 - Getting informed consent
 - Study procedures
- Appropriate handling of the Drug
- Communication with IRB
 - Approvals
 - Ensure compliance (ICH 4.1-4.9)
- Maintaining Records

*In short,
a PI is responsible for all that happens at his/her respective site*

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PI is Supported by a Team of Qualified Individuals

- Co-investigators, nurses, fellows, pharmacists, coordinators, data managers
- Delegation log defines the role of every personnel
- Documented qualification and training of all personnel
- Personnel changes are Ok
- PI cannot completely delegate supervision

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Detailed Records are Required

- Overall Study information
 - Qualification and training records
 - Common documents
 - Standard processes (study conduct, chronology of events, drug handling, etc)
 - CRF guidelines, study logs (screening, enrollment, adverse event, etc)
 - Regulatory documents
 - IRB communications
 - FDA communications
 - Financial disclosure documents
 - Ancillary documents: Notes to file

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Detailed Records are Required

- Subject Specific Records
 - Case histories
 - Case Report Forms (CRFs),
 - ALL supporting data (medical records, progress notes, laboratory reports, ECGs, etc.)
 - Informed Consents
- Safety Reports (each incidence)
 - Chronology of events
 - Reports to responsible parties (IRB, sponsor, FDA)
 - Supporting information (lab reports, X-rays, etc)

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General Rules About Documents

- Complete documentation
- Adequately coded and pre-defined format
- Good condition (e.g., torn pages unacceptable)
- Chronologically arranged
- Appropriately coded folders/binders
- Adequate storage and protection from elements
- Access controlled and readily accessible

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Staff Responsibilities

- Compliance with protocol-specific instructions
 - Follow standard processes
 - Use standardized documentation methods
 - Avoid "customization"
 - Follow time-lines for tasks and documentation
- Adherence to delegated responsibilities
- Follow chain of command for all activities
- Multi-tasking is fine

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IRB Responsibilities (21 CFR 56,50)

- Hands-on review of all clinical trials under supervision
 - Qualified reviewers
 - Proactive follow-up for protocol/ICD compliance
 - Monitoring of safety incidences
 - Qualification and training of personnel
- Expedited review process
- Standard processes
- Complete documentation and minutes of all meetings
- Appropriate action against non-compliance

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Sponsor Responsibilities

- Clinical trial design
- Study management: drug handling, data handling, record keeping, DSMBs
- Select and train investigators and monitors
- Review ongoing trial activities (monitoring)
- Review proof of compliance via documents
- Maintains an effective IND
 - Submit periodic updates and progress reports
 - Submit all changes to FDA
- Financing

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Sponsor-Investigator

- Both investigator and sponsor responsibilities
 - Study design and management
 - FDA communications
- Monitoring and auditing activities
- There is no special consideration for Investigator-initiated IND
 - Similar reporting requirements
 - No flexibility on compliance with laws
 - Reasonable compliance efforts

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Treatment- and Compassionate-Use-IND

- Need to be defined at the time of filing IND
- Regulatory responsibilities similar to regular INDs
 - Informed consent requirements
 - IRB approval and supervision
 - Justifiable rationale for IND
- Lower data collection and analysis requirements, except safety data
- Conducted both by for-profit and not-for-profit organizations

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FDA Audits are Increasing

Each year

- About 700 investigator audits
- About 50% audits lead to FDA 483
- Most FDA 483s are satisfactorily closed
- About 20 Warning letters
- About 5 investigator disqualifications

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What triggers an FDA Audit?

- When somebody cites your data
 - In an NDA, BLA or PMA
 - In a widely used publication
- When there is an accident
 - High profile serious adverse event
 - Complaint by a subject
 - Whistle-blowers
- Random surveillance audit
 - You ran out of luck!

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FDA Audits are Comprehensive

- All documents
- Every personnel
- All locations within a site
- Could take 2-10 days, average ~5 days
- Findings available right away
- Clarifications allowed
- Follow-up audits are rare
- Could take a long time to close-out (1+ yrs)

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Common Findings (Major)

- Informed consent violations
 - Improper
 - Not current
 - Recording errors
- Inclusion/exclusion violations
- Safety Reporting errors
 - Late reports
 - Incomplete address and follow-up
- Drug handling errors
 - Dose violations
 - Inadequate records

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Common Findings (Moderate)

- Inadequate supervision by PI
- FDA 1572 out-dated, incomplete and/or missing
- Bad documentation practices
- Training and qualification deficiencies

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Protocol Violations and Deviations

- Deviations are expected, violations are not
 - Both happen
 - Both need appropriate address
- Poorly designed protocol leads to more issues
- Failure to follow investigational plan, failure to conduct proper monitoring
- Error in recording data
 - Random
 - Systematic
- Error in data analysis

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Some tips....

- Maintain good documentation
 - Written standard processes
 - Detailed and defined information collection
 - Appropriate forms and checklists
 - Check for completeness and logic
- Monitor closely for quality and compliance
 - Independent checks
 - Timely training of all personnel
- Keep IRBs and FDA very informed about the conduct of the trial

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Questions and Comments

Mukesh Kumar, Ph.D.

Sr. Director, Regulatory Affairs and Quality Assurance

Amarex Clinical Research

20201 Century Boulevard, Suite 450

Germantown, MD 20874

Tel: (240) 454-6835

Fax: (301) 528-2300

Email: mukeshk@amarexcro.com

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