FDA Compliance Actions Against IRBs and Clinical Investigators

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Clinical Investigation

- Any experiment in which a drug is administered or dispensed to, or used involving one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

21 CFR 312.3(b)

Clinical Investigation

- In order to be the "practice of medicine"
  - Drug has to be approved for marketing
  - But not restricted to using it according to the labeled Indications for use. Therefore, off-label use falls within this definition.
- "In the course of medical practice" means non-research use.

Exemption from filing an IND (or FDA "research permit")

- Must be a lawfully marketed drug
- Exempt from 21 CFR 312 (filing an IND) if all five of the following apply
  - Not intended to be reported to FDA in support of a new indication for use
  - Not intended to support a significant change in advertising (if an Rx drug)

Exemption from filing an IND (cont.)

- no significant increase in risks or decrease in the acceptability of the risks, e.g.
  - Route of Administration
  - Dosage level
  - Use in patient population
- Conducted in compliance with Parts 50 and 56
- No promotional advertising of the product for the investigational use

21 CFR 312.2(b)(1)

Responsibility of Sponsors

- For drug/biologic studies, signs a form FDA 1571:
  - Prepare an accurate and adequate protocol
  - Comply with all requirements regarding obligations of sponsors including preparation and maintenance of records
  - Ensure informed consent and IRB requirements are met
  - Report Adverse Events to FDA
  - Prepare an accurate and adequate investigator's brochure, when applicable
  - Select qualified investigators
  - Prepare and submit progress reports to FDA in a timely manner
  - Drug substance: identity, strength, quality, purity, pharmacology, toxicology
  - Chemistry, manufacturing, and control of the finished dosage form
  - Previous human experience with the drug

Responsibility of Investigators

- An investigator fully commits to the following when she/he signs a form FDA 1572:
  - Personally conduct or supervise the investigation
  - Ensure that all associates, colleagues, and employees assisting in study conduct are informed about their obligations
  - Conduct the study in accordance with the protocol
  - Comply with all requirements regarding obligations of clinical investigators (including preparation and maintenance of records)
  - Inform subjects drugs are being used for investigational purposes and ensure informed consent and IRB requirements are met
  - Report Adverse Events to the sponsor
  - Read and understand the investigator's brochure

Responsibility of the IRB

- An IRB shall:
  - Be made up of at least 5 members, non-scientific, not affiliated
  - Have adequate and accurate written procedures
  - Perform adequate review of the investigation (56.111)
  - Records: (1) copy of proposed project, (2) minutes of meetings, (3) records of continuing review, (4) correspondence, (5) membership roster, (6) written procedures, (7) significant new findings
  - Assure the informed consent document adequately explains the elements of consent and meets the general requirements (50.20)
  - Assure informed consent interview process and setting is non-coercive
  - Have a process for handling Adverse Event reports
  - Assure identity, strength, quality, purity, pharmacology, toxicology of drug substances

Exempt Research

- Research with FDA regulated products generally must comply with IRB and informed consent requirements, whether or not an IND or IDE is needed

- Social and behavioral research may qualify for exemption, based on HHS, not FDA, regulations

45 CFR 46.101(b)

Waiver of Consent

- The HHS Regulations also provide for IRB to waive elements of informed consent, written documentation of consent, or to waive consent altogether
  - Social and behavioral research that is not exempt may still qualify for waiver of consent elements or waiver of consent
- The FDA regulations do not include these waiver provisions

45 CFR 46.116(c) or (d)

GCP Guidance

- ICH Good Clinical Practice, E6
  - Two Signatures on Consent

    http://www.ich.org/pdfICH/e6.pdf

- FDA Information Sheets for IRBs and Clinical Investigators

  http://www.fda.gov/oc/ohrt/irbs/default.htm

Conflicts of Interest
Financial Disclosure

- Financial Disclosure by Clinical Investigators file with sponsor 21 CFR 54

  http://www.fda.gov/oc/guidance/financialdis.html

- Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection

  http://ohrp.osophs.dhhs.gov/references/fr03-7691.pdf

Human Subject Protection

- FDA compliance activities
- Most common failures
- What can the institution do?

FDA Audits of Clinical Investigations

Types of Inspections

- **Pre-marketing audits**
  - Must be completed prior to approval of marketing permit (NDA, PLA, PMA)
- **For-cause audits**
  - F/U to complaints

Human Subject Protection

Notices of Inspection Results

- Form FDA 483
  - Issued at close of inspection
  - Response not required
- Follow-up letters
  - Issued after headquarters review
  - Response may be required

Recent FDA Enforcement Letters To Clinical Investigators

- Most common findings
  - Failure to follow the protocol
  - Failure to personally conduct or supervise the study
  - Failure to prepare and maintain adequate and accurate case histories
  - Failure to maintain drug accountability records
  - Failure to obtain valid informed consent

Typical FDA Actions

Against Clinical Investigator

- Warning letter
- Disqualification
  - NIDPOE (Notice of Initiation of
    - Disqualification Proceedings with an
    - Opportunity to Explain)
  - NOOH (Notice of Opportunity for Hearing)
  - Disqualified from receiving investigational products
- Prosecution

Recent FDA Warning Letters to IRBs

- Most common findings
  - Failure to prepare and follow written procedures
  - Failure to conduct adequate continuing review of ongoing studies
  - Failure to maintain records, meeting minutes

Typical FDA Actions

Against IRB

- Warning letter
  - No new subjects
  - No new studies
  - Suspend approval for ongoing studies

Responsibilities of Investigators and IRBs

- Are these just bureaucratic rules of DHHS and FDA?
- Does record keeping matter?

Responsibilities of Investigators and IRBs

- Correlation between inability to maintain records and inability to protect the rights and welfare of study subjects
- If it is *not* documented, it ***didn't*** happen
  - Not exactly true, but often said
  - FDA assurance of study integrity, including protection of the rights and welfare of human subjects, relies in large part on maintaining accurate and adequate study records

Responsibilities of Investigators and IRBs

- Humans are not machines
  - Do not perform repetitive tasks without occasional error
  - 1 in 100 error rate is unacceptable

- Checklist
- Written procedures
  - Otherwise dependent on skill of the
  - individual study coordinator

Responsibilities of Investigators

- "You stated that several subinvestigators would assist you, but as the clinical investigator you are responsible for all aspects of the study."

- "… you repeatedly or deliberately violated Federal regulations … ."

FDA NOOH

Responsibilities of Investigators (cont.)

- "Your signature on the informed consent form documents that you were present when the risks and benefits of the study were discussed and when each prospective subject was given the opportunity to ask questions prior to agreeing to participate in the research. The fact that you did not sign the forms until long after the subjects signed suggests that you may not have been present when the consent was obtained. Please respond."

FDA Warning letter

Responsibilities of Investigators (cont.)

- "You failed to obtain informed consent from study subjects in accordance with the provisions of 21 CFR 50 and the investigational plan.

  [The] protocol section 4.4.1 requires potential study subjects must sign the … consent prior to the initiation of the Preoperative Screening assessments."

FDA Warning Letter

University of Pennsylvania

September 1999 Jesse Gelsinger died
November 2000 NIDPOE letter issued
February 2002 NOOH letter issued

- Consent form deletions
- Failure to follow protocol stopping rules
- Failure to follow protocol exclusion criteria
- Failure to submit accurate reports to the IRB

- Institution had financial interest in sponsor
- PI had financial interest in sponsor company

Johns Hopkins Medical Research

- OHRP action

  July 2001,
  assurance for research at Hopkins
  suspended, stopping 2400 projects.

- FDA action

  March 2003,
  Warning letter issued to clinical investigator

The New York Times.

Research at

(Your Name Here)

On "The List"

FDA RESTRICTED LIST FOR CLINICAL INVESTIGATORS

- Clinical investigators who have agreed to certain restrictions with respect to their conduct of clinical investigations
- Where restrictions have been removed, it is so noted in the comments column

The List to Avoid

http://www.fda.gov/ora/compliance_ref/bimo/restlist.htm

FDA Disqualified/Totally Restricted List For Clinical Investigators

- Investigators who have been disqualified or "totally restricted"
- A disqualified clinical investigator is not eligible to receive investigational drugs, biologics, or devices
- Where an investigator has been reinstated it is so noted on the list

The List to Avoid

http://www.fda.gov/ora/compliance_ref/bimo/disqlist.htm

FDA DEBARRED LIST

- Individuals or firms barred from participating in the drug industry because they have been convicted of crimes related to FDA's regulation of drugs.

Sections 306(a) and (b) of the FD&C Act

The List to Avoid

http://www.fda.gov/ora/compliance_ref/debar/default.htm

Consequences of Not Doing the Right Thing

- FDA action in Federal District Court
- In addition there may be civil suits by
  - Study subjects
  - Sponsor
- There will be substantial legal costs
- Research cases may not be covered by malpractice insurance

Study Subject Lawsuits

- Two cases recently filed in state courts
  Naming sponsor, PI, IRB, CRO

- Orange County North Carolina
  - Hamlet vs. Genentech, et.al.

- Philadelphia County, Pennsylvania
  - Scheer vs. Burke, et.al.

Study Subject Lawsuits (cont.)

- Hamlet vs. Genentech, et.al.

- IRB duty:
  - Assist sponsor in developing screening protocol
  - Warn of danger of placebo
  - Investigator had conflict
  - “Worked a constructive fraud”

Study Subject Lawsuits

- Hamlet vs. Genentech, et.al.
- IRB duty:
  - Worked a constructive fraud
    - Said Hamlet was an appropriate candidate
    - Did not say risks to health could be substantial and potentially permanent
- Approved design of study
- Approved consent
- Did not adequately monitor study

Study Subject Lawsuits

- Scheer vs. Burke, et.al.
- ALLHAT study
  - Protocol not followed
    - Added hydralazine contrary to protocol
  - Consent materially misleading and deficient
    - Failed to describe potential SAE
    - Overstated benefits to subjects
    - “treatment” “regular medical care”
    - “your doctor” instead of “investigator” or “study coordinator”
    - “patient” instead of “subject”

Accreditation and Certification

- Human Research Participant Protection Program (HRPP)
  - IRB
  - Sponsor
  - Study site (investigator and other persons making study decisions)
- Certify clinical investigator, study coordinator, and IRB administrator
- Accredit IRBs

IRB's Responsibility

- When IRB learns of serious misconduct, it may suspend or terminate approval of the research.

- If it does, written notice to investigator, institution, and FDA, with reasons for the suspension/termination.

21 CFR 56.113 and 56.108(b)(3)

A System That Works

- Make sure all study staff and IRB staff have the necessary resources and support needed to accomplish their tasks
- Don’t place needless requirements or unreasonable demands on the IRB staff or study staff
- Effective QA system
- Pay attention to complaints from study personnel (grapevine)
- Minimize the use of enrollment incentives

The Emperor Has No Clothes Syndrome

"… even when his employees spelled out their suspicions (to monitors) about what was happening, it wasn't that he was particularly adept at dodging their questions. Rather, the monitors seemed reluctant to challenge such a prominent figure in the drug-testing business."

Personally Conduct or Supervise

Nobody was driving officer,
we were all in the back seat.

Researcher and Institution Reaction
or
Nobody Likes To Be Regulated

"The emotional reaction is: 'You know, I became a physician not to hurt people. Why do you have these regulations? You're questioning my integrity. How can you possibly think I'm going to do something bad?"'

Chi Van Dang
Vice Dean for Research, JHU, 2002

Overarching Concerns

- Is there a "culture of subject protection"?
- Does the institution support and respect the IRB and its mission?
- Are IRB members and investigators and IRB staff knowledgeable about regulatory requirements?
- Is there adequate documentation of IRB findings and actions?

Dale Hammerschmidt, M.D.,
IRB Chair, U. of Minnesota

THESE VALUES MUST BE ENCOURAGED RIGHT FROM THE TOP

"Credo values represent the foundation stone upon which leadership is built. Certainly, within Johnson & Johnson, you cannot be a good leader if you don't believe in and try to live up to the Credo."

Ralph S. Larsen, CEO of J&J

THESE VALUES MUST BE ENCOURAGED RIGHT FROM THE TOP

The goal. . .is to get every PI as engaged in the ethics of a study as he is in the methodology, so that ethics aren't considered solely the domain – and responsibility – of the IRB.

Ruth Faden, Director
Johns Hopkins Bioethics Institute

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