Conducting a Clinical Compliance Risk Assessment in the Pharmaceutical Industry

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Summary

- **Enforcement Environment:** The Government is focusing more investigative and enforcement resources on clinical research
- **Risks for Industry:** The major legal and business risks for sponsors (pharmaceutical and device companies) of clinical research
- **Specific Risk Areas:** The key risk areas for sponsors, including applicable legal and regulatory obligations and sanctions for non-compliance
- **Work Plan:** Key steps/issues in conducting a clinical research risk assessment

Why the Government is Increasing Scrutiny of Clinical Research

- Concerns about patient safety of clinical trial subjects
  - University of Pennsylvania
  - University of Oklahoma
  - Johns Hopkins University
- Concern about integrity of data supporting drug/device applications
- Growing volume of Federal dollars going to biomedical research
- The plaintiffs'/qui tam bar have identified suits against research institutions and sponsoring companies (*i.e.*, pharma and device companies) as promising areas
- General concern about practices of the pharmaceutical industry

What the Regulators Are Saying

HHS OIG (FY 2002 Work Plan)

> Will examine how sponsors of clinical trials monitor the implementation of the trials by clinical investigators. . . . [Sponsors] are responsible for ensuring that their clinical trials are conducted in accordance with FDA's regulations by selecting qualified clinical investigators, providing the clinical investigators with the information needed to conduct the investigation, and reviewing ongoing clinical investigations.

David Hoffman, AUSA/Philadelphia

> The growing number of incidents involving illegal conduct in the biomedical research context requires greater scrutiny from Government regulators and enforcement agencies. Serious instances of misconduct, particularly involving false statements to the Government or fraudulent activities, will be pursued using available civil and criminal statutes.

Major Risks for CR Sponsors (Legal & Business)

1. **Legal Risks**

   - **Criminal prosecution and fines** -- under the Food, Drug and Cosmetic Act, False Statements statute, and other Federal statutes
   - **Civil enforcement actions, including False Claims Act and qui tam suits**
   - **FDA/Regulatory sanctions, including disgorgement of profits**
   - **Product liability suits, including suits naming sponsors as defendants** (e.g., University of Oklahoma case, in which Immunex is named as a defendant)

Major Risks for CR Sponsors (cont'd)

2. **Business Risks**

   - **Shortage of Patients**
   - **Delays in/withdrawal of product approval** (can cost companies hundreds of millions or even billions of dollars in lost revenue)
     - FDA-imposed holds on clinical trials
     - Delays in the consideration of NDAs
     - Withdrawal of approval after a product is on the market
   - **Reputational harm** -- problems with data integrity, patient protections, fraud, etc., raise questions about the very mission of pharmaceutical companies, particularly those emphasizing the quality of their R&D/science

Risk Areas -- Summary

- Fraud and abuse
- GCPs and patient protections
- Data integrity and reporting
- Financial conflicts of interest
- Compliance with foreign regulatory requirements
- Cross-cutting risk: Use of CROs
- Miscellaneous and emerging issues
  - Improper marketing of investigational drugs or devices
  - Reimbursement
  - Fraud involving Government grants

Risk Area -- Fraud and Abuse

Issue:

- Whether arrangements between sponsor and physician-investigators are actually intended to influence or reward prescribing behavior

Sponsor Obligation(s):

- To ensure research grants and studies comply with Federal and state anti-kickback and related statutes

Risks of Non-Compliance:

- Criminal prosecution
- Civil FCA/whistleblower suits
- Exclusion or imposition of CIAs

Risk Area -- GCPs and Patient Protection

Issue:

- Whether sponsors have taken appropriate steps to balance health and safety risks to research subjects and whether such risks are adequately disclosed

Sponsor Obligation(s):

- recruitment of qualified investigators (including clinical experience, lack of conflicts of interest)
- protocols for recruitment of subjects
- IRB approval
- informed consent, privacy/confidentiality of patient data
- management of CROs and/or clinical lab (see later slide on CRO audit)
- adverse events and serious adverse events
- monitor clinical investigations

Risk Area -- GCPs and Patient Protection (cont'd)

Risks of Non-Compliance:

- Civil and criminal prosecution and fines
  - Tort liability (e.g., University of Oklahoma case in which Immunex was named as co-defendant)
  - Regulatory sanctions
    - Delay/withdrawal of FDA approval
    - Disgorgement of profits
- Reputational harm

Risk Area -- Data Integrity and Reporting

Issue:

- Whether data submitted by sponsors, and upon which regulators rely in approving product, is complete and accurate

Sponsor Obligation(s):

- Submission of protocol amendments to FDA
- Selection of qualified investigators
- Monitoring of investigators' compliance with protocol/regulations
- Accurate reporting of data to FDA (in NDA and otherwise)
- Data security, 21 CFR Part 11

Risks of Non-Compliance:

- Warning letters
- Criminal and civil enforcement (under FDCA and other statutes)
- Regulatory sanctions, including trial holds/product delays
- Disgorgement (under "fraud on the agency" theory")
- Tort liability

Risk Area -- Financial Conflicts

Issue:

- Whether financial conflicts pose a real or potential threat to the integrity of the results of the clinical research

Sponsor Obligation(s):

- Applicants are required to certify that clinical investigators do not have conflicts of interest or that such conflicts are disclosed

Risks of Non-Compliance:

- Criminal prosecution (false statements)
- Regulatory sanctions, including FDA audit, FDA request for additional information, exclusion of tainted data
- Tort liability (plaintiffs' lawyers in product liability suits have used financial conflicts to demonstrate negligence on the part of pharmaceutical manufacturers)

Risk Area -- Foreign Trials

Issue:

- Whether sponsors conducting clinical trials overseas comply with applicable US and local country laws

Sponsor Obligation(s):

- Compliance with all applicable US laws -- e.g., regulations governing patient recruiting, IRB approval (including informed consent), selection of qualified investigators, monitoring of progress, adverse event reporting, etc.
- Compliance with national laws of the country in which the trial is conducted

Risks of Non-Compliance:

- Criminal, civil and regulatory sanctions under US law
- Tort liability in US courts
- Enforcement actions under foreign law

Cross-Cutting Risk -- Use of CROs

Risks and concerns with CROs:

- Data rejected for fraud
- Missed serious adverse event
- Historical data lost due to CRO failure
- Study halted or delayed due to poor CRO performance
- Excessive costs due to poor planning
- Variable quality
- Requires considerable internal oversight/management

Auditing CROs

Goal:

- To understand how the CRO ensures the trial is conducted in accordance with the protocol and and in compliance with all applicable rules, regulations and sponsor policies.

Review against:

- The contract
- FDA Compliance Guidance
- The sponsor's compliance checklist
- The CRO's quality assurance program

Auditing CROs: Compliance Checklist

Sample Issues

- Review documentation related to milestone achievements
- Assess "earned" payments made to investigators
- Test to determine that payments to investigators and patients are in compliance with the contract and protocol
- Review of investigator credentials
- Assess patients against entrance requirements
- Privacy and security of patient data
- Assess compliance with GCPs (even compliance with their own or the sponsor' SOPs)
- Evaluate process for identifying and reporting adverse events
- Review of site visit protocol and reports

Risk Area -- Emerging Issues

Improper marketing of IND

Sponsors must adhere to strict limits on the distribution of investigational new drugs/devices and must not engage in pre-approval marketing efforts. Non-compliance can result in serious sanctions, including prosecution under the FDCA and other regulatory actions.

Reimbursement

Clinical researchers and sponsors may not charge for investigational drugs without FDA approval. Non-compliance can result in criminal prosecution and an action for disgorgement of profits (among other sanctions).

Fraud involving Government grants

Recipients of Federal grants (including pharma manufacturers) must comply with an array of requirements; the failure to do so may result in criminal prosecution or civil fraud actions under the FCA.

Off-label promotion

Work Plan for a Clinical Research Risk Assessment

- **Scope and oversight**
- **Identification of legal/regulatory obligations, company policies**
- **Gap analysis**
- **Development of findings, recommendations**
- **Presentation of findings to management**
- **Implementation of recommendations**

Work Plan -- Steering Committee

Decide on substantive scope of assessment

- Tailored to risks specific to your company and areas of Government focus
- Prioritization of areas to be addressed

Obtain buy-in prior to meetings, interviews, etc.

Provide on-going substantive expertise

Assist in the development of recommendations, presentation of recommendations to Senior Management

Assist with implementation of recommendations

Work Plan -- Identification of Obligations

Under agreed-upon scope, identify specific obligations of sponsors under FDA regulations and other applicable laws and regulations

Identify and collect company policies/SOPs

Identify and collect, to extent possible, industry “best practices”

Work Plan -- Gap Analysis

Review policies, SOPs in light of legal/regulatory obligations of sponsors:

- Selection of clinical investigators
- Identification, disclosure of financial conflicts
- Monitoring of IRBs, CROs
- Ensuring compliance with protocol
- Reporting of adverse events
- Collection, submission of data to FDA
- Compliance with anti-kickback and related statute
- Submission of claims for reimbursement

Review standard contracts and templates:

- Contracts with clinical investigators/trial sites
- Contracts with CROs
- IRB policies and procedures

Work Plan -- Gap Analysis (cont'd)

Perform audit (using sample methodology) in key areas, including:

- Contracts with CROs
- Trial protocols
- Informed consent forms
- IRB communications to investigators
- IRB procedures and membership
- Patient data sheets and medical records
- Statistical analyses
- Reports to the sponsor
- Patient recruiting/solicitation notices
- Clinical trial marketing
- Grants, payments to clinical investigators

Work Plan -- Findings and Recommendations

Develop initial findings on potential gaps in policies, SOPs

Validate findings with relevant functions

Develop recommendations to address compliance gaps

Brief senior managers within relevant functions

Brief senior corporate management

Develop implementation plans

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