The Laws and Regulations Governing Clinical Research 101

Health Care Compliance Association’s Research Compliance Conference
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The Speakers

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Today’s Agenda

- Overview of recent enforcement activity relevant legal authority
- Discussion of practical and operational implications
- Q&A
SELECTED CLINICAL TRIALS

1. The Healthy Volunteer Evaluation of an Aptamer-RNA Targeting Factor IXa

2. PROTECT AF – WATCHMAN Left Atrial Appendage System for Embolic PROTECTORion in Patients With Atrial Fibrillation

3. Premium Migraine Trial
Overview of Relevant Authority

- Focus on federal laws and regulations
- Discuss relevant requirements and government agencies with oversight responsibility
- Predictions about future anticipated legislative and regulatory activity
Practical and Operational Considerations

- The practical effect of legal requirements on clinical research programs
- Operational considerations
- Compliance priorities
- Highlight effective strategies for managing legal and regulatory compliance risk
Overview of Law and Regulations Governing Clinical Research

- Focus on the following federal agencies within the Department of Health and Human Services:
  - Food and Drug Administration
  - Office of Human Research Protection
  - Office of Research Integrity
  - Office of Inspector General
21 C.F.R. Part 50

- Scope: Protection of human subjects in clinical investigations regulated by FDA or used to support research applications or marketing permits for FDA-regulated products.
- Responsible agency: FDA
- General rule: Investigator may only involve a human being as a research subject if a legally effective informed consent is obtained.
21 C.F.R. § 50.20

General requirements for informed consent:

- Consent must be obtained beforehand and not obtained through coercion or undue influence.
- Research subject must understand the terms of the consent.
- Informed consents may not waive research subject’s legal rights or release investigators, sponsors, institutions, or agents from liability for negligence.
21 C.F.R. § 50.25

- Basic elements of informed consent include:
  - Notice that study involves research, the research’s purpose, and expected duration of subject’s involvement.
  - Description of reasonably foreseeable risks or discomforts.
  - Research benefits that can be expected.
  - Disclosure of alternative procedures or courses of treatment.
21 C.F.R. § 50.25 (cont.)

- Describes scope of record confidentiality.
- Contact person for questions regarding study.
- Statement that participation is voluntary and participants are not otherwise disadvantaged.
- When there is potential for more than minimal risk, notice regarding whether compensation and/or medical treatments are available should injury occur.
- Additional elements to address unique situations.
21 C.F.R. § 50.27

- Documentation of informed consent:
  - A comprehensive consent form signed by research subject; or,
  - A short form for consent, which accompanies oral presentation with a witness present.
  - Subject must sign short form and written summary.
  - IRB must approve written summary of oral presentation that is made to subjects.
Exemptions from informed consent:

- Human subject confronts a life-threatening situation necessitating use of test article.
- Informed consent cannot be obtained due to subject’s inability to communicate or lack of legal capacity.
- Insufficient time to obtain consent from subject’s legal representative.
- No alternative treatment with equal or greater chance of life-saving potential is available.
- IRB approves investigation without requiring patient consent.
- Presidential waiver to use investigational new drug for armed forces.
21 C.F.R. Part 54

- Scope: Financial disclosures required by applicants of FDA-regulated studies or products.
- Responsible agency: FDA
- General rule: FDA requires disclosure of certain financial relationships related to research which it will use when considering the reliability of study data.
21 C.F.R. §§ 54.3, .4

- Requirements apply to any applicant who submits a marketing application for a new drug, device, or biologic.
- Applicant must submit a list of all clinical investigators to be used in a study.
- Applicant is responsible for making certifications or disclosure statement for its investigators.
  - Applicant required to collect data from investigators.
  - Use FDA form 3454 to certify no financial relationship.
  - Use FDA form 3455 to report certain financial relationships.
21 C.F.R. § 54.5

- FDA will evaluate disclosure statement and steps taken to limit bias.
- FDA will consider study design and purpose in assessing potential bias.
- FDA may take “any action it deems necessary” to ensure reliability of data.
21 C.F.R. § 54.6

- Applicants are required to keep information on certain financial arrangements:
  - Financial arrangements and/or payments between sponsors and clinical investigators; and
  - Financial interests held by clinical investigators in the outcome of the research.

- Record retention period is for two years after the date of FDA approval for the test article.
21 CFR Part 56

- Scope: General requirements and standards for Institutional Review Boards (IRBs) that oversee clinical investigations regulated by the FDA.
- Responsible agency: FDA
- General Rule: IRBs must satisfy regulations related to composition, operation, and responsibilities for IRBs to be recognized by FDA.
IRBs are required to approve and monitor clinical investigations subject to FDA jurisdiction.

FDA may ignore clinical evidence derived from a clinical investigation that was not approved by an IRB.
There are several exemptions from the IRB requirements, including:

- Old, ongoing investigations (circa 1981);
- Emergency use of a test article;
- Qualifying taste and food quality evaluations; and,
- When FDA waives IRB requirements in response to a sponsor petition.
21 C.F.R. § 56.107

- IRB membership:
  - At least five members;
  - Varying professional backgrounds to reflect clinical and community perspectives;
  - Encourage members of both genders to participate;
  - One member with no affiliation to institution; and,
  - Protect against conflicts of interest in IRB review process.
21 C.F.R. § 56.108

- IRB functions and operations require written procedures:
  - For conducting initial and ongoing reviews of clinical investigations and other functions;
  - For reporting adverse outcomes or non-compliance to IRB, institution, or FDA.

- Majority of IRB members must be present for votes, and protocol approvals require a majority vote of attending members.
21 C.F.R. §§ 56.109, .111

- IRB’s scope of review:
  - Authority to approve, require modifications in (to secure approval), or disapprove all FDA-regulated research activities.
  - Require documentation of informed consent.
  - Ongoing reviews conducted at appropriate intervals based on degree of risk, but not less than once a year.
  - Apply regulatory criteria for approval.
21 C.F.R. Part 312

- Scope: Procedures and requirements governing investigational new drugs (INDs), including the IND application process for federal approval.
- Responsible agency: FDA
- General Rule: Use of a new drug subject to FDA approval must comply with these procedures and requirements until the IND application is approved.
21 C.F.R. Part 312

- Procedures and requirements governing use of investigational new drugs (INDs).
- Drugs under IND applications are exempt from FDA pre-market approval and can be lawfully shipped for clinical trials purposes.
- IND rules are extensive (35 pages of regs).
21 C.F.R. Part 312

- This Part addresses:
  - Labeling;
  - Promotion and charges for new drugs;
  - FDA waivers;
  - Phases of a new drug investigation;
  - Scope and content of required FDA reports;
  - Emergency use of new drugs;
  - Responsibilities of sponsors and investigators; and,
  - Special rules for drugs for life-threatening and severely debilitating illnesses.
21 C.F.R. Part 812

- **Scope:** Procedures and requirements governing investigational medical devices, including the process for seeking an investigation device exemption (IDE) and ultimate FDA approval.
- **Responsible agency:** FDA
- **General Rule:** Use of an investigational device subject to FDA approval must comply with the IDE procedures and requirements until FDA approves the device for marketing.
21 C.F.R. Part 812

- Medical devices under an IDE are exempt from FDA pre-market approval and can be lawfully shipped for investigatory purposes.

- IDE rules are constructed similarly to the IND rules, but are not as voluminous.
21 C.F.R. Part 812

This Part addresses:

- Labeling;
- Promotion and charges for investigational devices;
- FDA waivers;
- Prohibition of promotion and other practices;
- Investigational plan;
- Scope and content of required FDA reports; and,
- Responsibilities of sponsors and investigators.
Impact on Medicare Coverage

In its IDE approval letter to the sponsor, the FDA will categorize the device as either:
- Category A: Experimental/ Investigational
- Category B: Non-Experimental/ Investigational

FDA’s categorization affects Medicare coverage. Medicare permits coverage of Category B devices.

(42 C.F.R. Part 405, Subpart B).
Impact on Medicare Coverage

- Local Medicare contractors make decisions regarding coverage of Category B devices.
- Coverage of medical devices affects coverage of related services.
- All other Medicare coverage rules, national and local, apply.
Impact on Medicare Coverage

- Since September 2000, Medicare coverage for “routine costs” related to qualifying clinical trials and services necessary to address any complications. (Coverage Manual § 30.1).
- MMA requires coverage expansion of IDE related services to Category A devices effective January 1, 2005. (MMA § 731(b) added 42 U.S.C. § 1395y(m).)
45 C.F.R. Part 46

- Scope: Basic HHS policy, known as the Common Rule, for protection of human research subjects applicable to any federal department or agency that adopts it.
- Responsible agency: Office of Human Research Protection.
- General Rule: These regulations govern IRB proceedings and patient subject notice requirements that apply to HHS-related clinical research that is not FDA-related.
45 C.F.R. Part 46

- A model code for all federal agencies that is similar in structure to the FDA’s more comprehensive rules.
  - Addresses informed consent in the context of Public Health Service funded research.
  - Contains rules regarding composition of IRBs and their functions and powers.
45 C.F.R. Part 46

- Special rules that provide additional protection for clinical research involving:
  - Pregnant women;
  - Human fetuses;
  - Neonates;
  - Prisoners; and,
  - Children.
42 C.F.R. Part 50

- **Scope:** Rules that govern federal grantee’s response to, and reporting of, scientific misconduct. Also, regulations impose responsibility to promote objectiveness in research.
- **Responsible agency:** Office of Research Integrity (ORI), Office of Public Health Service and Science.
- **General Rule:** Instances of potential scientific misconduct must be reviewed, investigated, and, as appropriate, reported to ORI.
42 C.F.R. § 50.103

- Applicants must “inquire” immediately about potential misconduct and complete inquiry within 60 days.
- Report of inquiry is prepared and shared with individuals against whom the scientific misconduct allegations have been made.
- If further “investigation” is deemed to be warranted, a report to ORI is required.
- Impose appropriate sanctions on individuals when allegations are ultimately confirmed through an investigation.
42 C.F.R. §§ 50.601, .602

- Regulations promote objectivity in research and govern institutions that apply for PHS grants or cooperative agreements.
- Establish standards to ensure that the design, conduct and reporting on federally funded or directed research will not be biased by conflicting financial interests of an investigator.
42 C.F.R. § 50.604

- Institutional responsibility for conflicts of interest oversight.
  - Policies and procedures maintained and communicated to investigators.
  - Maintain records of all financial disclosures and conflict of interest remedial actions for three years after last report is filed.
42 C.F.R. § 50.605

- Designated official must review all conflicts of interests and work to manage, reduce, or eliminate such conflict.

- Conflicts may be managed by:
  - Public disclosure of conflict;
  - Monitoring research by independent reviewers;
  - Modified research plan;
  - Disqualification of investigator;
  - Divestiture of financial interest; or,
  - Severance of relationships that create the conflict(s).
42 C.F.R. § 50.606

- If a conflict of interest violation has biased the design, conduct or report of a study, then the institution must notify federal government.
  - Government may inquire regarding these issues at any time and may suspend grant funding if appropriate due to a violation.
Privacy and Research

- Health Insurance Portability and Accountability Act of 1996.
- Protected health information (PHI)
  - Created or received by a health care provider, health plan, or health care clearinghouse.
  - Either identifies or could be used to identify an individual.
  - Relates to a physical or mental health condition, the related patient care, and payment.
  - Transmitted or maintained in an electronic format or media.
Privacy and Research

- Notice of Privacy Practices
  - Informs patients regarding use and disclosure of PHI.
  - Patients sign an acknowledgement and consent for the use or disclosure of PHI for treatment, payment, or health care operations.
  - Usually included in patient consent forms for clinical research projects.
Privacy and Research

- The clinical research enterprise presents a privacy compliance challenge due to potential uses for study data.

- Uses and disclosures:
  - Patient consent in privacy acknowledgement;
  - Other disclosures not requiring patient consent;
  - “De-Identified” data (subjective and objective);
  - Limited data sets; and,
  - FDA-related activities.
International Clinical Trials

- International clinical trials
- Not just HIPAA!
  - Identifying applicable privacy laws (EU, Canada, Japan).
  - Understand networked data exchange and warehousing arrangements.
Office of Inspector General

- Increased focus continues on clinical research activities.
- FY 2005 Audit Plan indicates several related projects:
  - FDA’s financial disclosure requirements for clinical investigators;
  - FDA personnel’s outside activities;
  - Implementation of clinical trials data bank;
  - Review of adverse events reporting by IRBs; and,
  - Employee conflicts of interest at NIH.
- Proposed model compliance guidance for recipients of NIH grants expected in 2005.
Practical and Operational Implications

- How is it best to manage operations given the different sets of governing rules?
- Does clinical research compliance operate effectively within an overall compliance plan?
- What are the legal or regulatory issues that require most attention as a practical matter?
Practical and Operational Implications

- Are educational programs and training session helpful?
  - HIPAA and clinical research
  - Study initiation and enrollment
  - Regulatory documents
  - Contracts/conflicts of interest
  - IRB and informed consent
  - Introduction to Office of Sponsored Research Process
  - Medicare coverage and billing
  - Costs analyses/budget and payment terms
  - Documentation – preparation and retention
  - Research accounting/grant reconciliation
  - FDA audits
Practical and Operational Implications

- How does one manage the various domestic and international privacy rules applicable to clinical research?
- What other important functions do the IRBs serve for institutions?
- Is the financial management of clinical research separate from the IRB’s function?
Practical and Operational Implications

- What are effective strategies for managing conflicts of interest?
- What are proper sanctions to deal with conflict problems?
- Are higher level sanctions necessary for recurrent problems?
Questions?

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