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# 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

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# 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 PROTECTion in Patients With Atrial Fibrillation

3. Premium Migraine Trial

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# 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

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# 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

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# 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

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# 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.

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# 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.

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# 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.

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# 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.

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# 21 C.F.R. §§ 50.23, .24

- 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.

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# 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.

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# 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.

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# 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.

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# 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.

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# 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.

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# 21 C.F.R. § 56.103

- 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.

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# 21 C.F.R. §§ 56.104, .105

- 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.

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# 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.

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# 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.

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# 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.

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# 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.

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# 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).

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# 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.

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# 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.

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# 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.

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# 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.

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# 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).

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# 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.

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# 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).)

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# 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.

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# 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.

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# 45 C.F.R. Part 46

- Special rules that provide additional protection for clinical research involving:
  - Pregnant women;
  - Human fetuses;
  - Neonates;
  - Prisoners; and,
  - Children.

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# 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.

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# 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.

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# 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.

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# 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.

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# 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).

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# 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.

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# 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.

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# 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.

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# 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.

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# International Clinical Trials

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

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# 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.

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# 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?

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# 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

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# 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?

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# 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?

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# Questions?


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