EPSTEIN BECKER GREEN

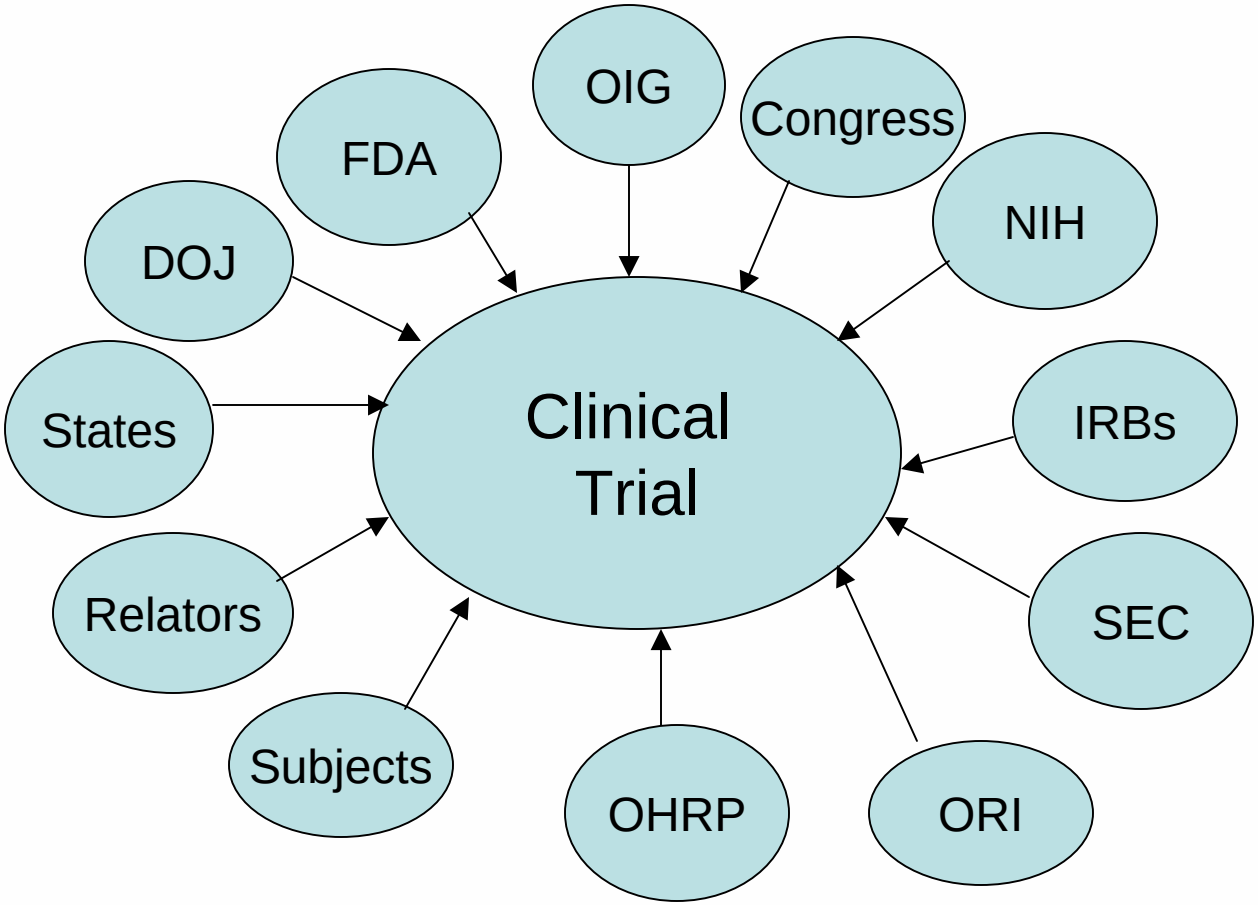
Clinical Trial Litigation and Enforcement Risks

Clinical Trials: Emerging Legal Threats
February 26, 2009

Robert Wanerman
Epstein Becker & Green, P.C.
rwanerman@ebglaw.com

EBG

Multiple Sources of Clinical Trial Oversight and Enforcement



Sponsored Research Projects

Informed Consent and Subject Injury

Abdullahi, et al. v. Pfizer, Inc., Nos. 05-4863-cv and 05-6768-cv (2d Cir. Jan. 20, 2009):

- Nigerian nationals sought damages under the Alien Tort Statute, 28 U.S.C. § 1350 (US district courts have jurisdiction over tort actions brought by aliens if it involves a violation of the law of nations or treaty of the United States)
- Alleged that Pfizer tested an experimental antibiotic on children with meningitis without the consent or knowledge of the children or their guardians, and without explaining the risks or availability of alternative treatments or available free care from Doctors Without Borders
- Second Circuit reversed district court decision that it lacked subject matter jurisdiction because the Alien Tort Statute did not apply, and that Nigeria was the proper forum for the action.
- Remanded for a hearing on the merits

Informed Consent and Subject Injury

The Second Circuit found that the Alien Tort Statute's prerequisites were satisfied:

(1) there is a norm of international law prohibiting medical experimentation on non-consenting human subjects, as embodied in the Nuremberg Code, the Declaration of Helsinki, guidelines published by the Council for International Organizations of Medical Services, and the International Covenant on Civil and Political Rights, although they are not necessarily binding law in the US;

(2) these principles prohibiting medical experimentation without informed consent have been the basis of US law since 1962, when informed consent was first required for drug trials;

(3) that under 21 C.F.R §§ 312.20 and 312.120, domestic and foreign clinical trial sponsors must obtain informed consent from subjects when enrolling them in a clinical trial;

(4) FDA regs require that foreign clinical studies without an IND must comply with GCPs, which require informed consent (21 C.F.R. § 312.120);

(5) the customary international law norms are specific; and

(6) the protections offered are of "mutual concern" to the nations involved

Informed Consent and Subject Injury

Johns Hopkins University (2001)

- Healthy volunteer in asthma study died after exposure to a drug intended to simulate an asthma attack
- Drug was not approved by the FDA, and no waiver was sought by the investigator
- Informed consent form approved by the IRB did not disclose that the drug was not approved by the FDA, and did not adequately disclose the risks of inhaling the drug
- Investigator failed to notify the IRB that the protocol had been altered, and failed to notify the IRB of published research discussing safety risks associated with the drug
- IRB did not do an independent literature search
- Hopkins' FWA was withdrawn by OHRP, but reinstated after voluntary remedies adopted by JHU (additional IRB, quality control checks)
- Private litigation settled

Clinical Trials and Insider Trading: It's Not a Good Thing

Drug Researchers Leak Secrets to Wall Street, Seattle Times (Sept. 12, 2005)

- Analysts and hedge funds contacting researchers directly and paying between $300 - $500/h for information on current clinical trials
- Most researchers had signed confidentiality agreements with sponsors
- Consulting firms are marketing access to panels of specialists
- Trading on the information violates insider trading rules

Clinical Trials and Insider Trading: It's Not a Good Thing

Securities and Exchange Commission v. Sanjiv S. Agarwala, Civil Action No. 06 CV 0352J (POR) (S.D. Cal.)(2006)

- Investigator in a clinical trial received three types of material non-public information:
  - Sponsor received FDA approval for a treatment protocol involving its drug for malignant melanoma
  - Results from a clinical trial for acute myeloid leukemia were positive, and
  - Results from a clinical trial for malignant melanoma were negative.
- SEC alleged that during 2004 the investigator used his father's brokerage account to purchase or sell stock in the sponsor before the public announcements of that information, and breached his duty to the sponsor not to trade on the basis of confidential information
- To settle the SEC's charges, Agarwala agreed to pay $44,750 in disgorgement of his illegal trading profits, civil penalties, and interest
- Also consented to the entry of a final judgment permanently enjoining him from future violations of the antifraud provisions of Section 17(a) of the Securities Act of 1933, Section 10(b) of the Securities Exchange Act of 1934, and Rule 10b-5

Congressional Oversight of Sponsored Research

House Energy and Commerce Committee

Investigation of Vytorin® clinical trials and safety and effectiveness, including:

- December 2007 letter requesting information relating to the delay in releasing clinical trial data and changing trial endpoints;
- January 2008 letters requesting information on DTC advertising, withholding of clinical data, and data safety monitoring;
- August 2008 request for records reaching back 10 years, focusing on financial relationships among sponsors and Oxford University Clinical Trials Service Unit and integrity of the data furnished to the FDA;
- September 2008 follow-up request for records and request to interview principal investigator; and
- February 2009 letter requesting information including:
  - Data safety monitoring board membership and minutes;
  - Clinical trial steering committees,
  - IRB membership and approvals,
  - Publication of trial data in the NEJM

FDA's Bioresearch Monitoring Program

- Intended to protect research subjects and the quality and integrity of data submitted to FDA
- FDA conducts onsite visits to investigators, sponsors, monitors, CROs, IRBs, and laboratories
- Inspection covers multiple facets of a clinical trial, including:
  - Who performed key tasks in the protocol (ex.: consent, data)
  - Degree of responsibility delegated by PI
  - How data is recorded and accuracy of records
  - Accountability for investigational item
  - Monitor's oversight of the investigation
- Deficiencies are reported on Form 483, and can trigger either:
  - Informational letter identifying deficiencies and requesting voluntary corrective action, or
  - Warning letter that identifies significant deviations from regulations and risks to health and safety; requests prompt written corrective action plan
- Repeated or deliberate failure to comply may result in penalties including a disqualification from receiving investigational products in the future, referral to OHRP, disqualification of data

FDA Civil Penalties

Leon LaHaye, M.D. and LaHaye Center (2003)

- FDA settled multiple civil charges against an ophthalmologist and his ASC involving laser eye surgery for $1.1M
- Used an unapproved laser on 110 patients before seeking approval for a study protocol
- The protocol was approved by CDRH for 754 eyes, but additional subjects were treated without first obtaining IRB or FDA approval
- Study protocol parameters ignored by treating nearsightedness beyond the permitted range and by treating astigmatism and both eyes of some patients
- Ophthalmologist failed to submit accurate and complete reports to the FDA indicating exposure of all subjects to the laser
- Improperly promoted the laser by omitting a statement that it was investigational

- 21 U.S.C. §§ 331 and 333

FDA Civil Penalties

Arizona Heart Institute/Edward Diethrich, M.D. (2003-2007)

- CDRH/BIMO on-site inspection to determine that data in an IDE application was scientifically valid and accurate
- Inspection triggered a Warning Letter
  - Four IDE Protocols using a stent
  - Stent was modified and implanted into 68 patients with thoracic and abdominal aortic aneurysms outside of an approved IDE protocol, and without informed consent
  - FDA concluded that this was unapproved research with a significant risk device
  - FDA rejected claim that the stents were exempt as “custom devices” that do not need FDA clearance
  - FDA mandated a plan of correction, including notice to patients that they were implanted with an unapproved device

FDA Civil Penalties

Arizona Heart Institute/Edward Diethrich, M.D. (2003-2007)

- Hospital and surgeon settled FCA claims for $5.8M and a five-year corporate integrity agreement
- Government alleged that defendants violated the FCA by submitting Medicare claims for procedures involving implantation of stent graft devices that were neither approved by the FDA approval nor were covered by an approved IDE

FDA Criminal Penalties

NuMed, Inc. (2004)

- Experimental stent implanted in 14 babies
- Procedures performed without any IDE or IRB approval
- Not used in an emergency situation or with FDA approval for compassionate use
- Informed consent for surgery did not explain that the stent was experimental
- No informed consent for research
- Researcher tried to obtain after-the-fact consents
- Triggered multiple enforcement actions
- 2009: Negligence claims against the surgeons dismissed due to lack of expert testimony as to causation of injury

FDA Criminal Penalties

NuMED, Inc. (2007)

- Manufacturer and its president pled guilty to distributing unapproved medical devices and paid criminal fines totaling $2,293,451
- Offenses involved distributing 2800 unapproved CP stents and 5200 balloon catheters
- Defendants acknowledged they had not sought pre-market approval or 510(k) clearance
- As part of the agreement, defendants agreed to (1) pay $2,230,103 to fund a clinical trial at Johns Hopkins using the stent, and (2) distribute the stent at no cost within the United States for five years following any FDA approval based on the clinical trial data.

FDA Criminal Penalties

Anne Butkovitz (2005)

- Clinical study coordinator for a clinical trial of rotavirus vaccine in children
- Responsible for contacting each subject's parent(s) at three intervals to determine if there were any serious adverse events and to report on a Case Report Form
- Did not make the required contacts with parents/guardians of the clinical study but stated on the Case Report Forms that she had made the contacts
- Entered a plea of guilty to one count of making a false statement, fined $1000 and sentenced to one year of probation
- Plea agreement included a lifetime debarment from any study involving a drug or biologic required or intended for submission to the FDA.

FDA Conflicts of Interest (21 C.F.R. Part 54)

At time of manufacturer filing, each investigator who participated in the clinical trial must disclose:

- Compensation made to the investigator in which the value of compensation could be affected by study outcome
- A proprietary interest in the tested product, which includes a patent, trademark, copyright or licensing agreement
- Any equity interest in the sponsor of a covered study (ownership interest, stock options, or other financial interest) whose value cannot be readily determined through reference to public prices
- Any equity interest in a publicly held company that exceeds $50,000 in value
  - This requirement applies to interests held during the time the clinical investigator is carrying out the study and for 1 year following completion of the study;

FDA Conflicts of Interest (21 C.F.R. Part 54)

- Any other compensation from the sponsor of the study to the investigator or the institution to support activities of the investigator that is worth more than $25,000 (not including the costs of conducting the study), which is given while the clinical investigator is conducting the study, or within one year after completing the study.
  - Includes grants for ongoing research, consulting arrangements, equipment, and honoraria
- Any steps taken to reduce the bias caused by the disclosed financial relationship(s)

FDA Conflicts of Interest (21 C.F.R. Part 54)

If FDA determines that the financial interests of any clinical investigator raise a serious question about the integrity of the data, its available remedies include:

- Conducting audits of the data derived from the clinical investigator in question;
- Requesting that the applicant submit further analyses of data to evaluate the effect of the clinical investigator's data on the overall study outcome;
- Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and
- Rejection or hold of the data generated as a result of a questionable financial relationship

Conflicts of Interest

- OIG Report: The Food and Drug Administration's Oversight of Clinical Investigators' Financial Information (January 2009):
  - Only 1% of investigators disclosed a financial interest in FY 2007 (compared with 23-28% disclosure to medical journals)
  - FDA cannot determine whether or not sponsors have submitted financial information for all investigators
  - 23% of approved applications were missing a certification or disclosure form
  - 28% of applications relied on a "due diligence" exemption from disclosure in 21 C.F.R.§ 54.4, and in 18% of those cases the applicant did not explain why the financial information could not be obtained
  - In 31% of cases, FDA did not document a review of financial information in a marketing application

Conflicts of Interest

Senate Finance Committee

- Sen. Grassley letters to pharma companies and institutions requesting information on payments to physicians
- Researchers failed to report income or underreported income
- Researchers and their institutions receive grants from NIH and other federal agencies
- Underreporting may have involved evasion of COI reporting thresholds
- Several manufacturers voluntarily disclose physician payments (Pfizer, Lilly)
- High-profile allegations of abuse:
  - Joseph Biederman, M.D. (Harvard/MGH): accused of failing to report $1.6M in consulting fees from manufacturers between 2000 and 2006; subsequently agreed to stop working on any sponsored research
  - Charles Nemeroff, M.D. (Emory): accused of failing to report more than $1.2M in consulting fees between 2000 and 2007; NIH suspended a $9.3M research grant and Dr. Nemeroff agreed to step down as chair of the medical school's psychiatry department
  - Frederick K. Goodwin, M.D.: former NIMH director and host of NPR show failed to report $1.3M in consulting fees; program cancelled

Conflicts of Interest

Physician Payments Sunshine Act of 2009

- Requires that drug, biological, and device manufacturers report information annually on “payments or transfers of value” to physicians
- Definition includes research, grants, and royalties
- Allows for reporting of payments or transfers of value in connection with a clinical trial to be made after the earlier of:
  - The date of FDA approval or clearance, or
  - Two calendar years after the date of the payment or transfer
- Data would be made available on a searchable website
- Civil penalty of up to $10,000 for a failure to report; a “knowing failure to report” can trigger a civil penalty of up to $100,000
- Statute would supersede state or local reporting laws

Conflicts of Interest

Massachusetts Pharmaceutical and Medical Device Manufacturer Code of Conduct

- 2008 statute; draft regulations pending that would require manufacturers to:
  - adopt Department's Code of Conduct
  - submit a description of its training program
  - certify compliance with the Code of Conduct and conduct annual audits
  - submit procedures for investigating non-compliance
  - submit contact information for compliance officer
  - report "the value, nature, purpose and particular recipient of any fee, payment, subsidy or other economic benefit with a value of at least $50 . . . ."

Conflicts of Interest

- Code of Conduct would not prohibit reasonable compensation for professional or consulting services in connection with a “genuine research project or clinical trial” or other costs as specified in a written research agreement
- Required disclosure would not include payments in connection with sponsored research that meets this definition

Grant-Funded Research Projects

Conflicts of Interest

Basic rules: Federal Grants

- Institution must have a process in place to ensure that conflicts of interest are "managed, reduced, or eliminated . . . ." 42 C.F.R. § 50.604
- Conflicts can be managed
- In the grant application, investigators must disclose "significant financial interests", which include
  - Salaries, royalties, or other payments in excess of $10,000 over 12-month period, and
  - Equity interests with a value over $10,000 and/or exceed 5% of the equity in a single entity
  - Excludes salaries for teaching, seminars, serving on advisory panels for non-for-profit entities
- Conflicts can be managed by a range of methods, including:
  - Public disclosure of significant financial interests;
  - Monitor of research by independent reviewers;
  - Modifying the research plan;
  - Disqualifying the conflicted investigator from any PHS-funded research;
  - Divestiture of the significant financial interests; and
  - Severance of the relationships creating the conflict.

Cost Transfers Under Research Grants

U.S. ex rel. Long v. Mayo Foundation (2005)

Relator and government alleged that Mayo's research accounting practices included:

- Spending down grant accounts at the end of the year to avoid returning unused funds to NIH
- Shifting costs from grant projects that were over-expended to grant projects that were under-expended without adequate documentation
- Retroactively altering effort and financial progress reports to reflect the reassignment of charges to the grants with remaining funds
- Not properly documenting transfers
- Not making transfers in a timely manner

- $6.5 million settlement

Time and Effort in Grant-Funded Research

Harvard/Beth Israel Deaconess (2004)

- Self-disclosure to NIH; referred to DOJ
- DOJ alleged that Harvard improperly charged for:
  - Costs of investigators not working on the grant
  - Supply and equipment expenses related to other projects
  - Salary of PI in excess of budgeted amount
- $2.4M settlement; DOJ acknowledged that settlement amount was reduced due to institution's disclosure and cooperation

Time and Effort in Grant-Funded Research

U.S. ex. rel. Schwiderski v. Northwestern University

- Clinical practice plan at an academic medical center is a separate legal entity from the grantee institution
- Relator (and later Government) alleged:

1. Northwestern overstated the description in the grant applications of the researchers' institution-based salaries and percentage of researchers' work effort devoted to the grants by leaving out clinical time and income
2. Northwestern knowingly failed to comply with time and effort reporting requirements and rebudgeting requirements as required under notice of grant award conditions

- $5.5 million civil False Claims Act settlement (qui tam)

Time and Effort and Cost Accounting

U.S. ex rel. Gober v. University of Alabama at Birmingham (2005)

- $3.39M settlement
- Whistleblower was UAB's compliance officer
- Whistleblower alleged UAB violated FCA by:
  - Drawing down NIH grant funds with insufficient documentation to support PI's efforts;
  - Failing to maintain adequate compliance mechanisms to reconcile effort commitments with actual effort expended as required by regulations
  - Billing Medicare for research-related services already paid by third parties

Take-Aways on Grant-Funded Research

- Don’t assume that time and effort reporting policies alone are enough
- Does your documentation match your polices?
- Are you seeking counsel or agency advice regarding grays areas under cost accounting principles or NIH policies?
- Charging salary costs for employees whose effort is also being accounted for by another legal entity requires good communication to avoid duplications

Take-Aways on Grant-Funded Research

- You can be liable for the actions of an affiliate
- The government does not view multiple grants as a fungible pool of money
- The government cares about data integrity
- There are no ad hoc cost transfers

Research Misconduct

- Falsification: Making up data or results and recording or reporting data
- Fabrication: Manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately reported
- Plagiarism: Appropriating another person's ideas, processes, results or words without giving appropriate credit

Research Misconduct

- Institutional Federalwide Assurance
  - Institution holding a grant must agree to have a process in place responding to allegations of research misconduct in PHS-supported research that complies with PHS Policies on Research Misconduct (42 C.F.R. Part 93)
  - Institution responsible for conducting inquiry and/or investigation into allegations of research misconduct and report findings to ORI
  - ORI may impose remedies, including exclusions from contracting or subcontracting with any agency of the federal government and from eligibility or involvement in federally-funded nonprocurement programs (including grants or contracts)

Research Misconduct: United States v. Poehlman

An example of what a researcher did wrong and a university did right

- University of Vermont researcher admitted fraud in grant data from 1992-2002
- Used false and fabricated data in published papers and relied on those papers in 17 grant applications
- Misconduct spanned more than 10 years, and involved approximately $3 million in grant funds
- Reported to the university by a student
- Poehlman allegedly destroyed evidence in a database, submitted false documents and testimonials to the investigation committee, and falsely accused collaborators

Research Misconduct: United States v. Poehlman

- UVM and ORI made over 50 findings of research misconduct, involving thousands of data points
- 10 scientific papers with falsified and fabricated data needed to be corrected or retracted

Investigator:

- Paid $180,000 in fines and penalties
- Agreed to a lifetime ban on receipt of federal funds
- Guilty plea to criminal fraud

University of Vermont:

- No penalties based on its internal investigation and cooperation with USA