Research Regulatory Issues

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Georgetown University Medical Center

Trust

"The scientific research enterprise, like other human activities, is built on a foundation of trust. Scientists trust that the results reported by others are valid. Society trusts that the results of research reflect an honest attempt by scientists to describe the world accurately and without bias.

From: Seberts, B., Shine, K. and White, R (1995) On Being a Scientist: Responsible Conduct in Research. National Academy of Sciences, Washington, D.C. National Press Academy http://www.nap/edu/readingroom/books/obas

"The successful conduct of research in a free society depends on trust between the scientific enterprise and the public, trust in the integrity of the discovery process, and especially trust in the safety of patients and healthy volunteers who participate in the process. In recent years, this essential trust has been shaken by a number of highly publicized events: tragic deaths of patients enrolled in clinical trials, high-profile allegations of financial conflicts of interest, and scientific misconduct by a few investigators."

From: Cohen, J.J. and Siegel, E.K. (2005). Academic medical centers and medical research. JAMA. Volume 294, No. 11

Fundamental Research Ethics Documents

- **Nuremberg Code**
- **Declaration of Helsinki**
- **Belmont Report - The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research - April 18, 1979**

  □

  Three Basic Ethical Principals:

  1. **Respect for Persons**
     - **Individual Autonomy - Cruzan**
     - **Protection of individuals with reduced autonomy**
  2. **Beneficence**
     - **Maximize benefits / minimize risks**
  3. **Justice**
     - **Equitable distribution of research costs and benefits**

- **Common Rule - IRBs**

Human Subjects Protection

Office of Human Research Protection (OHRP)
http://www.hhs.gov/ohrp/

The human subjects protection regulations (45 CFR Part 46) define **research** as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" [45 CFR 46.102 (d)]. A human subject is "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information" [45 CFR 46.102(f)].

Informed Consent Checklist

- Study involves research and purposes of research
  (Therapeutic Misconception)
- Duration of participation
- A description of the procedures to be followed
- Identify any experimental procedures
- Reasonably foreseeable risks or discomforts; if experimental, state that there may be unforeseeable risks
- Any benefits to the subject or to others
- Alternative procedures or courses of treatment, if any
- Extent to which confidentiality of records will be maintained
- If more than minimal risk, any compensation and/or available medical treatments if injury occurs, and where further information may be obtained
- 24-hour contact for answers to pertinent questions.

Continued on next slide

Informed Consent Checklist (cont.)

- Circumstances for termination of subject's participation
- Any additional costs as a result of participation in the research
- A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject
- Special Requirements RE: Children & Other Vulnerable Groups
- **Emergency Research Consent Waiver**
- Non English Speaking Subjects

http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm

Surrogate Decision Making

- **Legally Authorized Representative**
  - Next of Kin
  - Advanced Directives
  - Guardians

Placing Children in Jeopardy
Grimes v. Kennedy Kreiger Institute

- Study of lead abatement methods for low cost housing
- The study placed or retained children in areas with varying levels of lead dust - elevated blood lead levels not reported
- Court's concern for the particular child takes precedence over the interests of the parents and/or general public.

Grimes v. Kennedy Kreiger

We hold that...a parent, appropriate relative or other applicable surrogate, cannot consent to the participation of a child or other person under legal disability in nontherapeutic research or studies in which there is any risk of injury or damage to the health of the subject.

- Grimes v. Kennedy Kreiger Institute, et al., 366 Md. 29, 782 A.2d 807 (Ct App Md 2001)

Should students and employees be research subjects in non-therapeutic studies?

Should disabled persons participate in non-therapeutic studies in which there is risk of injury?

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Waiver of Consent

Emergency Research - no effective alternative treatment

- Anti-thrombolytics for acute stroke
- Traumatic blood loss - volume expanders

r/DNA Gene Transfer

- Institutional Biosafety Committees
- Office of Biotechnology Activities(OBA)
  - Recombinant DNA Advisory Committee (RAC)

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Animal Research

DOA registration; OLAW assurance; AAALAC accreditation [Site Visits]

Laws and regulations apply to vertebrate animals used in testing, research and training:

- Animal Welfare Act
- PHS Policy on the Humane Care and Use of Laboratory Animals
- Department of Agriculture Animal Welfare Regulations
- Guide for the Care and Use of Laboratory Animals
- U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training

Basic Principles of Animal Research

- Only if absolutely necessary
- Appropriate lowest species and minimum numbers
- Eliminate or minimize discomfort, distress, pain
- Use appropriate sedation, analgesia and/or anesthesia
- Euthanize when appropriate
- Appropriate living conditions for species
- Qualified personnel

Do the Right Thing

- Additional Motivation:
  - OHRP Enforcement Actions
    - Federal wide Assurance
    - Suspension / Restriction
  - False Claims Act
    - Civil and Criminal Liability
    - Treble Damages
    - Debarment
    - Actual knowledge or reckless disregard
    - Intentional ignorance not a defense
    - Qui Tam - Whistleblower (15-20%; 30%) *Healthcare & procurement fraud 79% of all qui tam cases - pursued more than any other types of fraud*
    - *HHS and DOD - agencies named most often as allegedly defrauded*
    - ***1986 – 2011 $30 Billion; 2011 - total $3 billion; 2012 - 4.2 Billion; 2013 - $3.8 Billion ($2.6 Billion Healthcare Fraud)***
  - Inspector General / US Attorney's Office

Sebelius, Holder Tout Recovered Funds From Health Care Fraud Investigations.

In continuing coverage, McClatchy (2/27, Pugh, Subscription Publication) reports that the Federal Health Care Fraud and Abuse Control Program, "a joint project" of the Justice Department and the Department of Health and Human Services, "recovered a record $4.3 billion" for fiscal year 2013, "up from $4.2 billion in 2012." That amounted to $8.10 "for every dollar spent investigating health care fraud and abuse in the last three years." Since its launch in 1997 the initiative has recovered "nearly $26 million" for the Medicare Trust Fund and the US Treasury. In a statement, HHS Secretary Kathleen Sebelius said, "We've cracked down on tens of thousands of health care providers suspected of Medicare fraud. New enrollment screening techniques are proving effective in preventing high risk providers from getting into the system, and the new computer analytics system that detects and stops fraudulent billing before money ever goes out the door is accomplishing positive results – all of which are adding to savings for the Medicare Trust Fund."

The Washington Times (2/27, Howell) quotes Attorney General Eric Holder, who said, "With these extraordinary recoveries, and the record-high rate of return on investment we've achieved on our comprehensive health care fraud enforcement efforts, we're sending a strong message to those who would take advantage of their fellow citizens, target vulnerable populations, and commit fraud on federal health care programs."

Failure to Comply with OHRP / FDA

- Duke University
  - (Not for Cause site visit)
- Johns Hopkins
- U Penn

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Johns Hopkins University
The death of Ellen Roche (2001)

- Study of airway obstructive disease (Asthma)
- Normal subjects
- Hexamethonium administered via inhalation
- 1st subject - cough, SOB not reported (cold or acidity?)
- Changed solution to reduce acidity (not reported)
- 2nd subject - no problem
- 3rd subject - Ellen Roche - 24 year old lab technician
- Students or employees as subjects?

Johns Hopkins University *cont.*

- Death due to acute respiratory distress
- Unaware of 1950's papers re: lung toxicity
- Not approved for human use (1972)
- 1978 asthma study at UCSF relied on by PI
  2 subjects with respiratory problems not reported

Johns Hopkins University *cont.*

- Inadequate IRB review of study
  - Inadequate IRB procedures
  - Failure to meet as a Full Board
  - Inadequate literature search
  - Overburdened
- Consent form deficiencies
- Insufficient minutes
- No FDA involvement
- Revocation of Assurances
- Re-review 2,400 protocols

University of Pennsylvania
The Death of Jesse Gelsinger (1999)

- Gene transfer protocol for rare metabolic disorder - ornithine transcarbamylase deficiency (“OTCD”) OTCD causes accumulation of ammonia [coma and death]
- 18 year old volunteer subject [stable on medication]
- OTC gene placed in adenovirus [vector] and injected - destination liver
- Death due to infection/inflammation, DIC

U Penn Findings

- Inadequate Animal Studies
- Failure to Report AE's – prior human toxicities (elevated liver enzymes) should have stopped study
- Noncompliance with inclusion/exclusion criteria
- Consent Form – Failure to disclose:
  - Financial conflicts of interest
    Individual and institutional
  - Risks adequately, including:
    Liver inflammation, DIC, Chills, N/V

U Penn/DOJ Settlement

- U Penn $517,496 Fine and Increased IRB oversight;
  Training and Education
- CNMC $514,622 Fine and Increased IRB Staff and Oversight
- PI:
  - 5-year ban as sponsor of FDA Regulated Clinical Trials
  - 5-year restrictions on PHS Grants
  - Training/Educational Requirements
  - Medical Monitor and /or CRO for clinical research activities
  - One study at a time
  - Lecture and author articles on "Lessons Learned" - include statements from family
- Co- PIs:
  - 3-year similar restrictions

US Attorney:

"This is a model enforcement action because it includes both individual researchers as well as research institutions in a civil matter..."

"Perhaps most significant is the impact that these settlements will have on the way clinical research on human participants is conducted throughout the country."

"Although gene therapy has tremendous potential to benefit patients, the tragic death of Jesse Gelsinger reminds us that sponsors who conduct clinical trials must take seriously their responsibility to make these trials as safe as possible."

- Dr. Lester M. Crawford, Acting FDA Commissioner

Death of Jolee Mohr

RA: Gene transfer research

intra-articular / AAV

Therapeutic Misconception

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Are all the problems in biomedical research?

- Milgram Experiments (Yale) on the conflict between obedience to authority and personal conscience.
- Tea Room Study (Wash U dissertation)
- VCU Twin Study (proxy consent)
- AAMC Graduation Survey

What are the risks in social and behavioral or educational research?

- Invasion of privacy
- Loss of confidentiality
- Psychological trauma
- Embarrassment and humiliation
- Social stigma
- What else?

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False Claims Act
Mid 90's PATH Audits (Clinical Billing)

- Not Pathology
- Physicians at Teaching Hospitals
- Low-lying Fruit
  - U Penn $30 M settlement
  - Thomas Jefferson U. $17M

That's why academic medical centers have mandatory billing compliance training!

False Claims Act
Research
(Billing, Pre & Post Award Grant Management)

- Research Billing Compliance
- Cost Reports / Time & Effort Reporting
- Research Misconduct

Grant Management / Cost Reports
Time & Effort Reporting

- US v. Thomas Jefferson University
  - June 2000 settlement $2.6M

NIH Grants - cancer and allergy & infectious disease

- PI was actually in Italy
- Postdoc paid from grant did not perform research
- Another allegedly used false or fabricated data to support grant application

US v. TJU

Prosecutor: *"Federal research grant funds are not to be considered 'entitlements' and educational institutions are not free to spend them as they deem appropriate."*

"The conditions attached to the award of a federal grant are vitally important to government."

US ex rel Gober vs. U of Alabama at Birmingham

- UAB $3.39M
- Whistleblowers (2) $395,000
- Allegations:
  - Billed federal healthcare programs (e.g. Medicare) for services billed to sponsors of clinical trials
  - Overstated or misstated percentage of effort that investigators worked on grant or contract or failed to properly disclose non-federal research activities

Mayo Foundation

- **$6.5 M settlement**
  - **Allegations:**
    - Improper cost transfers from overspent grants and internal cost centers to underspent grants
    - Inappropriately charged grant for costs unrelated to research sponsored by the grant
    - "Mayo had an accounting system unable to monitor and manage changes made to federal grant awards in the manner required by federal law"

Whistleblower = former accounting associate

V&E

Gary W. Eiland, Health Industry Group Vinson & Elkins LLP geiland @velaw.com (713-758-3474)

U.S. ex rel. Long v Mayo Foundation, No. CV02-522-ADM/SRN (D. Minn. Settlement announced May 26, 2005)

Harvard/Beth Israel Deaconess Medical Center

- **$2.4 M settlement**
  - **Allegations:**
    - Harvard/BIDMC improperly billed 4 NIH grants $1.9 M over 5-yr period
  - **Examples of inappropriate activity**
    - Salaries inappropriately paid for researchers who did not work on the grants
    - PI salary charged to grants in excess of budgeted amounts

(cont.)

Harvard/BIDMC (cont.)

- **Inappropriate activity, cont.**
  - Supply and equipment expenses incurred for projects unrelated to the grants
  - Additional expenses incurred
    - By researchers who were not eligible to work on or who did not work on the grant
    - For research animals used for unrelated projects

Johns Hopkins University

- **$2.6 M settlement**
  - **Allegations:**
    - Overstated percentage of effort; falsely reported T/E of employees who did not work on grants
    - Failed to maintain adequate compliance mechanisms to reconcile proposed effort commitments with actual effort

Whistleblower = office supervisor

V&E

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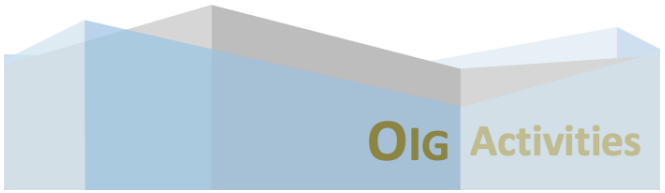
U.S. ex rel. Grau v. Johns Hopkins University, No. 99-1448 (D. Md. Feb. 26, 2004)

U.S. Department of Health and Human Services
Office of Inspector General

2014 HHS / OIG Work Plan

Work Plan
for Fiscal Year 2014



- CDC - oversight of HIV/AIDS Prevention and Research Grants
- NIH - college and university compliance with A-21 Cost Principles for Educational Institutions
- NIH - how universities meet cost sharing requirements
- With DOJ/FBI investigate compliance with select agent requirements for registration, storage and transfer of select agents and toxins

“But everybody does it that way”

is not an excuse!

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Is a Financial Incentive a Bad Thing?

US Constitution

Article 1, Section 8…

The Congress shall have the power:

- To promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries;

The Bayh-Dole Act (1980) (35 USC § 200) allowed non-profit organizations and small businesses to retain title to inventions arising from federally funded research.

- It is the policy and objective of Congress to use the patent system to promote the utilization of inventions arising from federally supported research or development;…to promote the collaboration between commercial concerns and non-profit organizations, including universities…
- to promote the commercialization and public availability of inventions made in the United States by United States industry and labor; to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against non-use or unreasonable use of inventions;…

A Fundamental Objective of GU Financial Conflict of Interest Policy and Practice:

To identify conduct that might constitute a conflict of interest, and to provide reliable and workable processes for resolving potential conflicts of interest.

With IP, inherent conflict [real or perceived] due to expectation of future financial gain.

What is our goal?

Preserve the integrity of research, researcher, and research institution; and the public trust in the results of the research

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Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought and Responsible Prospective Contractors

Published: August 23, 2011

Compliance Date: August 24, 2012

aka: PHS Financial Conflict of Interest rules

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Why?

PHS wants to ensure there is no reasonable expectation that the design, conduct or reporting of research funded by PHS will be biased by any conflicting financial interest of an investigator.

8/23/11 Telebriefing
Frances Collins, MD, PhD and Sally Rockey, PhD

- Aim of NIH is to see the relationship between AMCs and industry flourish

- Goal is not to discourage relationships between researchers and industry, because we depend on these relationships for the progress of biomedical research, but to make the relationships transparent and subject to scrutiny

From slides of Sally J. Rockey, PhD
Deputy Director for Extramural Research, NIH

Relationships between Academic Investigators and Industry are Important

- The public benefits when academic researchers collaborate with industry to develop products that promote individual and public health
- Academic researchers do most of the basic research that underpins much of the advances in medicine.
- Industry often builds on that basic research to develop therapeutic drugs and devices
- Therefore, it is essential not to stifle these relationships. This is even more important as we move towards a greater role for NIH in therapeutic development (e.g. NCATS)

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PHS COI Regulations Effective August 24, 2012

To ensure that PHS funded research is not biased by the financial interests of investigators

1. Definition of Significant Financial Interest [SFI] $10,000➔$5000 (compensation + equity), or any interest in non-publicly traded entity.
   - *SFI includes income from non-profit organizations*
   - *SFI excludes income from institution of higher education, AMC's teaching hospitals and government institutions*
   - *IP?*
   - *Must disclose sponsored or reimbursed travel*
2. "Investigator" is PI and any other person who is responsible for the design, conduct or reports of the research, including consultants and collaborators.
3. Investigator discloses all outside financial interests related to institutional responsibilities (this includes value of reimbursement for or company paid travel expenses); institution decides if related to research and if COI.
4. NIH must be informed of nature of conflict, value and CMP elements and how it relates to PHS funded research.
5. Public disclosure – either publicly accessible website or process for response within 5 working days of request for information re: COI plus update. Disclosure to include amount categories.
6. Training: every 4 years
7. Retrospective Review / Mitigation Plans
8. Subrecipient Agreements
9. SBIR/STTR Phase 1 grants

PHS: An investigator's significant financial interest is **related** to PHS-funded research when the Institution, through its designated official(s), reasonably determines that the significant financial interest: could be affected by the PHS-funded research; or is in an entity whose financial interest could be affected by the research.

PHS: A Financial **Conflict of Interest** exists when the Institution, through its designated official(s), reasonably determines that the Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the PHS-funded research

Examples of Conflict Management Plan Elements:

- Consent form disclosure of investigator and institutional interests ★
- Research monitored by independent reviewers: Dean's designee or oversight committee ★
- Disqualification from participation in all or a portion of the research [eg: consent, data analysis]; multi vs. single site; pre-clinical only; pre-clinical and clinical ★
- Independent evaluation for subject inclusion in clinical research
- Limitations on student assignments
- Divestiture of significant financial interests, or Severance of relationships that create actual or potential conflicts; escrow ★
- Limitation on role of investigator in outside company sponsor; executive position/BOD
- Limitations on transfer of institutional IP/data without fair/market based compensation
- Public disclosure of financial and IP interests in presentation/publications, in the educational setting and to collaborators
- Avoidance of therapeutic misconception

ICMJE:

"A conflict of interest exists when professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain). Perceptions of conflict of interest are as important as actual conflicts of interest."

The International Committee of Medical Journal Editors (ICMJE) has developed a uniform format for disclosure of competing interests for all member journals.

Financial relationships ... that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. [regardless of amount of compensation]

Patents (planned, pending or issued)

- ☐ Money paid to you
- ☐ Money to your institution

Research Misconduct
PHS Definition

fabrication, falsification, or plagiarism, in proposing, performing, or reviewing research, or in reporting research results.

Does not include honest error or differences of opinions.

- Plagiarism: Taking of the words and ideas of another as one's own, without crediting the source.

- Plagiarism tools

- Journal checks: "Similarity Report"

Research Misconduct Proceedings

Institutions have primary responsibility for hearing and deciding allegations of research misconduct in PHS supported research and for imposing sanctions where misconduct is found, and for providing notice to PHS.

- Institution must obtain and maintain custody of records
- Confidentiality for Respondent and Complainant
- Whistleblower protection for complainant making allegations in **good faith**

What is "good faith"?

"Good faith means having a belief in the truth of one's allegation or testimony that a reasonable person in the complainant's or witness's position could have based on the information known to the complainant or witness at the time. An allegation or cooperation with a research misconduct proceeding is not in good faith if made with known or reckless disregard for information that would negate the allegation or testimony."

US v. Breuning

University of Pittsburgh researcher guilty plea:

- 2 counts violating Fraud and False Statements Act for falsifying results of research regarding hyperactive and mentally retarded children in grant continuation application to NIMH
- 4-year sentence, majority suspended
- 5-year probation - barred from research
- $11,352
- Community service

University of Pittsburgh:

- $163,000 paid to NIMH

United States District Court
For The
District of Vermont

United States of America,	)	
Plaintiff,	)	
v.	)	Civil No. 2:05-cv-66
Eric T. Poehlman,	)	
Defendant	)	

Researcher admits fraud in grant data

Ex-Vermont Scientist won nearly $3M from US

(Source: Goldberg, C. and Allen, S. 2005, March 18. The Boston Globe)

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
- Reported to University by student lab technician - *"I felt that his behavior had to be exposed and that he should be removed from science."*

(UVM lab technician; Nature, May 3, 2006)

Summary of Poehlman's Massive Fraud

- Falsely accused collaborators
- Submitted false documents to investigation committee
- Solicited false testimonials
- Committed misconduct over 10 years with $3 million in funding
- Submitted false and fabricated data in 17 grant applications
- UVM and ORI found over 50 findings of research misconduct, involving thousand of data points
- 10 scientific papers have falsified and fabricated data and will be corrected or retracted

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From: Chris Pascal, JD, Director Office of Research Integrity, HHS

Poehlman and University of Vermont

- Investigator:
  - Pay back $180,000
  - Barred for life
  - Guilty plea to criminal fraud - (sentenced to serve 366 days in federal prison, permanently barred from federal research dollars, restitution: $180,000 to federal agencies)

- University of Vermont:
  - $0 because they cooperated

  (came to the attention of US Attorney because he sued U. VT over firing)

Office of Research Integrity

Press Release
Burlington, Vermont - March 17, 2005

The United States Attorney's Office for the District of Vermont, the U.S. Department of Health and Human Services (HHS) Office of Inspector General (OIG) and Office of Research Integrity(ORI) announced today that Dr. Eric T. Poehlman, 49, a former tenured research professor at the University of Vermont (UVM) College of Medicine in Burlington, Vermont, has agreed to a comprehensive criminal, civil, and administrative settlement related to his scientific misconduct in falsifying and fabricating research data in numerous federal grant applications and in academic articles from 1992 to 2002.

Source: http://ori/dha.gov/misconduct/cases/press_release_poehlman.shtml

U.S. Attorney David V. Kirby:

"Preserving the integrity of the grant process administered by the Public Heath Service is a priority for the Department of Justice. This prosecution demonstrates that academic researchers will be held fully accountable for fraud and scientific misconduct. Dr. Poehlman fraudulently diverted millions of dollars from the Public Health Service to support his research projects. This in turn siphoned millions of dollars from the pool of resources available for valid scientific proposals. As this prosecution proves, such conduct will not be tolerated."

Mass. Doctor Accused of Fraud by Faking Research

Updated: Thursday, 14 Jan 2010, 8:52 PM EST
Published: Thursday, 14 Jan 2010, 8:52 PM EST

BOSTON - Federal prosecutors have filed a health care fraud charge against a Massachusetts doctor accused of faking research for a dozen years in published studies that suggested after surgery benefits from painkillers.

U.S. Attorney Carmen Ortiz announced the complaint Thursday against Dr. Scott Reuben, the former chief of acute pain at Baystate Medical Center in Springfield.

Prosecutors say Reuben sought and received research grants from pharmaceutical companies but never actually performed the studies. Prosecutors say he fabricated patient data and submitted information to anesthesiology journals that published it.

The hospital said last year that it had discovered the alleged fraud. Reuben did not admit to it.

His attorney did not immediately return a call for comment.

Case of Emily Horvath

- Former graduate student, Indiana University
- Research supported by National Center for Complementary/Alternative Medicine and National Institutes of Health(NIH) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- Falsifying figures in grant applications, publications, thesis
- Falsifying the original research data when entering values into computer programs for statistical analysis with the goal of reducing the magnitude of errors within groups, thereby gaining greater statistical power

3 year voluntary exclusion

- From any PHS activity
- Supervision for any PHS sponsored research

Federal Register 4/13/10 (Vol 75, No70)

Case of Ryan M. Wolfort

- Former Louisiana State University Health Sciences Center-Shreveport House Officer, in the Department of Surgery, and a former graduate student Department of Molecular and Cellular Physiology
- Study on research examining the contribution of immune mechanisms to early oxidative stress and endothelial dysfunction in mice with induced dietary hypercholesterolemia
- Falsified/fabricated data reported in three publications and one manuscript that had been submitted for publication, reviewed, and returned for revision.

2 year voluntary exclusion

- Service, contracting or serving on an advisory board with any federal government

Federal Register 8/18/2009 (Vol 74 No 158)

Case of Scott Monte

- Clinical Research Associate, Huntington Memorial Hospital (HMH)
- Falsified and fabricated clinical research records in HMH cancer and prevention protocols
- Falsified/fabricated laboratory data or PE results on 5 subject case report forms
- Falsified GYN exam in physicians progress note and research chart
- Fabricated progress notes

3 year debarment

Federal Register 1/23/08 (Vol 73, No15)

U.S. v. Butkovitz Case
No. 05-CR-10128-DPW (D.Ma)

- Study coordinator accused of false statements in FDA approved clinical study, "Safety and Efficacy of Pentavalent…or Human-Bovine Reassortant Rotavirus Vaccine in Healthy Infants."

- Coordinator failed to make follow up contacts with parents/guardians to determine adverse events yet field Case Report Forms claiming she ha made the contacts.

Press Release: U.S. Attorney, District of Massachusetts, May 25, 2005.

"If convicted on these charges, Anne Butkovitz faces up to 5 years' imprisonment, to be followed by 3 years of supervised release and a $250,000 fine."

On September 16, 2005 she was sentenced to one year probation, fined $1,000 and ordered not to participate in any studies submitted to the FDA.

information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques when appropriate, and other forms of information technology.

The Older Americans Act (OAA) requires annual program performance reports from States. In compliance with this OAA provision, AoA developed a new State Program Report (SPR) in 1996 as part of its National Aging Program Information System (NAPIS). The SPR collects information about how State Agencies on Aging expend their OAA funds as well as funding from other sources for OAA authorized supportive services. The SPR also collects information on the demographic and functional status of the recipients. This collection was revised in November 2004 (OMB Approval Number 0985–0008). The proposed data collection continuation format remains unchanged from the November 2004 document. It may be found on the AoA Web site at *http://www.aoa.gov/prof/agingnet/NAPIS/docs/SPR-Modified-Form-11.08.04.pdf*. AoA estimates the burden of this collection of information as follows: 2,606 hours.

Dated: October 12, 2006.

Josefina G. Carbonell,

Assistant Secretary for Aging.

[FR Doc. E6–17251 Filed 10–16–06; 8:45 am]

BILLING CODE 4154–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2006N–0018]

Anne L. Butkovitz; Debarment Order

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing an order under the Federal Food, Drug, and Cosmetic Act (the act) permanently debarring Ms. Anne L. Butkovitz from providing services in any capacity to a person that has an approved or pending drug product application including, but not limited to, a biologics license application. FDA bases this order on a finding that Ms. Butkovitz was convicted of a felony under Federal law for conduct relating to the development or approval, including the process for development or approval, of a drug product under the act. After being given debarment and her opportunity to request a hearing within the timeframe prescribed by regulation, Ms. Butkovitz failed to request a hearing. Ms. Butkovitz's failure to request a hearing constitutes a waiver of her right to a hearing concerning this action.

DATES: This order is effective October 17, 2006.

ADDRESSES: Submit applications for termination of debarment to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Brenda R. Friend, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Background

On June 7, 2005, the U.S. District Court for the District of Massachusetts accepted Ms. Anne L. Butkovitz's plea of guilty to one count of making a false statement, a Federal felony offense under 18 U.S.C. 1001. This offense was committed while Ms. Butkovitz was the clinical study coordinator at a safety site for a clinical trial.

As a result of this conviction, FDA served Ms. Butkovitz by certified mail on March 7, 2006, a notice proposing to permanently debar Ms. Butkovitz from providing services in any capacity to a person that has an approved or pending drug product application including, but not limited to, a biologics license application. The proposal also offered Ms. Butkovitz an opportunity for a hearing on the proposal. The proposal was based on a finding, under section 306(a)(2)(A) and (c)(2)(A)(ii) of the act (21 U.S.C. 335a(a)(2)(A) and (c)(2)(A)(ii)), that Ms. Butkovitz was convicted of a felony under Federal law for conduct relating to the development or approval of a drug product, including the process for development or approval, of a drug product. Ms. Butkovitz was provided 30 days to file objections and request a hearing. Ms. Butkovitz did not request a hearing. Ms. Butkovitz's failure to request a hearing constitutes a waiver of her opportunity for a hearing and a waiver of any contentions concerning her debarment (21 CFR 12.22(b)(1)).

II. Findings and Order

Therefore, the Director of the Center for Biologics Evaluation and Research, under section 306(a)(2)(A) of the act, and under authority delegated to the Commissioner of Food and Drugs (21 CFR 1410.35), finds that Ms. Butkovitz has been convicted of a felony under Federal law for conduct relating to the development or approval, including the process for development or approval, of a drug product.

As a result of the foregoing finding, Ms. Butkovitz is permanently debarred from providing services in any capacity to a person with an approved or pending drug product application (section 306(c)(1)(B) of the act). A drug product means a drug, including a biological product, subject to regulation under sections 505, 512, or 802 of the act (21 U.S.C. 355, 360b, or 382), or under section 351 of the Public Health Service Act (42 U.S.C. 262). Any person with an approved or pending drug product application including, but not limited to, a biologics license application, who knowingly employs or retains as a consultant or contractor, or otherwise uses the services of Ms. Butkovitz, in any capacity, during Ms. Butkovitz's permanent debarment, will be subject to civil money penalties (section 307(a)(6) of the act (21 U.S.C. 335b(a)(6))). If Ms. Butkovitz, during her permanent debarment, provides services in any capacity to a person with an approved or pending drug product application including, but not limited to, a biologics license application, Ms. Butkovitz will be subject to civil money penalties (section 307(a)(7) of the act). In addition, FDA will not accept or review any abbreviated new drug applications submitted by or with the assistance of Ms. Butkovitz during Ms. Butkovitz's permanent debarment (section 306(c)(1)(B) of the act).

Any application by Ms. Butkovitz for termination of debarment under section 306(d)(4) of the act should be identified with Docket Number 2006N–0018 and sent to the Division of Dockets Management (see **ADDRESSES**). All such submissions are to be filed in four copies (21 CFR 10.20(a)). The public availability of information in these submissions is governed by 21 CFR 10.20(j). Publicly available submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday (21 CFR 10.20(j)(1)).

Dated: September 25, 2006.

Jesse Goodman,

Director, Center for Biologics Evaluation and Research.

[FR Doc. E6–17178 Filed 10–16–06; 8:45 am]

BILLING CODE 4160–01–S

Why People Cheat

- Publish or perish / intense competition
- Fear of loss of funding
- Greed - money, fame
- Reputation / Arrogance - so sure of the outcome
- Cultural differences - values, definitions

Poehlman colleagues speculate that either he bucked to an exaggerated perception of the pressure to publish papers and win grants to keep is laboratory going or he was just so sure that he knew the right answers that he cut corners to get them.

(Goldberg and Allan, 2005 Boston Globe)

Victims of Misconduct

- Erroneous and fraudulent research data and research findings can jeopardize the health of you and your family and the health of the general public.
- The reputations of the silent majority of honest scientists are victims of the few who cheat.
- The public is victimized by wasted taxpayer funds for fraudulent research.

From: Chris Pascal, JD, Director Office of Research Integrity, HHS

"We are still reeling from the shock…There is no worse feeling in the world than for a researcher to learn that he has put his name to a paper with fabricated data."

Dr. Leonard Zwelling, VP for Research, M.D.

Source: Wade, N. (2006, January 19), Cancer study was made up, journal says The New York Times
http://www.nytimes.com/2006/01/19/national/19fraud.html?pagewanted=print

Sponsor Limitations on Publication
Dr. Nancy Olivieri:
Hospital for Sick Children (Toronto) and University of Toronto

- Drug mfr, Apotex, sponsored Olivieri research of deferiprone for ion overload associated with thalassemia; compared to standard drug, deferoxamine
- She became convinced that study drug ineffective and caused liver damage; Apotex threatened legal action and tried to block reports to ethics committee, subjects and public
- Olivieri published findings in NEJM (1998) and presented findings at scientific meeting
- Apotex stopped all Olivieri clinical trials; ongoing legal warnings
- Olivieri terminated from hospital position, numerous legal actions followed
- Investigative report found lack of university support for academic freedom

ClinicalTrials.gov
Protocol Registration System

- Registration and results reporting of clinical trials is required
  - Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation.
  - Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
  - "Applicable clinical trials" generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the U.S., involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under and investigational new drug application (IND) or investigational device exemption (IDE).

- Penalties
- Loss of grant funds
- Financial penalty

- Must list registration number on CMS Claims

NIH Public Access - PubMed Central

- Effective 4/7/08
- Final, peer-reviewed manuscripts that arise in whole or in part from NIH funded research must be deposited in PubMed Central (digital archive of full text biomedical journal articles) upon acceptance for publication and available to public within 12 months
- Non Compliance may delay or prevent awarding of funds
- Progress reports / NIH applications that cite these articles must include PubMed Central cite
- Copyright issues in publication agreements: reserve the right to submit to PubMed Central

Export Control Laws/Regs

Export Control Restrictions

Export Administration Regulations (EAR) [Commerce]

- Governs dual use technologies (military and civilian)
- Commerce Control List: such as nuclear materials, chemicals, toxins, sensors and lasers, propulsion systems, etc.

International Traffic in Arms (ITAR) [Department of State]

- Munitions, defense articles and services

Office of Foreign Assets Controls [Treasury]

- Lists sanctioned countries (e.g. terrorist states)

Export:

1. Actual physical shipment or transmission out of U.S.
2. Disclosure to foreign national inside or outside of U.S. (Deemed Export)

Export Control / Fundamental Research Exemption

Research is not eligible for the fundamental research exemption if:

1. Publication restrictions

1. Restrictions on who can participate in research

1. Sponsor authorization to exclude certain sponsor information

Ownership of Tissue / Biological Materials

- Moore v. Regents of the University of California
- Washington University v. Catalona (8th Circuit held that Washington University in St. Louis owns tissue and serum that its medical faculty collected in a tissue bank, and the donors have no property interest in or right to direct transfer of the materials.)
- According to proposed guidance, OHRP and FDA reversing their prohibition against language in consent forms by which subject donates biospecimens or says no claim or right to compensation.

Example: "By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of research."

HIPAA

Health Insurance Portability and Accountability Act

- Medical Record Privacy provisions:
  - Protects individually identifiable health information = Protected Health Information (PHI)
  - Use and disclosure of PHI without authorization
    - Treatment
    - Payment
    - Operations

Patient Rights

- Receive copy of Privacy Notice
- File a complaint
- Request restrictions
- Select how to receive the information
- See and copy records
- Update / amend records
- Obtain list of disclosures (except T.P.O and if authorized)

Computer Security - now in effect

Permitted Disclosures

- Public Health activities (e.g. infectious disease tracking)
- Law Enforcement /Judicial Proceedings (e.g. victim of crime, valid subpoena)
- Deceased persons (e.g. coroner, organ donation)
- Patient Directories - with permission

Medical Record Privacy and Research

Research is NOT part of operations

Use & Disclosure of PHI for Research

- Authorization or

4 Exceptions:

- Waiver - Privacy Board or IRB
- Review Preparatory to Research
  - Protocol Development
  - Recruitment
- Decedent Information
- Limited Data Set

If you don't follow the rules, you cannot use the data; IRB has no authority to waive the HIPPA requirements

Waiver of Authorization

1. The use or disclosure of PHI involves no more than minimal risk to the individual's privacy.

2. The research could not practicably be conducted without the waiver.

3. The research could not practicably be conducted without access to and use of the PHI.

Trust that private information will remain private Certificates of Confidentiality

- Protect investigators and institutions from being compelled to release information that could be used to identify research study participants

- Allow the investigator and others who have access to research records to refuse to disclose identifying information in any
  - Civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level

Certificates of Confidentiality Kiosk:
http://grants1.nih.gov/grants/policy/coc/index.htm

Participation in Insider Trading

SEC and DOJ investigate claims that researchers and government officials [FDA] are selling confidential information about drug research to Wall Street investment firms or using it for personal gain.

What is RCR?
Office of Research Integrity
http://www.ori.hhs.gov

- Doing the right thing
- Conducting research with the knowledge and skills needed to conform to responsible practices
- Understanding and applying relevant regulatory requirements and scientific norms
- Much more than avoiding misconduct

From: Chris Pascal, JD, Director office of Research Integrity, HHS

Responsible Conduct of Research

- PHS requirements for trainees
  - Data Acquisition, Management, Sharing and Ownership
  - Conflict of Interest and Commitment
  - Human Subjects
  - Animal Welfare
  - Research Misconduct
  - Publication Practices and Responsible Authorship
  - Mentor / Trainee Responsibilities
  - Peer Review
  - Collaborative Science
- New NIH and NSF training requirements
- For NIH grants with any training component, electronic training alone is not enough

Gelsinger before financial conflict of interest was disclosed (according to PG)

"In late November 1999, the head researcher… traveled to my home in Tucson, AZ, where I met him for the first time, some two month's after Jesse's autopsy. My first question to him while sitting on my back porch was, 'What is your financial position in this?' His response was that he was an unpaid consultant to the biotech company, Genovo, behind the research effort. Being naïve, I accepted his word and continued my support for him and his work."

Paul Gelsinger, Father of Jesse, 18 years old and first person killed by gene therapy

~ Gelsinger, P (2001) Jesse's intent. http://www.circare.org/submit/jintent.pdf

Georgetown University Medical Center

Gelsinger after financial conflict of interest was revealed (according to PG)

"The over-enthusiasm of the clinical investigators painted a picture of safety and efficacy of their work. That enthusiasm led them to blind themselves to the ill effects that they were witnessing and not communicating to us or those with oversight for their work, the insitution's IRB and the FDA."

"...I still support our need for clinical trials, but with this caution: Informed consent is only possible if all the facets of the research endeavor are ethical and in the open. Because of the secretive and conflicting influences on clinical research, the average research subject has little hope of understanding and giving truly informed consent. *All research subjects really want is to be able to trust the system* (emphasis added)."

~ Gelsinger, P (2001) Jesse's intent. http://www.circare.org/submit/jintent.pdf

Help and Guidance

Any thoughts, concerns, and/ or suggestions - call us!

Research Integrity

202-687-8437

Georgetown University Medical Center