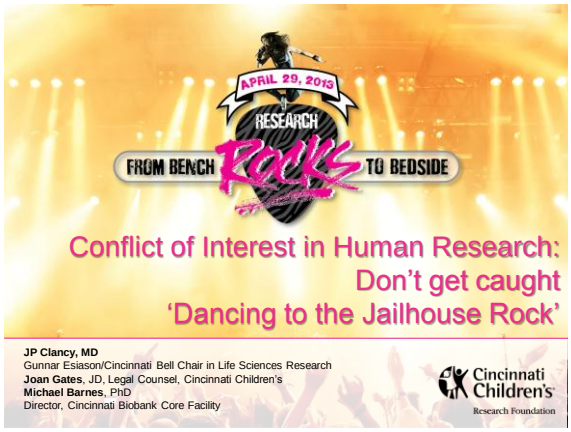

Conflict of Interest in Human Research: Don't get caught 'Dancing to the Jailhouse Rock'

JP Clancy, MD
Gunnar Esiason/Cincinnati Bell Chair in Life Sciences Research
Joan Gates, JD, Legal Counsel, Cincinnati Children's
Michael Barnes, PhD
Director, Cincinnati Biobank Core Facility

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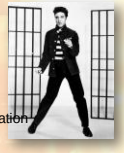
Disclosures



- JP Clancy, MD
  - Co-Chair, Biomarkers Consortium - Cystic Fibrosis Foundation Therapeutics (CFFT)
  - Member, Translational Advisory Committee (CFFT)
  - Member, CFFT/Vertex Pharmaceuticals Joint Development Committee
  - Member, Vertex Pharmaceuticals Global Advisory Board (Vertex Pharmaceuticals)
  - Member, Steering Committee, Arikace™ for Cystic Fibrosis program (Insmed Pharmaceuticals)
  - Member, Neurofibromatosis Translational Acceleration Program Scientific Advisory Board
  - Chair, scientific review committee for Gilead Sciences Research Scholars Program in Cystic Fibrosis
- Joan Gates, JD
- Michael Barnes, PhD

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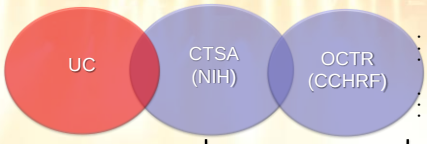
Who is the OCTR?

- Office of Clinical and Translational Research
  - Formerly CTO and TRTO
  - Director = Leslie Sullivan-Stacey



- CRPs
- Budgeting
- Multicenter trial design and execution
- Monitoring
- Marketing
- Education

T building

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Objectives – Conflict of Interest

- Upon completion of this program, participants should be able to:
  - Describe the various types of conflict of interest that can occur in medical research
  - Understand the potential risks that conflicts of interest can create
  - Discuss the mechanisms to avoid and manage conflicts of interest in clinical research

Summary

- High profile case reviews: Conflict of Interest in medical research
- Practical Guidance scenarios to avoid and manage Conflict of Interests in research

The sentinel case of Jesse Gelsinger

- 18 yo with ornithine transcarbamylase deficiency (OTCD)
  - The urea cycle (located in the liver), detoxifies nitrogen and converts it to urea which is nontoxic and is excreted in the urine.
  - Individuals with OTCD are unable to convert nitrogen (ammonia) to urea.
  - High levels of ammonia is toxic to the CNS, and as a result hyperammonaemic coma and death may occur with OTCD

University of Pennsylvania Almanac, February 9, 2005

The clinical trial

- Phase I safety study focused on determining the maximum tolerated dose of study drug in adult patients.
- The OTC gene was placed inside a virus (adenovirus) which was injected into the liver through blood vessels (hepatic artery).
- The virus carried the OTC gene into the research participant's liver where the subjects' liver cells would take up the OTC gene and produce the OTC enzyme (missing in OTCD).

University of Pennsylvania Almanac, February 9, 2005

The tragedy

- Jesse was the 17th of 18 patients in the study, and the youngest (18 yo)
- He had partial OTCD (diagnosed at age 2 yrs) managed with oral medications and diet. The study drug did not offer any direct benefit to him or his disease, but could be of great benefit to infants with OCTD.
- He received the hepatic artery infusion on Monday, September 13th, 1998.
  - That evening he developed a fever (104.5^{0}F)
  - By the next morning he had developed jaundice, disorientation and a rising ammonia level
  - He was placed on a ventilator, dialysis, and eventually ECMO, but eventually died of multisystem organ failure on Friday, September 17th.

Sheryl Gay Stolberg. The Biotech Death of Jesse Gelsinger. New York Times, Nov 28, 1999

The background…

- Director of the clinical trial and University of Pennsylvania Institute for Gene Therapy founded a biotech company called Genovo, Inc.
- Both the investigator and UPenn had equity stake in the company
- Investigators had patents on certain aspects of the procedure
- Genovo, Inc had invested 1/5th of the $25 million annual budget for the Institute for Gene Therapy
- The informed consent made no mention of the specific financial relationships between the investigator, company, and institution
- When Genovo, Inc was sold to a larger company, PI had $13.5 million in stock options, and the institution had $1.4 million

Sheldon Krimsky, Law and Ethics in Biomedical Research (2006)

The allegations

- The government alleged that the study had produced toxicities in humans that should have resulted in termination, but the study continued.
- Reports were submitted to FDA, NIH and to the Institutional Review Boards (IRBs) charged with oversight of this study that misrepresented the actual clinical findings associated with the study.
- Additionally, the consent form and process did not disclose all anticipated toxicities.

University of Pennsylvania Almanac, February 9, 2005

More allegations

- The government allegations contained in the settlements with Penn, CNMC and investigators address **several violations of the civil False Claims Act** that occurred between July 1998 through September 1999.
- The government contended that the individuals and their institutions (as the recipients of federal funding) submitted and/or caused to be submitted
  - False statements and claims in connection with the submission of grant applications, progress reports, and annual reports to, and receipt of federal funds from, the NIH
  - False statements and claims in connection with submissions to the FDA
  - False statements and claims in connection with the failure to obtain properly informed consent from human research participants
  - False statements made to IRBs charged with oversight of this research.

University of Pennsylvania Almanac, February 9, 2005

Settlements (PI and/or institution) (>$1,000,000 to government)

- **Five year restriction** - FDA-regulated clinical trials
- **Training/educational requirements**: human research participant protections and clinical research.
- **Restricted clinical activity** with a Medical Monitor and/or a Contract Research Organization for three years - restricted clinical activity in one study at a time
- A **Special Monitor (SM) oversight of animal research** that could influence the safety of human research participants.

Settlements (continued….)

- **SM oversight** of activities to: a) ascertain whether involvement constitutes Restricted Clinical Activity, b) ensure communication to the IRB, sponsor and grantee, and c) ascertain PI's compliance with regulatory requirements (semi-annual reports to NIH and FDA).
- **Notification t**o the Office of Policy for Extramural Research Administration (**OPERA**) of **new NIH submissions** involving human subjects research.
- **Agreement to lecture and author an article on the lessons learned from this study**. PI will advocate for the inclusion of any statements from those affected by the study, e.g., the Gelsinger family. This statement will be at the discretion of the Gelsingers.

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COI from the FDA to Hot-lanta…


THE WALL STREET JOURNAL.

Drug Chief at the FDA Is Accused Of Conflict

…OIG of the Dept of HHS is investigating a conflict of interest allegation involving the official in charge of drug approvals at the FDA…


Top Psychiatrist Didn't Report Drug Makers' Pay

…One of the nations most influential psychiatrists earned > $2.8M in consulting arrangements with drug makers…

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…from the Ivy League to the Bluegrass state…


Researchers Fail to Reveal Full Drug Pay

…A world-renowned Harvard child psychiatrist …earned at least $1.6M in consulting fees from drug makers…


Top Spine Surgeons Reap Royalties, Medicare Bounty

…The five surgeons are also among the largest recipients of payments from medical devise giant Medtronics…earned >$7M in first nine months of 2010..

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Practical Guidance to Avoid and Manage Conflict of Interests

- Joan Gates

John L.

- John is a researcher at non-profit medical center that receives federal funding.
- He studies noise induced hearing loss and his research is currently supported by a federal grant that will soon end.
- Since John moonlights in a rock band with his friends, Paul, Ringo and George, he is highly motivated to discover a means to prevent hearing loss for his fans and his friends.

Q: Is this a COI?

What is a Conflict of Interests ("COIs")?

Interests that affect or appear to affect a person's judgment when exercising their institutional obligations. Typically, COIs happen when an opportunity to influence institutional decisions to personal advantage occur (financial or otherwise).

COIs are the "temporal existence of conflicting primary and secondary interests."

Interests

Financial
- Money
- Employment
- Property/Stock Ownership

Non-Financial
- Professional
- Personal
- Physical
- Psychological

Further Defining COIs

- Acting in a professional or official capacity or in a position of trust
- While having a personal interest (usually financial)
- That interferes with objective decision making (or gives the impression that decision making is compromised)

Examples of COIs

- Maintaining roles that conflict
- Accepting personal gratuities
- Use of Institution's facilities to fulfill private obligations
- Conflicting outside employment or other allegiances (i.e., boards)

John L. (continued)

- John's wife Yoko owns a company that makes earplugs — Earpro, Inc.
- John's research has discovered a new way to prevent hearing loss that may revolutionize the design of earplugs. Recognizing the potential, Yoko wants Earpro, Inc. to sponsor John's continued research. John is thrilled since his federal funding is running out and due to recent cut backs, will not be renewed.
- Yoko has Earpro, Inc.'s legal counsel contact John's institution to set up a contract.

Q: Does John have a COI? What should John do, if anything, at this point?

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Addressing Conflict of Interests

- Disclosure
- Review
- Management

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John L. (continued)

- Earpro Inc. contacts Institution's Commercialization department to discuss the details of their monetary support for John's research.
- A Sponsored Research Agreement is reached that gives Earpro Inc. an option to an exclusive license to any invention that results from John's research in exchange for $200K to support John's continued research.
- John has not disclosed to Institution his wife's role with the company as he did not think it was relevant.

Q: Was John correct?

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Managing Provider/Industry Relationships

- Manufacturers will continue to interact closely with institutions/researchers in both traditional and leading-edge relationships.
- Financial relationships between industry and institutions/researchers are both complex and commonplace.
- Industry-sponsored research is a source of income/capital generation for institutions/researchers and participation in such research can enhance reputations.

Managing Provider/Industry Relationships

- Industry has resources to underwrite medical education and conferences, fund research, and provide philanthropic support for growth and development of physical plant and centers of excellence.
- These relationships have become a top enforcement priority for regulatory bodies, the plaintiffs bar, industry trade associations and the media (national, regional and local levels).

Managing Provider/Industry Relationships

As such, we must manage these relationships to assure they do not:

- *Impair judgment in research resulting in risk to human subjects, unreliable or biased data;*
- *Change medical prescribing behavior that can pose harm to patients and increase costs to government payment programs; or*
- *Diminish the objectivity and integrity of the content of medical educational programs and materials.*

John L. (cont.)

- John's technology is patented, he publishes his first paper and he is ready to develop a prototype. He needs to hire a specialized engineer and the $200K provided by Earpro, Inc. is not enough.
- While presenting at a conference, he is approached by a DOD representative that is very interested in his research and encourages John to apply for a DOD grant, which John does.
- Earpro is excited by this news and asks John to consult with Earpro on the side as a scientific board adviser to assure Earpro is kept in the loop.
- Earpro contracts with John directly and pays him $20K annually plus expenses.

Q: What, if anything should John do?

Handling Interests

Step One:

- Disclose, Disclose, Disclose!
- Apply the "Front Page of the "Cincinnati Enquirer" test

Handling Interests

Step Two: Mitigate/manage

- Transparency regarding interest (i.e., publications, informed consents)
- Modify research design
- Research monitored by independent reviewers
- Other alternatives?

Handling Interests

Step Three: If monitoring is not feasible, you may be required to:

- Discontinue the compensated activity
- Divest self of the financial interest
- Terminate the research

John L. (Cont.)

- With the support of the DOD funding, the prototype earplug is made and is ready for testing. An IRB protocol is submitted that will use human subjects to test the comfort and ease of use of the plugs, as well as the efficacy of the decibel reduction in field-like conditions.
- John uses the remainder of his DOD funding to partner with Earpro to manufacture the earplugs for this pilot.
- Earpro pays John's lab for the validation testing of the earplugs as concurrently, Earpro/Institution are negotiating the terms of Earpro's exclusive license agreement to make, use and sell the earplugs.

Q: Any issues/concerns?

Managing COIs

- All areas and relationships related to the potential conflict must be disclosed and considered; COIs cannot be managed in a vacuum;
- When real financial COIs exist, they must be addressed in the most conservative manner, especially when human subjects involved;
- The more complex and closer the activities of the researcher are to the business interests of a company, the more likely the institution will need to restrict or manage the researcher's multiple roles;
- Avoid conducting trials when researcher has financial interests in the outcome.

Comments and questions

- COI is everywhere
  - Disclose
  - Manage
  - Mitigate

Or else….

Research Rocks

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