Financial Conflict of Interest (FCOI) and Human Subjects Research: Opportunities and Challenges in the Device World

Harry Greenberg, M.D.
Senior Associate Dean of Research
Director Of Spectrum
Harry Greenberg, M.D.
Relationships with Industry
2010

Biota
Symphogen
Vical
Novartis
Ligocyte
Functional Genomics
Vaxart
What is an FCOI?

“Financial conflicts of interest occur when people are tempted to deviate, or do deviate, from their professional obligations for economic gain.”

Brennan et al. JAMA
2006; 295:426
“Conflicts of interest are common and practically unavoidable in a modern research university. Conflicts of interest can arise out of the fact that a mission of the University is to promote public good by fostering the transfer of knowledge gained through University research and scholarship to the private sector.”

Stanford University Research Policy Handbook
Personal Conflicts of Interest: Many Motivators, not all Financial

- Contribution to science
- Career advancement
- Opinion of peers and hierarchy
- Prestige -- fame -- status
- **Financial gain**
FCOI in Education

- Educator **objectivity ↔ financial** incentive
- Speakers Bureau = **company’s agent**
- Stanford SoM policy prohibits serving on a Speakers Bureau
- Faculty can give talks as part of educational mission as long as they control content and materials and the purpose is not primarily for marketing
- Meeting (or talk) on **one** product is not education; it is **advertisement**
“Individuals must consciously and actively divorce clinical care decisions from any perceived or actual benefits expected from any company. It is unacceptable for patient care decisions to be influenced by the possibility of personal financial gain.”

Stanford Industry Interactions Policy (SIIP) 2010
Today’s concern:

Financial Conflict of Interest in **Human Research**

- for the inventor/investigator
- for the institution
- for the sponsoring company
- government oversight

Jesse Gelsinger
(1981-1999)
Medical Industry Ties Often Undisclosed in Journals

Lots of Money, Not So Much Disclosure
A study of 32 doctors who had each received $1 million or more from medical device makers in 2007 found that those payments were disclosed in less than half of a sample of the medical journal articles they published in 2008.

DISCLOSURE IN: EVERY ARTICLE
7 doctors: 15 articles

SOME ARTICLES
14 doctors: 29 articles with, 22 articles without

NO DISCLOSURE
11 doctors: 30 articles without

Articles by one doctor

Source: Susan Chimonas, Zachary Frosch and David J. Rothman, College of Physicians and Surgeons, Columbia University
Areas of Concern for FCOI

1. Protection of human subjects
2. Data integrity & study validity
3. Reputation of the investigator
4. Reputation of the institution
5. Reputation of the sponsoring company
Types of Financial Relationships with Industry

- Consultant - Expert
  - Advisor
    - Basic Research and Product development
    - Market development
      - Study Designer
      - DSMB member
- Speakers Bureau
- Investor
- Inventor
- Founder
- Advisory Board Member
- Board of Directors
- **Investigator**
Protection of Human Subjects In Device Research

First: Do No Harm

• You do NOT know if the device will work
• Study pts cannot expect to benefit personally
• Devices are often not optimal when 1st tested
• All devices fail sometimes
• Safety requires restraint in pressing on
• Technical prowess is not uniform
• There must be no coercion to participate
• (Amazingly, pts generally agree to participate in the face of FCOI)
Some Assumptions

• News media can make any physician relationship with industry look nefarious

• Physicians must exercise diligence and good judgment to ensure that industry relations fall within policy and common sense guidelines

• There is a delicate balance between the value of these personal financial relationships and their risk to the individual (and the institution)
Protection of Human Subjects
“The Rebuttable Prohibition”

• Assume a conflicted investigator cannot carry out the HSR investigation if financial interests are above pre-specified thresholds:
  – $10,000 in income
  – $10,000 in equity in publicly traded company
  – Any equity in privately held or start up company

• Investigator can rebut this prohibition with compelling justification for an exception
Some “Rebuttable” Circumstances

- The conflicted investigator is uniquely qualified to conduct the study
- It serves the subjects’ interests to have conflicted investigator involved
- There is a plan/process for protecting the research from the introduction of bias
- There is a plan for efficiently passing expertise to other non-conflicted investigators
“Rebuttable” Management Strategies

Plans to protect research integrity include:

- PI not involved in recruitment, selection, consenting, or data analysis
- PI not allowed to do treatment except in rare cases of device development
- Data blinded and “locked” prior to analysis
- Inclusion of independent biostatistician on data analysis
- Other management approaches as needed
Unique Attributes of Physician-Inventor

- Often knows the device best
- Usually has most experience with device
- His/her 1st use in humans likely to be safest for pts
- Design modifications frequently come from 1st use experience
- They are *Never* objective about the device merits or results
Important Differences in Device vs. Drug Evaluation

• The skill and experience of physician investigator can strongly impact the outcome of device use

• A device may result in acute complication that requires an immediate and “creative” intervention

• Device trials at all stages are typically much smaller than drug trials – beginning with the First-in-Human trials

• Significant results from device use (good and bad) may be immediately apparent --and can lead to early and major changes in the device

• It is common (and useful) for a device to undergo iterative improvements even in the early stages of clinical testing
Some reasons to involve the device inventor in the early device evaluation in people

• There are often major, unanticipated issues as a device moves from bench and animal testing to the initial clinical trials

• The inventor may able to appreciate nuances of device function that someone less experienced with the device would miss

• The inventor is particularly well suited to make improvements on the device as a result of experience in the first clinical cases
Choices for Conflicted Investigator

- Divest to below the financial threshold
- Get others without conflict for key functions [PI, protocol director, etc.]
- Do not carry out the proposed investigation; leave it to others
- Make the case for unique circumstances [device inventor is 1° one]
- (Some PIs divest rather than give up the investigation)
First in Man Case

Dr. Jones created a novel “smart” catheter to more safely and efficiently clear occlusions of peripheral blood vessels. She filed patent applications on the device through her University OTL. A device manufacturer (Heart-a-Tech) took an exclusive license. Dr. Jones consults for H-a-T as an SAB member for which she earns $60,000/ year. She also has stock options currently worth $100,000.
First in Man Case

She now wishes to initiate a sponsored research contract with H-a-T to use the device in a phase 1 ‘first in man’ study enrolling 10 patients. She proposes that she should be allowed to do this study despite her FCOI since she is the most familiar with, and skilled in the use of, the new device. She proposes to select, consent, treat and evaluate the subjects as she knows most about how the device works.
First in Man Case: Questions

1. Does Dr. Jones present a compelling argument rebutting the prohibition of her involvement?

2. Should Dr. Jones be allowed to be protocol director on the study?

3. Should she be allowed to select patients for the study?

4. Should she be allowed to explain the study/consent to prospective patients?

5. Should she be allowed to do the procedure and if so, under what circumstances? Should she be allowed to evaluate the results of the procedure on the subject?

6. Should she be allowed to analyze the data on the trial after it has been gathered and/or be the primary (another) author of reports coming from the study?

7. Would she need to disclose her company relationship as inventor/consultant/owner with the subjects?
Safer Wafer Case

• Dr. Jefferson and Dr. Suarez have invented an implantable wafer containing chemotherapeutic agents believed to be active in treating brain tumors. Based on their animal studies they hypothesize that slow release of chemotherapy at the tumor site will extend the patient’s life and reduce toxicity. Drs. Jefferson and Suarez propose to be co-PIs on a Phase I safety study of the wafer in 10 patients.
Safer Wafer Case

• Drs. Jefferson and Suarez’s wafer was licensed by their University to NeuroX, a company founded by them. The University has taken equity in NeuroX and has a royalty agreement. At the time of licensing Dr. Jefferson bought out all of Dr. Suarez’s future financial interests in NeuroX, so Dr. Jefferson is the sole investigator with a financial interest in the technology now.

• NeuroX is funding this study as sponsored research.
Safer Wafer Case

- Given that both investigators invented the device and took it through animal studies is there a compelling justification for the involvement of one or both of them in this HSR?
- Are there risks posed by either investigator recruiting, selecting, consenting, or treating the subjects?
- In a limited safety study are there safeguards that can protect the subject and the data?
- Is Dr. Suarez, who no longer has any financial interests related to this technology, free of bias?
- Is there an institutional FCOI here and if so, how might it be handled?