

CONFLICTS OF INTEREST





Historical Evidences

- **1980- Massachusetts Eye and Ear Infirmary and Harvard Medical School-** Ophthalmology fellow trial on Vit-A based ointment for dry eye syndrome, he owned half million shares of company Spectra Pharmaceutical Services, his mentor also had stocks.
- More patients were enrolled than required, Fellow sold stock when he realized the product was ineffective



Examples

- **Duke's University -**

In 1999 OHRP had shut down Duke's University as Grant Officer was on IRB and should not be a voting member, and thus there was inadequate IRB supervision of human subject experiments

Fred Hutchinson Cancer Research Center (FHC), Seattle



- Researchers were charged with financial conflicts of interest related to a bone marrow transplantation study.
- Several key researchers including Nobel Prize winner Donald Thomas had stock shares in Genetic Systems
- FHC had financial relationships relating to commercial rights to antibodies produced by its researchers-
- 20 out of 82 patients died as a result of participation in study.



Jesse Gelsinger

- 1999- Death of 18 yr old male with genetic disorder that impairs ammonia metabolism
- Underwent gene therapy at University of Pennsylvania
- Injected with adenovirus carrying the gene - developed serious problems and died in 4 days
- Later it was found that
 - Two Rhesus monkeys had died in tests involving a gene delivery system similar to the one used with Jesse; four other human patients had suffered toxicity to their livers earlier in study
 - PI and Head of Instt had 30% shares in Genovo, pvt company producing the gene-altered adenovirus
 - Genovo was sponsoring research for its product.



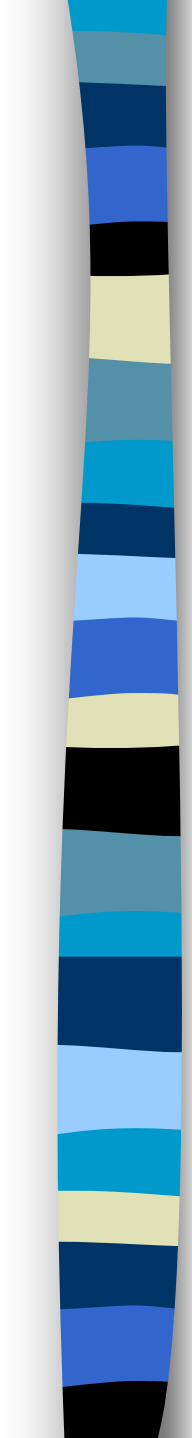
Critics Charge

- Academic Researchers are for sale !
- Multibillion dollar activity !
- Outcome of research is biased by academic-industrial liaisons !
- Quality of research is being challenged !
- Outcome of research may be prejudiced !
- Academia not driven by Altruistic societal mission!
- Highest standards of intellectual integrity !



What is happening

- Number of clinical trials is exploding
- Recruitment of large number of subjects to fill trials and expedite dissemination of results
- Faculty members commonly paid per participant recruited/ enrolled
- Awareness of institutional and personal incentives to generate income from clinical trials

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- Awareness is non-existent
 - It is important that we at least start thinking about it
 - Half the problem would be solved if their presence is recognized



Conflict of Interest

- Situations in which financial or other personal considerations may compromise, an investigator's professional judgment in conducting or reporting research.
- The bias such conflicts may affect
 - collection, analysis and interpretation of data, hiring of staff, procurement of materials, sharing of results, choice of protocol, and use of statistical methods.
- Conflicts of interest can affect other scholarly duties in both biomedical and behavioral research



Understanding Conflicts of Interest

- Any professional has a primary as well as a myriad of secondary interests
- A conflict of interest occurs when the secondary interests “unduly influence” the persons “professional judgments concerning a primary interest”



Medicine

- Three Primary Interests
 - Patient Health and well being
 - Clinical Research
 - Education of future health professionals
- Secondary Interests
 - Financial gain
 - promotion
 - grants for research
 - publication of research results
 - desire of fame
 - family obligations



Conflicts

- Secondary Interest are usually not illegitimate but frequently necessary and desirable
- Problem occurs when secondary interests dominate, unduly influence, distort, corrupt the integrity of a physician's judgment in relation to patients health, clinical research or medical education
- Fortune, fame, family preference threaten the integrity of the professional judgment

***Dennis F Thompson.
Understanding Financial Conflicts of Interest,
NEJM 329 (1993): 573-76***



COI

- COI are inherent/always present or exist
 - On one hand researchers are the guardians of public/patients interests and on other hand in making scientific advances and translating through industry
- COI cannot be totally eliminated but aim should be to minimize
- Management of COI very importance



Conflicts of Interest vs Conflicts of Commitment

■ COI

- between primary and secondary interests
- Secondary interests are not part of physician's duty
- Secondary interests should not influence on professional judgment

■ COC

- arises between primary interests
- e.g, caring of a patient and educating medical students and completing research study
- Not very problematic from ethical point of view



Risk Benefit Compromise ?

- Subjects safety may be compromised
- Knowledge produced may be biased to serve the interests of a few rather than those of the society and have long term adverse effects



Evaluating COI

- Probability that judgment will be distorted
 - If the secondary interest is small unlikely to corrupt decision making
 - Large financial incentive influence is great
- Potential magnitude of harm
 - If small or transient in nature, concern is less
 - Harm life threatening or disabling or lead to loss of public confidence, concern is heightened
- Difficult to determine when secondary influences have improper influence or not



Types of COI

■ Financial

- Stock Ownership
- Equities
- Consultancies
- Patent - licensing arrangements
- Research Grants with Pharma, or manufacturers of research products

■ Non-Financial

- Publications
- Promotion
- Peer recognition
- Grant renewals



Influences of Financial COI

- Which treatments to test ?
- Whether to have placebo?
- Endpoints of the trial
- Inclusion exclusion criteria
- Information in IC form and process
- Rules for stopping trial if efficacy proven or adverse events
- Whether clinical trial will be stopped due to evidence from other studies?
- Which eligible patients will be enrolled?

Baruch A. Brody.

“Conflicts of Interests and validity of clinical trials” in Conflicts of Interest in Clinical Practice and Research, ed Roy G Spece, David S Shimm, Allen E Buchanan (New york: Oxford University

Prerss, 1996), 407-17.



Researchers Conflicts of Interest

- Key issue to worry is that some interest might threaten
 - Valid research design
 - Data integrity
 - Patient safety
 - Dissemination of results



Key Questions

- Is there need to emphasize on financial COI ?
- Are COI new ?
- How frequent are they ?
- Do financial interests really compromise judgment ?
- Are patients worried about these ?
- What protections against adverse consequences should be in place ?



Financial COI

- Are not the only one, but the more dangerous ones
- Money as key motivating factor, the more the better
- Financial ties between researchers and industry in US (by Dr E.Emmanuel, NIH)
 - 34% occasional speaking engagements
 - 33% consulting arrangements
 - 32% paid position on board of directors
 - 14% equity in company- mean value \$100,000



Financial COI

- Investigator or immediate family have material interests in sponsoring company, including speaking fees, consultation fees, stock ownership, equity interests, patents, trademarks, copyrights, licensing agreements, Ownership in company
- Small interests under ~10,000\$ or <5% ownership for e.g., may not be considered to be COI
- Diversified mutual funds where shareholder has no control over the equities held by the fund do not present COI
- Financial interests of IEC member's spouses, partners, dependents should be also reported



Reviews and Meta-analysis

- Clinical trials and meta-analyses sponsored by drug companies favored the product produced by the funder
 - Lexchin et al. BMJ, 2003
- Conclusions of trials were significantly more likely to recommend the experimental drug as the treatment of choice if the trials were funded by for-profit organisations
 - Nielsen et al. JAMA 2003



Protections for Conflicts of Interest

- Small amounts may be acceptable
- Middle amounts need to be disclosed or watched
- Large amounts need to be prohibited
- Reducing the magnitude of harm is difficult but requires additional oversight



Conflict of Interest Policy

- 3 elements

- Requirement for regular disclosure to Institution of potential conflicts by faculty members with appropriate administrative scrutiny of financial interests
- Monitoring by a standing or specially appointed oversight committee
- Mechanism of granting exceptions to the policy when they are warranted by extraordinary circumstances

***Martin JB & Kasper DL,
In whose Best Interest? Breaching the Academic-Industrial Wall
NEJM 343 (2000): 1646-49***



Management Strategies

- Disclosure of all financial relationships-
to IEC, COI Committee, Subjects
 - Subjects may not understand how to interpret or act on the information
 - Information may create anxiety, distress, reducing confidence in participation



Management Strategies

- IEC to decide and manage,
- Oversight, (e.g., quarterly reports)
- DSMB (oversee protocol integrity, data analyses, safety),
- Re-assign responsibilities between investigators (change key roles-determining patient eligibility, obtaining IC, grading adverse events)



Management Strategies

- Prohibition- change researcher as the one with control over design should have no financial interests with sponsors
 - Or PI makes adequate plans for managing the financial and decision making conflicts



Other Remedies

- NEJM has a requirement
 - “Authors to disclose any financial arrangement with the company whose product figures prominently in the submitted manuscript or with the company making a competing product”
 - “Authors of such articles will not have significant financial interest in a company that makes a product discussed in the article”
- Many Universities in US-
 - disclosure policies and Conflicts of Interest Committees



Other Remedies

■ Mediation

- Placing financial incentives in a trust/ donation to Institutions for educational or research support, prevent funds be targeted to individuals

■ Elimination Approach

- “Investigators involved in post coronary artery by-pass graft (CABG) study will not buy, sell, or hold stock options in any companies providing or distributing medications under study”



Conflicts of Interest among Researchers

■ Conflict of Time

- May make a commitment but may not have enough time
- Investigators motivation/demotivation can affect subject safety



Conflict of Interest Committee

- Advisory Committee to advise
- > 5 members
 - COI acceptable without further action
 - Disclosure to subjects necessary
 - Controls need to be in place
 - extra monitoring, consent process performed by someone other than conflicted party, or other measures
 - Conflict is unacceptable and must be eliminated for research to proceed



Reviewing COI

- Are all relevant information concerning PI's activities been disclosed?
- Are financial interests excessive ?
- Is there an indication that research results have not been faithfully and accurately reported?
- Is there any indication that PI's professional role has favored any outside entity?
- Has the PI inappropriately represented the institution to outside entities?
- Does the PI appear to be subject to incentives that might lead to inappropriate bias?



Reviewing COI

- **Is the PI involved in a situation that might raise questions of bias, inappropriate use of university assets, poor data management?**
- **Could the PI's circumstances represent any possible violation of state, or local laws and requirements?**
- **Will the research work plan receive independent peer review prior to its initiation?**
- **Are there mechanisms in place to prevent the introduction of bias into research projects**



Reviewing COI

- **Will the project be supervised by someone with no conflicting interests?**
- **Are there means to verify research results (e.g., independent corroboration in another lab, FDA review)?**
- **Will data and materials be shared openly with independent researchers?**
- **Will the product of the collaborative effort with an outside party be published in the peer-reviewed scientific literature?**



Regulatory Framework

- Not well defined and concerns only data integrity
- Need for additional oversight
- No govt requirements on managing or disclosing COI
- No requirements coordinated with subject protections like IEC review or informed consent
- Institutions to develop their own mechanisms
- Recognition, Disclosure and management
 - The important point is recognition of COI and then decide on strategies for management



Conclusions

- With the growing links between clinical researchers and industry, conflicts of interests are likely to increase and occur in new situations so there is a need to craft better ways of regulating them
- Many potential conflicts of interest do not constitute actual conflicts or may be acceptable with proper oversight and safeguards.



Conclusions

- Implement a diverse set of principles:
 - maintaining academic freedom and an atmosphere that promotes free and open scholarly inquiry without bias;
 - facilitating the transfer of technology and other developments for the benefit of the public;
 - serving as the steward of public and private resources entrusted to it.



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