

PAST EVENTS GUIDES CONFLICTS OF INTEREST TODAY

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Cancer research hospital Seattle 1981 – 1993

- Researchers - trying to reduce graft versus host disease (GVHD) in bone marrow transplantation
- Protocol 126 – T cells were removed from the patient bone marrow (thought to cause GVHD)
- Eight antibodies were used to remove the T cells
- Outcome of study – over 12y 20 out of 82 died due to T cells depleted bone marrow failing to regraft and produce blood cells
- Conclusion - death direct result of participating in the study
- Several key researchers including the Nobel prize winner Donald Thomas had stock shares in Genetic systems (3 antibodies were produced by this company)

Gelsinger case - 1999

- Jesse Gelsinger: 18y, male
- Diagnosis: ornithine transcarbamylase deficiency
- Was in relatively good health using special diet and medications
- University of Pennsylvania's institute for human gene therapy – underwent gene transfer experiment – injected with adenovirus carrying gene for ornithine transcarbamylase (Genovo)
- Result: serious CVS /CNS problem
- Outcome – death in 4 days
- Principal investigator and head of the institute had substantial financial stake in Genovo
- Genovo was providing substantial funds to finance research at the institute for Human gene therapy

Massachusetts hospital and Harvard medical school – 1980s

- Clinical trial on vitamin A based ointment for dry eye syndrome
- Ophthalmologist owned half a million shares of the company manufacturing the ointment
- Fellow mentor also had stocks in the company
- Enrolled more patients than required in the trial
- Before results were published sold stocks
- Why?
- Few harms but violations of moral rights

Events led to guidelines

- January 2001: US office for human research protection issued interim guidelines on conflict of interest
- Executive council of the Association of American Medical Colleges approved the first report of its task force on financial conflicts of interest in clinical research

Guidelines – ? sufficient

- Some felt that they were not comprehensive
- Bekelman, Yan Li and Gross carried out a meta-analyses to review original, quantitative studies on the extent, impact, and management of financial conflicts of interest in biomedical research

Scope and Impact of Financial Conflicts of Interest in Biomedical Research JAMA, January 22/29, 2003—Vol 289, No. 4

Meta-analyses

- Search: MEDLINE (1980-2002), Web of Science citation database, references of articles, letters, commentaries, editorials, and books and by contacting experts - 1664 citations screened, 144 potentially eligible full articles retrieved
- 37 studies met criteria
- The main outcomes were the
 - prevalence of specific types of industry relationships
 - the relation between industry sponsorship and study outcome or investigator behavior
 - the process for disclosure, review, and management of financial conflicts of interest

Results of meta- analyses

- 1/4th of investigators have industry affiliations,
- 2/3^{rds} of academic institutions hold equity in start-ups that sponsor research performed at the same institutions.
- Eight articles evaluated 1140 original studies – statistically significant association between industry sponsorship and pro-industry conclusions (pooled Mantel-Haenszel odds ratio, 3.60; 95% confidence interval, 2.63-4.91).
- Industry sponsorship was also associated with restrictions on publication and data sharing.
- The approach to managing financial conflicts varied substantially across academic institutions and peer-reviewed journals.

Conflicts of interest

“a set of conditions in which professional judgment concerning a primary interest tends to be unduly influenced by a secondary interest”

Thompson D. Understanding financial conflicts of interest.
N Engl J Med. 1993;329:573-576.

Medical - Primary interests

- Patient health and well being
- Clinical research
- Medical education of future health professionals

Medical - secondary interests

- Financial gain
- Promotion
- Grant renewals for research
- Publication of research results in prominent journals
- Desire for fame
- Interest in avocational pursuits
- Family obligations
- Other hidden factors

Secondary interests

- They should not dominate / unduly influence /distort / corrupt the integrity of a physicians judgment in relation to primary interests
- Includes individual and his or her spouse and dependent children

Basic Conflicts Rule Includes:

- Spouse and minor children



- Your best friend



Conflicts of interest

Not equal, some greater concern than others -
sliding scale of conflicts of interests

Severity depends on 2 factors

- The probability that judgment will actually be distorted
- The potential magnitude of the harm

Least when the secondary interest is unlikely to corrupt decision making or when potential harm is transient or of small consequence

Indirect types of financial conflicts of interest

Paying physicians who are not investigators and not linked to the scientific aspects of research

Paying physicians to enroll patients in research studies

Some condemn double billing – paying the same physician for tasks that are not reimbursed such as submitting protocol for IRB approval, screening potential subjects, completing research forms, documenting outcomes, reporting adverse events

Indirect types of financial conflicts of interest contd

In USA it is possible for an investigator to get approximately USD 475,000 for enrolling 100 patients into a research study (Shimm and Spece) as un-reimbursed costs of clinical research

Finders fee – a financial incentive (or otherwise) for referring patients for enrollment

“ can pose a temptation to enter a patient into an experiment for which another treatment is more effective

Decisions in design and conduct of clinical research → conflicts of interest

Which treatments to test in the trial

Use placebo or an active control arm

Endpoints

Inclusion exclusion criteria

Information provided in informed consent form

Rules for stopping the trial

Whether clinical research will be stopped due to evidence from other clinical trials

Which eligible patient will be enrolled

Company sponsored trials - issues

Asserts control over the data –
researchers at University of California
attempted to publish data showing that a
new drug (HIV immunogen) to prevent
HIV was ineffective

Company refused to release the data to
the investigators and attempted to prevent
publication of negative result

Eventually published

Assessing conflicts of interest

Difficult for external observer to determine

Public confidence in the integrity of
professional judgment is important

Standard guidelines should be in place



Possible remedies

Remedy 1


- have guidelines in place – national and institutional both for basic and clinical research
- professional regulation by relevant associations
- Institutions should have clear policies, that address the reporting and management of conflicts of interest of IRB members

Remedy 2

- Make a formal disclosure of possible conflicts of interests. Now common practice
 - Most journals
 - Most universities
 - WHO
 - National committees
- Full disclosure to patients about source of funding and investigators potential conflict of interest in receiving industry funding for enrolling patients

Remedy 3 – Mediation

- Placing financial incentives in a blind trust or donating funds to institutions to use for educational purposes/ research
- Prohibitions



**Protecting Patients, Preserving
Integrity, Advancing Health:
Accelerating the Implementation of COI
Policies in Human Subjects Research**

***A Report of the AAMC-AAU Advisory Committee on Financial
Conflicts of Interest in Human Subjects Research***

February 2008

- Thank you

- You may not seek or accept
- directly or indirectly
- anything of value

