

*How to Make Good Clinical Trials*  
***How and What To Disclose:***  
*Conflict of Interest in Clinical Trial Conduct*

*Ted Feldman, M.D., FSCAI*

**Summit** Angioplasty **TCT Asia Pacific 2008**

Wednesday, April 23 ~ Friday, April 25, 2008

The Convention Center of Sheraton Walkerhill Hotel, Seoul, Korea



Ted Feldman MD, FACC, FSCAI

*Disclosure Information*

The following relationships exist:

Grant support: Abbott, Atritech, BSC, Cardiac Dimensions, Edwards,  
Evalve, Myocor, St Jude

Consultant: Abbott, Cardiac Dimensions, Coherex, Cordis, Myocor

Speaker: Boston Scientific

*Off label use of products and investigational devices  
will be discussed in this presentation*

# Industry Influence

- The pharmaceutical industry spends approximately \$12 billion annually on gifts and payments to physicians
- Pharmaceutical companies' share of funding for clinical trials is more than 70%
- The industry also shoulders more than half of the costs of formal programs of continuing medical education

- Katz D, Caplan AL, Merz JF. All gifts large and small: toward an understanding of the ethics of pharmaceutical industry gift-giving. *Am J Bioeth* 2003;3:39-46
- Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003;289:454-465.
- DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ* 2003;22:151-185.
- Bodenheimer T. Uneasy alliance: clinical investigators and the pharmaceutical industry. *N Engl J Med* 2000;342:1539-1544.
- Morin K, Rakatansky H, Riddick FA Jr, et al. Managing conflicts of interest in the conduct of clinical trials. *JAMA* 2002;287:78-84.
- Greider K. The big fix: how the pharmaceutical industry rips off American consumers. New York: Public Affairs, 2003.
- Relman AS. Defending professional independence: ACCME's proposed new guidelines for commercial support of CME. *JAMA* 2003;289:2418-2420.
- Steinman MA, Shlipak MG, McPhee SJ. Of principles and pens: attitudes and practices of medicine housestaff toward pharmaceutical industry promotions. *Am J Med* 2001;110:551-557.
- Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? *JAMA* 2000;283:373-380.

# The New York Times

## Diagnosis: Conflict of Interest

By DANIEL CARLAT  
Published: June 13, 2007

Boston

THE revelation that the heart disease is the latest disappointment. Violated the risks for \$750 million to settle the Food and Drug Administration.

While those criticisms continue medical education doctors how to practice result, dangerous side

Most states require the medical education each of these courses were provided has changed drastically

Essentially, this is a new twist on that well-known instrument of corruption, money laundering. Drug companies don't directly pay doctors to teach courses. Instead, they pay someone else to cut the checks. Similarly, the drug companies don't explicitly tell doctors to say good things about their products. Instead, they hire a company to write good things about their products and to pay doctors to deliver the messages.

These shenanigans were recently spotlighted by Senator Max Baucus, Democrat of Montana, and Senator Charles Grassley, Republican of Iowa, of the Senate Finance Committee. In April, their committee released a report, two years in the making, concluding that drug companies have used educational grants unethically as a way of marketing their products.

In response, the guidelines regarding commercial support for continuing medical education are being reviewed. The solution could hardly be simpler: any continuing medical education that is paid for by the drug industry should not be accredited. Drug companies could still pay for any educational event, article or pamphlet they choose, but their courses and materials would no longer bear the imprimatur and implied credibility of accreditation.

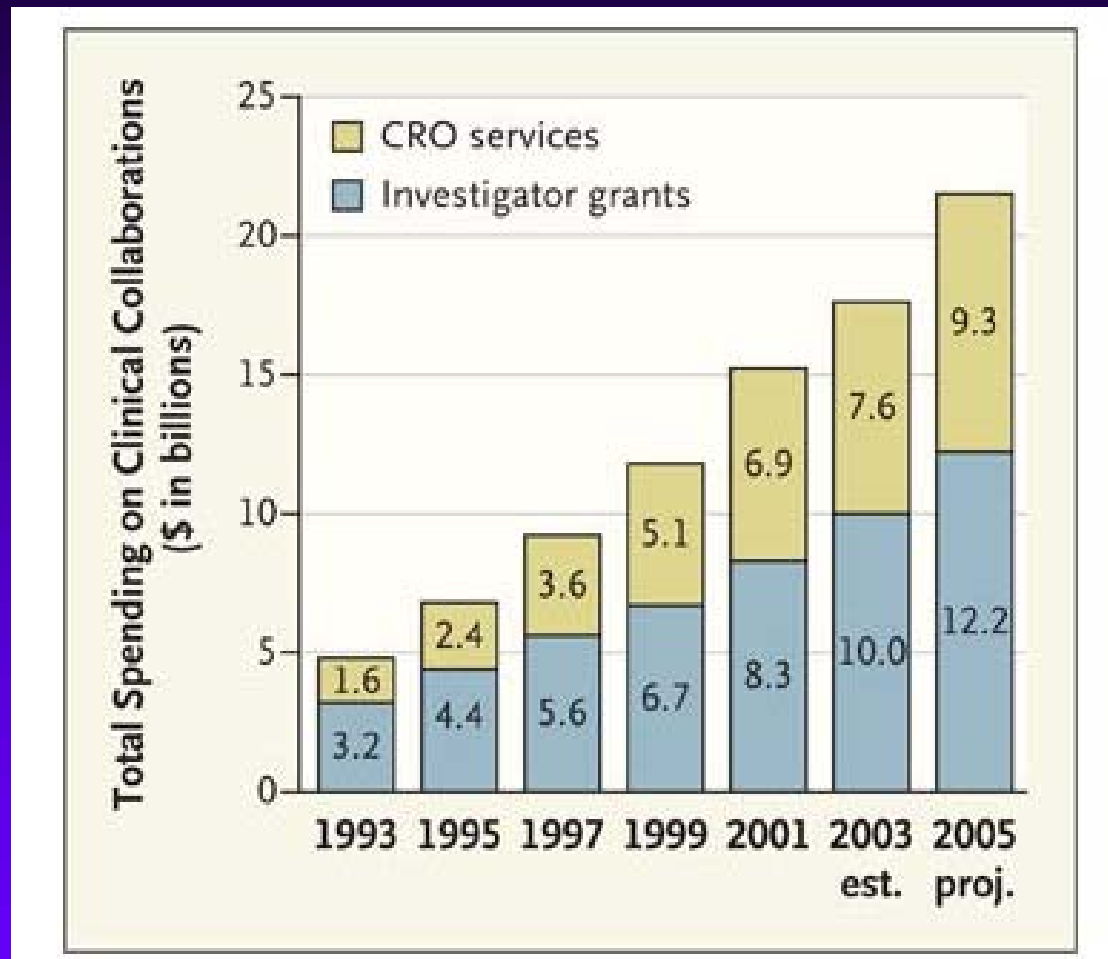
According to the most recent data available from the national organization in charge of accrediting the courses, drug-industry financing of continuing medical education has





## Commercializing Clinical Trials

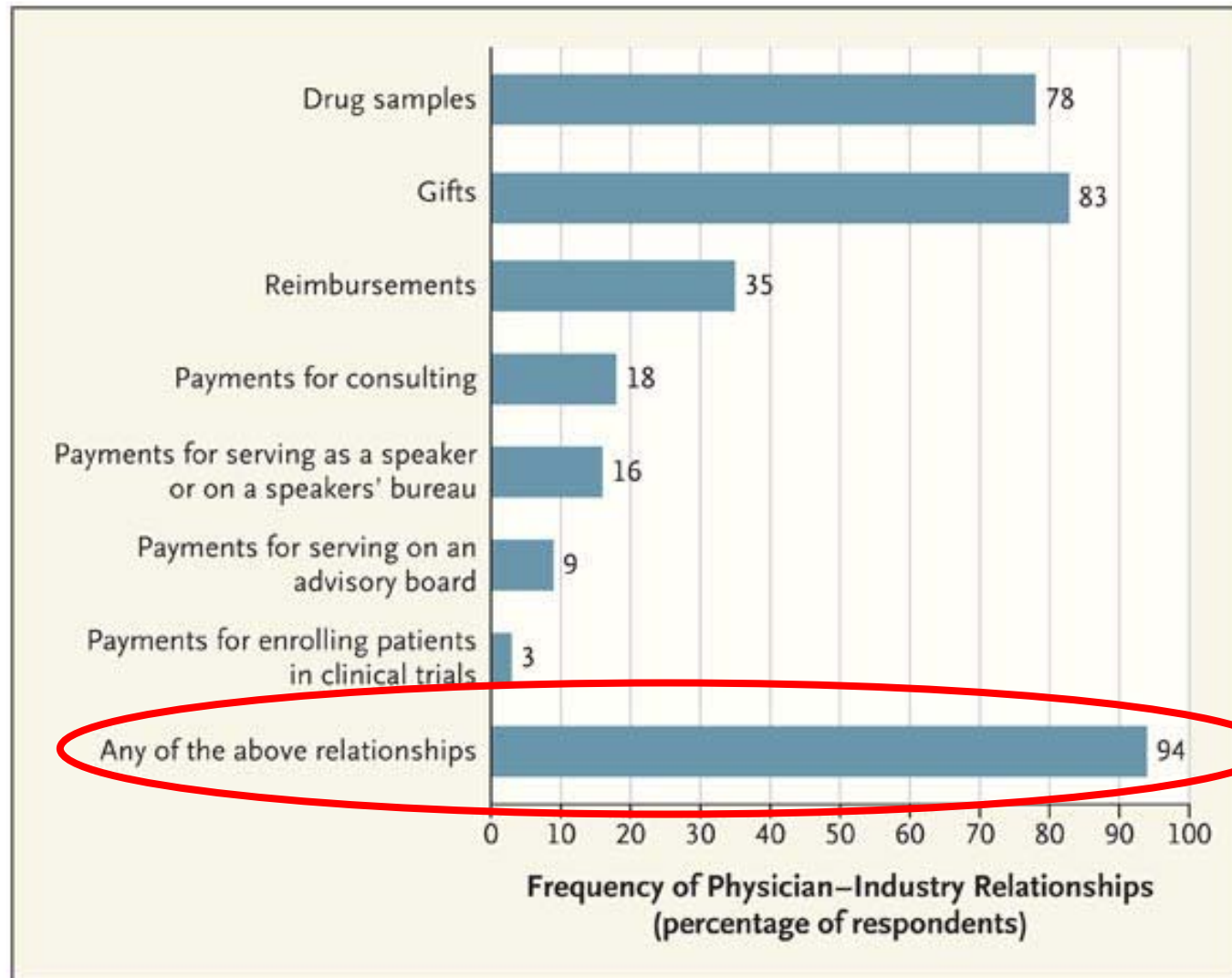
### *Risks and Benefits of the CRO Boom*



Total Spending on Clinical Collaborations by Member Companies of the Pharmaceutical Research and Manufacturers of America



## Frequency of Various Types of Physician-Industry Influences



# Industry gifts to physicians

Receiving gifts is associated with positive physician attitudes toward pharmaceutical representatives.

Physicians who request additions to hospital formularies are more likely to have accepted free meals or travel funds from drug manufacturers.

The rate of drug prescriptions by physicians increases after they see sales representatives, attend company-supported symposia, or accept samples.

A systematic review of the medical literature on gifting found that an overwhelming majority of interactions had negative results on clinical care.

Sandberg WSet al. The effect of educational gifts from pharmaceutical firms on medical students' recall of company names of products. Acad Med. 1997;72:916–918.

Brotzman GL, Mark DH. Policies regulating the activities of pharmaceutical representatives in residency programs. J Fam Pract. 1992;34:54–57.

Chren MM, Landefeld CS. Physicians' behavior and their interactions with drug companies: a controlled study of physicians who requested additions to a hospital drug formulary. JAMA. 1994;271:684–689.

Lurie N, Rich EC, Simpson DE, et al. Pharmaceutical representatives in academic medical centers. J Gen Intern Med. 1990;5:240–243.

Orlowski JP, Wateska L. The effects of pharmaceutical firm enticements on physician prescribing patterns: there's no such thing as a free lunch. Chest. 1992;102:270–273.

Peay MY, Peay ER. The role of commercial sources in the adoption of a new drug. Soc Sci Med. 1988;26:1183–1189.

Cleary JD. Impact of pharmaceutical sales representatives on physician antibiotic prescribing. J Pharm Technol. 1992;8:27–29.

Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? JAMA. 2000;283:373–380.

Wall LL, Brown D. The high cost of free lunch Obstetrics & Gynecology. 110(1):169-73, 2007



# Areas for Conflicts of Interest

- Patient care
- Institutional
- Educational programs & CME credit
  - Accreditation Council for Continuing Medical Education (ACCME)
- Professional organizations
  - SCAI, etc
- Clinical Trials
  - Steering committee, Trial PI
  - Site investigator
  - presenter



Conflicts in clinical practice are the least discussed...



"Under disclosure rules, I'm required to tell you I own stock in the company whose drug I'm prescribing."

## Conflict-of-interest concerns raised over Cleveland Clinic doctor who led drug study

Posted by [Harlan Spector](#) April 07, 2008 19:59PM

Categories: [Breaking News](#), [Business Impact](#), [Impact](#), [News Impact](#)

When Dr. Steven Nissen, the Cleveland Clinic's top heart doctor, exposed to the world that the diabetes drug Avandia increased the risk of heart attack, he was working on behalf of the maker of a competing drug, Actos.

Should it have been disclosed to readers of the New England Journal of Medicine (NEJM), which published the Avandia findings, that Nissen also was leading a study financed by Actos maker Takeda Pharmaceutical Co.



About the Avandia study published last May, Steiner said he was concerned that Nissen and a colleague "wrote such a harshly critical article and did not inform the readers that they were 'under contract' with the prime competitor."

that showed Actos offered a heart benefit.

About the Avandia study published last May, Steiner said he was concerned that Nissen and a colleague "wrote such a harshly critical article and did not inform the readers that they were 'under contract' with the prime competitor."

Nissen and a spokeswoman for the journal said he followed disclosure policies. The article listed several pharmaceutical companies that pay for research at the Clinic, including Takeda Pharmaceuticals.

“A conflict of interest occurs when there is a divergence between an individual's private interests and his or her professional obligations to [the institution] such that an independent observer might reasonably question whether the individual's professional actions or decisions are determined by considerations of personal gain, financial or otherwise. A conflict of interest depends on the situation, and not on the character or actions of the individual.”



# Federal regulation of educational activities

**Elements of the federal government have indicated the importance of this independence. In 1997, the FDA wrote:**

*"The FDA has not regulated and does not intend to regulate ... Industry Supported Scientific and Educational Activities that are independent of the influence of the supporting company. Companies and providers who wish to insure that their activities will not be subject to regulation should design and carry out their activities free from the supporting companies' influence and bias . . ."*

**In 2003, the Office of Inspector General of the U.S. Department of Health and Human Services wrote:**

*"... grants or support for educational activities sponsored and organized by medical professional organizations raise little risk of fraud or abuse, provided that the grant or support is not restricted or conditioned with respect to content or faculty . . . Codes of conduct promulgated by the CME industry may provide a useful starting point for manufacturers when reviewing their CME"*



Accreditation Council for Continuing Medical Education ACCME

# Values Underlying the ACCME Standards for Commercial Support

- 1. Accredited CME providers must place a higher priority on the health and well being of the public than on individuals' personal economic interests.
- 2. Some people in CME have personal economic interests derived from financial relationships with commercial interests that create a personal sense of duty or loyalty to the commercial interest.
- 3. Some financial relationships with commercial interests are important enough to conflict with the person's responsibility to CME learners and to conflict with the public interest.
- 4. If a person in CME has a conflict of interest, the CME provider must manage the conflict in a manner that is in the best interest of the public.



## Accreditation Council for Continuing Medical Education ACCME

- **The ACCME Standards for Commercial Support:** voluntary self-regulation
- 2004 Standards for Commercial Support
- Six Standards:
  - (1) independence,
  - (2) resolution of personal conflicts of interest,
  - (3) appropriate use of commercial support,
  - (4) appropriate management of associated commercial promotion,
  - (5) content and format without commercial bias, and
  - (6) disclosures relevant to potential commercial bias.



Accreditation Council for Continuing Medical Education ACCME

# STANDARD 1: Independence

**1.1** A CME provider must ensure that the following decisions were made free of the control of a commercial interest.

- a) Identification of CME needs;
- b) Determination of educational objectives;
- c) Selection and presentation of content;
- d) Selection of all persons and organizations that control content of the CME;
- e) Selection of educational methods;
- f) Evaluation of the activity.

**1.2** A commercial interest cannot take the role of non-accredited partner in a joint sponsorship relationship.





Accreditation Council for Continuing Medical Education ACCME

## STANDARD 2: Resolution of Personal Conflicts of Interest

- 2.1 The provider must be able to show that **everyone** who is in a position to control the content of an education activity **has disclosed** all relevant financial relationships with any commercial interest to the provider.
  - *The ACCME defines “relevant” financial relationships as financial relationships in any amount occurring within the past 12 months that create a conflict of interest.*
- 2.2 An individual who **refuses to disclose** relevant financial relationships will be disqualified from being a planning committee member, a teacher, or an author of CME, and cannot have control of, or responsibility for, the development, management, presentation or evaluation of the CME activity.
- 2.3 The provider must have implemented a mechanism to identify and **resolve all conflicts of interest prior** to the education activity being delivered to learners



Accreditation Council for Continuing Medical Education ACCME

- STANDARD 3: Appropriate Use of Commercial Support
- STANDARD 4. Appropriate Management of Associated Commercial Promotion
- STANDARD 5. Content and Format without Commercial Bias



Accreditation Council for Continuing Medical Education ACCME

## **STANDARD 6. Disclosures of Potential Commercial Bias**

- **6.1** An individual must disclose to learners any relevant financial relationship(s), to include the following information:
  - The name of the individual;
  - The name of the commercial interest(s);
  - The nature of the relationship the person has with each commercial interest.
- **6.2** For an individual with no relevant financial relationship(s) the learners must be informed that no relevant financial relationship(s) exist.

### **Commercial support for the CME activity.**

- **6.3** The source of all support from commercial interests must be disclosed
- **6.4** 'Disclosure' must never include a trade name or a product-group message.

### **Timing of disclosure**

- **6.5** A provider must disclose prior to the beginning of the educational activity.



- Code of Federal Regulations
- Responsibility for Promoting Objectivity in Research
- Institutional responsibility
  - (a) Maintain an appropriate written, enforced policy
  - (b) Designate an institutional official to solicit & review financial disclosure statements
  - (c) Require that each Investigator submits Significant Financial Interests (and those of his/her spouse and dependent children):
    - (i) reasonably appear to be affected by the research for which PHS funding is sought
    - (ii) In entities whose financial interests would reasonably appear to be affected by the research.
  - (d) Provide guidelines to identify conflicts and take actions to manage, reduce, or eliminate conflicts.
  - (f) Establish adequate enforcement mechanisms and provide for sanctions where appropriate.





## Responsibility of Applicants: Management of conflicting interests

- *A conflict exists when a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the PHS-funded research.*
- Examples of conditions or restrictions that might be imposed to manage conflicts of interest include, but are not limited to:
  - (1) Public disclosure of significant financial interests;
  - (2) Monitoring of research by independent reviewers;
  - (3) Modification of the research plan;
  - (4) Disqualification from participation in all or a portion of the research funded by the PHS;
  - (5) Divestiture of significant financial interests; or
  - (6) Severance of relationships that create actual or potential conflicts.



- **Which financial interests do I need to disclose?**
- The regulation requires the disclosure of all “Significant Financial Interests”
  - (1) that would reasonably appear to be affected by the research for which funding is sought from the NIH; and
  - (2) in entities whose financial interests would reasonably appear to be affected by the research need to be disclosed to your Institution.



A "Significant Financial Interest" is defined by the regulation as anything of monetary value, **including** but not limited to:

- salary or other payments for services (e.g., consulting fees or honoraria);
- equity interests (e.g., stocks, stock options or other ownership interests);
- intellectual property rights (e.g., patents, copyrights and royalties from such rights).



The term does **not** include:

- salary, royalties, or other remuneration from the Institution;
- any ownership interests in the Institution, if the Institution is an applicant under Phase I of the SBIR and STTR programs;
- income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities;
- income from service on advisory committees or review panels for public or nonprofit entities;
- an equity interest that, when aggregated for the Investigator and the Investigator's spouse and dependent children, does not exceed \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a five percent ownership interest in any single entity;
- salary, royalties or other payments that when aggregated for the Investigator and the Investigator's spouse and dependent children over the next twelve months, are not expected to exceed \$10,000.





- **What about enforcement mechanisms and/or sanctions?**  
Each Institution is required to establish adequate enforcement mechanisms and provide for sanctions where appropriate; however, the Institution may determine the nature of the enforcement mechanisms and sanctions.
- Examples of conditions or restrictions that might be imposed to manage conflicts of interest include, but are not limited to:
  - public disclosure of Significant Financial Interests;
  - monitoring of research by independent reviewers;
  - modification of the research plan;
  - disqualification from participation in all or a portion of the research funded by the NIH;
  - divestiture of Significant Financial Interests; or
  - severance of relationships that create actual or potential conflicts.

## When in doubt, disclose



See Comment page 355 and  
Department of Error page 370

When do a researcher's financial or personal interests constitute a conflict that warrants disclosure? Financial interests are the easiest to recognise, but other interests can be more subtle. The desire to advance professionally or to defend an idea one believes in deeply can undermine objectivity as much as a financial stake.

The safest course is to identify and disclose any interest that could undermine the credibility of the research. The decision by Athena Kolbe not to disclose to *The Lancet* that she was the author of two papers cited in her article written under the pen name Lyn Duff opened her work to attacks that could have been, if not prevented, blunted by disclosure.

Could more explicit conflict of interest guidelines be of help to authors? Right now, guidelines vary from journal to journal and are constantly being revised, either because they are felt to be too strict or not strict enough. A more systematic approach may be in order.

A paper in the current issue of *IRB: Ethics & Human Research* describes one such approach. The paper presents model language for disclosing the

financial interests of participants in clinical research. Surprisingly, few institutions have standard language for disclosing such conflicts. The model was developed by the Conflict of Interest Notification Study (COINS), a project funded by the US National Heart, Lung and Blood Institute.

Working with institutional review boards and conflict of interest committees, the COINS team identified nine major forms of financial conflicts of interest, including salary support, payment of finder's fees, and the holding of a patent or ownership of equity. They then drew up draft disclosure statements that were not only reviewed by experts but also presented to potential research participants and focus groups. The responses were used to draw up a statement that could be adapted to suit different situations.

Their method was a thoughtful and systematic approach that could be adapted to draw up other models for conflict of interest statements, including, perhaps, one for publication. In the meantime, the best rule remains "when in doubt, disclose". ■ *The Lancet*

See Weinfurt KP  
*IRB: Ethics & Human Research*  
2007; 29: 105.



## Dancing with the porcupine

*Armstrong and Yusuf go head-to-head over industry's role in research funding*

- competing interests of each of the players
  - Industry follows a "better, faster, cheaper" model
  - investigators concerned with quality, ethics, scholarship, and the public eye.
- extreme lack of government funding for clinical research
- Industry funding fills a void that has been created by an abdication of responsibility by peer-review funding bodies
  - privatization of research with emphasis on marketing
  - trials designed to establish equivalency instead of superiority
  - for-profit clinical research organizations (CROs) play a bigger role
- Collaboration of industry and academia has led to health benefits that outweigh the real and perceived dangers

# Has the hunt for conflicts of interest gone too far?

- strangely, financial transactions between patients, insurance companies, hospitals, and doctors, encompassing 85% of the medical marketplace, do not count as conflicts of interest
- conflict of interest policies exclude the best experts from providing education and advice
- private companies bring new products to patients and medical care has improved steadily and spectacularly because of them
- no evidence supports that corporate detailing and gifting adversely affect patient care

# Conflicts of interest in clinical research: *opprobrium\* or obsession?*

the case in favour of full disclosure rests on three large fallacies

- 1<sup>st</sup> fallacy of objectivity, the notion that scientific writing can be free from the common prejudices found in other literatures or journalism—or that if prejudice does exist it can be easily neutralised by a statement of disclosure
- second fallacy—that it is financial conflicts of interest which “cause the most concern”. Financial conflicts may be the easiest to identify but they may not be the most influential. Academic, personal, and political rivalries and beliefs are less easily recognised, but each may affect an interpretation
- third fallacy is that disclosure can heal the wound inflicted by a financial conflict.

\*cause of shame or disgrace

*The Lancet 1997; 349:1112-1113*



# Non-Financial Investigator Interests

- Professional status (eg, personal, departmental, or institutional)
- Research funding
- Patient-related (eg, as a personal physician; payment for study recruitment)
- Institutional (eg, ethics committee)
- Grant-related
- Regulatory (eg, FDA)
- Scientific publication
- Mass media
- Legal (eg, patent protection)
- Sociopolitical
- Public interest (eg, research support through taxes, charitable)

## *Conflict of interest:*

### Disclosure is not enough to offset betrayal of trust

- The basic problem with conflict of interest is betrayal of trust. If you engage in a form of relationship that would cause the average reasonable onlooker to lose trust in your independent scientific judgment, you do not magically regain that trust simply through disclosure.

Brody, Howard. *Hooked: Ethics, the Medical Profession, and the Pharmaceutical Industry*. Lanham MD. Rowman and Littlefield, January 2007.

Perhaps part of the difficulty with conflict of interest lies in the phrase itself, which has disparaging connotations. The *Annals of Internal Medicine* uses the term “**dual commitment**” and asks authors to disclose these to editors. *The Lancet's* policy is much the same.