Built in Bias

How Conflicts of Interest Pervade the Health Industry and What is Being Done About It

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Pharmaceutical and medical device companies receive intense criticism for their marketing practices and untoward consequences of their products.

Physicians working in clinical research and their organizations have been tainted as well. These problems lead to loss of confidence in the medical and translational research enterprise.

There is enough blame for everyone.
University-industry collaborations continue to be crucial to achieve a continued high degree of technological innovation in biology and medicine, blurring roles between academic research and the commercial world.

The resources for innovation will involve government, philanthropy and industry, with industry playing an increasingly important role.

This means that extraordinary care has to be taken to preserve the objectivity of research and development in medicine.
Proposition

The clinical research enterprise has a built-in bias toward more diagnoses and more treatments.

This is what our society has wanted and may still want.

This talk relates to the impacts of conflicts of interest (COI)s fueled mainly by money derived from selling those drugs and devices.
Americans Want the Latest Thing
How the Health Industry is Sometimes Perceived
Recognition

The Federal Government, AAMC, and Academic Medical Centers are progressively recognizing the insidious effects of COIs in:

1. Research
2. Education, mainly continuing education
3. Health care

and are trying to do something about them.
Definitions

**Interest**

An interest may be defined as a commitment, goal, or value held by an individual or an institution.

**Conflict of Interest (COI)**

A conflict of interest occurs when two or more contradictory interests relate to an activity by an individual or an institution. The conflict lies in the situation, not in any behavior or lack of behavior of the individual.
“Situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator’s judgment in conducting or reporting research.”

AAMC, 1990

“A conflict of interest in research exists when the individual has interests in the outcome of the research that may lead to a personal advantage and that might therefore, in actuality or appearance compromise the integrity of the research.”

NAS, Integrity in Scientific Research

Avoid the appearance of wrongdoing
The financial circumstances underlying COIs of concern in research are not entirely a bad thing. They motivate innovation and they are inevitable in the real world.

They have to be disclosed and managed
Institutional COIs

Equity in startups

Taking money aimed at subverting freedom to publish

Arrangements with companies to support research with first right to license resulting technologies.

Interest in clinical research outcomes

Allowing donors to distort mission
Institutional COIs

Penn – Jesse Gelsinger case
NIH – Sanctioned major conflicts of top personnel
Johns Hopkins – Cosmedicine
Harvard – Licensing privileges
Va. Commonwealth – Gave up academic freedom to a tobacco company
BP grants to co-opt marine biologists
Disclosure

In research, the people who need to know about the COI are the research participants and those who interpret the results of a study.

The decision about disclosure of a COI should never be left to the possessors of the COI because they are susceptible to self-deception or worse about the influence of the COI on them.
Bias Is Hard to Spot in Ourselves

The human capacity for self-deception is infinite.

Korenman, 2004
## Reporting Requirements

<table>
<thead>
<tr>
<th></th>
<th>Income</th>
<th>Equity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>500</td>
<td>2,000</td>
</tr>
<tr>
<td>Feds</td>
<td>10,000</td>
<td>10,000 or &gt; 5% of Company</td>
</tr>
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</table>

School of Med: all outside activities
Disclosure should be strengthened but not to the point where people know what actually is going on.

Disclosure To Participants

Widespread

Can have perverse effects

• Affects willingness to say no

• May limit liability
Systematic Bias Due to COIs

Basic scientists – push toward drug development
Clinical trial study design – for FDA approval
Investigators co-opted voluntarily to be supporters
“Thought leaders” become paid enthusiasts
Preparation of publication
Journal review
FDA approval process
Professional Societies
Databases for meta-analysis
Clinical practice guidelines
Continuing medical education
Marketing
Sponsored trials are designed to prove the validity of the proposed benefit. Comparison of pharmaceutically-sponsored versus NIH-supported clinical studies indicates a substantially higher frequency of success for the sponsored studies.

To some degree this may be a comparison of apples and oranges because the NIH studies include attempts to resolve disputes.
Phase III Clinical Trial

The acid test
Negotiated with FDA
Agreed upon statistical power
Sponsor tries for narrowest possible scope
Focus on primary end point
25% of investigators have industry affiliations. And two thirds of academic institutions hold equity in start-ups that sponsor research at the institution. Industry sponsorship is associated with a statistically significant increase in favorable conclusion. Odds Ratio 3.60, (2.63-4.91)

Bekelman et al, 2003, JAMA 289:454
IRB Members and Industry

IRB members sometimes participate in discussions of protocols in which they have interests in the sponsor or a competitor of the sponsor.

Removing persons with interests from IRBs is not likely to improve the review process.

Disclosure at the time of review and recusal are critical.

Cambell, EG et al 2006 NEJM; 355:2321
Phase Three Trial Investigators

Are or become experts
Become consultants
Join speaker’s bureaus “Key Opinion Leaders”
Become advocates
Sometimes behave badly

Martinson et al, Nature 2005; 435:737
Pharma’s Thought Leaders
<table>
<thead>
<tr>
<th>Key Opinion Leaders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practices</td>
</tr>
<tr>
<td>Professor</td>
</tr>
<tr>
<td>Presence</td>
</tr>
<tr>
<td>Payroll</td>
</tr>
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</table>
Physician Payments

<table>
<thead>
<tr>
<th>Company</th>
<th>Payments (in million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eli Lilly</td>
<td>$124.7</td>
</tr>
<tr>
<td>GSK</td>
<td>86.9</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>22.8</td>
</tr>
<tr>
<td>Pfizer</td>
<td>19.8</td>
</tr>
<tr>
<td>Merck</td>
<td>9.4</td>
</tr>
<tr>
<td>J &amp; J</td>
<td>5.2</td>
</tr>
<tr>
<td>Cephalon</td>
<td>13</td>
</tr>
</tbody>
</table>

Keep in mind that our database only includes the seven companies that have disclosed payments nationwide. The provider may or may not get money from companies not included in this database.

propublica.org
## Distribution of 2007 Company Payments

<table>
<thead>
<tr>
<th>Company</th>
<th>Total Value of Payments to All Individuals</th>
<th>Median Value of Payments to Individuals</th>
<th>Total Value of Payments of ≥$1 Million</th>
<th>Mean Value of Payments of ≥$1 Million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomet</td>
<td>$19,148,000</td>
<td>$13,000</td>
<td>$7,175,000</td>
<td>$1,794,000</td>
</tr>
<tr>
<td>DePuy</td>
<td>4,734,600</td>
<td>9,000</td>
<td>31,663,000</td>
<td>4,523,000</td>
</tr>
<tr>
<td>Smith &amp; Nephew</td>
<td>19,296,000</td>
<td>22,000</td>
<td>12,663,000</td>
<td>2,533,000</td>
</tr>
<tr>
<td>Stryker</td>
<td>36,906,000</td>
<td>38,000</td>
<td>19,149,000</td>
<td>2,394,000</td>
</tr>
<tr>
<td>Zimmer</td>
<td>61,049,000</td>
<td>18,000</td>
<td>43,408,000</td>
<td>2,412,000</td>
</tr>
<tr>
<td>Total</td>
<td>183,744,000</td>
<td>18,000</td>
<td>11,405,700</td>
<td>2,716,000</td>
</tr>
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</table>
### Number of Publications and Disclosures of Payment of $1 Million or More per Company

<table>
<thead>
<tr>
<th>Company</th>
<th>Articles in Sample Written By Payment Recipients</th>
<th>Articles in Sample Identifying Company Name</th>
<th>Articles in Sample Disclosing Payment “Exceeds $10,000”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomet</td>
<td>8</td>
<td>6 (75)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>DePuy</td>
<td>19</td>
<td>10 (53)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Smith &amp; Nephew</td>
<td>9</td>
<td>3 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Stryker</td>
<td>17</td>
<td>12 (71)</td>
<td>0</td>
</tr>
<tr>
<td>Zimmer</td>
<td>38</td>
<td>10 (26)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>41 (45)</td>
<td>7 (8)</td>
</tr>
</tbody>
</table>

Data and Safety Monitoring Boards (DSMB)s

Enhance objectivity, protect participants.

Power to stop trials for **efficacy** or **safety**

Knowledgeable members,

No COIs
Preparing Papers for Submission

- Requires considerable skill.
- Science must satisfy reviewers.
- Artfully written so that physicians will focus on the benefits and not on the risks.
- In fact, the abstract, which is the only part many physicians read, might not mention adverse effects at all, as occurred in the Vioxx trial.
Sponsors still often do the statistical analysis in-house and engage a writing company to compose the paper.

Investigators are still sometimes sent a completed manuscript and asked whether they would like to sign on as an author.

Those practices were banned by the most prestigious journals in 2005.
New Conflict Rules at Leading Medical Journals

International Committee of Medical Journal Editors
Oct. 2009

Broad array of financial disclosures including relatives.

Include consulting work, Medicallegal activities, grants, payments for manuscript preparation, patents and royalties going back three years

Includes non-financial COIs as well
Implementation of the ICMJE Form for Reporting Potential Conflicts of Interest

Beginning Nov 1, 2010

Concept is “what a reader might wish to know”

Identifying Information

Work under consideration (funding sources)

Any relevant financial activities outside of the submitted work (36 mos. prior to submission).

Any other relationships or activities that a reader would wish to know about that might have influenced the authors.
Publication Bias

Burying negative results  Many examples: SmithKline-Beecham study of Paxil in teenagers.

Trial registration
Sec 801 of FDA Amendments Act
Must register summary protocol, population, design, outcome measures, recruitment, location and contacts for new agents and devices, and old ones for a new use
Not for existing approved drugs
Adverse events
Technical or lay summaries, complete protocol, other information
Huge results database now available
Recognizes for the first time the FDA’s critical role in assuring the safe and appropriate use of drugs after they are marketed. Tries to make safety after release as strong as regulations before release.

Includes imported products and devices.

“Promotional speech” vs Education
Failures of Gatekeepers of Science

JAMA – Overestimation of deaths due to obesity
Science – retraction of 2 Hwang Woo Suk papers
Lancet – retracted data on NSAIDS and oral Ca
NEJM – Statement of concern on Vioxx
Ann Int Med – retracted Poelman postmenopause
Journals also have conflicts of interest. The best journals compete ferociously. Besides prestige and readership, publishing successful clinical trials generates huge numbers of reprint orders. In the case of Vioxx, 904,000 reprints were ordered at substantial profit to the NEJM.

Armstrong, D 2006 NY Times 5/15
Moral Responsibility of Journals

Such is the power of the leading journals that they have a great responsibility to the profession and the public to maintain the very highest publication standards including to reveal COIs.

They must find ways to admit errors.

Professional Societies

Once the fountainhead of the newest and best research and clinical care information
Now undertake complex and expensive tasks
  Influencing legislation
  Supporting trainees
  Carrying out dialogue with the NIH, the media and the public.
  Producing a sophisticated multifaceted meeting
  Providing additional educational programs

Professional societies now depend on income from drug and device companies for survival
Commercial Income

May unbalance the science and bias education including highly biased CME segments.

Foster over-the-top media presentations

Permit biased articles and supplements in their journals.

Sponsor biased clinical practice guidelines.

AAMC Council of Academic Societies working on this.
Bias Is Hard to Spot in Ourselves

The human capacity for self-deception is infinite.

Korenman, 2004
Clinical Practice Guidelines

33% of authors have financial COIs
50% of guidelines had no COI documentation
34% of guidelines stated no COIs
50% had at least one author receiving research support
43% had at least one author who had been a speaker for the company

Derived from National Guideline Database Nature, Oct 20, 2005

No evidence found that guidelines improve outcomes, but they do change process somewhat.
Gifts to Doctors

Proposed U.S. Bill:
Drug and device manufacturers would need to publicly disclose all doctor payments and gifts exceeding $100 per year in a national database. Built into health care reform.

Serious penalties to PhARMA

Universities now have to disclose to the NIH etc. if the faculty does not tell them – what to do?
Grassleying Psych

Psychiatrists get lots of money from drug Cos. to promote treatments. Vermont. Average $56,000

Some fail to report earnings as required.

Psychiatrists set up companies including president of the APA valued at 4.8 mil.

APA get 30% of its funding from Pharma, some for ads and some as donations.

The problem is bias!
Psychiatry Prof. and Department Chair Alan Schatzberg has stepped down from his position as principal investigator on a federal research grant, following what has now been six months of Congressional scrutiny regarding the professor’s financial ties to the drug industry.
Reporting COIs In Research

NIH issued new guidelines now undergoing comment 7/21/2010.

Investigators must reveal significant financial interests (amount to be determined).

Institution will decide with the investigator which ones to reveal for each NIH study.

Institutional policies and performance subject to audit and penalties.

Problem: Sponsors revealing payments; very difficult to reconcile with institutional data.

Processes must be improved at great expense.

What’s Going On in CME

FDA now active in post-approval oversight:
Promotional material vs education with enforcement powers.
Institutions are banning memberships in speaker’s bureaus
Educational programs have to demonstrate independence of sponsors for CME approval. Still too easy to get CME approval.
Marketing Approaches

Speaker’s bureaus
Trying to enhance indications
(hypertension, diabetes, hyperlipidemia, sepsis)
Sometimes promoting off label use (illegal)
Funding and seeding practice guideline committees
Sponsoring continuing education in many tricky ways
Courting care providers
Financing meetings,
Meals, sampling
Direct advertising to patients

What’s Going On In Clinical Care

Keeping detail persons out of clinical areas.
Eliminating gifts large and small (meals)
Limiting sampling
Trying to develop objective approaches to training clinical teams in the use of devices.

Problem: A huge outpouring of E-invitations to participate in questionnaires, discussions or “educational” programs on the use of relevant drugs.
Innovation and Interdependence

University-industry collaborations continue to be crucial to achieve a continued high degree of technological innovation in biology and medicine, blurring roles between academic research and the commercial world.

The resources for innovation will involve government, philanthropy and industry, with industry playing an increasingly important role.

This means that extraordinary care has to be taken to preserve the objectivity of research and development in medicine.
PhRMA’s New Code

1. We provide information that is useful for patient diagnosis and care and that is good.
2. We will not bribe people as companies but will continue to ask consultants for help.
3. We will support education and research by providing support for organizations.
4. We support disclosure of financial funding by us.
5. We don’t give out little things any more.
6. We train reps to be very ethical.
7. We will report adherence to the Code.
Most big PhARMA get in trouble because of excesses of their marketing divisions. Examples are everywhere. But marketing makes the profits that fund the research.

Top management needs to better control marketing with an eye to the overall consequences of recurrent bad behavior.
Americans Want the Latest Thing
Remediations from Academia

1. Tighter COI policies
2. Firewalls between institutional management and industry relations with strong rules.
3. More emphasis on research integrity rather than profitability
Systematic Bias Due to COIs

Basic scientists – push toward drug development
Clinical trial study design –
Investigators co-opted (voluntarily)
“Thought leaders” become paid enthusiasts
Preparation of publication
Journal review
FDA approval process
Professional Societies
Databases for meta-analysis
Clinical practice guidelines
Continuing medical education
Marketing

DSMB
New Rules for Faculty Behavior
New transparency rules for publication.
Enhanced post-approval monitoring
Study registration
More attention to COIs
Assuring objectivity, faculty limits
FDA, Watch dogs and media
Society has concluded that drug and device companies are fiduciaries for the public just as doctors are fiduciaries for their patients.

“One party, the beneficiary, entrusts the other with discretionary power over some interests and the other, the fiduciary, exercises that power in the beneficiary’s interest.”

Miller, P 2006 Fiduciary Obligation in Clin Res. 34:424
Where we fall down

Companies tend to talk the talk but do they walk the walk?

Academia tends to talk the talk, but do they walk the walk?
Bias Is Hard to Spot in Ourselves

The human capacity for self-deception is infinite.

Korenman, 2004
Marcia Angell Big Pharma – Bad Medicine

- Academia’s roles blurred
- Pharma don’t have education budgets, they have marketing budgets
- Pharma gave up most of their R&D work to academia and biotech companies and just buy what they want
- Academe depends on Pharma to survive

May 2010 Bostonreview.net/BR35.3/angell.php