Built in Bias

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

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Perception = Reality

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.
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.
Institutional COIs as Well as Individual 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 not 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
Systematic Bias Due to COIs

Basic scientists – irreproducibility of results suggests bias
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
Basic Science Irreproducibility

Ioannides, J: Why most published Research Findings are False. PLOS Med 2e124;2005 Positive Bias!

Begley, Amgen Nature 483, 531,2012: Comment: 53 foundational basic science articles on cancer were only reproducible 11% of the time. But they generated much additional research including clinical trials. Sloppy and Positive Bias

<table>
<thead>
<tr>
<th>REPRODUCIBILITY OF RESEARCH FINDINGS</th>
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<tbody>
<tr>
<td>Preclinical research generates many secondary publications, even when results cannot be reproduced.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Journal impact factor</th>
<th>Number of articles</th>
<th>Mean number of citations of non-reproduced articles*</th>
<th>Mean number of citations of reproduced articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20</td>
<td>21</td>
<td>248 (range 3–800)</td>
<td>231 (range 82–519)</td>
</tr>
<tr>
<td>5–19</td>
<td>32</td>
<td>169 (range 6–1,909)</td>
<td>13 (range 3–24)</td>
</tr>
</tbody>
</table>
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 – and if p > .05 --
Safety quite secondary
### Key Opinion Leaders

<table>
<thead>
<tr>
<th>Practices</th>
<th>Uses the drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor</td>
<td>Looks the part</td>
</tr>
<tr>
<td>Presence</td>
<td>Enthusiastic and energetic</td>
</tr>
<tr>
<td>Payroll</td>
<td>30% of marketing budget</td>
</tr>
</tbody>
</table>
Gifts to Doctors

Proposed U.S. Bill:

Drug and device manufacturers must 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 have to disclose to the NIH re COIs of NIH awardees and to the public if asked.
Physician Payments

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.

<table>
<thead>
<tr>
<th>Company</th>
<th>Amount (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>

As of July 2011, Payments = to 763 million from 12 companies. Go to Propublica.org to learn about a specific doctor.
Last week we published a big update to Dollars for Docs, our interactive news application of payments made to U.S. healthcare providers by 15 pharmaceutical companies. Compared to when we launched the project in 2010, the amount of data we’re collecting has grown enormously: The list of payments increased from around 750,000 to almost 2 million, and the grand total of the payments grew from around $750 million to just under $2 billion.

Compiling the data for it has been an enormous project right from the beginning. This year’s update took more than eight months of full-time work by me, working with other news-app developers. It was a massive effort and presented huge technical and journalistic challenges.
## Payments by Device Companies


<table>
<thead>
<tr>
<th>Company</th>
<th>Total Value of Payments millions</th>
<th>Total Payments of &gt;1 Million millions</th>
<th>Articles by Recipients No.</th>
<th>Articles with Company Name No. (%)</th>
<th>Articles Disclosing Payment “Exceeds $10,000” No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomet</td>
<td>$19,148</td>
<td>$7,175</td>
<td>8</td>
<td>6 (75)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>DePuy</td>
<td>47,346</td>
<td>31,663</td>
<td>19</td>
<td>10 (53)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Smith &amp; Nephew</td>
<td>19,296</td>
<td>12,663</td>
<td>9</td>
<td>3 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Stryker</td>
<td>36,906</td>
<td>19,149</td>
<td>17</td>
<td>12 (71)</td>
<td>0</td>
</tr>
<tr>
<td>Zimmer</td>
<td>61,049</td>
<td>43,408</td>
<td>38</td>
<td>10 (26)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>183,744</td>
<td>114,057</td>
<td>91</td>
<td>41 (45)</td>
<td>7 (8)</td>
</tr>
</tbody>
</table>
Data and Safety Monitoring Boards (DSMB)s

- No COIs, Enhances objectivity, protects participants.
- Knowledgeable
- Power to stop trials for **efficacy** or **safety**
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.
New Conflict Rules at Leading Medical Journals

International Committee of Medical Journal Editors
Oct. 2009

Broad array of financial disclosures including close relatives.

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

Includes non-financial COIs as well
Publication Bias

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

Trial registration: clinical trials.gov

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.

Adverse events

Lay summary
Role of FDA H.R. 3580, the FDAAA Sept. 2007

Recognizes 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

However, many COIs in FDA deliberations
Annals of Internal Medicine
Established in 1927 by the American College of Physicians

THE LANCET

JAMA
The Journal of the American Medical Association
September 2, 1992

The NEW ENGLAND JOURNAL of MEDICINE

AMERICAN ASSOCIATION FOR THE
ADVANCEMENT OF

SCIENCE
6 January 1989
Vol. 243 • Pages 1–140
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
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
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.
## Reported FCOI among Panel Members by Category of Guideline Sponsor

Neuman, J et al BMJ2011;343:d5621

### All Guidelines

<table>
<thead>
<tr>
<th>Guideline Type</th>
<th>#</th>
<th>% with COI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>7</td>
<td>56</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>Government</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>69</td>
</tr>
<tr>
<td>US specialty</td>
<td>4</td>
<td>58</td>
</tr>
<tr>
<td>Canadian specialty</td>
<td>2</td>
<td>83</td>
</tr>
</tbody>
</table>

### Guidelines with declared COI

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</thead>
<tbody>
<tr>
<td>Diabetes</td>
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</tr>
<tr>
<td>Other</td>
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**CHOLESTEROL OVERHAUL**

**NEW STATIN GUIDELINES FROM YOUR BIG PHARMA FRIENDS**

**CHECK YOUR PULSE. IF YOU HAVE ONE, YOU SHOULD BE TAKING STATIN DRUGS.**

**CANCEL THE GYM MEMBERSHIP YOU DON'T USE AND SPEND THAT MONEY ON A PRESCRIPTION YOU DON'T NEED.**

**WIPE DOWN THE COUNTER WHEN YOU'RE DONE.**

**STATINS SHOULD BE RECLASSIFIED AS A SCHEDULE 1 CONDIMENT.**

**ALTHOUGH CHEMICALLY IDENTICAL, GENERIC STATIN DRUGS WON'T MAKE YOU AS COOL AS THE MORE EXPENSIVE NAME BRANDS WILL.**

**FACE IT, YOUR KIDS WON'T EXERCISE, SO START THEM ON STATINS EARLY.**

**LET'S MOVE ... TO THE PHARMACY.**

**STATINS SHOULD BE SERVED AS THE MAIN COURSE AT EVERYONE'S THANKSGIVING DINNER.**

**WARNING: THESE GUIDELINES SHOULD BE IGNORED ONCE THEY ARE NO LONGER PROFITABLE TO THE DRUG INDUSTRY.**

**WE FOUND A BETTER DRUG ... FOR OUR SHAREHOLDERS, THAT IS.**

**NAME BRAND: COOL DUDE WITH LOW CHOLESTEROL.**

**GENERIC: NERD WITH LOW CHOLESTEROL.**
Reporting COIs In Research

NIH issued new guidelines.

Investigators must reveal significant financial interests related to their employment.

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.
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.
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.
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