CONFLICTS OF INTEREST IN MEDICAL RESEARCH: Facts and Friction

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Financial Disclosure

• NO NOT NEVER
Definition of conflict of interest

• Main Entry: conflict of interest
  Date: 1850
  “Conflict between the private interests and the official responsibilities of a person in a position of trust”

  – Merriam-Websters Collegiate Dictionary
  http://www.m-w.com/cgi-bin/dictionary
Conflicts of Interest

- May be perceived or real, potential or actual, inconsequential or harmful.
- Are ubiquitous and inevitable
- Differ from conflict of commitments (competing demands on a person’s time/resources)
Investigators/Authors and Reviewers

- Career Advancement
- Peer Recognition
- Competing Research Interests
- Competition for Research Grants
- Garnering High Profile Publication
- Intellectual Biases/Passions
- Financial
Editors

Promotion of Journal or Self

- Improve Impact Factor
- Increase subscriptions
- Increase financial profitability
- Eliminate or decrease stress, hostility or harassment
Financial Conflicts of Interest

- Any paid affiliation or financial involvement with any entity with an interest in the subject of or materials in the study
- Pervasive
- Increasing
- Intense Scrutiny
Financial Conflicts of Interest

- Payment / Remuneration
- Material / Financial interest
- Affiliations
- Consultancies
- Competing interests
- Current, recent, remote, future
Science and profit
Are they partners or enemies?
Increased Scrutiny

- Skeptical Public
- High Profile Lapses of Business Ethics
- Transformation of Research Enterprise
  - Privatization of Biomedical Research
- Financial Self-interests of Investigators
- Increased Awareness and Attention in Biomedicine
Literature on Conflicts of Interest

- Focus on Industry - Investigator Relationships
- Ethical Considerations
- Issues of Influence
## Leader of the Lobby Push

### 1999-2000 Political Spending in Millions

<table>
<thead>
<tr>
<th>Industry</th>
<th>Lobbying</th>
<th>Campaign Contributions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>$177</td>
<td>20</td>
<td>$197</td>
</tr>
<tr>
<td>Insurance</td>
<td>128</td>
<td>41</td>
<td>169</td>
</tr>
<tr>
<td>Telephone companies</td>
<td>123</td>
<td>21</td>
<td>144</td>
</tr>
<tr>
<td>Electric companies</td>
<td>120</td>
<td>19</td>
<td>139</td>
</tr>
<tr>
<td>Commercial banks</td>
<td>66</td>
<td>25</td>
<td>91</td>
</tr>
<tr>
<td>Oil &amp; Gas producers</td>
<td>31</td>
<td>33</td>
<td>64</td>
</tr>
<tr>
<td>Automobile manufacturers</td>
<td>55</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>Tobacco</td>
<td>45</td>
<td>8</td>
<td>53</td>
</tr>
<tr>
<td>Food processors &amp; manufacturers</td>
<td>21</td>
<td>14</td>
<td>35</td>
</tr>
</tbody>
</table>
Pharmaceutical US Promotional Spending

# Table 1. Funding for Biomedical Research by Source, 1994-2004

<table>
<thead>
<tr>
<th>Data Source</th>
<th>1994 (100)</th>
<th>1995 (100)</th>
<th>1996 (100)</th>
<th>1997 (100)</th>
<th>1998 (100)</th>
<th>1999 (100)</th>
<th>2000 (100)</th>
<th>2001 (100)</th>
<th>2002 (100)</th>
<th>2003 (100)</th>
<th>2004 (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other federal</td>
<td>Calculation*</td>
<td>2.1 (6)</td>
<td>2.3 (6)</td>
<td>2.2 (5)</td>
<td>2.1 (4)</td>
<td>2.4 (5)</td>
<td>3.4 (6)</td>
<td>5.2 (7)</td>
<td>6.7 (8)</td>
<td>7.6 (8)</td>
<td>6.9 (7)</td>
</tr>
<tr>
<td>State and local government</td>
<td>US Department of Health and Human Services</td>
<td>2.3 (6)</td>
<td>2.5 (6)</td>
<td>2.7 (6)</td>
<td>2.8 (6)</td>
<td>3.0 (6)</td>
<td>3.2 (6)</td>
<td>3.5 (5)</td>
<td>3.7 (5)</td>
<td>4.0 (4)</td>
<td>4.3 (5)</td>
</tr>
<tr>
<td>Foundations, charities, and other private funds</td>
<td>US Department of Health and Human Services</td>
<td>1.4 (4)</td>
<td>1.4 (3)</td>
<td>1.6 (4)</td>
<td>1.6 (3)</td>
<td>2.0 (4)</td>
<td>2.1 (4)</td>
<td>3.4 (5)</td>
<td>2.6 (3)</td>
<td>2.6 (3)</td>
<td>2.5 (3)</td>
</tr>
<tr>
<td>Pharmaceutical firms</td>
<td>Pharmaceutical Research and Manufacturers of America</td>
<td>11.1 (30)</td>
<td>11.9 (30)</td>
<td>13.6 (32)</td>
<td>15.5 (33)</td>
<td>17.1 (32)</td>
<td>18.5 (32)</td>
<td>21.4 (30)</td>
<td>23.5 (30)</td>
<td>25.7 (28)</td>
<td>27.0 (29)</td>
</tr>
<tr>
<td>Biotechnology firms</td>
<td>Biotechnology Industry Organization</td>
<td>7.0 (19)</td>
<td>7.7 (19)</td>
<td>7.9 (18)</td>
<td>9.0 (19)</td>
<td>10.6 (20)</td>
<td>10.7 (18)</td>
<td>14.2 (20)</td>
<td>15.7 (20)</td>
<td>20.5 (23)</td>
<td>17.9 (19)</td>
</tr>
<tr>
<td>Medical device firms</td>
<td>Benchmark study published in In Vivo; Boston Consulting Group</td>
<td>2.7 (7)</td>
<td>3.4 (8)</td>
<td>3.8 (9)</td>
<td>4.4 (9)</td>
<td>4.7 (9)</td>
<td>5.3 (9)</td>
<td>6.3 (9)</td>
<td>7.3 (9)</td>
<td>8.25 (9)</td>
<td>9.2 (10)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>37.1 (100)</td>
<td>40.1 (100)</td>
<td>43.1 (100)</td>
<td>47.6 (100)</td>
<td>52.9 (100)</td>
<td>58.2 (100)</td>
<td>71.0 (100)</td>
<td>79.4 (100)</td>
<td>90.9 (100)</td>
<td>94.3 (100)</td>
<td>94.5</td>
</tr>
<tr>
<td>Adjusted total†</td>
<td>47.8</td>
<td>50.3</td>
<td>53.1</td>
<td>57.6</td>
<td>62.6</td>
<td>66.9</td>
<td>78.9</td>
<td>85.1</td>
<td>94.6</td>
<td>94.3</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.
*Estimated as the difference between total federal funding and funding for the National Institutes for Health.
†Adjusted by the Biomedical Research and Development Price Index.
‡Budgeted spending, actual not available until late 2005.
$Actual spending data not available until late 2005.

Funding for Biomedical Research by Source, 1994-2003
Why Does it Matter?

- Financial Interests / Relationships Can:
  - Bias *what* authors publish
  - Affect *when*, *how*, and in some cases, *if* research is published
Scope of Financial Interests

- Systematic review - 37 studies
- Prevalence - 1 in 4 investigators have industry affiliations
- Association between industry sponsorship and pro-industry conclusions (OR 3.6)

- Berkelman et al JAMA. 2003;289:454-465
Why Does It Matter?
Financial Interests and Study

Conclusions

• Authors who supported use of calcium channel blockers were more likely than neutral or critical authors to have financial relationships with manufacturers (96% vs 60% vs 37%).
  Stelfox et al. *NEJM* 1998;338:101

• Industry sponsored studies of cancer drugs reached unfavorable conclusions much less often than studies with nonprofit funding (5% vs 38%).
  Frieberg et al. *JAMA* 1999;282:1453
Financial Interests & Recommendations
192 authors of 44 practice guidelines, 1991-1999

- 59% - Had relationship with companies whose drugs were in the guideline
- 7% - Believed relationship influenced personal recommendations
- 19% - Believed relationship influenced colleague’s recommendations

Delay of Publication
Study of 2,157 life science faculty in top 50 NIH-funded Universities, 1995

19.8% of respondents delayed publication of articles for more than 6 months to serve proprietary needs:

- to allow for patent application or negotiation
- to protect scientific lead
- to slow dissemination of undesired results
- to resolve intellectual property ownership disputes

Suppression of Results

- Legal action to suppress / delay publication

- Olivieri - Deferiprone (iron chelation therapy) worsened hepatic fibrosis - company delayed publication 3 years (NEJM. 2002;347:1368)
Suppression of Results

• Dong - Synthroid shown to be bioequivalent to generic thyroxine - company delayed publication 3 years (“Thyroid Storm” *JAMA*. 1997;277:1238)

• Kahn - HIV Immunogen not effective - company sued UCSF for $8M over publication; arbitration ruling in favor of university (*JAMA*. 2000;284:2193)
Deliberate Lying

Class Study

• Celecoxib associated with lower incidence of gastric ulcers and ulcer complications combined

• BUT only reported 6 months data when author had 12 months data. Lied to us.  
  (JAMA. 2000;284:1247)

Clarification letters and reply  
  (JAMA. 2001;286:2398)
Sponsor Termination of Research

- CONVINCE Trial - Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (*JAMA*. 2003;289:2073)
- 16,602 hypertensive patients (1996-98)
- Sponsor terminated trial “for commercial reasons” - 2 years early
- Violation of Pact with Patients and Investigators
Potential FDA Approval

• Muraglitazar: billion dollar oral drug to control blood glucose and triglycerides
• Sept 8, 2005 FDA Advisory Committee voted 8:1 to approve
• Early October, 2005 press conference by pharmaceutical company to announce probable approval letter with clarification
• October 20, 2005 JAMA publication on line
• November, 2005 pharmaceutical company withdraws request for approval
HIDE BAD NEWS

VIGOR (Vioxx Gastrointestinal Outcomes Research) Trial

Expression of Concern
Curfman GD, Morrissey S and Drazen JM

Expression of Concern Reaffirmed
Curfman GD, Morrissey S and Drazen JM
*N Eng J Med* 2006; 354:1193
FACTORICATION

Patient-Specific Embryonic Stem Cell Derived From Human SCNT Blastocysts
Hwang WS et al.
*Science* 2005;308:1777

Expression of Concern
Kennedy D
*Science* 2006;311:36
Whether or not warranted, the total result arouses public concerns and threatens the credibility of biomedical research.
“Conflict of interest for a given manuscript exists when a participant in the peer review and publication process — author, reviewer, and editor — has ties to activities that could inappropriately influence his or her judgment, whether or not judgment is in fact affected.”

- ICMJE. http://www.icmje.org/
Disclosure of Financial Interests

- Prospective, complete, detailed
- During course of the study and up to time of publication
- Past and future considerations
- “When in doubt, disclose.”
Reporting Financial Aspects of Research

• Source of Funding
• Individual Financial Interests
• Must be Transparent to Reader
• Enables Interpretation in Light of Financial Information
• Essential to Merit Public Trust

DeAngelis C. *JAMA* 2006;296:996-998
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* I certify that all financial and material support for this research and work are clearly identified in the manuscript.

* I certify that all my affiliations with or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties) with any organization or entity with a financial interest in or financial conflict with the subject matter of materials disclosed in the manuscript are disclosed completely here: ________________________________

or are disclosed in an attachment.

* I have no relevant financial interests in this manuscript.
Industry-Investigator Relationships

- Who designed the study?
- Who controls the data?
- Who performs the statistical analysis?
- Who are the authors?
- Who controls publication?
Publication of Industry Sponsored Research

- Funding source / support clear and complete
- Role of the sponsor in study
- Disclosure of contributions of employees
- An Academic Researcher must indicate that:
  “Dr X, as principal investigator of the XYZ study, had access to all of the data and takes full responsibility for the integrity of the data and the accuracy of the data analysis.”
Conclusions

• Financial interests are ubiquitous
• Involve researchers, authors, reviewers, and editors
• Policies on disclosure are essential and must ensure transparent reporting
• Managing conflicts of interest appropriately is essential to ensure the Public’s Trust