“Promotion Bias” in Clinical Research

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Clinical Research Under Suspicion

• Groundswell of skepticism in the medical community, spreading to the public, about industry-funded clinical medical research. Why?
  – Perceived conflicts of interest among scientists, primarily physician researchers.

• One initiative to address such concerns:
  – pre-publication review and reanalysis of industry-sponsored studies by academic statisticians.

• This initiative, adopted by and now advocated universally by *JAMA: The Journal of the American Medical Association*, the world’s largest circulation medical journal, is understandably problematic for industry biostatisticians.
Clinical Research Under Suspicion

Less widely recognized:

The circumstances prompting it
  – pose ethical challenges to Statistics as a profession
  – call for discipline-wide responses
Outline

• What is “promotion bias”?

• Forms of and evidence for promotion bias in clinical medical science.

• Ramifications for the biostatistical community?

  All highly-condensed.

• Caution: Not a Manichean, few villains, not on a high horse “search and destroy mission.”
Promotion bias

• Distortion of the production and communication of scientific information, and/or misrepresentation of its source(s), by the commingling of marketing and clinical investigation.

• Such commingling generates
  – directional pressures on scientific reporting, and
  – perceptions of conflict-of-interest

• Claim: risk of promotion bias is high in complex organizational settings with diffused responsibility.
The Nature of Conflict of Interest (COI)

• Multidimensional, including financial conflicts and desires
  – prestige, and to feel useful.
  – protect job or please superior.
  – support a scientific group, grant application, or student.
  – help friends and colleagues succeed.

• Potential present in all work environments

• American Association of Medical Colleges (AAMC) definition equates actual conflict and appearance of conflict.
  – COI can be inherent in an environment.

• Inevitably, scrutiny/enforcement emphasizes the measurable, hence financial issues.
Professional context and societal expectations of marketing and clinical scientific research

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The Clinical Research COI Problem

• Perceived selective data suppression
  – Medical journal editors “found themselves playing a game of research hide-and-seek….”
    Jeffrey Drazen, Editor-in-Chief
    *New England Journal of Medicine (NEJM)*
  – “In one sense, all journals are bought—or at least cleverly used—by the pharmaceutical industry.”
    Richard Smith, Former Editor
    *British Medical Journal (BMJ)*
  – “We were burned very badly.”
    Catherine D’Angelis, Editor-in-Chief
    *Journal of the American Medical Association (JAMA)*
  – “The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols….”
    Chan, Hrobjartsson, Haahr, Gøtzsche, Altman, JAMA 2004;291.
Lack of Trust: Selective Data Reporting (Publication and/or FDA Submission)

Safety

– Cyclooxygenase-2 (Cox2) inhibitors (Vioxx)
– Selective serotonin reuptake inhibitors (SSRIs)
– Implantable Cardioverter-Defibrillators
– Aprotinin (peri-operative anti-clotting agent)

Efficacy

– Cox2 inhibitor (Celebrex)
– Thyroxine bioequivalence (“Thyroid Storm”)
– HIV-1 Immunogen Trial (Study 806)
Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.
Lack of Trust: January 2008

“Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall.”
Lack of Trust: January 2008

• Among the 11 studies published as positive that the FDA viewed as negative or questionable

“Although for each of these studies the finding with respect to the primary outcome was nonsignificant, each publication highlighted a positive result as if it were the primary outcome. The nonsignificant results for the prespecified primary outcomes were either subordinated to nonprimary positive outcomes (in two reports) or omitted (in nine).”
Lack of Trust: January 2008

- 22 unpublished studies

“…since the protocols were written according to international guidelines for efficacy studies and were carried out by companies with ample financial and human resources, to be fair to the people who put themselves at risk to participate, a cogent public reason should be given for failure to publish.”

Cleveland Clinic
Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment
A Case Study Based on Documents From Rofecoxib Litigation

Sponsors have a marketing interest to represent their products in the best light. This approach conflicts with scientific standards that require the symmetric and comparable reporting of safety and efficacy data. Selective reporting of the results of clinical trials can misrepresent the risk-benefit profile of drugs. We summarize how the sponsor represented...
In contrast, in April 2001, the company’s internal intention-to-treat analyses of pooled data from these 2 trials identified a significant increase in total mortality (hazard ratio [HR], 4.43; 95% CI, 1.26-15.53 for protocol 091, and HR, 2.55; 95% CI, 1.17-5.56 for protocol 078), with overall mortality of 34 deaths among 1069 rofecoxib patients and 12 deaths among 1078 placebo patients (HR, 2.99; 95% CI, 1.55-5.77). These mortality analyses were neither provided to the FDA nor made public in a timely fashion.
The data submitted by the sponsor to the FDA in a Safety Update Report in July 2001 used on-treatment analysis methods (which) … minimized the appearance of any mortality risk.

In December 2001, when the FDA raised safety questions about the submitted safety data, the sponsor did not bring these issues to an institutional review board for review and revealed that there was no data and safety monitoring board for the protocol 078 study.
Lack of Trust: Selective Reporting

• Perception that physicians are deprived by industry of data, especially safety data, needed for patient care.

• Stakes?
  – Synthroid’s manufacturer settled class action lawsuit for $135 million. But gain from publication delay from retained share of $600 billion/year market, and related sale price of company, thought far higher.
  
  – During 5+ years on US market, estimated ~100,000 excess Vioxx-associated heart attacks, ~30-40% fatal. (From associate director, US FDA's office of drug safety)
Lack of Trust: Science as Marketing

• Seeding trials
  – Products of marketing departments.
  – Address medically minor or marketing-specific questions.
  – Pay 100s to 1000s of physicians to enroll patients in trials of company product.
  – Use fairly few patients per physician.
  – Empirically, influence physicians to adopt the company’s product.
  – Priorities:
    ❖ drug dissemination high
    ❖ results dissemination low
Lack of Trust: Science as Marketing

• Ghost authorships
  – Late involvement of academics as primary authors for studies conceived, executed, and interpreted by sponsor.
  – Papers largely written by sponsor or retained medical writing/communications/public relations firm.
  – Research programs may export serial publications this way. Responsibility for data analyses in ghost authored manuscripts is implicitly accepted by and attributed to the academic authors, though really attributable to sponsor ghost authors.
Lack of Trust: Science as Marketing

• ADVANTAGE: A ghost-authored seeding trial.
  – Refocoxib (Vioxx) vs. naproxen (Naprosyn).
  – 600 clinical investigators recruited.
  – The paper, controversially, excluded 3 of 8 Vioxx-associated cardiovascular deaths, of which the first author was not informed.

• First author:

  “[The sponsor] designed the trial, paid for the trial, ran the trial… [The sponsor] came to me after the study was completed and said, ‘We want your help to work on the paper.’ The initial paper was written at [the sponsor], and then it was sent to me for editing… Basically, I went with the cardiovascular data that was presented to me.”
Guest Authorship and Ghostwriting in Publications Related to Rofecoxib
A Case Study of Industry Documents From Rofecoxib Litigation

Joseph S. Ross, MD, MHS
Kevin P. Hill, MD, MHS
David S. Egilman, MD, MPH
Harlan M. Krumholz, MD, SM

Context  Authorship in biomedical publication provides recognition and establishes accountability and responsibility. Recent litigation related to rofecoxib provided a unique opportunity to examine guest authorship and ghostwriting, practices that have been suspected in biomedical publication but for which there is little documentation.

Objective  To characterize different types and the extent of guest authorship and ghostwriting in 1 case study.
“This case-study review of industry documents demonstrates that clinical trial manuscripts related to rofecoxib were authored by sponsor employees but often attributed first authorship to academically affiliated investigators who did not always disclose industry financial support. Review manuscripts were often prepared by unacknowledged authors and subsequently attributed authorship to academically affiliated investigators who often did not disclose industry financial support.”
So is this unusual, and where do we fit in?

Ghost Authorship in Industry-Initiated Randomised Trials

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Background

Ghost authorship, the failure to name, as an author, an individual who has made substantial contributions to an article, may result in lack of accountability. The prevalence and nature of ghost authorship in industry-initiated randomised trials is not known.
“We found evidence of ghost authorship for 33 trials (75%; 95% confidence interval 60%–87%). The prevalence of ghost authorship was increased to 91% (40 of 44 articles; 95% confidence interval 78%–98%) when we included cases where a person qualifying for authorship was acknowledged rather than appearing as an author. In 31 trials, the ghost authors we identified were statisticians. It is likely that we have overlooked some ghost authors....”
Lack of Trust: Science as Marketing

• CONSIDER: Research program conceived to both produce informative data and meet marketing objectives, e.g.,
  – Develop prevalence and progression data on a common condition.
  – Demonstrate unmet need for/underutilization of company product.

• Funded by corporate marketing unit. Academics imported, ask scientific questions, function like a board of directors.

• Unattributed contract public relations firm and medical editors coordinate meetings, some analyses, and production of papers.

• Company provides resources, manages data collection, conducts some analyses.

• Polished drafts furnished to academic physician-scientist board member “primary authors.”
Lack of Trust: Science and Marketing

• Papers to *JAMA, BMJ, Lancet, NEJM, etc.* by academic authors

• Quality of science depends on timing and distribution of responsibilities and authority between
  
  – Medical scientists, academic and industry
  
  – Corporate public relations/medical writing support unit
  
  – Corporate marketing sponsors

• In such a structure, who ensures scientific integrity of the result? Is scientific attribution valid? Sometimes? What if some data are omitted from reports?
Lack of Trust: Science as Marketing

“Who We Are

"If you've got a good story to tell—people will want to hear it“ ...

Our services are designed to help market a product from preliminary concept to launch and beyond....

We reach further than other medical communication companies by blending creative strategy and scientific content to set your product apart from the competition....

Our medical writers are among the best in the field. Every year, we publish hundreds of medical manuscripts and abstracts. Our list of noteworthy achievements includes citations in prestigious high-impact journals, ample presence at major congress, and excellent ongoing relationships with key opinion leaders in many therapeutic areas.”
Lack of Trust: Science as Marketing
Lack of Trust: Science as Marketing

- **Associate Scientific Director**  You may be wondering, how can I possibly get this kind of job? Well, it’s simple. All we ask is that you have and/or possess: An advanced degree such as a PhD, MD, PharmD, and 2+ years in any of or more of the above mentioned therapeutic areas. The ability to interpret data. Must have supported experience of medical/scientific writing skills. Experience with peer review of scientific/medical publications, especially in developing scientific manuscripts from study data.
Lack of Trust: Science as Marketing

• From the web site of a major public relations firm, in reference to its internal group supporting the writing of manuscripts for a large international research effort, and managing the process by which they are reviewed and approved by an academically-based governance body:

“However, the [company’s group] does not ghostwrite articles for authors, in keeping with the uniquely independent nature of the [academic governance group].”
Article 15

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person.
WMA DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

• Article 27

– In publication of the results of research, the investigators are obliged to preserve the accuracy of the results.

– Negative as well as positive results should be published or otherwise publicly available.

– Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication.
If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach, and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.
Medical Community Responses

• Four dimensions, by and directed at medical research institutions and **physician-researchers**:

• Tightened financial disclosure policies for authorship and regulatory and/or advisory activities.

• Requirements for attribution of authorship roles, and public acknowledgement of scientific responsibility.

• Tightened institutional restrictions on consulting, medical gifts, some forms of fraternization. No free lunches.

• Initiatives to increase transparency of the clinical research enterprise.
  
  • Clinical trial registries
  
  • Clinical research data disclosure
Medical Community Responses

• **World Association of Medical Editors (WAME):**
  Journal management of COI (2002); Clinical trial registration (2005); Ghost writing (2006); Authorship (2007)

• **International Committee of Medical Journal Editors (BMJ, Lancet, NEJM, JAMA, AIM, other general medicine journals):**
  Updated requirements for manuscript submissions (2006).

• **Federation of American Societies in Experimental Biology (FASEB):**
  Updated COI guidelines (2006)

• **American Association of Medical Colleges:** Principles for protecting integrity of clinical trials (2006)

• **JAMA:** Update on COI policy (2006)

• Many more.
And Biostatistics?

- To what discipline are recognizing and understanding sources of bias, and controlling their influences on inferences and decisions, most technically and philosophically central?
- Does any profession depend more on unfettered information flow than does (applied) Statistics?
- My personal answers to these questions imply that the medical research community is addressing concerns important to our future as well.
  – Perhaps their problem is ours too!
What do you think?

Comments?
Thanks for your attention!

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