

Recognizing and Addressing Conflict of Interest

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Conflicts of interest (Col) are increasingly recognized as important considerations for those involved in the delivery of health care and conduct of research. Col is known to exist and can affect a wide variety of entities including clinicians, academic researchers, institutions, scientific journals, the pharmaceutical industry, federal regulators, policy-makers, and professional organizations. Recent reports highlight an apparent pattern of Col that has many questioning the validity of published research papers, Food and Drug Administration (FDA) advisory committee recommendations, and clinical practice guidelines.¹⁻⁶ The intent of this article is to assist clinicians in recognizing and addressing apparent Col. Col has been defined as a set of conditions whereby judgment concerning a primary interest is subjugated by a secondary interest.⁷ In addition to this theoretical definition, the National Institutes of Health (NIH) and the FDA (among others) have promulgated financial definitions. The secondary interest can arise from any number of sources ranging from financial gain to prestige or career advancement.⁸ While most clinicians and researchers report they are able to separate potential conflicts from their decision making process, a wide body of medical and social science literature suggests otherwise.⁹

Research

Funding for clinical and basic sciences has dramatically changed in the last several decades. The proportion of privately funded research increased from 32% in 1980 to 62% in 2000.⁴ While the NIH remains the primary funder of basic biomedical research, pharmaceutical companies finance more than 70% of all clinical trials.^{10,11} In a recent systematic review, it was estimated that 25% of all investigators in academic medical institutions received research funding from industry and that research with industry support was 3.6 times more likely than non-industry sponsored research to report a conclusion favorable to industry.¹² Others report industry sponsorship is associated with lower quality research and research that is delayed or not published.^{11,13,14}

Col in research can lead to biases in study results and conclusions, some of which are difficult to detect. It has been suggested that data from both pivotal clinical trials of rofecoxib and celecoxib were not presented in full making their results more favorable.^{1,2,15-19} In the wake of the withdrawal of rofecoxib from the US market, editors at the New England Journal of Medicine (NEJM) issued an Expression of Concern about the data integrity of the Vioxx GI Outcomes Research (VIGOR) trial, the pivotal clinical trial published in 2000.^{1,2,15} In their editorial, the editors indicated that cardiovascular events known by investigators prior to publication, were not reported, leading to an underestimate of the myocardial infarction risk associated with rofecoxib.^{1,2} Similar allegations were leveled at the outcomes study for celecoxib.^{17,19} The Celecoxib Long-term Arthritis Safety Study (CLASS) published in 2000 presented data demonstrating significant safety advantage of celecoxib over diclofenac or ibuprofen after 6 months of follow-up.¹⁶ It was later revealed that 12-month follow-up data presented to FDA, and available at publication time, negated the clinical benefit of celecoxib over traditional NSAIDs.¹⁸ The CLASS investigators defended selective submission of data based on a high and differential drop-out rate after 6 months, a rationale disputed by the FDA statistical reviewer.

While suppression of negative results and overt manipulation of data is likely rare, selective underreporting of outcomes is surprisingly common.^{20,21} Studies that have compared research protocols to published papers have observed that 60%-71% of all outcomes, both efficacy and harm, go unreported.²⁰ Based on data gathered from corresponding authors of these studies, outcomes reaching statistical significance were 2.4-4.7 times more likely to be reported compared to non-statistically significant findings.²⁰ The selective reporting of non-significant, but clinically important outcomes, can culminate in biased meta-analyses and reviews such as those concerning the safety and effectiveness of selective serotonin reuptake inhibitors in children.²² Finally, a number of subtle design tactics can be used to attain positive

results.^{1-3,17,23} Drugs may be paired against an alternative that is known or highly suspected to be inferior.²⁴⁻²⁶ This was a major criticism of esomeprazole (Nexium) which, in clinical trials, may have been compared to inadequately dosed alternatives.²⁷ Another strategy is to inadequately power studies to produce equivocal results. It has been suggested that the large salmeterol safety study was prematurely terminated after unfavorable interim data were observed.²⁸⁻³⁰

Practice Guidelines, Professional Associations, Advocacy Groups

Recent investigations revealed over 50% of authors revising the Diagnostic and Statistical Manual of Mental Disorders (DSM) had financial ties to the pharmaceutical industry.³¹ Within the "Mood Disorders" and "Schizophrenia and Other Psychotic Disorders" panel, 100% of members had financial ties. The next version of the DSM (DSM-V), scheduled for 2011, will include a more formal financial disclosure section.³² The National Cholesterol Education Program guidelines for cholesterol management and the American Society of Hypertension guidelines for hypertension treatment have been subject to similar controversy.³³⁻³⁵

The journal Nature evaluated Col declarations in 215 practice guidelines added to the US National Guideline Clearinghouse in 2004.⁵ Of those reviewed, 125 (58%) guidelines contained no Col disclosures. Only 31 of the remaining 90 guidelines (34%) claimed no Col, 50% of guidelines had at least one member with an advisory board or consultancy position for a reviewed company, and 11% had at least one author owning stock whose product is included in the guideline. The International Committee of Medical Journal Editors' Uniform Requirements on disclosure have included strengthened recommendations about sponsorship, authorship, and accountability since 2001.³⁶

Finally, many professional organizations and non-profit disease advocacy groups have strong financial ties to the pharmaceutical industry.³⁷ These organizations are not required to disclose specific amounts contributed by industry, but their annual reports generally acknowledge dollar ranges for different corporations and individuals. Investigations into these groups report them to be relatively quiet with regard to information pertaining to drug safety issues of many of their corporate sponsors.^{38,39}

Regulation

The FDA relies on advisory panels composed of outside experts to give recommendations about drug approval. Current policies require all advisory panel members to submit detailed and confidential Col disclosures that are used by the FDA to decide who should be on a panel. In general, prospective advisory committee members are prohibited from serving if they have a financial Col particular to the matter discussed in committee. However, the FDA has the authority to grant waivers, depending on the magnitude of financial interest or if the need for the candidate's expertise outweighs the potential Col created by the appointment.⁴⁰ In February 2005, the New York Times reported that 10 of the 32 advisers on the COX2 safety advisory group had ties to companies associated with the drugs being reviewed and their votes were significant in the committee's recommendation to allow the drug valdecoxib (Bextra) to remain on the market and allow rofecoxib to return to market.⁶ An analysis conducted by Public Citizen found that while 73% of meetings had at least one member with a Col, there was no association between conflict rate and voting outcomes.⁴ It was noted, however, that excluding members with Col did produce voting margins which were less favorable to the drug being discussed in a majority of the meetings. The FDA is currently considering new rules that would prohibit advisory members who have received financial support from pharmaceutical marketing departments from serving while at the same time relaxing restrictions for those who are associated through research grants.⁴¹

Addressing Apparent Conflict of Interest

Disclosure is one of the most frequently encountered methods to address potential Col. However, the extent of disclosure in research publications is not always clear or uniformly validated. The Journal of the American Medical Association (JAMA) recently experienced a run of unreported Cols in published studies.⁴²⁻⁴⁴ JAMA has a rigorous conflict disclosure policy and stipulates that authors disclose all financial Cols regardless of whether they pertain to the research submitted. However, while disclosure may reveal many potential Cols it does not provide any guidance for interpreting or resolving conflicts. Furthermore, research from the social science discipline suggests that disclosure may cause those with a competing interest to more strongly favor that interest.^{9,45}

For original medical research, there is no substitute for careful evaluation of methods, results, and interpretation of the data. Review papers and editorials are particularly prone to unconscious bias. To accommodate this, the NEJM briefly introduced a policy prohibiting authors of reviews and editorials from having financial interests in any of the products discussed in their article. The journal later retracted this policy because of the scarcity of expert authors without said financial conflicts and now only restricts authorship to those without "significant" interests.⁴⁶ Articles published in journal supplements are typically heavily subsidized by the pharmaceutical industry, are performed with less scientific rigor, and are frequently not given the same level of peer review as articles in the main journal.^{47,48} Academic institutions may have additional Col management strategies limiting an investigator's role in specific research activities, such as consenting and enrolling human subjects, reporting adverse events, evaluating outcomes, and data analysis.

Reading and interpreting the volume of published medical literature existing today is beyond the ability of even the most diligent clinician. While practice guidelines and topic reviews are particularly attractive because they summarize these massive data, the number of evidence summaries is also large and clearly not created equal. Systematic evidence reviews, with documented methods for finding and evaluating the data are preferred over unstructured review articles where studies can be selected and emphasized in unknown and potentially biased ways. Formal recommendations should have an explicit link to the evidence from which they are based. While it may be difficult to discern, it is important that evidence summaries have not only content experts but also individuals skilled in critically evaluating clinical research. The methods used to evaluate and interpret the evidence should be described in detail as well as disclosures of research funding and individual Col. Systematic reviews are widely produced today; however, data suggests that those produced by industry are less transparent, of lower methodological quality, and more likely to be favorable compared to those produced by the Cochrane Collaborative.⁴⁹

Sources of Evidence-Based Drug Information

Agency for Health Research and Quality:

<http://effectivehealthcare.ahrq.gov/aboutUs/index.cfm>

Drug Effectiveness Review Project: www.ohsu.edu/drugeffectiveness

Canadian Agency for Drugs and Technology in Health: www.cadth.ca

National Institute for Clinical Excellence (UK): www.nice.org.uk

Therapeutics Letter (Canada): www.ti.ubc.ca

Drug and Therapeutics Bulletin (UK): www.dtb.org.uk

Medical Letter: www.medletter.com

Prescriber's Letter: www.prescribersletter.com

A number of organizations have established robust and defensible processes for producing systematic evidence available to the public. The Oregon-based Drug Effectiveness Review Project is comprised of public purchasers who have consolidated resources to produce systematic reports comparing the effectiveness and safety of pharmaceuticals. These exhaustive evidence reports are available to the public on their website. Unfortunately, they may be impractically large for the practicing clinician. The table provides sources of evidence-based information which vary from exhaustive to brief reports.

Connections between industry and medical research are pervasive and to a large extent necessary. Given the subtle ways in which competing financial interest manifest, it is critical that readers are made aware and cautious of potential conflicts.

Reviewers: Alison S. Little, MD, MPH, Drug Effectiveness Review Project; Marian McDonagh, PharmD, OHSU Evidence-based Practice Center; Michel Boucher, BPharm, MSc, Canadian Agency for Drugs & Technologies in Health; Gary T. Chiodo, DMD, FACC, OHSU Center for Ethics in Health Care.

References

1. Curfman GD, Morrissey S, Drazen JM. Expression of concern: Bombardier et al. "Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis." N Engl J Med 2000;343:1520-8. N Engl J Med 2005; 353:2813-4.
2. Curfman GD, Morrissey S, Drazen JM. Expression of Concern Reaffirmed. N Engl J Med 2006; 354:1193-.
3. Couzin J. SCIENTIFIC PUBLISHING: Echoing Other Cases, NEJM Says Vioxx Safety Data Withheld. Science 2005; 310:1755-.
4. Lurie P, Almeida CM, Stine N, Stine AR, Wolfe SM. Financial conflict of interest disclosure and voting patterns at Food and Drug Administration Drug Advisory Committee meetings. JAMA 2006; 295:1921-8.
5. Taylor R, Giles J. Cash interests taint drug advice. Nature 2005; 437:1070-1.
6. Harris G, Berenson A. 10 Voters on Panel backing Pain Pills Had Industry Ties. New York Times. New York, 2005.
7. Thompson DF. Understanding financial conflicts of interest. N Engl J Med 1993; 329:573-6.
8. Levinsky NG. Nonfinancial conflicts of interest in research. N Engl J Med 2002; 347:759-61.
9. Dana J, Loewenstein G. A Social Science Perspective on Gifts to Physicians From Industry. JAMA 2003; 290: 252-255.
10. Zerhouni EA. US Biomedical Research: Basic, Translational, and Clinical Sciences. JAMA 2005; 294:1352-1358.
11. Bodenheimer T. Uneasy Alliance -- Clinical Investigators and the Pharmaceutical Industry. N Engl J Med 2000; 342:1539-1544.
12. 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.
13. Rennie D. Trial Registration: A Great Idea Switches From Ignored to Irresistible. JAMA 2004; 292:1359-1362.
14. Studdert DM, Mello MM, Brennan TA. Financial Conflicts of Interest in Physicians' Relationships with the Pharmaceutical Industry -- Self-Regulation in the Shadow of Federal Prosecution. N Engl J Med 2004; 351:1891-1900.
15. Bombardier C, Laine L, Reicin A, et al. Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis. N Engl J Med 2000; 343:1520-1528.
16. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal Toxicity With Celecoxib vs. Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis: The CLASS Study: A Randomized Controlled Trial. JAMA 2000; 284:1247-1255.
17. Hrachovec JB, Mora M. Reporting of 6-month vs. 12-month data in a clinical trial of celecoxib. JAMA 2001; 286:2398; author reply 2399-400.
18. Lu H. Statistical Reviewer Briefing Document for the Advisory Committee, 2000.
19. Fontanarosa PB, DeAngelis CD. Conflicts of Interest and Independent Data Analysis in Industry-Funded Studies--Reply. JAMA 2005; 294:2576-2577.
20. Chan AW, Hrobjartsson A, Haahr MT, Gotsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA 2004; 291:2457-65.
21. Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. BMJ 2005; 330:753.
22. Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. BMJ 2004; 328:879-83.
23. Rennie D. Thyroid storm. JAMA 1997; 277:1238-1243.
24. Kahrlas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. Alimentary Pharmacology and Therapeutics 2000; 14:1249-1258.
25. Richter JE, Kahrlas PJ, Johanson J, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. The American Journal of Gastroenterology 2001; 96:656-665.
26. FDA. Medical Review of Nexium (Esomeprazole Magnesium) Delayed-Release Capsules., 2001.
27. McDonagh MS, Carson S. Drug Class Review on Proton Pump Inhibitors. Portland, Oregon: Evidence-Based Practice Center at Oregon Health & Science University, 2005.
28. Lurie P, Wolfe SM. Misleading data analyses in salmeterol (SMART) study. The Lancet 2005; 366:1261-1262.
29. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, the SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol. Chest 2006; 129:15-26.
30. Medical Officer Review Division of Pulmonary and Allergy Drug Products: US Food and Drug Administration, 2004.
31. Cosgrove L, Krinsky S, Vijayaraghavan M, Schneider L. Financial ties between DSM-IV panel members and the pharmaceutical industry. Psychother Psychosom 2006; 75:154-60.
32. Vedantam S. Experts defining mental disorders are linked to drug firms. Washington Post. Washington, D.C., 2006.
33. Gozner M. Petition To the National Institutes of Health Seeking an Independent Panel to Re-evaluate the National Cholesterol Education Program Guidelines. Washington, D.C.: Integrity in Science Project - Center for Science in the Public Interest, 2004.
34. Lenzer J. US consumer body calls for review of cholesterol guidelines. BMJ 2004; 329:759.
35. Saul S. Unease On Industry's Role In Hypertension Debate. The New York Times. New York, 2006.
36. Davidoff F, DeAngelis CD, Drazen JM, et al. Sponsorship, Authorship, and Accountability. N Engl J Med 2001; 345:825-827.
37. Lifting the Veil of Secrecy - Corporate Support for Health and Environmental Professional Associations, Charities, and Industry Front Groups. Washington, D.C.: Integrity in Science Project - Center for Science in the Public Interest, 2003.
38. Ready T. Divided Loyalties? Washington Post. Washington, D.C., 2006.
39. Ginsberg T. Donations Tie Drug Firms and Nonprofits. Philadelphia Inquirer. Philadelphia, 2006.
40. Food and Drug Administration. FDA Guidance on Conflict of Interest for Advisory Committee Members, Consultants and Experts, 2000.
41. Harris G. Rules Planned for Industry Ties on F.D.A. Boards. New York Times. New York, 2006.
42. Ridker PM. Incomplete Financial Disclosure for Study of Funding and Outcomes in Major Cardiovascular Trials. JAMA 2006; 295:2725-a-2726.
43. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Unreported financial disclosures in a study of migraine and cardiovascular disease. JAMA 2006; 296:653-4; author reply 654.
44. Urato AC. Antidepressant treatment and relapse of depression during pregnancy. JAMA 2006; 296:166; author reply 166-7.
45. Wang S. Simply Disclosing Funds Behind Studies May Not Erase Bias. Wall Street Journal. New York City, 2006.
46. Drazen JM, Curfman GD. Financial Associations of Authors. N Engl J Med 2002; 346:1901-1902.
47. Lexchin J, Light DW. Commercial influence and the content of medical journals. BMJ 2006; 332:1444-1447.
48. Rochon PA, Gurwitz JH, Cheung CM, Hayes JA, Chalmers TC. Evaluating the quality of articles published in journal supplements compared with the quality of those published in the parent journal. JAMA 1994; 272:108-113.
49. Jorgensen AW, Hilden J, Gotsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. BMJ 2006; 333:782.