bioethics

Bioethics ISSN 0269-9702 (print); 1467-8519 (online)
Volume 24 Number 6 2010 pp 273–283

doi:10.1111/j.1467-8519.2008.01702.x

PUBLICATION ETHICS AND THE GHOST MANAGEMENT OF MEDICAL PUBLICATION

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Keywords
publication ethics, research ethics, sponsorship bias, ghost management

ABSTRACT

It is by now no secret that some scientific articles are ghost authored – that is, written by someone other than the person whose name appears at the top of the article. Ghost authorship, however, is only one sort of ghosting. In this article, we present evidence that pharmaceutical companies engage in the ghost management of the scientific literature, by controlling or shaping several crucial steps in the research, writing, and publication of scientific articles. Ghost management allows the pharmaceutical industry to shape the literature in ways that serve its interests.

This article aims to reinforce and expand publication ethics as an important area of concern for bioethics. Since ghost-managed research is primarily undertaken in the interests of marketing, large quantities of medical research violate not just publication norms but also research ethics. Much of this research involves human subjects, and yet is performed not primarily to increase knowledge for broad human benefit, but to disseminate results in the service of profits. Those who sponsor, manage, conduct, and publish such research therefore behave unethically, since they put patients at risk without justification. This leads us to a strong conclusion: if medical journals want to ensure that the research they publish is ethically sound, they should not publish articles that are commercially sponsored.

Medical research is risky. This is particularly true of clinical trials that test new drugs or devices. Such risks are justified on the basis of the potential benefits of increased medical knowledge, and so publicity is necessary for ethical research. Publicity in this context generally means publication in a medical journal, so publication is a central element in ethical research. Nonetheless, *publication ethics* generates little attention relative to *research ethics*. It is generally assumed that 'there's no such thing as bad publicity': as long as the results of the research are published in an appropriate forum so that others can learn from them, the research is assumed to have met the publicity criterion for ethical research. This assumption is profoundly mistaken. While the public good cannot be served by keeping the results of research from the public eye, mere publicity, even in a reputable medical journal, is not sufficient. In order to know if published research is ethically justified, it is important to ask not only *if* the results have been published, but also *why* and *how* they were published.

This article aims to reinforce and expand publication ethics as an important area of concern for bioethics. We argue that the commercial management of much of the scientific literature has worrying implications for the ethics of a significant amount of medical research. This leads us to a strong conclusion: if medical journals want

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to ensure that the research they publish is ethically sound, they should not publish articles that are commercially sponsored.

PUBLICATION ETHICS

Research ethics is largely concerned with the treatment of patients, and so addresses issues such as dangerous research, equipoise, patient consent, and paternalism. The ethics of publication are relatively ignored. Some discussions of research ethics, however, do consider issues surrounding publication, largely under the guise of 'research integrity.'[1] Such discussions address violations of specifically scientific or academic norms, such as those dealing with plagiarism, fabrication of data, duplicate publication,[2] and, in particular, authorship.[3] The last of these has become an issue because of the prevalence of multi-authored articles produced in a distributed way, which has led some to suggest abandoning 'authorship' in favour of 'contributorship.'[4]

Just as interest in research ethics led to the creation of Institutional Review Boards and the requirement that research proposals receive ethics approval, specific interest in publication ethics has led to the creation of several institutions to that aim to foster ethical publication practices. Prominent among these are the Committee on Publication Ethics (COPE) and the International Committee of Medical Journal Editors (ICMJE), whose criteria for authorship have been widely adopted.[5]

Scientific misconduct in publication, from plagiarism and fabrication to duplicate publication and questionable authorship practices, is frequently explained by pointing to the pressures generated by the 'publish or perish' culture of academia.[6] Efforts to regulate or improve publication ethics therefore either have a moralistic tone, encouraging individual researchers to act with integrity,[7] or else focus on the role that institutions most directly connected to academic science – scientific societies, universities, and teaching hospitals – can play in regulating publication practices.[8]

Focusing exclusively on professional 'publish or perish' pressures ignores an important additional source of violations of publication ethics in medicine: commercial pressure from the pharmaceutical industry for publications that reflect favourably on their products. The effects of this pressure can be seen in concern over conflicts of interest, publication bias, withholding of data, duplicate publication, 'salami slicing', and other practices designed to shape the scientific literature favourably.

While commercial pressures have serious effects on the integrity of publication, they are relatively ignored in discussion of publication ethics.[9] Both professional and commercial pressures, however, play important roles in many of the most important breaches of publication ethics, when, for example, pressures to publish meet opportunities to publish presented by commercial interests.

Violations of publication ethics are not separate and distinct from violations of the ethical norms governing the treatment of patients in research. Meeting the

[1] M. Iverson et al. Scientific Societies and Research Integrity: What Are They Doing and How Well Are They Doing It? *Sci Eng Ethics* 2003; 9: 141–155; N.H. Steneck. Fostering Integrity in Research: Definitions, Current Knowledge, and Future Directions. *Sci Eng Ethics* 2006; 12: 53–74.

[2] J. Brice & J. Bligh. Author Misconduct: Not Just the Editors' Responsibility. *Med Educ* 2004; 39: 83–89; A. Caelleigh. Roles for Scientific Societies in Promoting Integrity in Publication Ethics. *Sci Eng Ethics* 2003; 9: 221–241; I. Chalmers. Role of Systematic Reviews in Detecting Plagiarism: Case of Asim Kurjak. *Br Med J* 2006; 333: 594–596; R.B. Daroff & R.C. Giggs. Scientific Misconduct and Breaches of Publication Ethics. *Neurology* 2004; 62: 352–353; M.J. Farthing. Authors and Publication Practices. *Sci Eng Ethics* 2006; 12: 41–52; F.J. Gilbert & A.R. Denison. Research Misconduct. *Clin Radiol* 2003; 58: 499–504; Iverson et al., *op. cit.* note 1; A.V. Neal et al. Correction and Use of the Biomedical Literature Affected by Scientific Misconduct. *Sci Eng Ethics* 2007: 13; Steneck, *op. cit.* note 1.

[3] P. Borry et al. Author, Contributor or Just a Signer? A Quantitative Analysis of Authorship Trends in the Field of Bioethics. *Bioethics* 2006; 20: 213–220; Farthing, *op. cit.* note 2; A.H. Jones. Can Authorship Policies Help Prevent Scientific Misconduct? What Role for Scientific Societies. *Sci Eng Ethics* 2003; 9: 243–256; M.T. Laflin et al. Publication Ethics: An Examination of Authorship Practices. *Am J Health Behav* 2005; 29; A. Sheikh. Publication Ethics and the Research Assessment Exercise: Reflections on the Troubled Question of Authorship. *J Med Ethics* 2000; 26; K.L. Woolley et al. Declaration of Medical Writing Assistance in International Peer-Reviewed Publications. *JAMA* 2006; 296: 932.

[4] D. Rennie et al. When Authorship Fails: A Proposal to Make Contributors Accountable. *JAMA* 1997; 278: 579–585; R. Smith. Reinventing the Biomedical Journal. *J Neurosci* 2006; 26: 9837–9838.

[5] COPE. 2003. Committee on Publication Ethics Guidelines on Good Publication Practice. Available at http://www.publicationethics.org.uk/guidelines [Accessed 23 June 2008]; ICMJE. 2006. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. Available at www.icmje.org [Accessed 23 June 2008].

[6] Borry et al., *op. cit.* note 3; Brice & Bligh, *op. cit.* note 2; Gilbert & Denison, *op. cit.* note 2; Sheikh, *op. cit.* note 3.

[7] Brice & Bligh, *op. cit.* note 2.

[8] Caelleigh, *op. cit.* note 2; Iverson et al., *op. cit.* note 1.

[9] COPE, for example, puts anonymized summaries of the cases it considers on its website. As of 2008, it listed 20 cases of disputes between authors, 20 of failure to obtain informed consent, and 18 of plagiarism. By contrast, only 4 cases were categorized as 'Drug Company' and 4 as 'Financial Interest,' and one of these was categorized as both, making for a total of only 7 cases. COPE. Cases. Available at http://www.publicationethics.org.uk/cases [Accessed 23 June, 2008].

publicity criterion is required if putting patients at risk is to be justified; but this criterion cannot be met by publicity that violates the ethical norms governing publication. A closer look at publication practices is therefore a vitally important part of research ethics: in ignoring breaches of publication ethics, the scientific community risks allowing as ethically sound research that it should find deeply worrying.

GHOST MANAGEMENT[10]

Pharmaceutical companies perform and sponsor a significant amount of medical research and analysis, especially clinical trials, but also meta-analyses, reviews, epidemiology, laboratory science, and health economics research. Especially in the past two decades, these companies have developed systems that treat knowledge as a resource to be carefully developed and used to affect the opinions of researchers and practitioners. Publication of pharmaceutical company-sponsored research in medical journals, and its presentation at conferences and meetings, is now governed by 'publication plans' that extract more scientific and commercial value out of data and analyses through carefully constructed articles. This has brought medical publishing into the 'marketing era.'[11] The number of articles that pharmaceutical companies produce is large, and the numbers on particular drugs are tightly correlated with the sales of those drugs. Research is created with publication and marketing in mind. As expressed by industry experts, 'Historically, Phase IV studies were primarily conducted to support a product's commercialization; now they are increasingly conducted to maximize it.'[12]

The work of publication planners is largely unseen. To gain commercial value from research, articles publicizing it are written under the names of independent medical researchers, though company authors may also be recognized. The work of pharmaceutical company statisticians, reviewers from a diverse array of departments, medical writers, and the publication planners themselves is only rarely acknowledged in journal publications.[13] Even sponsorship, the company funding of the trial, is omitted from many meeting abstracts.[14] For this reason we might see publication planning as the 'ghost management' of medical research and publication. We apply the term *ghost management* when pharmaceutical companies and their agents control or shape several crucial steps in the research, writing, and publication of articles: these articles are ghostly because signs of their actual production are largely invisible, and managed because the companies shape the eventual message conveyed by the article or suite of articles. Companies aim to maximize the number of publications from positive trials, minimize those from negative trials, and ensure that the results of the study are published promptly and in prominent journals.[15] Ghost management makes apparently scientific research a marketing tool.

There have been a number of individual reports of the ghost management of medical journal articles and meeting presentations.[16] However, because it is typically invisible, some of the best demonstrations of the existence and effects of ghost management have resulted from legal action.

Court proceedings showed that in 1996 Wyeth hired the medical education and communication company (MECC) Excerpta Medica to prepare ten manuscripts to help market its diet drug dexfenfluramine (Redux) in

[10] In this section we summarize and amplify an earlier description by one of us of the 'ghost management' of medical research and publication. S. Sismondo. Ghost Management: How Much of the Medical Literature is Shaped Behind the Scenes by the Pharmaceutical Industry. *PLoS Med* 2007; 4: e286.

[11] K. Applbaum. 2004. *The Marketing Era: From Professional Practice to Global Provisioning*. New York: Routledge.

[12] H.E. Glass & D.W. Dalton. Profiles of Phase IV Investigators and Subsequent Prescribing of the Study Drug. *J Pharm Mark and Manage* 2006; 17: 3–17.

[13] P.C. Gøtzsche et al. Ghost Authorship in Industry-Initiated Randomised Trials. *PLoS Med* 2007; 4: 47–52; B. Moffatt & C. Elliott. Ghost Marketing: Pharmaceutical Companies and Ghostwritten Journal Articles. *Perspect Biol Med* 2007; 50: 18–31.

[14] T. Finucane & C. Bolt. Association of Funding and Findings of Pharmaceutical Research at a Meeting of a Medical Professional Society. *JAMA* 2004; 117: 842–845.

[15] H. Melander et al. Evidence B(i)ased Medicine – Selective Reporting from Studies Sponsored by Pharmaceutical Industry: Review of Studies in New Drug Applications. *Br Med J* 2003; 326: 1171–1173.

[16] A. Barnett. 2003. Revealed: How Drug Firms 'Hoodwink' Medical Journals. *The Observer* Dec. 7, 2003; P. Baty. 2005. When Access to Data is a Real Bone of Contention. *Times Higher Education Supplement* Nov. 25, 2005; D. Blumenthal et al. Withholding Research Results in Academic Life Science. Evidence from a National Survey of Faculty. *J Am Med Assoc* 1997; 277: 1224–1228; A. Fugh-Berman. The Corporate Coauthor. *J Gen Intern Med* 2005; 20: 546–548; M. Gruzuk & C. Jones. 2003. CBC Marketplace: Inside the Business of Medical Ghostwriting. Canadian Broadcasting Corporation. Available at http://www.cbc.ca/consumers/market/files/health/ghostwriting/ [Accessed 6 Dec 2008]; M. Larkin. Whose Article Is It Anyway? *The Lancet* 1999: 354; A.W. Matthews. 2005. Ghost Story: At Medical Journals, Writers Paid by Industry Play Big Role; Articles Appear Under Name Of Academic Researchers, But They Often Get Help; J&J Receives a Positive 'Spin'. *Wall St J* December 13; S. Ngai et al. Haunted Manuscripts: Ghost Authorship in the Medical Literature. *Account Res* 2005; 12: 103–114; M. Peterson. 2002. Madison Ave. Has Growing Role In the Business of Drug Research. *New York Times* Nov 22.

medical journals. Excerpta wrote the manuscripts and located authors, paying them between $1000 and $1500 for their editing work.[17] Most of those manuscripts never saw print, because the drug was withdrawn from the market.

Internal documents about Parke-Davis's promotion of its drug gabapentin (Neurontin) in the 1990s became available through litigation. Steinman and co-workers examined approximately 8000 pages of these court documents to identify promotional strategies through research and publication, continuing medical education, advisory boards, and consultants meetings.[18] Parke-Davis employed a 'publication strategy' in order 'to disseminate the information as widely as possible through the world's medical literature' (including information relevant to off-label uses). The company had a stated goal of publishing the positive studies, and there are instances of non-publication of negative studies. As part of the same strategy, Parke-Davis supported further publications through MECCs. One 'grant request' from a MECC proposed developing a group of 12 articles on gabapentin with a 'consistent message' and a focus on, among other things, 'emerging uses.' The proposal suggested topics, journals, titles, and authors.

Lawsuits about rofecoxib (Vioxx) allowed a systematic study identifying 96 published articles (24 on clinical trials and 72 review articles) on which Merck had worked prior to their publication, and which were later published mostly under the names of academic first authors.[19] For example, one document lists eight review articles for which the MECC Scientific Therapeutics had intended authors and journals, and estimated delivery dates of first or second drafts. Ghost-managed review articles were likely to be single-authored by academics, who were especially likely not to declare financial support for the work.[20]

A legal action gave psychiatrist David Healy access to a document listing 85 articles on the drug sertraline (Zoloft or Lustral) being handled by a public relations firm Current Medical Directions (CMD) for Pfizer.[21] All of the manuscripts were carefully managed, as CMD was aware of submission dates, requests for revisions, target dates for those revisions, and projected publication dates. The document includes comments such as 'First draft with author for review,' and 'Manuscript submitted to American Journal of Psychiatry 7/98. Confidence intervals requested by journal. Revised manuscript resubmitted 9/98.'[22] Most of these manuscripts were published in important medical journals between 1998 and 2000, with academic researchers listed as their authors. This group of 85 manuscripts became 40% of articles published between 1998 and 2000 containing 'sertraline' in the title.[23] The articles were published in more prominent journals than were others on sertraline, had nearly twice as many authors per article, had authors who were on average twice as prolific, and were cited three times as often.[24]

In a separate phenomenon, some trials are 'seeding trials,' created to increase physician familiarity with a drug or directly increase prescriptions. A US Federal investigation revealed that in some of Schering-Plough's post-marketing trials of its hepatitis C treatment Intron A, liver specialists were paid between US$1000 and $1500 per patient enrolled in the trials; patients' insurance plans paid the $20,000 annual cost of treatment.[25] Merck's large ADVANTAGE trial of Vioxx, involving more than 5500 patients, was similarly a seeding trial. It was created by its Marketing Department, as internal documents state, to allow investigators to '[g]ain experience prior to and during the critical launch phase.'[26] The trial was nominated for an internal Merck marketing award.

Cases revealed by litigation are not isolated or unusual. While MECCs doing publication planning generally do not reveal details of their work – to either potential critics or competitors – they promote themselves and the services they offer. Many have flashy websites highlighting their ability to write, track, and publish journal articles, and to produce transparent and attractive outputs displaying the results of their work. In 2001 there were 182 established MECCs in the United States and many more elsewhere.[27] More than 50 (!) of these, some of them

[17] C. Elliott. The Drug Pushers. *The Atlantic Monthly* April 2006: 82–93.

[18] M.A. Steinman et al. Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents. *Ann Intern Med* 2006; 145: 284–293.

[19] J.S. Ross et al. Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: A Case Study of Industry Documents From Rofecoxib Litigation. *J Am Med Assoc* 2008; 299: 1800–1812.

[20] Ross et al., *op. cit.* note 19.

[21] D. Healy & D. Cattell. Interface between Authorship, Industry and Science in the Domain of Therapeutics. *Br J Psychiatry* 2003; 183: 22–27.

[22] Current Medical Directions. 1999. Worldwide Publications Status Update: Zoloft (Sertraline HCl). New York: 37.

[23] Sismondo, *op. cit.* note 10.

[24] Healy & Cattell, *op. cit*. note 21.

[25] G. Harris. 2004. Medical Marketing Treatment by Incentive; As Doctor Writes Prescription, Drug Company Writes a Check. *New York Times*, June 27.

[26] K.P. Hill et al. The ADVANTAGE Seeding Trial: A Review of Internal Documents. *Ann Intern Med* 2008; 149: 251–258.

[27] G. Golden et al. Medical Education and Communication Companies: An Updated In-Depth Profile. *J Contin Educ Health Prof* 2002; 22: 55–62.

having hundreds of employees, advertise publication-planning services on the Internet (list available from the authors).

To take only one example, Watermeadow Medical describes in some detail how it engages in strategic communications activities at every stage of the product life-cycle. The goal is to ensure that, well before and after a new drug receives regulatory approval and is brought to market, 'decision makers are aware of its attributes and benefits, through appropriate communication channels and within an ethical framework.' To this end, early in the process Watermeadow identifies 'high-profile opinion leaders' who can act as advocates for a new drug. The firm coordinates the production of 'abstracts, posters, white papers, primary manuscripts, review articles, etc.' The company taps into 'strong relationships with international academic thought leaders' to 'fuel clinical debate, educate on cutting-edge developments and encourage product use.' Publication planning is only one aspect of the overall communications plan, but it is a major one: 'By maximizing the product support in the scientific literature, [Watermeadow clients] can take advantage of one of the most influential communication channels for healthcare and scientific audiences. Importantly, this also ensures optimal return from other marketing and promotional activity.' These broad-spectrum communications activities are undertaken not only to increase doctors' awareness of the drug's existence and confidence in its alleged efficacy; they are also 'pivotal in achieving an effective return on the investment for a product, maximizing adoption on the basis of clinical benefits.' In a delightfully ambiguous phrase, Watermeadow says their services can 'establish unmet medical need', leaving it unclear whether they aim merely to *discover*, or actually to *create* a need for their sponsor's products. Whichever it is, Watermeadow's self-promotion makes it quite clear that publication planning is an integral part of a marketing campaign.[28]

Pharmaceutical companies also do some publication planning in-house, though industry sources estimate that in-house planning makes up only 20% of that business.[29] Several MECCs – including Carus Clinical Communications, Excerpta Medica, Wolters Kluwer Health and Thomson Scientific Connexions –are divisions of major publishing houses.[30] 'Synergies' result from improved access to those publishers' journals, and possibly through reprint sales and supplement fees. Vertical integration may be attractive in the industry as a whole: at least three of the world's largest advertising agencies own not only medical communication companies, but also contract research organizations (CROs).[31]

Ghost management is a large enough trade for the industry to have established two professional associations: The International Publication Planning Association (TIPPA), and the International Society for Medical Publication Professionals (ISMPP).[32] Both organize meetings, have committees to develop policy, post job advertisements, and provide useful links. ISMPP has developed a set of ethical guidelines for medical writing, discussed briefly below. These associations compete with for-profit companies offering similar services, like the Center for Business Intelligence.[33]

As should be already clear from the above, publication planning is an activity that spans both research and publishing, and even extends to the downstream uses of publications. Publication planners would ideally be involved at early stages of research, to achieve consistency in the message of publications, to maximize their number, to allow later publications to refer to earlier ones, and to ensure the number of publications peak at the launch of the product.[34] As one planner at the 2007 ISMPP meeting said:

> This is what utopia looks like from an industry perspective. We have agreement and alignment on a plan, not even just a publication, a full plan, investigators on board, agencies lined up, everybody ready to play and we're going to get this done in a timely way, in an orderly fashion, and things work like clockwork.[35]

Ghost management of medical research and publication, then, is a substantial business, employing substantial numbers of marketers, writers, and managers. Given Healy's results, described above, it is reasonable to conclude that approximately 40% of journal reports of clinical trials of new drugs (and, more anecdotally, perhaps

[28] Watermeadow Medical. 2008. http://www.watermeadowmedical.com/ [Accessed 5 Sept 2008]

[29] Medical News Today. 2005. 80% of Pharmaceutical Medical Publications Spending Outsourced in 2004. *Medical News Today* 7 Mar.

[30] Carus Clinical. 2008. http://carusclinical.com/, Thompson Scientific Connexions. 2008 [Accessed 5 Sept 2008]. http://www.sciconnex.com/ [Accessed 5 Sept 2008], Wolters Kluwer. 2008. http://www.wkhealth.com/ [Accessed 5 Sept 2008], Excerpta Medica. 2008. http://www.excerptamedica.com//index.cfm [Accessed 5 Sept 2008].

[31] Peterson, op. cit. note 16.

[32] TIPPA. 2008. http://www.publicationplanningassociation.org/about.aspx [Accessed 5 Sept 2008]. ISMPP. 2008. http://www.ismpp.org/ [Accessed 5 Sept 2008].

[33] Center for Business Intelligence. 2008. http://www.cbinet.com/ [Accessed 5 Sept 2008].

[34] S. Sismondo. Ghosts in the Machine: Publication Planning in the Medical Sciences. *Soc Stud Sci*, forthcoming.

[35] Ibid.

a higher percentage of meeting presentations on clinical trials) are ghost managed through to publication.

ETHICAL PROBLEMS OF GHOST MANAGEMENT

Multiple factors work to create the conditions for ghost management: Unsurprisingly, when companies control research and publication, the medical literature tends to contain much more positive views of those companies' products. This makes it easier for pharmaceutical companies to use scientific research to market their products. Publications have more marketing value if they appear to be at least somewhat independent of the companies themselves. Therefore their prominent authors are typically affiliated with universities or other research institutions. Meanwhile, academics have a strong interest in publications, particularly in prominent journals. They are therefore often willing to participate in ghost-managed work, even to the point of serving as authors on publications when they have not met ICMJE requirements for authorship. Medical journals also benefit from the publication of ghost-managed medical articles, because these articles tend to be well cited, and because pharmaceutical companies may want to purchase thousands of reprints for distribution to physicians, giving journals another source of profit.

Many different parties – pharmaceutical companies, MECCs, academic researchers, and medical journals – therefore have reasons to collude in the ghost management of the medical literature. Each of these reasons is ethically problematic on its own. Combined, they lead to a situation where very little of the research carried out by authors or published by medical journals should be counted as ethically justified.

Medical journal articles that form parts of publication plans are pieces of medical science: they represent scientific research and conform to the standards of science well enough to pass peer review and be published in scientific journals. But they, like the science they represent and embody, are driven by marketing concerns. In addition to the evidence offered in the last section, we can see clear evidence of the driving role of marketing in the strong pro-sponsor bias that much of that research displays. Pharmaceutical company funding has been repeatedly shown to affect published results strongly.[36] Company-sponsored research is roughly four times more likely to report results favorable to the company than is independent research.[37] Undoubtedly, ghost management is part, though only part, of the cause of this phenomenon.[38] In general, we have reason to believe that any time strong interests fund research, that funding will bias the results.[39]

Precisely because sponsorship biases results so strongly, industry management of research needs to be 'ghostly.' Biased literature can have its effects only if it appears to be independent, and so ghost management is hidden because pharmaceutical companies know that they have something to hide: guest authors are part of a largely successful attempt to disguise conflicts of interest and the biases that they create. Pharmaceutical companies and publication planners are willing to risk the minor scandals that come from occasional revelations of ghost-written journal articles, because the value of academic sponsorship outweighs the cost of those scandals. Authors and researchers who participate in such research are allowing themselves to be used in the service of pharmaceutical profit. Worse, as we argue, they are putting trial subjects at risk without justification.

If ghost-managed research is primarily undertaken in the interests of marketing, then this suggests that significant quantities of medical research involving human subjects is performed not primarily to increase knowledge for broad human benefit, but to disseminate results in the service of profits. Since the risk of medical research on human subjects is justified by the prospect of health benefits from increased knowledge, as required by the Nuremberg Code, the Declaration of Helsinki, and subsequent guidelines, much of the scientific research currently published in medical journals is ethically problematic. This is a major problem for research ethics. It means that apparently ethically sound research, carried out with patient consent, approved by ethics boards, and appearing to respect the principle of equipoise – though given the way funding biases results, equipoise is typically violated[40] – is nevertheless deeply suspect. Research carried out primarily for marketing purposes places

[36] For example, J. Bekelman et al. Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review. *JAMA* 2003; 289: 454–465; J. Lexchin et al. Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review. *Br Med J* 2003; 326: 1167–1170; S. Sismondo. Pharmaceutical Company Funding and its Consequences: A Qualitative Systematic Review. *Contemp Clin Trials* 2008; 29: 109–113.

[37] Bekelman et al., *op. cit.* note 36; Lexchin et al., *op. cit.* note 36.

[38] S. Sismondo. How Pharmaceutical Industry Funding Affects Trial Outcomes: Causal Structures and Responses. *Soc Sci Med* 2008; 66: 1909–1914.

[39] D. Bloor. 1976. *Knowledge and Social Imagery*. London: Routledge & Keegan Paul.

[40] J. Fries & E. Krishnan. Equipoise, Design Bias, and Randomized Controlled Trials: The Elusive Ethics of New Drug Development. *Arthritis Research and Study* 2004; 6: 250–255.

patients at risk for the sake of private profits, not public knowledge. Pharmaceutical companies and their agents are not the only parties to blame for this violation of research ethics: both the academic researchers who participate in such research or allow it to be published under their names, and journal editors who publish it are also deeply implicated in unjustifiably placing human research subjects at risk.

ADDRESSING GHOST MANAGEMENT

At the root of the problem is the fact that pharmaceutical companies are engaged in both research and marketing. There are strong interests, then, in shaping the research to serve marketers' ends. Thus we support the call for the sequestration of drug research from drug marketing.[41] That is both a laudable goal on the largest scale and can inform more local responses to ghost management.

While ghost-managing research is ethically problematic for pharmaceutical companies and MECCs, we do not believe that either will stop doing it in the absence of strong pressure or sanctions from other actors, on whom we focus here. Those other actors are regulators, academics, and medical journals.

(a) Regulators

Governments, acting together, could end monopoly rights on pharmaceuticals. Without exclusive rights, producers of drugs would face generic competition across the board. They would, then, have little incentive to engage in expensive marketing of their products, because that marketing would benefit competitors as well as themselves. Pharmaceutical companies will argue that such a regime would reduce the incentive for research and development, but that is not obvious. Only a small minority of drugs are genuinely novel and are improvements over their forerunners.[42] The basic research leading to new drugs is more often supported by governments and foundations than by pharmaceutical companies.[43] As for clinical trials and related research, we have already shown that much pharmaceutical company research is in the service of marketing, and so could be simply unnecessary. Though it remains to be empirically demonstrated, we believe that drug development – i.e. turning novel research into products – can be done by generic companies and government agencies.

Alternatively, governments, again acting together, could force the division of pharmaceutical companies into entities that do research and development and entities that produce and distribute drugs, with strict limits – along the lines of anti-monopoly strictures – on the amount of contact between them. To the extent that drug research by non-state agencies is valuable, it should find support between grants and market mechanisms.

On a more modest scale, and not requiring coordination, regulators such as the FDA and the European Medicines Evaluation Agency could prohibit pharmaceutical companies and their agents from distributing scientific data, by prohibiting them from stating anything about their products other than what would be very closely specified upon approval of the drug. This would dramatically reduce the promotional role of drug representatives. Complementing this policy would be a prohibition on pharmaceutical company sponsorship of continuing medical education. Thus, physicians who wanted to learn more about particular drugs would have to themselves turn to the scientific literature, somewhat reducing the value of the ghost management of research. In the US, the trend is in the opposite direction, with legislation, court rulings, and regulatory change tending to grant companies more freedom in their ability to promote drugs; both the FDA and the courts seem to be leaning toward allowing unlimited distribution of published scientific articles.[44]

One form of regulation that will *not* work is self-regulation. ISMPP, for example, has recently adopted a code of ethics.[45] The code encourages ISMPP members to apply the standards of professional organizations such as

[41] M. Angell. 2004. *The Truth About Drug Companies: How They Deceive Us and What to Do About It*. New York: Random House; M. Doucet & S. Sismondo. Evaluating Solutions to Sponsorship Bias. *J Med Ethics* 2008; 34: 627–630; T. Hubbard & J. Love. A New Trade Framework for Global Healthcare R&D. *PLoS Biol* 2004; 2: 147–150; A. Schafer. Biomedical Conflicts of Interest: a Defence of the Sequestration Thesis – Learning from the Cases of Nancy Olivieri and David Healy. *J Med Ethics* 2004; 30: 8–24.

[42] Food and Drug Administration. 2004. CDER NDAs Approved in Calendar Years 1990–2004 by Therapeutic Potential and Chemical Type. Center for Drug Evaluation and Research. Available at http://www.fda.gov/cder/rdmt/pstable.htm [Accessed 6 Dec. 2008].

[43] US Congressional Joint Economic Committee. 2000. The Benefits of Medical Research and the Role of the NIH. Washington, DC. Accessible through the US Federal Government's Document Services.

[44] Food and Drug Administration. 2008. Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Draft Guidance) http://www.fda.gov/oc/op/goodreprint.html [Accessed 30 April 2008]; Sismondo, *op. cit*. note 34.

[45] International Society for Medical Publication Professionals. 2007. ISMPP Code of Ethics. Available at http://www.ismpp.org/pdf/94_80_ISMPP%5b1%5d.Code.of.Ethics.pdf [Accessed 6 Dec. 2008].

the ICMJE and the Consolidated Standards for Reporting Trials (CONSORT).[46] Other industry guidelines include the Good Publication Practices (GPP) for pharmaceutical companies and the guidelines of the European Medical Writers Association (EMWA).[47] Such self-imposed standards miss the point, since they do not address the conflict between science and marketing that leads to biased literature. Merely regulating MECCs while preserving the current institutional structure will ensure that trials continue to be ghost managed, and that patients continue to be put at risk for commercial gain.

(b) Authors

It is abundantly clear that academic researchers who appear as authors on articles to which they have contributed little or nothing are behaving unethically. Such authors violate accepted norms of authorship, but much more importantly they help to hide conflicts of interest.[48] They lend their credibility to research that is likely to be biased and is performed for its marketing value, and is therefore, as we have already argued, ethically flawed from the beginning. For the sake of some academic credit and perhaps a small consulting fee, then, these authors unnecessarily put patients at risk, and directly contribute to pharmaceutical companies' marketing efforts. Those marketing efforts are intended to convince physicians to see health conditions differently, to think more – and more highly– of particular drugs, and to be more likely to prescribe those drugs. Thus academic deception is in this case a serious breach of responsibility to the public.

But such behaviour is simply at the end of a spectrum that includes activities few find remarkable. Although many authors could act with a great deal more integrity than they do, the vast majority of authors do not act with malign intent: they are simply doing research within the institutional contexts in which they find themselves. Many discussions of publication ethics adopt an overly moralistic tone, as if a lack of 'integrity' among researchers, rather than the economic influence of the pharmaceutical industry, is the main cause of ethically flawed research. If such authors are to avoid unethical and deceptive practices, they need more than moralistic scolding. They require, most of all, genuine alternatives to engaging in hidden marketing.

Authors need such alternatives if their research is to be ethically defensible; but they also require them for self-interested reasons. They might believe that participating in industry-funded, ghost-managed research is the only way for them to do cutting edge science but, in fact, they are ensuring that such research is actually carried out by others. 70% of pharmaceutical company funding goes not to academic researchers but to CROs that do not expect to publish their research under their own names.[49] Even part of the remaining 30% of industry-funded research is likely to include some that is ghost-managed from beginning to end.[50] The current system of industry sponsorship, then, is one in which academic researchers do little truly independent research and where they are valued more for contributing a façade of independence than scientific insight. This puts such researchers in a dangerous position: by participating in ghost-managed research they undermine the independence for which the pharmaceutical industry values them. Each scandal diminishes their value; and they would do well to wonder whether the pharmaceutical industry might eventually decide to abandon the façade and simply take ownership of its research. If so, then academic researchers would lose both their sources of funding and their claim to do independent and cutting edge science. If they want to do the ethically right thing, or if they simply want to do real, independent science, academic researchers would be better served by a system that allowed them to carry out their research without interference from pharmaceutical companies and their ghost-manager proxies.

It would be unfair, then, to focus criticism entirely on such authors and researchers, who are, after all, caught in an unethical system that they had little part in designing. Moreover, ghost management is a completely normal part of medical science: those who, for the best of reasons, want to do interesting medical research might understandably feel that they have little choice but to

[46] CONSORT. 2006. The CONSORT Statement. Available at http://www.consort-statement.org [Accessed 6 Dec. 2008].

[47] E. Wager et al. Good publication practices for pharmaceutical companies. *Curr Med Res Opin* 2003; 19: 149–154, also available at http://www.gpp-guidelines.org/ [Accessed 6 Dec. 2008]; A. Jacobs & E. Wager. European Medical Writers Association (EMWA) guidelines on the role of medical writers in developing peer-reviewed publications. *Curr Med Res Opin* 2005; 21: 317–321, also available at http://www.emwa.org/Mum/EMWAguidelines.pdf [Accessed 6 Dec. 2008].

[48] For our purposes we can ignore issues of fairness in violations of norms of authorship: The under- or unacknowledged contributors – medical writers, company statisticians, and others – are part of different economies of authorship, and while the inappropriate academic credits accumulated by over-acknowledged contributors are real, their importance fades in relation to the health consequences of ghost management.

[49] P. Mirowski & R. van Horne. The Contract Research Organization and the Commercialization of Scientific Research. *Soc Stud Sci* 2005; 35: 503–584.

[50] Blumenthal et al., *op. cit.* note 16; J. Lexchin. Implications of Pharmaceutical Funding on Clinical Research. *Ann Pharmacother* 2005; 39: 194–197; M.M. Mello et al. Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry. *N Engl J Med* 2005; 352: 2202–2210.

participate in pharmaceutical industry structures. In order to carry out research that is both scientifically meaningful and ethically sound, authors require help from other agents.

(c) Medical Journals

Medical journals are an essential link in the chain that connects research and marketing: since major medical journals have the most authority among sources of medical information, considerable work of ghost management is aimed at placing articles in such journals. Journals make some efforts to prevent ghost management and ghost authorship. The most important set of criteria for authorship of medical papers is that of the ICMJE, adopted by most journals. According to these criteria,

> Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.[51]

Ghost-managed papers will typically violate one or more of these requirements of authorship. When publication planners and industry researchers, rather than the academic authors whose names appear on the paper, do most of the work of designing the trial, analysing the data, and drafting the article, the academics who receive credit do not truly meet the ICMJE criteria. Despite this, medical journals publish large numbers of ghosted papers: again, roughly 40% of articles on recent drugs are managed by publication planners.

Journal editors might plead ignorance, but implausibly, at least in general. At a recent meeting of ISMPP, one of the two international associations of publication planners, the speakers included editors of three of the very best regarded medical journals, one person representing a journal editors' organization, and a representative of a major international publisher of many journals. Some of these people took the opportunity to promote their journals during their talks. A few other publishers and journals were represented by booths at the trade show associated with the meeting.[52] Moreover, it was clear from the conference as a whole that editors recognized the roles of their audience, and that there is routine communication between publication planners and journal editors. For example, the editor of a top-ranked journal said, 'The way to get an article published easily, which is what our goal is and yours, is to avoid practices that are going to slow things up and slow the period of time before you can start enjoying the acclaim and the revenue that comes with successful publication in a big journal.' Another expressed appreciation for medical writers, and suggested that to meet ICMJE guidelines *authors* have a responsibility to insist on 'early active involvement in the research project' not 'to sign off on already-written manuscripts, particularly in review articles'. This editor clearly understood the planners' activities and goals.[53]

These journal editors are violating the spirit of their own rules. They do so because publication planners handle some of the more important manuscripts they can publish: reports of randomized, controlled trials or other major studies authored by well-regarded researchers. These manuscripts will go on to be cited much more often than others on the same topic,[54] both on their own apparent strengths and because publication planners will themselves cite them. Drug representatives will use reprints of these articles to buttress their sales pitches, in the process earning the journals reprint fees and further promoting the articles themselves. Clearly, medical journals face substantial conflicts of interest when dealing with ghost-managed manuscripts, as they do with sponsored manuscripts in general.[55]

Medical journals should be concerned with advancing medical knowledge in the service of human health, not with acting as part of the marketing arm of the pharmaceutical industry. They should therefore make every effort to ensure that they do not publish ghost-managed articles. No doubt many editors, like many researchers, see themselves as engaged in the publication of honest scientific research, and as doing so within a commercial system that they had no part in designing. They would be understandably offended to be accused of being corporate shills. Despite their noble intentions, however, these journal editors are –perhaps unknowingly or unintentionally – engaged in the publication of unethical research. It is true that they are often unable to determine positively whether authorship on a particular article is illegitimate or inappropriate. However, at a minimum, they should refrain from dealing with MECCs, and insist that contact people on submitted manuscripts be authors. This would at least force authors to serve as intermediaries on manuscripts, which

[51] ICMJE, *op. cit.* note 5.

[52] ISMPP. Program of The 3rd Annual Meeting of ISMPP. Philadelphia, 2007 [available from authors].

[53] Sismondo, *op. cit.* note 34.

[54] Healy & Cattell, *op. cit.* note 21.

[55] J. Lexchin & D. Light. Commercial Influence and the Content of Medical Journals. *Br Med J* 2006; 332: 1444–1447.

is more contact with manuscripts than authors sometimes now have. Journals, acting together, should also develop and enforce much more strict penalties for violation of ICMJE rules. For example, they should bar anybody found guilty of illegitimately serving as an author from publishing in *any* medical journal for some considerable period.

As a further step, journals should not provide reprints for commercial purposes. Former BMJ editor Richard Smith reports a case in which a journal sold $1 million worth of reprints of a single article to a company, enough to provide copies to most practising physicians in North America and Western Europe.[56] Authors may want a reasonable number of copies of an article to distribute to colleagues, but numbers in excess of a few hundred are being used for marketing purposes.

Ideally, though, journals should refuse to publish any industry-sponsored trials. There is no other way entirely to remove commercial conflicts of interest and their resulting biases. If journals want to avoid being morally implicated in putting patients at risk for the sake of commercial gain, they must stop publishing articles that do just that. Certainly the dozen most major journals are in a good position to do so. Their rejection rates are so high that they could easily afford to do so without running short of high-quality articles to publish. JAMA and the NEJM, for example, have rejection rates as high as 94%.[57] If they refused sponsored trials, publication in their pages could become even *more* prestigious, since articles appearing in their pages would be free of commercial bias and so much more likely to be ethically sound.

We do not mean to suggest that suppressing data is the solution to unethical research. The results of ethical research should certainly be widely publicized, because of their value to medical knowledge. But, if many trials are carried out primarily for the purposes of marketing rather than increasing medical knowledge, then our proposal will not lead to the suppression of data. Without prestigious publication venues, companies will have no reason to undertake marketing-oriented research. Far from leading to a glut of suppressed data, our proposal would lead to fewer trials. This is no bad thing: if some industry-sponsored trials are unethical, then we should want there to be fewer of them. And companies can still post data from their other trials to public databases, as they have largely committed to do in any case. If, on the other hand, journals insist on continuing to publish the results of industry-sponsored trials, then they should publish the data in the closest to raw form as possible, and engage in serious critiques of the trials that they publish, rather than simply printing industry-approved advertisements.

In refusing to publish industry-funded or ghost-managed articles, journal editors can avoid the moral stain of putting patients at risk for commercial profit. On its own, this is an important reason to reject such articles. But journal editors have an additional reason: refusing to publish sponsored articles can help researchers escape from a system that pushes them to conduct unethical research. Medical journal editors occupy a position of relative power compared with individual authors and researchers. As long as MECCs can boast of acceptance rates of 80%[58] in journals that have *rejection* rates above 90%, researchers will quite understandably feel that the only way for them to publish in major medical journals is to accept pharmaceutical funding and the ghost management that often accompanies it. A refusal on the part of medical journals to publish industry-sponsored trials would give authors and researchers an important reason to refuse to engage in industry-funded research, and it would give them a prestigious venue for such research. Journals would not only be protecting their own ethical integrity; they would also be helping researchers and authors to act with integrity.

CONCLUSION

We have argued that authors and journal editors are complicit in unjustifiably putting trial participants at risk. On its own, this is bad enough, and would be a serious breach of research ethics even if it rarely, or even never, led to significant adverse health effects. But such practices *do* have serious effects on health. Moreover, these effects are not confined to trial participants but potentially extend into the general public.

Studies that display a significant pro-sponsor bias play an important role in the drug approval process, in clinical practice guidelines, in physicians' prescribing practices, and even, in some cases, in patients' beliefs about which treatments they should pursue. Sometime, this means that drugs that should be neither approved nor prescribed end up in wide use, the recent Vioxx controversy being only one prominent example. In such cases, patients are not merely put at risk by the way ghost management uses medical research for marketing purposes: they are actually harmed. Not only does ghost-managed research put

[56] R. Smith. Medical Journals and Pharmaceutical Companies: Uneasy Bedfellows. *Br Med J* 2003; 326: 1202–1205.

[57] A. McCook. Is Peer Review Broken? *The Scientist* 2006; 20: 26–35.

[58] See, for example, Gardiner-Caldwell Group. 2007. http://www.thgc-group.com/ [Accessed 15 Dec 2007].

trial participants at risk, it threatens the health of millions of patients who take drugs that might otherwise not be prescribed. It may, through disease-mongering, alter physicians' and potential patients' conceptions of health and disease, leading to more perceptions of disease and more prescriptions.[59]

Ghost management therefore has serious implications for health, both for trial participants and for the public at large. The best way to eliminate the dangerous health effects of ghost management would be to separate pharmaceutical research from marketing completely. Short of such a radical solution, however, authors and journal editors still have an obligation to the public to refrain from engaging in, or publishing, ghost-managed research. Otherwise, they are putting public health at risk for the sake of private profit.

[59] R. Moynihan & A. Cassels. 2005. *Selling Sickness: How the World's Biggest Pharmaceutical Companies are Turning Us All into Patients*. Vancouver: Greystone Books.

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