ARTICLES

Conflicting interests: The evolution of an issue

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ABSTRACT
The systematic funding of University research has brought into relief a question of conflicting interests. The potential in funded research for conflict and the damaging effects that conflicting interests might have on civil society had been first noted by Eisenhower in the context of State-funded research. Since the 1980s, there has been greater concern with the corrosive effects of private or corporate funding on research. Initial efforts to manage the problems have focused on authorship declarations, but recent controversies with the SSRIs suggest the only way to manage the problem is by placing all clinical trial data in the public domain.

Introduction

The issue of conflicts of interest in medicine has grown in salience in recent years, marked by a series of defining moments roughly twenty years apart – 1961, 1984 and 2002, all of which have been American, before coming to a moment of clear crisis in 2004. Rather than trying to analyse the elements that make conflicting interests a problem, this paper seeks to offer a chronology of the key moments and background changes against which the issue of conflict of interests became the problem it now is.

1961

The role of conflicting interests in medical research arguably opened in January 1961, when Dwight Eisenhower in his last speech as US president noted the growing power and influence of what he termed the military-industrial complex:[1]

'In the councils of government, we must guard against the acquisition of unwarranted influence whether sought or unsought by the military-industrial complex. The potential for the disastrous rise of misplaced power exists and will persist.

'We must never let the weight of this combination endanger our liberties or democratic processes. We should take nothing for granted. Only an alert and knowledgeable citizenry can compel the proper meshing of the huge industrial and military machinery of our defense with our peaceful methods and goals, so that security and liberty may prosper together.

'Added to and largely responsible for the sweeping changes in our industrial-military posture has been the technological revolution during recent decades. In this revolution, research has become central; it also becomes more formalised, complex and costly. A steadily increasing share is conducted for, by, or at the direction of the Federal Government.

'Today the solitary inventor, tinkering in his shop, has been overshadowed by the task forces of scientists in laboratories and testing fields. In the same fashion, the free university, historically the fountainhead of free ideas and scientific discovery has experienced a revolution in the conduct of research. Partly because of the huge costs involved, a government contract becomes virtually a substitute for intellectual curiosity …

'The prospect of domination of the Nation's scholars by Federal employment project allocations and the power of money is ever present and gravely to be regarded.

'Yet, in holding scientific research and discovery in respect, as we should, we must also be alert to the equal and opposite danger that public policy itself could become the captive of a scientific and technological elite.'

Eisenhower's concern stemmed from the highly visible emergence of a research establishment that had not been present before the Second World War. The concern in 1961, perhaps more clearly obvious to a Republican president, was the influence of government on academics. The historical context also linked the emergence of the problem with government funding, leading many to focus on the relative novelty of government having a role in research and to overlook the age-old adage about pipers and tunes. In broader terms the concerns were with the notion of made-to-measure or applied research. Government, especially the American government, remained the focus of conflict of interest concerns through the mid-1970s.

Eisenhower's speech did not mention medical research overtly, but the War effort had included substantial government funding of and involvement in medical research, which led after the war to the establishment of the National Institutes of Health in the United States and comparable medical research establishments in other countries. During the 1950s and 1960s, academic careers in medicine for the first time required a research component and the phrase 'publish or perish' first appeared.[2]

1984

When the question of conflict of interest next emerged in 1984, the context had changed completely. Arnold Relman, then editor of the *New England Journal of Medicine*, brought to light the issue of conflict of interest.[3] He outlined that there had always been links between academics and industry but that the scope for a commercial application of research had grown, and that this brought with it new risks. A few years before, the president of Harvard, Derek Bok, had begun the process of questioning the position of academia in the new

world of university campuses penetrated not by the government or the military but by commercial science.[4]

The emergence of a debate about conflict of interest in medicine in the early 1980s suggests that developments in the previous decade were impacting on the world of academic medicine. In fact, in the course of the 1970s, there had been a series of linked developments that are clearly pertinent to this issue.

First, the science behind both psychiatry and many other branches of medicine became Big Science in a way that it had not been before. Through to the late 1960s, while a host of new treatments were introduced to psychiatry, the discipline remained one in which senior clinicians undertook experiments with drugs that determined whether these drugs worked or not, and the testing of drugs both in clinical trials and in clinical practice remained closely tied to the impact these drugs had on patients. Feedback from patients still played a part in this scientific world.

However, starting from the 1970s, clinical trials were conducted on multiple sites and were often multi-national, and the trials were increasingly coordinated by either the pharmaceutical companies themselves or by a new breed of organisations, CROs (Clinical Research Organisations), that emerged in the late 1970s. The upshot of these developments was that clinicians involved in trials were increasingly less likely to have a good picture as to what a drug actually did. The role of senior clinicians vis-à-vis new drugs and pharmaceutical companies became increasingly ornamental rather than substantive. These clinicians became the figureheads who often presented company-generated material with which they themselves had little or no personal familiarity. Their role increasingly was one of educating or leading by example their fellow clinicians into the use of these drugs.

Operating at one remove from patients in this way meant that clinicians no longer had the authority that had previously stemmed from personal hands-on research experience with a drug. In an academic world growing increasingly busy, senior clinicians were also less likely to be actually treating patients, and thus they were also less likely to have direct feedback on the effects of the drugs from the patients to whom they had given the drug. Finally, they were increasingly less likely to be able to scrutinise an entire database themselves and try to extract a valid picture of what this new agent might do, as the data from the multiple sites of a trial were increasingly held centrally in pharmaceutical company archives rather than in a lead investigator's files.

A second way in which medical science became Big in the 1970s was with the development of an increasing array of technologies designed to establish what drugs were actually doing or where they might actually be working in the body. Technologies such as scintillation counters and later brain scans of various sorts produced data that only the experts could interpret. Where before both patients and their advocates could contest the meanings that were being put on an experience by an expert, in the case of the new technical data the only way for patients or anyone with a dissenting point of view to

contest the data would have been to hire their own experts. Increasingly patients and the general public had to rely on the hope that their experts would be genuine.

A third factor also came into play in the late 1970s. Pharmaceutical companies and their marketing departments became more heavily involved in the business of imparting clinical information about new compounds. The first satellite symposia at scientific meetings began to appear at this time and by the 1990s satellite symposia were a regular feature. For example, in the mid 1990s American Psychiatric Association Meetings might have as many as 40 Satellite Symposia with companies paying several hundred thousand dollars for the privilege of hosting each of these. Increasingly, Satellite Symposia came with journal supplements which featured new research data or review articles on issues of interest to the company and their product, and increasingly these articles were 'apparently' written by some of the most senior figures in the field. In order for this to happen efficiently, and particularly given that these same senior figures were in great demand from a range of different pharmaceutical companies, it was simply not feasible for these authors to write all their own articles and an industry grew up around providing ghost-written articles for both companies and authors.[5]

The extent to which ghostwriting was a new factor to be taken into account by journals and the scientific field began to register in the early 1990s. In 2000, journal editors attempted to tackle the problem by putting in place procedures requiring authors to offer some specification of their role in the production of an article.[6]

A final change of note was the passage of the Bayh-Dole Act, which came into force in 1981.[7] The background to this piece of legislation lay in concerns about an apparently slowing rate of growth in the American economy. One way to stimulate productivity in research-led areas, it was proposed, was to re-organise the academic system in a manner that enabled academics and institutions to hold patents and thereby profit from developments that had come about by virtue of support from federally-funded projects.

Bayh-Dole marks a point of transition to a new focus on what is now termed the knowledge-based economy. This refers to the production of a new set of manufactured goods regarding which intellectual property rights are of importance and whose value lies in the intellectual artefacts associated with the basic product rather than in the commodities themselves. Pharmaceutical products are among the leading items in this new economy.

2002

The issue of academics holding patents was at the heart of the next defining moment in the conflict of interest debate in 2002, when MJ Owens, along with a co-author, Charles Nemeroff, a Professor of Psychiatry in Emory University, had a review paper published in *Nature Neuroscience*. In this paper, Nemeroff argued first, that a transdermal patch for the delivery of lithium might be clinically useful, second, that emerging aspects of the neuroscience of mood disorders pointed to a

utility for mifepristone in the treatment of psychotic depression, and third, that milnacipran, a drug available on some European and Asian markets, might be useful for the treatment of fibromyalgia.[8] Readers of the review were not made aware that Dr Nemeroff held a patent on a transdermal patch for the delivery of lithium, or that he was a member of the Scientific Advisory Board of Corcept Therapeutics who were conducting the trials on mifepristone, or that he was Director and Chairman of the Psychopharmacology Advisory Board of Cypress Bioscience which was hoping to bring milnacipran to the US market for fibromyalgia.

Drs Bernard Carroll and Robert Rubin wrote to *Nature Medicine* pointing out these undeclared conflicts of interests. *Nature* refused to publish their letter, arguing the journal did not have a clear conflict of interest policy that Dr Nemeroff had violated. Where journals had clear conflict of interest policies, Dr Nemeroff had in fact probably been more than usually forthcoming in complying with such policies and declaring his interests. The issue moved from *Nature* to the *New York Times*. Following a *New York Times* article,[9] a letter to *Nature* from a number of senior figures within the American scientific establishment advocated that *Nature* beef up their conflict of interest policy.

Nature complied, stating that: 'The argument for extending existing disclosure policy to reviews is strong. Studies of the clinical literature have concluded that industry funding is associated with pro-industry results, so there is a clear prima facie case for concern. One can argue that because review articles are inherently selective and opinionated, they provide more scope for bias than do reports of research results. Moreover there have been clear examples of abuse, in which academic authors have been paid by pharmaceutical companies to put their names and credibility to reviews produced by ghost writers employed to boost company products. The most compelling argument for disclosure, however is to remove suspicion. When scientists offer their professional expertise without disclosing potential financial benefits to themselves, it threatens to undermine public trust, not simply in a particular paper or journal, but in the integrity of the scientific enterprise as a whole. The main purpose of our disclosure policy therefore, is to maintain the credibility of the material we publish, in the eyes of the scientific community and the public.'[10]

The journal further added that: 'the public interest is not served by stigmatising commercial research. Academia and industry are increasingly intertwined, particularly in the US, and such partnership can offer significant benefit to scientific progress. The challenge is to manage the relationship in a way that does not undermine academic values such as open communication, prompt publication and the perceived integrity and objectivity of the scientific community. Many of these concerns are best addressed by public disclosure, which journals are uniquely well placed to promote. Journals cannot eliminate all tensions arising from commercialisation of academic research, of course, and ultimately these issues must be resolved in the marketplace of ideas.'[11]

This series of events became grist to the mill of a range of conflict of interest debates in medical and psychiatric meetings in the course of 2003/2004. What gave the incident extra spice was that Dr Nemeroff had links to almost all of the major pharmaceutical companies in addition to other companies, and had been described as the most powerful man in American psychiatry.[12]

The editorial response from *Nature Neuroscience* makes it clear that, as of 2002, the question of disclosing conflicts of interest was bound up in the broader issue of the dependability of the scientific literature. Conflict of interest had become something of a code for lack of access to the raw data underpinning experiments. Having begun a policy of asking authors to declare conflicts of interests in the 1980s, journals had moved on by 2000 to in many cases requiring authors to complete authorship declaration forms in an effort to ensure that someone at some point in the chain of events that proceeds from scientific experiment to the publication of results of that experiment was in a position to take responsibility for any claims being made.[13] Despite this, the new authorship matrix is consistent with many articles being ghostwritten,[14] and the notional authors never in fact having seen the raw data on which they appear to report.

Science and Journal-ism

As the leading journals in medicine began to tighten their conflict of interest policies through the 1980s, they drew a hostile response from many academics. Critics offered arguments to the effect that it almost cannot in principle make any difference to the progress of science whether an author has a conflict of interest or not.[15] The response from *Nature* makes it clear that it remains their expectation that the marketplace of ideas is still the guarantor that truth will emerge. The example of Thomas Edison and the light bulb is commonly cited – surely, it is argued, neither the scientific community nor its journals would have wished to block someone like Edison from reporting the effects of his experiments in trying to produce light bulbs, phonograms or other technical developments. Edison is a carefully chosen figure in this regard in that he was clearly motivated by commercial concerns, but equally clearly, contributed significantly across a range of applied developments.

Arguments in this vein typically appeal to philosophies of science, such as that put forward by Karl Popper, namely that science advances by refutation. The implication here is that science is a process that will inevitably find out any flawed statements, as its practitioners will at some point take statements that appear likely to be false and will test these for their reproducibility. This process could, conceivably, even be enhanced by misleading statements put forward by individuals who are led to such positions by conflicts of interest. The success of science in other words lies in the fact of its being a communal and empirical process rather than a process whose success depends on the motives of individual practitioners.

Against this argument, it seems necessary to distinguish between the process of science, which is often laboratory-based and is always

empirical, and the subsequent communication of scientific results. The first scientific societies, such as the Royal Society, operated on the basis of a public demonstration of results in the form of scientific experiments conducted in the presence of peers. The scientific article is an off-shoot of these demonstrations, which through peer review aims at reproducing something of the conditions present at the first Royal Society Meetings.

Since then the communication of scientific results has developed in a number of different dimensions and the uses to which such communications can be put have become increasingly rhetorical. Claims first made in scientific forums, acquire a cloak of legitimacy derived from science when later put to use in political debates, for social purposes, or for other ends. These other ends include an increasing use of certain scientific products in medico-legal settings or for other persuasive purposes. Within medicine, perhaps linked to the need to sell medicines through physicians, scientific papers portraying evidence of treatment efficacy have become a marketing tool.

Given this latter proliferation of both the amount of literature and the uses to which this literature is put, there would seem to be an increasing need to recognise that what is involved here is essentially a journal-ism that should be subject to all the rules of mainstream journalism. This is particularly the case given that an increasing proportion of the medical literature is associated with pharmaceutical companies and this literature reports on findings not readily open to independent replication. Were others able to undertake comparable studies and generate competing results or otherwise refute the claims made by pharmaceutical companies or their experts, then it would be more reasonable to argue that the laboratory-based or replicating arm of science might be able to correct for any corruptions stemming from conflicts of interest in its associated journalistic processes.

The Greatest Divide in Medicine

In 2002, the issue of *Newsweek* coinciding with World Mental Health Day carried a cover feature of a depressed teenage girl.[16] The inside story outlined that there were 3 million depressed teenagers in the United States, and that if left untreated this situation would lead to unacceptable levels of substance abuse, failed marriages and careers and deaths from suicide. The article noted that there were a number of new antidepressants, such as Selective Serotonin Reuptake Inhibitor (SSRI) drugs Paxil, Zoloft and Prozac, which could help. Such articles commonly have input from PR companies working for pharmaceutical companies. The expectation in this case would appear to have been that a number of SSRIs would shortly thereafter have a licence to treat teenage depression.

There had in fact been approximately 21 randomized trials of SSRI drugs in children, giving rise to 6 full articles with 3 abstracts, as well as approximately 70 publications of open studies or case reports with Celexa, Prozac, Paxil (Aropax/Seroxat), Zoloft, Luvox and Efexor. The open studies and published double blind trials universally portrayed these drugs as safe, well-tolerated and effective when given to

children. The most famous of these studies, study 329, involved Paxil,[17] stated that Paxil was safe, well-tolerated and effective in children, but noted that some children became emotionally labile while taking it. The question of what was happening to children, who were deemed to have become emotionally labile, was picked up by journalists and lawyers rather than scientists or regulators.

As a result of a Glaxo SmithKline application to the regulators for a license for Paxil to treat childhood nervous disorders, the raw data from clinical trials were lodged with a number of national regulators. Within a fortnight of seeing the raw data in May 2003, after the events lying behind the term emotional lability had been clarified, the regulators in the United Kingdom issued a warning against the use of Paxil for minors. A few weeks later, Glaxo SmithKline wrote to all doctors noting that Paxil use was linked to suicidality and that withdrawal from Paxil was also linked to an apparent doubling of the rate of suicidality. Three months later, Wyeth recommended against the use of Efexor in children, in similar terms. In December 2003, British regulators issued a position statement in which they stated that none of these drugs had demonstrated efficacy in depression in children. This reassessment of the data does not however represent a triumph of scientific method – it indicates rather a crisis triggered by media concerns.

These developments led to a projected FDA hearing for February 2nd 2004. Ten days before this hearing, in what was widely seen as a pre-emptive strike, a working group for the American College of Neuropsychopharmacology reported that after reviewing the evidence it was the task force's view that SSRI drugs were safe and effective and well-tolerated by children.[18] The authors of this report included Emslie, Wagner and Ryan who had all been authors on study 329, and between them had been authors on most of the published randomized trial literature on SSRIs given to children. These three authors and their co-authors, however, noted that they might not be correct in their conclusions that there were no problems with SSRIs in that they had not seen the raw data.

The apparent anomaly of authors not having seen their own data was compounded in this instance by the very report having been in fact authored by GYMR, a Washington based public relations company, who specialise 'in translating the language of science and medicine into the more understandable language of health' (From GYMR.com). GYMR was 'founded in 1998 by a team of experts in healthcare and social change… [it] offers clients marketing and communications expertise that strategically support public policy goals… [clients] include many of the nation's most respected associations, government agencies, pharmaceutical companies, philanthropic organizations and health initiatives.' 'Whether it's provoking action on a national health issue or crafting an organizational image that appeals to internal and external audiences, GYMR excels at designing and implementing issue and image campaigns.'

In this case, GYMR was delivering perhaps the premier organisation in the world of psychopharmacology and a slate full of the

most prominent names in the field to support a company position. It transpired however that internal documents made clear the key company in the field had reneged from this position in 1998 – a SmithKline Beecham assessment of the Paxil studies, which had been completed at that time, including study 329, indicated that the drug did not work for depressed children, but that the data would not be submitted to the regulators, as a statement to the effect that the drug had not been shown to work for children would have a negative commercial impact.[19] Selected positive data, however, would be progressed to publication. Subsequently, other investigators have made it clear that this state of affairs was not confined to SmithKline and Paxil.[20]

Despite the pre-emptive strike, the February FDA hearing recommended strengthening the warnings on these drugs, against a background of regulatory assessments that at least 13 of the 15 studies undertaken of antidepressants in children failed to show efficacy for the drug, and panel views that there appeared to be an activation syndrome on these drugs.

We have here the greatest divide in medicine between the raw data on an issue on the one side and the published accounts purporting to represent those data on the other. The divide, it is important to note, only came to light as a result of the efforts of journalists and lawyers. No clinician or scientist had a hand in questioning the validity of the 'science'. What lessons can be drawn from this situation?

First, the entire set of open and randomized trials germane to both the safety and efficacy of these drugs in children would seem to have the appearance but not the substance of science. The discrepancy between the papers and the underlying data is comprehensive and would appear to stem in part from the possibility that many if not close to all of the key studies have been ghost-written. It is difficult to avoid such a conclusion when even the notional authors of the key papers claim not to have seen the raw data. This latter point transforms this issue from a matter of one group of drugs causing a hazard in one group of subjects into a problem for evidence-based medicine.[21]

A second point about this current crisis is that while pharmaceutical companies know exactly how many prescriptions are issued for a drug, extraordinarily, no-one knows how many children or adults are on any drugs. When this fact is allied to evidence that serious adverse events are reported by physicians to regulators in no more than one in one hundred cases, it is clear that the situation is one in which the dominant interests of industry could not be better served. The degree to which conflicting interests affect clinicians becomes clear in this case also, in that when it comes to reporting on the hazards posed by SSRIs, the quality of the information reported by patients on adverse events appears to be much better than that reported by physicians.[22]

Finally, the issue of the reporting of the results of SSRI trials done in children gives us an instance in which a set of what appeared superficially to be scientific communications were in fact functioning as

a rhetorical device rather than as the products of a science exercise. In this case the rhetoric was aimed at gaining a marketing advantage. What better marketing position to adopt than one which advocates a course of treatment on the basis of an evidence-based scientific consensus? There would however appear to be reasonable grounds to state that there must be some fundamental opposition between marketing and science, in that the former operates to build consensus,[23] while the latter supposedly moves forward by fracturing consensus. When we have arrived at a situation in which the mental sets of clinicians have been captured so that it is difficult for them to conceive of alternatives to those being sold to them, there are reasonable grounds to state that such a field is no longer scientific. When there is almost no possibility of discrepant data emerging to trigger a thought that might be unwelcome to the marketing department of a pharmaceutical company, the situation would seem appropriately described as totalitarian.

One of the ironies of the current situation is that those concerned about developments often lobby for public or state funding of studies, unaware of the history of these issues – namely that governments were once thought even less disinterested than private companies who are in principle perhaps subject to the discipline of the marketplace. Part of the solution to this crisis would appear to lie not so much in the funding source that leads to conflicting interests, but in independent access to the raw data from clinical trials. If companies want to market their product under the banner of science, they can be required to conform to the norms of science, but this will require journal editors and academic meeting organizers to refuse access to articles or presentations on data that is not in the public domain. This, rather than conflict of interest or authorship declarations, would seem to offer a way forward.

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