

Confronting the conflict of interest crisis in medical research

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ABSTRACT

In the last couple of years, serious controversies have raised doubts over the reliability of research supporting the efficacy and safety of Selective Serotonin Reuptake Inhibitors, popular drugs used for the treatment of depression and a variety of related conditions. These controversies have also evoked concerns over the promotional tactics used by industry to promote these drugs. In another article in this volume, David Healy argues that the tactics highlighted by these and some other recent controversies in psychiatry have brought medical research itself to the level of commercial publicity. In the following article, I provide some additional first-hand information about controversies in which David Healy was involved. I then situate these controversies within the context of the increasing commercialization of medical research. I discuss how the controversies highlight the failure of existing regulatory regimes in curbing inappropriate industry influence over research. I critically analyse some of the measures recently promoted by the medical research community, such as the introduction of a clinical trial registry, and I indicate why these measures are insufficient. In conclusion, I highlight how a more radical reform of the clinical trials scene is needed.

Introduction: David Healy and the pharmaceutical goliaths

David Healy's article is one among many articles published in the last couple of years that highlight how commercial interests of pharmaceutical companies impact on medical research and practice. In his earlier writings, Dr. Healy, a psychiatrist and Director of the North Wales Department of Psychological Medicine, analyzed how commercial drug development has influenced the development of modern-day psychiatry in the second half of the last century. In his influential book *The Anti-Depressant Era*, for example, he shows very poignantly how the financial interests of pharmaceutical companies have contributed to shaping the nature of some psychiatric diseases.¹ Healy and others after him have argued that pharmaceutical companies are under pressure to find markets to sell their drugs.² To do so, pharmaceutical companies not only defend their turf within existing markets and aggressively promote prescription of their drugs, but they also have developed complex marketing structures aimed at creating new consumer demands, by moulding the concept of disease itself. Once a

particular patient population is saturated in terms of drug consumption, a new disorder and thus a new patient population can be found for which treatment with the same or a similar drug can be recommended. For example, pharmaceutical companies have been actively involved in increasing the public's 'awareness' that minor depression, anxiety, social phobia, post-traumatic stress disorder and pre-menstrual dysphoric disorder are diseases or mental illnesses for which pharmacological treatments are available.

A wide range of strategies have been used to publicize pharmacological treatment of these diseases. In North America, famous hockey stars, football players, pundits and former politicians have been enrolled by pharmaceutical companies to promote the public's understanding of newly-established diseases and their treatment. Radio hosts are paid or otherwise lured into talking about these conditions on prime-time shows, and video-clips prepared by communications firms, with not very subtle publicity for particular treatments, increasingly find their way as fillers for dead moments in local news bulletins.

The tendency to medicalize variable aspects of the human condition has been particularly poignant in some areas of psychiatry, where the line between disease and a variable mental state is often difficult to define, and where diagnostic criteria are often vague. Dr. Healy has been among the first to analyze this phenomenon in detail and based on a thorough understanding of pharmacology and its historical development.

While Healy's past analysis of this development already sheds a critical light on the practices of some pharmaceutical companies and on the impact of commercial drug development on medicine, Healy has lately become an even more vehement critic of industry practices. He has been very vocal in expressing concerns about the lack of information on the potentially serious side effects of Selective Serotonin Reuptake Inhibitors (hereafter SSRIs). According to Healy, there have been clear indications for years now that several SSRIs may induce serious agitation, suicidal ideation and dependencies in some patients. Without rejecting the potential usefulness of these drugs, he and others have argued that there is a need for further studies on the side-effects of these drugs, and that in the absence of such studies, physicians and patients should be warned about the increased risk of suicide or agitation among those starting to take these drugs. Healy has appeared as an expert in American lawsuits against some of the major pharmaceutical companies, defending his view that the use of these anti-depressants can cause significant agitation and can lead to suicide and violent acts. In these cases, he was a witness for families of people who had committed suicide, sometimes accompanied by homicide, after starting to take an SSRI. He also appeared at recent U.S. Food and Drug Administration (hereafter FDA) hearings where the concerns about potential side-effects of some SSRIs on children and adolescents were discussed.

Healy's criticism and his appearance as an expert witness have brought him on a collision course with various pharmaceutical

companies. When the *Hastings Center Report* published a special issue on the 'Prozac phenomenon'³ and included an article of his, the drug's producer, Eli Lilly, withdrew its funding from the Hastings Center. More troubling events were awaiting Healy. Some time after the Hastings Center controversy, he was offered the position of the Director of the Mood and Anxiety Disorders Program at the Centre for Addiction and Mental Health (CAMH), the leading psychiatric research institution in Canada, affiliated with the University of Toronto. Prior to settling in Toronto, he gave a public lecture at a special conference organized by the Department of Psychiatry at the CAMH in which he reiterated his controversial but well-known view that pharmaceutical companies should have investigated further the link between suicide risk and SSRIs, and that they had failed to do so. Shortly after his lecture, the offer — which he had already accepted — was withdrawn, and Healy became entangled in a bitter lawsuit against the CAMH and the University. Healy had been hired by the CAMH and not by the University, but his appointment at the CAMH came with a 'status only' appointment in the Department of Psychiatry. As can be expected in these circumstances, associations were made in the media between this development and the high percentage (about 40% of the overall budget) of pharmaceutical funding for the Mood and Anxiety Disorders Program, as well as a close institutional research collaboration between the CAMH and Eli Lilly.

But contrary to the more easy and sinister interpretation given to this controversy in the media, Healy himself, in an article in *Perspectives in Biology and Medicine*⁴ and in his recent book *Let Them Eat Prozac*,⁵ expressed doubts about the idea of direct interference by the drug company Eli Lilly, or other pharmaceutical companies. The official explanation given was that Healy's provocative presentation in an academic setting had created unease among the members of the program that he was supposed to lead. Healy, for his part, suggests that Dr. Charles Nemeroff, a leading American psychiatrist with very close ties to the pharmaceutical industry, may have used his influence and academic standing within psychiatry to discredit him and to create doubts about the decision to hire him. He had previously indicated his utter disapproval of Healy's outspoken criticism of SSRIs and of drug companies' lack of research on side-effects. According to Healy, Nemeroff had made intimidating comments when Healy had presented data about the link between suicide and SSRIs at an earlier conference. Nemeroff was present at the Toronto conference, and had made public comments about Healy's dismissal before Healy was officially informed. Moreover, considering Nemeroff's personal financial relations with the industry, it is fair to say that he had an interest in isolating a critic of industry's tactics and in undermining his credibility.

Where there other factors at play? Healy's unwavering criticism clearly may have offended colleagues in his future institution, because it could have been understood by them as an indirect suggestion that they were all exposing their patients to serious risks and may have been participating in a pharmaceutical scam. It is also worth pointing out that some people argued that public criticism of SSRIs amounted to

fear-mongering, which could undermine the efforts to promote awareness of treatment options for people suffering from depression. Creating fear of potential side-effects, in this view, would be more harmful and lead to more suicide and suffering than remaining silent about the potential side-effects of these drugs. Controversial statements about the risk of SSRIs, on that view, would be seen as irresponsible for someone who is supposed to promote appropriate treatment for patients suffering from a debilitating disease.

Did these ideas play a role in the rescinding of CAMH's appointment of David Healy? Concerns about the potential atmosphere within the new department, or concerns about the need for a high-ranked psychiatrist within a university department to promote depression treatment rather than create fears about treatments, seem to be the most charitable explanations of the reasons behind the decision. However, revoking an appointment on the basis that a person's views are perceived as harmful to the public seems remarkable in an academic research context. It also seems odd that his views, which were well-known, would come back to haunt him after the offer was made. It also raises interesting questions about the limits of academic freedom. Should concerns about the public's interpretation of one's views be a reason not to express these views, or to express them more prudently? In this case, should the concern about the potential negative impact on the promotion of anti-depression treatment be a reason not to voice — or not to voice too publicly — one's view that SSRIs may cause suicide or have other negative side-effects? This argument, in my opinion, is particularly problematic in an academic research setting. It undermines the ability to have meaningful debate among specialists. In the end, the fact that only a couple of years later so many regulatory agencies have issued public warnings about the potential side-effects of several SSRIs in children and adolescents, including suicidal ideation, seems at least already a partial vindication of Healy. Rather than being irresponsible, these developments suggest that by voicing his concerns publicly and by criticizing the lack of research and information sharing on these issues, he was fulfilling a crucial public duty.

It will likely remain unknown what determined CAMH's decision and whether or to what extent Nemeroff and others played a role in his dismissal. Healy and the CAMH obtained a settlement, as part of which Healy was appointed as visiting professor at the Faculty of Medicine of the University of Toronto for a period of three years.

This appointment as visiting professor must have been of some importance to David Healy. From my peripheral involvement in the controversy, I witnessed the fierce legal battle over the academic standing of David Healy. After his offer of employment was withdrawn in 2001, concerns were raised within the university about the reasons for this decision and the potential implications for academic freedom within affiliated research institutes.

Clearly, the academic standing of David Healy was an important factor in litigation that bore enormous financial consequences. It was important for those on whose side David Healy appeared as an expert

witness to confirm his academic credentials, and it was as important for the opposite side to discredit him. The appointment as chair of a department at the University of Toronto would have made it, in the American context, much harder to discredit him. It has to be pointed out that attempts to have David Healy disqualified as an expert witness had already failed in court, even without an appointment in Toronto.

The personal saga of David Healy, including his run-in with Charles Nemeroff, is worth keeping in mind when reading his article. Not that his personal involvement discredits his arguments — on the contrary, one must appreciate the personal drive with which Healy continues to speak out in this area, and the energy he finds to provocatively embrace new controversies. At the same time, it seems appropriate to realize that claims about the importance of some controversies may be influenced by his personal attachment and detailed knowledge of these particular cases.

Two defining moments in the debate over conflicts of interest?

David Healy describes two different aspects of the new strategies for pharmacological promotion in scientific publications. He argues that two pivotal events in the last couple of years have fundamentally altered the debate about conflicts of interest in medicine. One of them was the public exposure of significant undeclared conflicts of interest in a review article in the journal *Nature Neuroscience*. The other was the controversy surrounding the hiding of negative results of clinical trials and the selective release of positive data by a major pharmaceutical company.

Undisclosed financial interest in scientific publications

The first pivotal case discussed by Healy in his article involves Dr. Charles Nemeroff. David Healy must have been pleased by the negative publicity surrounding this influential psychiatrist who, in Healy's view, has been on a mission to destroy his reputation. But his personal satisfaction about the muddy waters in which Dr. Nemeroff has found himself does not in and of itself diminish the value of Healy's criticism. The story speaks for itself. Here we have a very influential psychiatrist, who publishes a review of novel and promising neurological treatments, without disclosing that he has major financial interests in several of the recommended products. In what other walk of life would influential professionals be allowed to make recommendations, based on their perceived 'special knowledge and expertise' in favour of products in which they have significant financial interests? It is hard not to see the lack of disclosure as an expression of either a lack of judgment or a total indifference towards the concerns about conflict of interest.

This controversy is also interesting because it exposes the inadequacy of the approach taken until recently by one of the leading science journals. As Healy mentions, it was only after the controversy became publicized that the journal *Nature Neuroscience* agreed to revise

its policy. Until then, it had clung to the idea that science is science and that disclosure of financial interests is irrelevant in an objective exchange of scientific opinions.

But while the case is a rather extreme example of conflict of interest in scientific publications, this is hardly a 'new' or pivotal case of conflict of interest. Financial conflicts of interests of authors and investigators have been exposed in many other contexts in the past. And it has been associated with very serious consequences. The most dramatic example is the case of Jesse Gelsinger, an 18-year-old volunteer who died in a gene transfer study for the treatment of OTC, a rare and potentially lethal liver disease. The research took place in a research institute affiliated with the University of Pennsylvania, sponsored with a US\$20 million contract by the company GENOVO. The director of the institute and lead investigator in the trial, Dr. Wilson, held 30% of the stock in GENOVO, which had an estimated value of US\$13.5 million.⁶ Other researchers in the institute, as well as the University of Pennsylvania itself, had major stock holdings in the company. Moreover, the former dean of the Faculty of Medicine, who had appointed Dr. Wilson, held a patent on the gene vector that was being used in the trial. If successful, this study would have been published in the scientific literature, and depending on the journal, disclosure of financial interests may not have been required. Long before the case involving Nemeroff, the case of Jesse Gelsinger had stirred a major debate about the impact of financial interests on the conduct of clinical trials,

The fact that medical experts are allowed to make recommendations in highly ranked science journals, notwithstanding their large financial interests, also reverberates with reports that insider trading occurs frequently in the context of medical research. Cases have been brought against biomedical researchers for insider trading, and a recent study seems to suggest that this practice may be widespread.⁷ If financial interests are sufficiently tempting to lure some researchers into white-collar criminal behaviour, it seems plausible that a reviewer with a serious financial interest in the outcome of a review may be tempted to 'skew' some data, or conveniently overemphasize the benefits of a study treatment. It is odd that some leading medical journals still seem to doubt that this is a serious concern.

The SSRI controversy

Healy's detailed discussion of the controversial role of a medical communications agency in the promotion of and the selective publication of data regarding the drug Paxil is extremely disturbing and reveals a callous attempt by a pharmaceutical company to hide research results, with serious implications for public health. The controversy surrounding the SSRIs highlights issues that are also not necessarily entirely new. Conflict of interest issues in research have been discussed extensively in the past. Various publications have indicated, for example, that there is a clear association between sources of funding and research outcomes. Research that is funded by

industry is significantly more likely to come to a conclusion that is financially rewarding for the sponsor. Industry-sponsored research is much more likely, for example, to conclude that a new therapy is better than standard therapy, or to state that a class of drugs produced by the sponsor is effective.⁸

The facts described by Healy go further, though, than the subtle and often unconscious impact of conflicts of interests on research outcome. They amount, to use the words in the lawsuit by the Attorney General of the State of New York against GlaxoSmithKline for the facts described by Healy, to 'deception, misrepresentation, concealment and suppression' of important information.⁹

But however serious these facts may seem, they are not unique. In the last couple of years, several controversies have revealed remarkable tactics by various pharmaceutical companies involving hiding data that could financially damage them, or using skewed or selective results to promote drug prescriptions. It suffices here to mention just a few of the recently exposed controversies. In 2000, media reports, quoting David Healy, accused Eli Lilly of playing down potential side-effects of its popular drug Prozac by altering the terms used in reports about negative side effects in clinical trials.¹⁰ In May 2004, the pharmaceutical giant Pfizer agreed to pay US \$430 million to settle a lawsuit by a former employee turned whistle-blower, who was joined in the lawsuit by the U.S. federal government and eleven state governments. The former employee helped to expose various marketing practices by the company Warner Lambert — later bought by Pfizer — to promote off-label use of its epilepsy drug Neurontin. Medical researchers affiliated with leading American universities were paid to deliver promotional lectures at educational events and to publish favourable reports on the off-label use of Neurontin.¹¹ One professor at the University of Minnesota received more than \$300,000 from Warner Lambert for the publication of a book on the treatment of epilepsy. In July 2004, Belgian drug maker Janssen Pharmaceutica, a subsidiary of Johnson and Johnson, admitted in a letter to doctors that its promotional materials had 'minimized potentially fatal risks, and made misleading claims' about the safety of its schizophrenia drug Risperdal.¹² The same company also came in the news for its financial involvement in a campaign to promote the adoption of guidelines recommending the use of, among others, Risperdal for the treatment of patients covered under state-sponsored health insurance plans.¹³ In the same month, a *New York Times* article exposed various gaps in the labeling of side-effects of several drugs, including another drug produced by Pfizer.¹⁴ These are only some of the most recent pharmaceutical controversies that were exposed in the media.

Concerns have also been raised in the past about the phenomenon of ghost-authorship.¹⁵ In a 1998 article in the *Journal of the American Medical Association*, Annette Flanagin and colleagues discussed their analysis of 809 articles in six leading medical journals. They come to the conclusion that up to 11% of articles published in these journals used ghost authors, while 19% of them used honorary authors, even though both practices violate existing authorship

guidelines.¹⁶ Healy himself, with his colleague Dinah Cattell, published an interesting study that highlights the remarkable success of medical communication bureaus in getting these ghost-written articles published in the most influential peer-reviewed journals.¹⁷ The boom in these commercial communication agencies, which offer a variety of services aimed at promoting pharmaceutical products – from organizing and writing up medical studies, designing brochures, preparing infomercials, and designing educational materials for physicians – is in and of itself a remarkable phenomenon.

While the phenomena described by Healy may not be particularly novel, Healy has a point in emphasizing that the debate about conflicts of interest has reached a new level, and that the recent developments seem to constitute a culmination of the industry's impact on medical research. Healy's examples are also remarkable in that they seem to combine examples of the inordinate and serious impact of financial interests on the health and well-being of consumers. It makes the example of SSRIs an exquisite 'case study' for the teaching of conflict of interest problems.

The seriousness of the situation is reflected in the flood of professional and regulatory initiatives in this area that have come out in the last couple of years. In the remainder of this commentary, I want to discuss some of the remedies that have been proposed in the context of conflict of interest, and focus in particular on two approaches that go much further than what I would call intra-professional approaches to dealing with conflict of interest.

Remedies to curb the impact of commercial interests in medical research

Conflict of interest policies of medical journals.

As Healy emphasizes, medical journal editors started long ago to try to address concerns about inappropriate authorship and authors' conflicts of interest. They introduced authorship sheets for submission of articles, requiring people to explicitly indicate and endorse their level of involvement in the authorship of an article. These 'declarations', if filled out properly, should have helped to get rid of ghost authorship. But it is not clear that they work well. Authorship guidelines have existed for a long time, but social practices die hard. Honorary authorship by directors of laboratories and senior supervisors is a longstanding tradition in medical research, even if the widely accepted Uniform Requirements for Manuscripts Submitted to Biomedical Journals prescribe that only those who (1) contribute substantially to the conception and design, or acquisition of data, or analysis and interpretation of data; (2) draft the article or revise it critically for important intellectual content; and (3) give their final approval, qualify as authors.¹⁸ Many of those involved in medical research probably share the experience of having clinicians demand co-authorship in response to a request for help in recruiting their patients. Moreover, laboratory directors still add their names to publications of junior

researchers. Within medicine, researchers are used to operating in a culture where authorship is not strictly determined on the basis of direct participation in the preparation of the manuscript. The provisions of the guidelines are not clearly respected. In this culture, it may seem less of an issue to accept ghost authorship: the line between adding one's name to an article written by a junior researcher and adding one's name to an article prepared by a medical writers' bureau seems narrow. And both actions gratifyingly pad an academic researcher's CV. In fact, considering the successful publication strategies of some of these writers' bureaus, joining an industry-organized publication as author seems more likely to increase someone's academic status.

Medical journals generally also ask in their submission sheets whether any author involved in the publication has a conflict of interest. Some journals only use these disclosures internally to assess the submission, but most publish a note indicating any financial interest authors in the study may have. Medical journals have further insisted for some time that stricter conflict of interest rules should apply in the context of review articles and editorials. Because of their importance for medical practice, many of the leading medical journals have insisted that authors of review articles and editorials cannot have any financial interest in a product discussed, or in any competitive product. It is significant for the current medical research environment that the editors of the *New England Journal of Medicine* felt obliged to become more lenient. In 2002, editors Jeffrey M. Drazen and Gregory D. Curfman declared that they had revised the journal's policy about review articles and editorials and that from then on, the journal 'expects that authors of such articles will not have any *significant* financial interest in a company (or a competitor) that makes a product discussed in the article [my emphasis].'¹⁹ However, the editors also emphasized that this requirement is only a 'guideline', and that the editors would evaluate on a case-by-case basis whether a financial interest constitutes a problem for a review article or editorial. As justification for this change, they indicated, among other things, that in the previous two years, allegedly because of the strict conflict of interest requirements, they had managed to obtain only one drug therapy article about a novel form of treatment. Because of the financial relations of most working scientists with industry, there seems to be a scarcity of scientists without conflicts of interest.

The obligation to divulge the authors' financial interests seems to reflect a basic common-sense concern, based on the realization that, in John Stuart Mill's words, 'the love of money is one of the strongest moving forces in human life.' This concern is accepted as a basis for policy in various other walks of life, such as journalism, the judiciary and government, where it leads to much stricter policies – for example, prohibiting financially interested persons from involvement in decision making, consulting or evaluation of products. In this context, it seems odd, as the controversy described by Healy indicates, that some journals still have trouble with the most basic disclosure requirements.

It is, however, far from clear that disclosure of sponsorship of studies and of other financial interests of authors is a sufficient remedy. Publications can still be used as part of marketing schemes, and it is unclear how readers of these journals should weigh the impact of a researcher's financial interests on the credibility and integrity of the published study. Readers, particularly clinicians who are often overworked and unable to find time to read the details of the published literature, will not be able to evaluate the impact of these conflicts. Clinicians are also not trained to assess the validity of published articles. How could they determine what these published disclosures mean with respect to the integrity of a study? An older study is revealing in that respect. In 1982, a study by Avorn, Chen and Hartley showed that a majority of clinicians erroneously believed that their knowledge of two widely-prescribed drugs came from the scientific literature. In fact, their understanding of the drug was based on deceptive advertisements of the drug.²⁰ This study suggests that physicians simply absorb information provided to them, without being able — because of lack of time or training — to critically assess its value and origin. If clinicians cannot even determine whether their knowledge is based on advertising or on scientific literature, how can they be expected to make an appropriate judgment about the potential bias resulting from a small disclosure provided on the bottom of the first page of an article? They later forget where the information came from.

Clinical trials registry

A second solution that has been widely recommended in the context of the controversy surrounding SSRIs, in particular with that surrounding GlaxoSmithKline's concealment of research data concerning Paxil, is the establishment of a clinical trials registry. For years, commentators have argued that too many drug trials are never reported and that negative results often do not find their way into the medical literature. The problems described by Healy go much further. They involve the very conscious hiding of questionable efficacy and side-effect data and the active promotion of drugs that are potentially ineffective and, for some patients, dangerous. It is not surprising that this extreme example of an attempt to manipulate publication has led to such an outpouring of support for clinical trials registries.²¹

What are the advantages of a clinical trials registry? Marcia Angell, former editor-in-chief of the *New England Journal of Medicine*, is among those who forcefully defended such a registry in an editorial article in the *Washington Post*.²² A clinical trials registry, if appropriately designed, would make it impossible for pharmaceutical sponsors to selectively publish only positive trial results. The registry should also contain information on the drugs and dosages to be tested, as well as details of the trial methodology. By having an obligation to state beforehand the trial's endpoints, comparison drugs, and methods of measurement, sponsors would not be able to change their research approach in light of interim outcomes without public scrutiny. According to Marcia Angell, the registry should also contain the names

of researchers as well as information on their financial relations to the sponsors and the products tested.

With respect to the issue of a clinical trials registry, the controversy surrounding the SSRIs described by Healy can indeed be considered a defining moment. It clearly has given the movement demanding a clinical trials registry the necessary momentum. Recently, the World Health Organization (WHO) became the first large organization to announce the establishment of a comprehensive clinical trials registry.²³ Other organizations followed suit. Immediately after the Attorney General of New York launched the aforementioned lawsuit against GlaxoSmithKline, the American Medical Organization called upon the U.S. government to create a public registry of all clinical trials.²⁴ At least two large pharmaceutical companies, including GlaxoSmithKline, also indicated their willingness to establish or contribute to some form of public database of clinical trials. Not surprisingly, GlaxoSmithKline did so only after it had felt the heat of the courtroom. Its proposal to publish the data of all of its trials was turned into a court-controlled commitment as part of a settlement of the case.

The most influential move toward a clinical trial registry probably came in September 2004, when the International Committee of Medical Journal Editors, which includes the editors of 13 major medical journals, including the *Journal of the American Medical Association*, the *New England Journal of Medicine*, the *Lancet* and *The Medical Journal of Australia*, issued a joint statement that they would require, 'as a condition of consideration for publication,' registration of clinical trials prior to patient enrolment.²⁵ The Committee will require such registration for all research projects in which research subjects are assigned to intervention or comparison groups. It can be expected that many other medical journals will follow in the footsteps of this initiative.

Will such a clinical trials database be sufficient? It will surely help. Access to data is a precondition for any reasonable debate about the validity and limitations of a clinical trial. If all trials are registered, independent scrutiny of the reasons for halting trials becomes possible. Researchers can also put pressure on sponsors and researchers to release data when it becomes clear that a registered clinical trial is finished and its results have not been publicized. Without full disclosure of research data, no appropriate verification can be undertaken and pharmaceutical sponsors can continue to hide data that do not favour their commercial plans.

It should be clear that a clinical trials registry is only part of the solution, and that such a registry can only function appropriately if it is part of a government-enforced system. The registry requirement introduced by the *International Committee of Medical Journal Editors* seems to reflect a profound sense of crisis. It seems to be an attempt to show the public that the medical profession and the research community can clean up their own mess. But it clearly does not solve all of the problems, since it does not bind all medical journals and does not prevent other questionable forms of distribution of research results.

The registry requirement would have made it much harder for GlaxoSmithKline's medical communications bureau to have selective results published in the most influential peer-reviewed journals. This is to some extent reassuring, but industry tactics may now shift to involve the use of less rigorous journals. Further, it is not clear that this registry will contribute to the promotion of appropriate comparative trials that will challenge the biased studies which can still be controlled by pharmaceutical sponsors. Even if clinical trials are registered and later published in leading medical journals, will there be independent scrutiny of the methodology, data analysis and interpretations? The problems of potential bias in industry-sponsored studies still remain a major challenge.

The journal editors acknowledge the limitations of their initiative, qualifying it as 'only part of the means to an end: that end is full transparency with respect to performing and reporting clinical trials.'²⁶ In an interview with the *New York Times* following the settlement with GlaxoSmithKline, New York's Attorney General Spitzer also recognized that a registry is not a panacea. Interestingly, he lashed out at the regulatory authorities, asking rhetorically where they had been all these years, failing to deal with what he termed 'consumer fraud.'²⁷

This is indeed, a very poignant question. Conflicts of interest have been raised for years as a major challenge for medical research. Several regulatory authorities have drafted discussion papers and guidance documents, or even have strict policies on certain conflicts of interest. Two areas of regulatory oversight are worth mentioning here. The first is the research review system, built around local review of research protocols, prior to commencing a study, by Research Ethics Committees (RECs, otherwise known as Institutional Review Boards [IRBs] in the U.S.A.). The second is the review structure by the governmental drug regulators, such as the U.S. Food and Drug Administration. What indeed, are they doing in this context and why have they not been able to curb the type of abuses that Healy describes?

REC review of research

As has been extensively documented elsewhere in the research ethics literature, various research scandals in the twentieth century have made the research community accustomed to some form of external review of medical research projects involving human subjects.²⁸ The controversies that constituted the direct impetus to the development of research review structures generally involved overzealous researchers who ignored the interests and well-being of individual research subjects. Researchers involved in these projects often seemed blinded by their desire to obtain results, driven by a misguided sense of contributing to the public good, or simply lacked appropriate sensitivity toward the suffering of their research subjects. The research projects in which these mishaps occurred were generally investigator-driven, and often government-sponsored research projects. An obsession with the research questions and a desire to obtain

interesting, publishable results also seemed to be common factors underlying this behaviour.

Research ethics committees (RECs) — referred to as Research Ethics Boards (REBs) in Canada and as Institutional Review Boards (IRBs) in the U.S.A. — were established to deal with what became perceived as an inherent conflict of interest in medical research conducted by physicians. This type of conflict of interest is very different from that described by Healy. The conflict with which RECs were established to deal was that between the inherent duties of physicians towards their patients and the duties of clinician-researchers towards the advancement of science. It is a fundamental tenet of the ethics of the medical profession that they have a primary obligation towards their patients. This is recognized in the Hippocratic Oath, and in various medical research codes, including the Nuremberg Code and the Declaration of Helsinki. National laws also impose this primary duty of care towards patients. The imposition of review by RECs constituted recognition of the danger that physician-investigators can be tempted to relinquish this duty by giving priority to their scientific endeavours.

Various national funding agencies and national and international medical organizations, in particular the World Medical Association, with its Declaration of Helsinki,²⁹ promoted this review system. Drug regulatory agencies also introduced the requirement for REC review as a layer of administrative protection focusing on respect for the rights and well-being of research subjects. International initiatives, such as the *International Conference on Harmonization of Good Clinical Practice Guideline*³⁰ further promoted the idea that REC review was an essential requirement to protect research subjects in clinical trials.³¹ Review by an appropriately constituted REC developed into an explicit requirement for most — if not all — research involving human subjects in industrialized countries. RECs' mandate became gradually more clearly defined so as to include a review of: the value and validity of the research protocol; subject selection; the risk-benefit ratio; and informed consent procedures.³² In many countries, the administrative procedures involved in REC review also became more formally defined, either through guidelines of funding agencies, or through regulations emanating from the government. Since the REC was an administrative body developed to deal with an inherent conflict in the practice of medical research, some governmental agencies simply seemed to rely on them as the answer to all concerns about conflicts of interest. Health Canada's Therapeutic Products Directorate, for example, stated in an Impact Analysis Statement accompanying regulations on clinical trials very confidently that REBs help to 'ensure that conflict of interest situations are avoided and that the health and safety of the trial subjects remain the paramount concern.'³³

Changes in the nature of medical research brought with it new controversies and new foci for research ethics review. Controversies such as that surrounding the death of Jesse Gelsinger stirred a heated debate about the role of REC review in the context of the commercialization of research. Clearly, RECs also have to be concerned

when financial conflicts of interest appear to affect the safety and well-being of human subjects. In May 2004, the U.S. Department of Health and Human Services, for example, issued a new *Guidance document on Financial Relationships and Interests in Research Involving Human Subjects*, in which it confirmed that IRBs have to evaluate the potential impact of financial interests on the safety and well-being of subjects.

But it is unclear how far the RECs' role extends, and even less clear how efficacious they are in this context. They may be able to deal to some extent effectively with specific aspects of the commercialization of research, such as the phenomenon of paying research subjects for their participation, or the use of financial incentives for investigators and clinicians to recruit their patients into specific research projects. Dealing with the more systemic impact of the commercialization of research clearly constitutes a formidable challenge for these already overburdened, understaffed, and largely voluntary committees. And yet, as the controversies discussed above indicate, the impact of commercial interests on the integrity of science is of direct relevance to the work of RECs. If the integrity of research is affected by commercial interests, how can RECs appropriately evaluate the scientific value and validity of protocols?

In addition, as the International Committee of Medical Journal Editors acknowledges, publication of research results is also required out of respect for research subjects.³⁴ REC review has as one of its major obligations to ensure that research subjects are respected and not harmed. It has to be concerned about what happens with research results and should therefore as part of its job ensure that research subjects do not participate in a study when there is a possibility that the results will be hidden for commercial reasons.

Over the last couple of years, the more systemic impact of conflicts of interests has received much attention from various professional organizations. The Association of American Medical Colleges, for example, set up a Task Force on Financial Conflicts of Interest with the mandate to make recommendations to deal with individual and institutional financial conflicts of interest. In its first report, it indicated clearly how the concerns about the impact of financial conflicts of interest go further than concerns about enrolment practices, and how the threat to scientific integrity has wide implications. 'Financial interests threaten scientific integrity,' the Task Force stated, 'when they foster real or apparent biases in study design, data collection and analysis, adverse event reporting, or the presentation and publication of research findings.'³⁵

Issues such as adverse event reporting and bias in design which may affect the validity of a study is of direct relevance to REC review. But is REC review up to the task? While its role in dealing with conflicts of interest is increasingly recognized, the REC review system itself has become the target of criticism. Even in the U.S.A., where more than in most countries IRBs have been integrated into the regulatory system, various reports and commentators have questioned the efficacy and appropriateness of the existing IRB system in the changed research environment.³⁶ It exceeds the scope of this paper to

discuss all of the problems identified in these reports. But one problem in particular should be mentioned: the conflict of interest embedded in the REC system itself. Ironically, just when RECs are being called upon to improve their role in evaluating the impact of conflict of interest, their own structural flaws are being exposed.

RECs, as several commentators have emphasized, are in most countries part of established academic institutions and their members are connected to the research interests within these institutions.³⁷ Membership of RECs is dominated by medical professionals and/or people with research interests within the institution. Although community representation has gradually been added as a core requirement, it seems fair to argue that REC review in most countries currently remains a form of peer-based, internal review system. Local internal review by an institutional REC has often been defended because of its ability to shape local norms and to respect local values better. The values it serves are those of the local research community. Even in recent years, when these RECs have become more bureaucratized and formally regulated, particularly in the U.S.A., the philosophy that underlies their functioning remains one of local 'dialogue' with 'stakeholders'.

As RECs have assumed a more significant administrative role, with a mandate to evaluate the potential impact of individual and institutional conflicts of interest, this model seems much less appropriate. Institutionally-based RECs, generally staffed with people who in their capacity as researchers or clinicians report directly to institutional officials with vested interests in the conduct of research, are asked to make decisions that may affect the financial interests of superiors and of the institution, bring them on a collision course with their superiors, and ultimately even threaten their employment.

In addition, the commercialization of medical research has also led to a remarkable new phenomenon: the development of commercial RECs.³⁸ Some Contract Research Organizations have set up their own internal RECs, while several private RECs have found a niche in the commercialized research environment. The latter are for-profit organizations which have as their sole commercial activity the review of research protocols for a fee. These RECs are increasingly important and have developed into a thriving industry, as more and more research has moved out of the academic setting and into the community. They have definitely filled a gap in the North American research market. However, especially when dealing with concerns over the impact of commercialization on research, it seems to me inappropriate to rely on these commercial RECs. These are in a client-provider relationship and have a direct financial interest in offering a service that pleases their client. Refusal to approve a study may have huge financial consequences for the contract research organization or sponsor who contracts with the private REC. And since nothing in the system prohibits these sponsors from seeking approval of another REC and from breaking their commercial relationship, these RECs clearly cannot be perceived as independent administrative bodies.

In view of the limitations of RECs when it comes to reviewing financial conflicts of interest, recommendations have also been made to develop specialized Conflict of Interest Committees within institutions. The Association of American Medical Colleges recommended in its two reports that specialized committees should be established to review individual and institutional conflicts of interest.³⁹ These committees would have an explicit and clear mandate to review financial relations between individual researchers, the institution and research sponsors, and would have to make recommendations about how to deal with these conflicts. The committees would serve as an important resource for the review by RECs and would inform the REC of potential problems and recommend strategies to deal with them. Delegation of conflict of interest review to such specialized committees would help to prevent RECs from becoming even more overburdened with yet another complicated task, and could help to establish more effective control of financial interests.

It is not clear, however, why they would not face similar problems as RECs with respect to the lack of independence from the institution's financial interests. It is also interesting to point out that RECs and conflict of interest committees have been around for some time, but did not prevent some of the most serious research controversies of the last years. As the father of the late Jesse Gelsinger pointed out at a conference in Toronto: the University of Pennsylvania had a conflict of interest committee and it had its research protocols reviewed by an appropriately constituted IRB. Yet, major conflicts of interests were not dealt with. Moreover, the AAMC's recommendations target the academic institutions, but the problem of the integrity of research clearly extends much further. It seems unlikely that private Contract Research Organizations would ever consider establishing a COI committee to determine whether a study should not be undertaken because of the significant financial interest of the CRO.

Regulatory review of pharmaceuticals by governmental agencies

The controversy surrounding the promotion of SSRIs has exposed the inadequacy of the drug regulatory system in dealing with selective publication of research data and the manipulation of research results. While the development of research ethics review committees aims at protecting those participating in research by providing prior review of research protocols, the drug regulatory system focuses on the protection of consumers, by regulating the entry into the market and the sale and promotion of new drugs. The two systems are not hermetically sealed. Prior review of research protocols by RECs has been integrated as a fundamental part of the drug regulatory system, but the focus of the discussion here is on the end-point of the process: the evaluation of the efficacy and safety of a drug and the determination of the parameters of its use.

Unlike the more peer-based review conducted by RECs, the drug and medical devices approval system is more solidly based on state

authority over issues related to public health and safety. It involves governmental agencies, such as the U.S. Food and Drug Administration, which are directly accountable to the government and which receive a clear regulatory authority. Control is exercised by a specialized professional administration that should function independently from the researchers and the industry that submits its drugs for review.

Over the years however, the independence of these regulatory bodies from the interests of researchers and industry has come under siege. With funding for regulatory review being reduced, several regulatory agencies now obtain a significant part of their core funding directly from review fees paid by pharmaceutical companies. In the U.S., for example, the FDA expects to collect, for the fiscal year 2005, \$350 million of its expected \$1.845 billion overall budget in user fees. Industry has thus become, in a way, a significant client and revenue source of the FDA. This is in and of itself not sufficient to totally undermine the independence of the FDA. The payment of a review fee does not necessarily give much control if the regulatory agency has a monopolist position and if industry cannot avoid submitting its applications to the agency. However, the payment of a fee contributes to potential regulatory capture. The pharmaceutical industry is a powerful economic force, and to make the FDA's budget dependent on its payments increases its leverage. It has used this position, for example, to put pressure on the FDA with respect to how it should spend a significant part of its budget, i.e. on faster drug approval and not on the development of research to support its review function.⁴⁰ In addition, the FDA's more cautious approach towards the approval of new drugs has certainly been weakened in the last decades. In the wake of the HIV/AIDS crisis, patient advocacy groups put pressure on the regulatory agencies to speed up the approval of new, potentially life-saving drugs. Pharmaceutical companies have also challenged the more cautious approach, invoking both patient interests and financial costs resulting from delays in drug approval.

And while drug development has significantly increased over the last couple of years, the administrative support of the drug regulatory agencies has not been proportionally expanded. Regulatory agencies are often short-staffed and can review only a limited number of drugs carefully. The increased number of submissions, the proportional reduction of regulatory review, and the overall reduced review times for new drugs may explain why in the last two decades, several drugs have been taken off the market after a significant number of patients were seriously harmed. As in many other areas of government, drug regulatory agencies have suffered from an ideological era of 'less government' and 'more self-regulation.' Regulatory agencies rely to a large degree on self-reporting and the self-monitoring of pharmaceutical companies. While there is a drug regulatory review process in place, it functions in an environment where excessive reliance is placed on good corporate behaviour.

Another interesting development is the way in which drug regulations, originally intended to focus on consumer protection, have

increasingly become a tool to protect the financial interests of pharmaceutical companies who invest in drug development. Most changes to the regulatory structure surrounding drugs in the last decades aimed at speeding up the approval process. In addition, as Rebecca Eisenberg emphasizes, various amendments to the FDA regulations aim at linking these regulations with the patent protection regime. While the FDA review system was developed to provide an independent review of the safety and efficacy of drugs, focusing on the protection of consumers, it has, according to Eisenberg, *de facto* become an important regulatory means to obtain market exclusivity for new drugs and to guarantee financial returns for investments.⁴¹ One example of this development is the FDA's authority to extend patent protection by providing market exclusivity to pharmaceutical companies for making changes to a previously approved product. Another example given by Eisenberg is the *Food and Drug Administration Modernization Act* of 1997, which aims at promoting pediatric trials for existing drugs. It gives six months of exclusivity for products used in pediatric clinical trials. One should ask whether this confusion of the FDA's role brings it into conflict with its mandate to protect the public and undermines its accountability to the public. Indeed, its role in protecting patent interests may clash with the need for openness of clinical trial results, which is a pre-condition for a transparent scientific debate.

The FDA does impose strict reporting obligations upon sponsors. Before commencing clinical trials, sponsors have to file an Investigational New Drug Application, with data to support the claim that research subjects will not be put at unreasonable risk. They have to keep the agency informed of any serious and unexpected adverse events associated with the experimental treatment and any other data that suggests risks to human subjects. After having tested the drug through various clinical trial stages, they have to submit data supporting the efficacy and safety of the product. However, the system is largely based on self-regulation, and fundamentally respects the proprietary nature of research data. As Michael Baram observes, the reporting obligations are extremely flexible, and 'riddled with legalistic exceptions and deference to investigator judgment on critical matters.'⁴²

It is clear also, from the controversy described by Healy, that the FDA does not sufficiently control whether there is a discrepancy between the published data and the data submitted to support drug approval. In that sense, the FDA's review system does not necessarily help to make pharmaceutical sponsors publicly accountable. The SSRI controversy raises general doubts about the efficacy of the system and its ability to respond quickly to significant public health concerns.

Regulatory reform: Where do we go from here?

This discussion of the lacunae in the regulatory system surrounding medical research seems to explain not only why the controversies described by Healy could happen, but also why they constitute such a significant threat to the integrity of medicine. When

commercial sponsors design the protocol of a study, select its research subjects, conduct the research, collect the data, interpret the results, control publication of the outcome, fund advocacy and support groups to lobby governments for approval or funding of the drug, and spend millions on commercial campaigns to promote a new drug, there is reason to worry about the integrity of the process, particularly in the absence of a strong regulatory sector. There are too many messy aspects inherent in the practice of medical research to eliminate bias in research design, selection of subjects, data collection and/or presentation of results.

Protecting the integrity of medical research will require a strengthening of the regulatory review at different levels. First of all, as emphasized above, it is untenable to maintain that RECs can play a role in reviewing conflicts of interest in an increasingly commercialized research context, when they themselves are affected by significant conflicts of interest. It will be important to look at international developments, and to determine whether some of the review systems that are based on mandatory regional review boards and on direct regulatory oversight by governmental agencies could defuse the concerns raised by flaws in the North American system of REC review.⁴³

Drastic interventions will be needed to promote the independence of the drug regulatory system. Sheldon Krimsky, in his recent book on the commercialization of medical research, recommends the establishment of an independent National Institute for Drug Testing (NIDT). The establishment of this institute would allow the government to prevent those with a direct financial interest in the outcome of the study from controlling the design of the protocol, conducting the study itself, selecting the data, interpreting the results in the scientific literature and using selective publications for marketing purposes.⁴⁴ Under Krimsky's proposal, a company wishing to apply for approval of a new drug would negotiate with this NIDT an appropriate research design to test the efficacy and safety of the drug. The Institute would then invite various qualified drug assessment centers to submit proposals for conducting the trials. Although Krimsky does not discuss this, it seems that academic research centers could replace much of their current corporate funding from clinical drug trials by participating in this more rigorous and independent system of drug evaluation.

Improving an independent and critical research sector, for example, by ensuring truly independent and well-funded academic research sectors, should certainly be a core component of any solution. The commercialization of medical research and in particular the intrusion of commercial strategies at all levels of society, including academia, has made it increasingly difficult to find an independent voice.

If there is one uplifting element in the controversies discussed here, it must be that there are still researchers out there like David Healy who are willing to take a critical stand, sound the alarm if needed, and who manage, often slowly and sometimes at considerable personal cost, to make changes happen. The personal price some of

them pay may have considerable public benefit: it makes them so much more personally motivated to expose the flaws in the system.

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