Dr. H is an expert on the treatment of depression. A pharmaceutical company, Calaxy Inc. signed a contract with Dr. H and his institution for a multisite three-year study on the efficacy and safety of a new antidepressant, Xanadu, for use in pregnant women. The contract stipulates that Dr. H will have access to all data for final analysis and that all publications based on the study will be submitted for final approval to the sponsor before public disclosure. Dr. H’s budget includes money for finder’s fees for clinicians who recruit patients into the trial and rewards for clinician-researchers whose patients remain in the trial for the duration of their pregnancy. In the course of the trial, Dr. H becomes worried about potential negative effects of Xanadu on newborns. He reveals his concern to the company, requests immediate access to all the data, and indicates that he will reveal his concerns at an upcoming International meeting. The company refers to a contradictory opinion of an internal data-monitoring committee set up by the sponsor, refuses to provide full access to the data, and points out that researchers have to obtain final approval of the sponsor before any public discussion of the results. Shortly after, Dr. H receives from Calaxy an abstract discussing the interim results of the study, accepted for presentation at an International conference. Dr. H is first author on the abstract, which does not contain any reference to his concerns. Dr. H contacts the chair of his department, Dr. I, who is a remunerated board member of Calaxy. She points out that Calaxy is a trusted and transparent partner in research, that it has its own data-monitoring committee, that it is ultimately responsible for the safety and efficacy of its products, and that contractual obligations have to be respected. She mentions also in passing that Calaxy provides close to 20% of the research funding of the institution and that discussions are underway for the funding of a Calaxy research chair, for which Dr. H would be an excellent candidate.

What is financial conflict of interest in research?

Thompson (1993) defined a conflict of interest as “a set of conditions in which professional judgment concerning a primary interest tends to be unduly influenced by a secondary interest.” When clinician-researchers engage in research, tensions can exist between their interests as researchers and their primary obligations as clinicians. While Ch. 29 considers these divergent roles, we will focus specifically on financial conflicts of interest (COIs).

Several reasons justify the focus on financial COIs. Firstly, financial interests in research have exponentially increased in the last decades as a result of legislative (Bayh-Dole Act, 1980; Eisenberg, 2003; Lemmens, 2004) and funding agency initiatives that promote commercial matching funding (Downie et al., 2002; Atkinson-Grosjean, 2006; Downie, 2006; Lemmens, 2006). Medical research is increasingly submerged in the competitive context of a lucrative biotechnology industry. Secondly, many significant
recent controversies that have affected the public trust in the medical research enterprise are associated with financial COIs (Silberner, 2000; Healy, 2002; Krimsky, 2003, 2006; Angell, 2004; Viens and Savulescu, 2004; Revill, 2005; Armstrong, 2006a; Gelsinger, 2006). Thirdly, an array of reports, initiatives, and regulations emanating from official organizations and governmental agencies reflect an awareness that the potential negative impact of financial interests is a serious cause for concern (Office of the Inspector General, 2000; American Association of Medical Colleges, 2001, 2002; Canadian Institutes for Health Research, 2001, 2005; Institute of Medicine, 2001; US Department of Health and Human Services, 2004; UK House of Commons Health Committee, 2005). Fourthly, the tensions described in Ch. 29 are an inherent part of research while financial interests are more objective, tangible, and measurable, and can in theory be separated from the conduct of research itself (Thompson, 1993).

Types of financial interests of clinician-researchers

Researchers can have various financial interests. Some have stock in the company whose product they are testing or significant interests in spin-off companies set up for the purpose of commercializing research results. The controversy surrounding the death of Jesse Gelsinger, for example, revealed that the director and lead investigator of the Human Gene Therapy Institute, several of its researchers, and the University of Pennsylvania all had substantial equity stakes, reportedly in the millions of dollars, in a company that had invested in the genetically altered virus used in the experiment (Gelsinger, 2006; Krimsky, 2006).

Others are consultants for sponsoring companies or are remunerated members of advisory boards. Many receive significant payment for conference presentations or as members of speaking bureaus set up by pharmaceutical companies to promote their products at academic, educational, and promotional venues.

Financial rewards are also offered to researchers for research recruitment, as described in the case study (Lemmens and Miller, 2003). Financial recruitment incentives can be offered as finder's fees (i.e., per capita payments for every research subject recruited) or as bonuses for speedy recruitment, recruiting extra subjects, or keeping subjects in a trial (Office of the Inspector General, 2000). Finder's fees are often part of more general compensation for the costs of being involved in research, making it hard to identify whether and how much researchers receive for the mere recruitment of research subjects.

Even when clinician-researchers have nothing to gain from being involved in a research project, their institutions can be financially dependent on, or have close relations with, commercial sponsors, creating institutional COIs (Emanuel and Steiner, 1995). This may have an influence on institutional policies and behavior and create pressure on individual researchers. Financial interests of individuals with decision-making authority within institutions (e.g., departmental chairs, heads of research) can transform an individual COI into an institutional one (American Association of Medical Colleges, 2002).

The mere sponsorship of a clinical trial may create financial COIs that impact on research. The conflict resides then in the fact that commercial sponsors have a direct interest in obtaining commercially favorable results, while the goal of research is to obtain reliable and scientifically accurate information that benefits patient care.

Why is it important to deal with financial conflict of interest in research?

Ethics

Safety and well-being of research subjects

Financial interests in research may influence how researchers recruit subjects and how they treat them in the course of a clinical trial. When significant
amounts of money can be gained by recruiting more subjects, or for recruiting them faster, researchers may be tempted to be more lenient with inclusion criteria. Financial interests in the results of a study or in keeping subjects enrolled can negatively impact on the decision to withdraw research subjects or to halt a trial when this is in the subjects' best interests.

**Integrity of research**

Commercial interests may threaten the integrity of the research process in two ways. Firstly, financial interests may impact on the design of the study, the conduct of the study itself, the interpretation of research data, and the presentation of the results in publications. Empirical studies establish a statistically significant link between source of funding and research outcome. Industry-sponsored research is more likely than research sponsored by non-commercial sources to lead to a conclusion that a new therapy is better than the standard therapy (Bekelman et al., 2003; Lexchin et al., 2003; Bhandari et al., 2004; Chalmers, 2004). Commentators have pointed out that positive results are more likely to be published than negative ones and that industry-organized studies in which adverse effects of new drugs are discovered often remain unreported (Chan et al., 2004; Chan and Altman, 2005; Chalmers, 2006).

Secondly, recent controversies have indicated how pharmaceutical sponsors and academic investigators have participated in the conscious control over, or even manipulation of, research questions and dissemination of results. Research is increasingly coordinated by specialized contract research organizations, which either conduct research in specialized research centers or involve a multitude of clinicians. Sponsors increasingly control the design of the study, the recruitment of subjects, the collection and analysis of data, and the publication of the results. The final results are often written by ghost authors, offered as easy publications to established academics and published in the most prestigious medical journals (Healy and Cattell, 2003; Tereskerz, 2003; Angell, 2004; Lemmens, 2004). Academic authors are accustomed to giving credibility to publications. Instances of such practices are documented, for example, in a 2004 lawsuit of the Attorney General of New York against GlaxoSmithKline, which was settled out of court (*AG New York v. GlaxoSmithKline*, 2004; Lemmens, 2004).

Particularly when companies have already invested significantly in product development and expect to market a blockbuster drug in the near future, they have significant financial interest in emphasizing benefits more and harms less. Careful selection of comparators and overemphasis of positive findings is a tempting business strategy (Aronson, 2006). Concerns about biased reporting, lack of transparency, and research manipulation are not limited to commercially sponsored research, yet ample empirical evidence combined with various reports suggest that the problem is more prevalent in this area. This creates reasonable doubts about the validity of clinical treatment recommendations based only on publicly available data (Bhandari et al., 2004; Marshall, 2004).

**Distortion of the research agenda**

The increase of industry funding and the growing commercial focus of funding agencies also has an impact on the health research agenda. Researchers funded to conduct research with a commercial focus are not available for other research endeavors. Since commercial sponsors are able to offer higher recruitment incentives to researchers and research subjects, it may become harder to launch other studies. Commercial interests also create incentives for pharmaceutical companies to conduct research that contributes to the creation of new categories of disease or that influence the level of diagnosis of existing illnesses (Lexchin, 2006; Moynihan and Henry, 2006; Tiefer, 2006).

It is less likely that research will be conducted on diseases affecting only few people ("orphan
diseases") or poor people (e.g., uninsured people in industrialized countries or the majority of people in developing countries). Proportionally less research funding is available to study the impact of other health factors, non-commercial products, or drugs that are no longer protected by patents.

Another cause for concern is that pharmaceutical sponsors are currently not required to conduct research on the long-term health effects of their products (Editorial, 2004; Lemmens, 2004). Indeed, they may have significant financial interests in avoiding long-term follow-up studies. If no one else is conducting these studies, significant adverse effects may remain undetected for a long period.

Policy

The nature of conflict of interest regulations

Clearly, commercial interests of research cannot justify exposing research subjects to direct harm. Researchers who include non-eligible subjects in a clinical trial because of the financial rewards involved clearly violate widely accepted ethical norms of research. In the same vein, those who participate in the falsification of research, or who misrepresent research findings, are guilty of research misconduct or fraud (Anon., 2002; Holden, 2005; Couzin and Unger, 2006; Cyranoski, 2006). In these cases, it is clear that moral culpability is associated with behavior that is per se reprehensible, whether it is stimulated by financial greed or not.

In reality, it is hard to determine whether and to what extent financial interests are the primary motive behind reprehensible behavior. It is impossible to enter into the mind of investigators. In the Gelsinger case, there is no direct evidence that the investigators acted because of financial gain. We can only identify the fact that there were huge financial interests at stake, and that there was research misconduct. Subtle influence of commercial funding of research is also possible. Involved researchers may simply be unaware of the extent to which they are influenced by commercial interests in the research.

This explains the growing interest for precautionary approaches. They are based on the presumption that financial interests are likely to influence some to behave in ways that may expose people to risks or that may affect the integrity of research. Rules for COIs do not suggest that all those who are in COI situations are necessarily morally culpable. However, they reflect a growing awareness of the impact of COIs and of the need to set regulatory standards. A violation of these standards becomes an issue of professional misconduct. The sanctions associated with these rules are imposed not because subjects are directly harmed, or because the research they are involved with is fraudulent or bias, but because we know that this can be the result.

Regulatory remedies

Many universities, professional organizations, and medical journals have established guidelines that reflect the precautionary approach. Regulations for COIs are further introduced by drug regulatory and healthcare agencies. There is also growing attention for the use of criminal law and professional misconduct rules to deal with COIs (Kalb and Koehler, 2002; Lemmens and Miller, 2003). The procedural mechanisms introduced by these organizations and agencies include disclosure of COIs, review by research ethics committees (REC) or specialized COI committees, increased monitoring, and outright prohibition.

Disclosure is the most basic requirement. The idea behind disclosure is that people who have been informed of the existence of COI can make a well-informed judgement about its potential impact. Many medical journals have clear disclosure policies in place, obliging authors to reveal financial relations with sponsors (International Committee of Medical Journal Editors, 2006), although some established journals are still struggling to impose
Disclosure is also a core component of respect for research subjects. Indeed, it seems crucial to disclose to those who accept at times significant risks in research the various interests that may impact on research. Yet some guidelines, such as those issued by the American Association of Medical Colleges (2001, 2002) and the US Department of Health and Human Services (2004), remain surprisingly vague about the requirement of disclosure and do not endorse a strict disclosure obligation. Instead, they give institutional authorities, such as RECs, leeway in determining when and to what extent financial interests ought to be disclosed (Lemmens and Miller, 2003). In our opinion, disclosure is a necessary although not always sufficient condition for dealing with COIs.

Disclosure is also the basis of other procedures. Academic institutions, journals, and funding agencies submit COI situations to a review process. Based on this review process, researchers can be told to disclose the conflicts, or to make required changes to, for example, the Informed consent procedure. Such COI committees or RECs may further recommend that independent investigators be added to a research project, or that an independent data-monitoring committee be established to monitor the safety of clinical trials, analysis of data, and presentation of findings.

The financial COI may be deemed so significant that a prohibition is warranted. The American Association of Medical Colleges (2001, 2002), for example, recommends that institutions introduce in their COI policies a rebuttable presumption that researchers with significant financial interests ought not to be involved in the research, and that institutions with significant interests ought not to have research take place in their establishments.

Finally, COIs may be the subject of specific prohibitions. Various academic centers, for example, have issued guidelines prohibiting the use of finder's fees (Lemmens and Miller, 2003). Researchers who violate these guidelines can be held accountable by their institution for these violations.

**Novel approaches**

Many of these remedies have been in place for some time without preventing major controversies. Several authors have called for more radical and stricter COI approaches. For example, to counter the overall impact of financial interests on the focus of research, some have suggested that public funding for research should be significantly increased (Downie, 2006; Lemmens, 2006), or even that research on healthcare products should be fully publicly funded (Brown, 2000, 2006).

To deal with the phenomenon of ghost authorship (Flanagin et al., 1998), stricter sanctions have been proposed. Two medical journals have announced that they would ban those who have been involved in submitting a ghost-authored article from submitting new articles for several years (Brownlee, 2004). Others have recommended that more details ought to be provided as to who contributed to a study and that academic institutions ought to diminish the focus on quantity of publications in the assessment of academic performance and ought to recognize better other contributions to research (Davidoff, 2000).

Commentators and official reports have pointed out that the regulatory structures set up to deal with COIs are themselves affected by COIs and are in need of significant reform (Office of the Inspector General, 2000; Institute of Medicine, 2001; Lemmens, 2004; Viens and Savulescu, 2004; Ferris and Naylor, 2006). For example, REBs are increasingly expected to deal with COIs while they are themselves affected by COIs and are in need of significant reform. It is also not clear that internal COI committees are independent enough to curb significant institutional COIs.

The idea of mandatory registration of clinical trials has also been gaining ground. This would track trials before they begin, which would avoid secrecy and ensure full reporting of results. Registration is already a regulatory requirement in the
USA for all clinical trials involving serious and life-threatening diseases. It has been recommended by the International Committee of Medical Journal Editors (2006; see also De Angelis et al., 2005) a group of international experts (Kreža-Jerlč et al., 2005), and the World Health Organization (2006a,b,c). Participation in clinical registration is a major step toward transparency and accountability (Horion, 2006; Sim et al., 2006) but should not be regarded as a panacea to COI concerns (Lemmens, 2004).

Another more drastic suggestion is to separate those who conduct medical research from those who have a financial interest in the outcome of the research through the establishment of a new drug-testing agency (Krimsky, 2003; Angell, 2004; Lemmens, 2004). The agency, in dialogue with the submitting company, would determine the appropriate design of clinical trials aimed at testing efficacy and safety of the new compound and would rely on independent accredited drug-testing centers to conduct the trials and analyze the results.

How should I approach financial conflict of interest in research in practice?

The mounting evidence and exposures of the impact of financial COIs should alert for clinician researchers. Disclosure of financial Interests to RECs, COI committees, research subjects, and in publications is necessary although not sufficient. Clinician-researchers should help to promote in their institutions a system of oversight that incorporates regulation, includes assessment and analysis independent of commercial interests, protects patients from harm, improves transparency in clinical research, and contributes to restoring public trust.

Clinician-researchers should obviously respect institutional COI policies and procedures. They should consult with professional organizations and institutions when they are in doubt about how to deal with COIs. They should refuse to be involved in research fully controlled by sponsors and should insist on full access to the data before accepting to sign on to any publications reporting the results of the study. Institutions should develop more stringent COI policies and should have the courage to prohibit research projects when personal or institutional financial Interests may impact or appear to impact on the integrity of the research. They should also be willing to sanction those who violate COI policies. It is, for example, remarkable that so many instances of ghost authorship have been documented, yet that no significant sanctions have been enacted.

Clinician-researchers ought not to rely on institutional policies and initiatives alone. Increased vigilance, informing oneself about the empirical evidence on COIs, and educational initiatives to explore and resolve financial COIs may all help in the long run to create a new research culture and to restore integrity in research. Clinician-researchers ought to critically determine how they can best contribute to promote independent and socially relevant medical research. Finally, clinical investigators ought to ensure that clinical trials in which they participate are registered, even if it is rarely a legal requirement at this point in time.

The case

The research contract signed by the institution and Dr. H gives the sponsor too much control over future publications. Although it is common to allow the sponsors to see the results before final publication and provide time for the potential filing of patent applications, sponsors ought not to be given the power to prevent publications. Dr. H should refuse to sign this stipulation and the institutional review should also screen out these clauses. In addition, clinician-researchers have a primary ethical and professional obligation to ensure the well-being of research subjects. When in their professional opinion, safety is at stake, they have to disclose this to research subjects and to their colleagues regardless of contractual clauses (Thompson et al., 2001; Viens and Savulescu, 2004).

Dr. H is in a difficult position to enforce his obligations. Clearly, he should not be swayed by
Dr. I's assertions and promises. He should contact the chair of the REC over his concerns related to the safety of the product tested and people higher up in the hierarchy of the institution with respect to the pressure put on him. Dr. I's personal interests and the relationship between the institution and the sponsor reveal a significant institutional COI. The potential impact of these institutional interests ought to have been evaluated by the REC or a COI committee before the research started.

At a minimum, the institution ought to investigate what happened and ought to support Dr. H fully in pressing for access to the full data and withdrawal of the abstract. If the conference is organized by a professional organization, that organization ought also to investigate allegations of ghost authorship and misrepresentation. If no support is forthcoming and institutional support is lacking, Dr. H has an ethical obligation to go public. This may come at a high personal and professional cost, as indicated by several recent controversies (Thompson et al., 2001; Viens and Savulescu, 2004; Revill, 2005). In an increasingly commercialized research context, professional organizations, academic institutions, and governments ought to develop adequate procedures to evaluate allegations of misconduct and appropriate remedies to protect whistle-blowers.

Dr. H ought not to have accepted the funder's fees and competitive enrollment fees provided for in the budget and the REC ought to also have spotted these. Although it is appropriate to remunerate clinicians for the work they perform for the study – these services ought not to be covered as a clinical service by the healthcare system – financial perks for mere recruitment are unacceptable.

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