Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards

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At a 1997 congressional hearing on research involving human subjects, Representative Christopher Shays (R-Conn.) was startled to hear of the existence of institutional review boards (IRBs) set up as profit-making ventures (Stolberg 1997). The congressional hearing marked one of the first public discussions of the issue of private, commercial review of research involving human subjects. Only recently has the phenomenon of commercial review attracted limited scholarly attention (Tendy 1996; Wadman 1997; Heath 1998; Kefalides 2000). More surprisingly, no governmental agency has systematic data on commercial IRBs. This comes as a surprise, considering the fact that many commercial IRBs have been inspected for years by the Food and Drug Administration (FDA) or received formal assurances from the Office for the Protection from Research Risks (OPRR) (Office of Inspector General 1998d).

The growth of the market for commercial research review is the latest development in the history of IRBs. Since the 1960s, federal funding agencies and the FDA have gradually introduced approval by an IRB as a precondition for research involving human subjects. Originally required only for research undertaken within specific research centers, granting agencies soon expanded the requirement of IRB review to all federally funded institutions. In 1981, the FDA also clarified that any medical

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research used to support an application for approval of new drugs or medical devices, whether the research is performed within institutions or by private physicians, has to obtain approval from a duly constituted IRB. Many states have integrated the system of research review into their regulations and require IRBs to review all research protocols within an institution, regardless of the source of funding (Office of Inspector General 1998d).

Internationally, research review has also more clearly become a crucial element in the protection of research subjects over the last two decades. In 1975, for instance, the World Medical Association revised its Declaration of Helsinki to include a requirement that experimental procedures involving human subjects be reviewed by an independent committee (World Medical Association 1964; 1975). Furthermore, international guidelines for research requiring ethics approval were promulgated in 1991 and 1993 by the Council for International Organizations of Medical Sciences (Council for International Organizations of Medical Science 1991, 1993), and in 1995 by the World Health Organization (World Health Organization 1995). This international trend is reflected in the recent adoption of the International Conference on Harmonisation's Good Clinical Practice Guideline (hereafter ICH GCP Guideline) (International Conference on Harmonisation 1996) by several national regulatory agencies. The ICH GCP Guideline represents an effort on the part of several national regulatory agencies (in particular from the United States, Europe, and Japan) to develop a common standard for the conduct of clinical trials and the regulation of medical research (Hirtle, Lemmens, and Sprumont, 2000). The Guideline will likely set the international standard for clinical research involving human subjects, and it clearly identifies review by an independent committee as a precondition for medical research involving human subjects.

In this context of increasing need for efficient IRB review and significant growth in industry funded research, commercial IRBs found their niche. They have become very visible participants at the commercial exhibits of drug or therapeutics conferences, where fast research ethics review has become a marketable item, promoted in the well-designed brochures of contract research organizations (CROs) or commercial IRBs. Commercial research review is gaining importance as research and development of new drugs, particularly phase I studies, increasingly take place in research centers of pharmaceutical companies, in CROs, or through physicians independent from academic research centers (Office

of Inspector General 1998c; Bodenheimer 2000). Researchers do not have access to IRBs established in academic centers. Thus, commercial IRBs have become crucial players in the rapidly expanding national and international drug and research industry.

Commercial IRBs can be divided in two categories: (1) freestanding commercial committees without institutional affiliation, established for the purpose of reviewing protocols for compliance with ethical and regulatory standards, often referred to as non-institutional review boards (NIRBs) or independent review boards, and (2) research review boards set up by CROs or pharmaceutical companies to review research for products developed or tested by the company itself, which we call proprietary IRBs. Often, the work of proprietary IRBs is an integral part of a wide array of services offered by the CRO. While NIRBs, by definition, review research undertaken elsewhere, proprietary IRBs typically review in-house studies. The division is far from absolute; some of the IRBs connected to CROs function as proprietary IRBs when reviewing protocols for research undertaken by the CROs themselves but also offer research review as a separate marketable product. For the sake of clarity, we will discuss proprietary and NIRBs as separate entities.

The purpose of this paper is to discuss one particular aspect of commercial research review that has been mentioned in the literature (Francis 1996; Office of Inspector General 1998a; Cho and Billings 1997) but has yet to be fully analyzed: the risk that fundamental conflicts of interest undermine the structure of commercial research review. Focusing on commercial IRBs, we point out why conflict-of-interest rules should be better developed and why they should prescribe more clearly what types of relationships are appropriate between IRBs or IRB members and research sponsors. In doing so, we recognize that the issue of the impact of financial interests on the independence of IRBs is not exclusive to commercial IRBs.

Nevertheless, we want to focus here on financial conflicts of interest that inhere in the structure and context of commercial IRBs. Two reasons justify our restricted focus. First, conflict of interest in academic research review has been discussed more extensively in the literature (Glass and Lemmens 1999; Cho and Billings 1997; Francis 1996; Jones 1995). As we will point out further, some of these conflicts are specific to research review in academic settings, and thus differ from the ones discussed here. The inherent financial conflict of interest underlying commercial IRB review has received less attention. Second, the conflicts of interest

we analyze in commercial IRBs can be seen as a paradigm that has relevance for dealing with some forms of conflicts of interest affecting research review in the academic setting. We aim to clarify which conflicts are created by the commercialization of research review, and which are currently endemic to research in general. We argue that regulations do not adequately address the special nature of financial conflicts of interest affecting commercial and, increasingly, academic IRBs.

Commercial Review: A Thriving Business Escaping Public Scrutiny

The difference between commercial and academic IRBs lies primarily in the context in which they operate and, to some extent, in the goals of the medical research that these IRBs are reviewing. Traditional IRBs are generally established by nonprofit educational and research organizations, such as universities, nonprofit hospitals, granting agencies, or professional associations. Commercial IRBs, by contrast, mostly review studies on behalf of for-profit companies, such as CROs (Office of Inspector General 1998d). While this distinction is beginning to fade as a result of the significant increase in the proportion of industry-sponsored research in academic centers (Grob 1998; Maatz 1992; Kefalides 2000), it remains fair to distinguish private from academic IRBs in light of the former's focus on commercial studies. Even when private IRBs are involved in the review of research undertaken at academic health care centers, which is increasingly the case, they are primarily involved in the review of commercially sponsored research for these institutions (Office of Inspector General 1998d). Moreover, by focusing strictly on commercial IRBs, lessons can be learned about the potential need to restructure academic IRBs in the context of increasing academic entrepreneurialism. Several academic institutions have formed partnerships with CROs and set up academic IRBs to review in-house research, for example. These academic IRBs share many of the characteristics of proprietary IRBs, and our discussion of commercial IRBs is clearly relevant for determining what conflicts can arise from this situation.

The keys to the success of NIRBs seem to be the increasing demand for review of research protocols from CROs and independent physician-researchers, the speed of the review, the quality and variety of services offered, and the ability to review multisite projects (Office of Inspector

General 1998d; Heath 1998; Kefalides 2000). As Erica Heath, president of one of the largest American NIRBs, puts it: "We certainly cannot market approvals. But we can market in terms of speed, efficiency, expertise, customer relations, and complete information on readable forms" (Heath, personal communication, 1997). Unlike most academic IRBs, many NIRBs can guarantee a very short review time. The average review time of the NIRBs contacted by the Office of Inspector General was 11 days (Office of Inspector General 1998c). One survey found that some NIRBs guarantee review in as little as 5 days (Lemmens and Thompson 2000). Because of the high volume of protocols they review and the concomitant expertise of their members, many NIRBs are likely capable of giving coherent and clear instructions to improve protocols. Their reviews might be more predictable than those of some academic IRBs with more fluctuating and often less experienced membership. The latter have come under increasing criticism for their members' lack of training, administrative understaffing, and disregard of regulatory requirements (Office of Inspector General 1998a; 1998c; Kefalides 2000). Some NIRBs take a very active role in educational programs for IRB members. They sometimes have much stricter educational requirements for their members than many academic IRBs, which often hesitate to impose education on their volunteer members, who are frequently hard to recruit. Finally, many multisite trials can be efficiently reviewed by one NIRB, thus avoiding the lengthy process of going through multiple reviews, which often lead to contradictory instructions (Office of Inspector General 1998d; Heath 1998).

Proprietary IRBs offer a number of other advantages. They are directly accessible and may be under the authority of the CRO, so that research protocols can be reviewed even faster and upon special request. Setting up a proprietary IRB may be cheaper than paying an outside IRB, particularly if the CRO has a high volume of studies. Finally, a CRO may feel more comfortable in granting access to confidential information to an IRB that has a formal link with the company and adheres to its policies.

Surprisingly, notwithstanding their importance, official information on the number of NIRBs or proprietary IRBs functioning in the United States or Canada is lacking. Even the Department of Health and Human Services mentions in its official report only that there are "at least 15, and perhaps quite a few more" NIRBs and takes this guesstimate from a consortium of NIRBs (Office of Inspector General 1998d). Similarly, the Canadian Health Protection Branch has no official information on

NIRBs, although several of them are active in Canada and are recognized as playing an important role within the drug approval system.

The Health Industry Manufacturers Association's website recently listed 21 U.S. and one Canadian CROs or commercial IRBs (Health Industry Manufacturers Organization 2000). While preparing a survey on NIRBs, we found that there are at least two other Canadian NIRBs (Lemmens and Thompson 2000). Moreover, several European NIRBs and proprietary IRBs advertise their services at American conferences. These services include access to the booming European CRO industry, which benefits from the easy recruitment of human subjects in eastern European countries. While the Office of Inspector General's reports provide some information on NIRBs, there is no public information on proprietary IRBs set up within private commercial companies. The lack of clear, official information on NIRBs and the absence of any information on proprietary IRBs raise concerns in light of the public role these IRBs fulfill.

Since the congressional hearing, there have been signs in Canada, the United States, and Europe that governmental agencies are paying more attention to the phenomena of for-profit and proprietary review. In 1998, the three major federal funding agencies in Canada introduced a uniform Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (Medical Research Council, Social Sciences and Humanities Research Council, and Natural Sciences and Engineering Research Council 1998). The policy statement includes, among other things, more detailed instructions on how IRBs have to be set up. In discussing what constitutes a conflict of interest, there is a prudent reference to commercial IRBs. The statement gives, as an example of conflict of interest, a member's acceptance of "undue or excessive honoraria for their participation in the REB (e.g., *on commercial REBs*)" [the Research Ethics Board (REB) is the Canadian equivalent of the IRB] (Medical Research Council, Social Sciences and Humanities Research Council, and Natural Sciences and Engineering Research Council 1998). Unfortunately, the document offers no further discussion of commercial IRBs, nor does it clarify why commercial IRBs are singled out. As we will discuss further, undue payment may be a concern, but it is not clear why that would be an issue only for commercial IRBs.

In the United States, federal agencies involved in human subjects research took several initiatives following the congressional hearings on the protection of research subjects. The Department of Health and Human Services (Office of Inspector General 1998a; 1998b; 1998c; 1998d) and

the National Institutes of Health (Bell Associates 1998) published detailed reports that critically assess the adequacy of the current research review system. One report of the Office of Inspector General focuses exclusively on the emergence of "independent boards," another common term for NIRBs (Office of Inspector General 1998d). The first official report on the subject, it indicates very clearly that commercial NIRBs have become crucial players within the current review system and identifies the advantages of NIRBs as well as their potential problems, with conflict of interest among the latter. The National Bioethics Advisory Council is also looking into the adequacy of the current system of human subjects protection (Moreno 1998), and it is hoped that they will deal with the phenomenon of private commercial review and problems associated with it in their final recommendations. Recent suspensions of research institutions by OPRR have increased the calls for a major reform of the system, and it remains to be seen what the role of commercial IRBs in any new structure will be and whether the concerns raised in this paper will be addressed.

In Europe, a recent scandal involving the alleged "importation" of research subjects from eastern European countries (Estonia, Poland, and perhaps even the war-torn former Yugoslavia) by a research company located in Switzerland has raised awareness among regulatory agencies of the loopholes in the regulation of medical research. It provoked an official investigation into the activities of the CRO and the private IRB responsible for reviewing the importation scheme (Hirtle, Lemmens, and Sprumont 2000; Schaad 1999a; 1999b; 1999c). This case serves to highlight some of the potential consequences arising from a lack of clear conflict-of-interest guidelines. Sometime after the importation of research subjects was exposed and became the subject of an investigation, it was discovered that the director of the CRO had, for a long time, also been the main administrator of the private ethics committee. While this one incident does not represent a standard practice among CROs or NIRBs, it does highlight the need for analysis and regulation of conflicts of interest affecting such boards.

What Constitutes a Conflict of Interest?

While the concept of conflict of interest is clearly in vogue in discussions around health policy and the term is used in many different contexts, it is

hard to find a clear definition of it. *Conflict of Interest in Academic Health Centers*, a 1990 report of the Association of Academic Health Centers (AHC), mentions the importance of professional norms for determining what conflicts of interest are. It states that a conflict exists "when legal obligations or widely recognized professional norms are likely to be compromised by a person's other interests" (Shipp 1992). James P. Orlowski and Leon Wateska define conflict of interest more narrowly as "a discrepancy between the personal interests and the professional responsibilities of a person in a position of trust" (Orlowski and Wateska 1992). Dennis Thompson defines a conflict of interest as "a set of conditions in which professional judgment concerning a primary interest (such as patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)" (Thompson 1993). Other authors also stress that conflicts of interest arise when professional obligations clash with other interests (Shipp 1992; Erde 1996).

Secondary interests are not in themselves improper, but they should be subservient to primary interests. Secondary interests are often financial, but they can also be intangible ones, such as gaining professional advantage, prestige, or power. Following this definition, the central questions arise: what are the primary obligations of IRBs, what is the role of IRB members *qua* members, and how seriously can these obligations be affected by other interests? The impact of conflicts of interest can only be understood when the primary obligations of IRBs and IRB members are clarified.

IRBs have a protective public role. "The primary purpose [of IRB review]" according to the FDA Rules and Regulations, "is to assure the protection of the rights and welfare of the human subjects" (21 CFR 56). The ICH GCP Guideline refers to "the protection of the rights, safety and well-being of subjects" in its definitions of "independent ethics committee" and "institutional review board" (International Conference on Harmonisation 1996). As thus defined, an IRB's primary duty is to protect human subjects of research (Levine 1988).

In light of their public policy role, we argue that rules of administrative law ought to inspire us in refining the rules by which IRBs are organized. Rules of administrative law apply to a variety of judicial bodies and governmental agencies and may vary accordingly. It is not easy to determine which of these bodies resembles the IRBs most closely. In many respects, the role of IRBs can be situated somewhere between, for example, the roles of public curators and administrative licensing boards.

Licensing boards are similar to IRBs in that they often have an important public policy goal, they are given much discretion in the implementation of their policies, and their decisions often have a major impact on the activities they regulate. Moreover, administrative licensing boards are often specialized bodies, dealing with issues that require particular expertise from board members. The same is true for IRBs, which function within highly specialized areas of medical research. On the other hand, the IRB's role is clearly more intimately related to individual people's rights and welfare than, say, a land development, transportation, or liquor licensing board. Because of their protective role and their responsibility with respect to the rights, integrity, and well-being of individual research participants, IRBs have some of the characteristics of public curators. They are first and foremost obliged to look after the welfare and rights of research subjects. In addition, the IRB's mandate also resembles that of human rights commissions, when these are involved in policy rather than litigation. Finally, while specialized knowledge on the part of some IRB members is required, representation by the community and by members of different disciplines are core requirements for IRB review. Thus, IRBs differ from highly specialized administrative or professional bodies in that there is clearly public involvement and public responsibility directed toward the physical and emotional well-being of individual research participants.

Bias and Conflict of Interest in Administrative Law

Because of this resemblance to administrative bodies, administrative law on conflict of interest (discussed under the heading "bias") can inspire this debate. The independence and impartiality of judges and administrators are major principles of judicial and administrative review (Flick 1984). In common law, an essential principle of natural law is expressed in the adage *nemo judex in causa propria sua debet esse* ("no one ought to be judge in his or her own case"). In American law, conflict of interest falls under the due process clause, enshrined in the 14th Amendment to the Constitution, which guarantees the right to a fair hearing before an *impartial* tribunal.

This is not to say that IRBs ought to be treated entirely as tribunals. The rules on bias and conflict of interest in administrative law are a

reflection of the general concern for independence and neutrality as essential ingredients for a good administration, particularly when administrators are given a specific public duty (Dickens 1995). They apply to a wide variety of administrative and judicial bodies.

As we have pointed out, IRBs are situated on a continuum somewhere in between administrative tribunals and administrative licensing boards. Where they are placed on this continuum between administrative and judicial bodies is important, if we want to apply rules of administrative law with respect to conflicts of interest in research review. While administrative adjudicators are held to the same requirement of impartiality as judges (*Tennessee Cable Television Association* v. *Tennessee Public Service Commission* 1992), the interpretation of what constitutes a conflict of interest may differ depending on the type of administrative board involved. Conflict-of-interest rules are context-specific; the assessment of conflict of interest can differ according to the type of administrative board or judicial body. The closer an entity approaches judicial decision-making, the stricter the rules of conflict of interest are. Clearly, judges presiding in a criminal procedure ought to have the highest level of detachment from financial or personal interest in a case. The same level of detachment is not necessary, possible, or always desirable when we are dealing with highly specialized administrative bodies. When dealing with a motion for preliminary injunction against an IRB's rejection of a research protocol, the Minnesota District Court recognized explicitly that there are due process standards in the IRB process, but that they are different from the ones in criminal procedures. "An IRB proceeding is, simply, not a federal criminal prosecution," the Court stated. "Such a proceeding is governed by contracts and federal regulations which do not require, or provide, the full panoply of criminal procedural rights" (*Halikas* v. *University of Minnesota* 1994).

IRBs need some specialists who, for example, may be very strongly committed to a certain area of research and may have strong personal bias toward seeing this research being undertaken. At the same time, membership of boards is precisely balanced, or is at least intended to be so, to ensure that these interests of individual members do not dominate the review process. For the same reason, a quorum of the IRB has to be weighed and, if majority rule rather than consensus is used, should not lead to a systematic outvoting of community members.

While IRBs are specialized entities, they do have general protective obligations toward the public. IRBs and their members have this

protective role in a particular circumstance: research participants are often in a vulnerable position. They may suffer from disease; their financial and social situation may push them to participate in trials; in some cases, they may participate in research to try to obtain access to quality care. This situation warrants careful consideration because of the risk of undue influence or manipulation.

Writing about professional advisory relationships, Bernard Dickens (1995) points out that "dependent parties at disadvantage enter [these] relationships for their own protection against their ignorance and vulnerability to exploitation and abuse. These relationships impose special duties on those whose protection is sought and who undertake to afford that protection." The diligent exercise of responsible review by the boards should compensate partially for the vulnerable position of research subjects. In these circumstances, higher duties of protection are imposed on the party with more power. While IRB members have no direct relationship with research subjects, IRBs have special duties as organizations and their members have a professional obligation to fulfill their work in accordance with the mission of the IRB. Patients who participate as research subjects should be able to trust the health care institution in which they are treated to look after their well-being and respect their rights. The fiduciary nature of the doctor-patient relationship remains a cornerstone of medicine and should not be abandoned when physicians and patients are involved in research. Likewise, this fiduciary relationship should extend to the institutional bodies that are set up to protect patients and others who participate in medical research.

The need to create trust in IRBs as institutions can also be given a very practical justification. When IRBs function in a transparent way, they inspire public confidence. Public trust in the ethical conduct of trials is essential to the success of medical research, which relies on volunteer participation. Creating public trust in research and research review is therefore essential, not only to respect the subjects of research but also to ensure long-term research participation. Paul Finn's argument about the importance of conflict-of-interest rules for professionals rings very true in this context. He argues that "there can be a public interest in reassuring the community that even the appearance of improper behaviour will not be tolerated. The emphasis here seems to be the maintenance of the public's acceptance of, and the credibility of, important institutions in society which render 'fiduciary services'" (Finn 1987).

The idea that public trust is an important aspect of conflict-of-interest rules seems to be confirmed by the standards used in American and common law to determine whether the impartiality of the administrative decision maker is affected by bias. In both systems of law, the test is whether it is reasonable to consider that secondary interests may have an influence on the decision-making process. The Canadian Supreme Court describes the "reasonable apprehension of bias" test as determining whether a "reasonably well-informed person" would consider the secondary interest to be so significant that it is likely to undermine the independence of the decision maker (*Pearlman* v. *Manitoba Law Society Judicial Committee* 1991). American law seems more lenient toward conflict of interest, by requiring that a party seeking to demonstrate bias must overcome the presumption of honesty and integrity on the part of decision makers and the presumption that decisions affecting the public are done in the public interest (McDonald 1999). Nevertheless, this can be done by using a "realistic appraisal of psychological tendencies and human weaknesses" (*Valley* v. *Rapides Parish School Board* 1997) to show a serious risk of actual bias or prejudgment. Other cases also refer to the test as simply requiring that an adjudicator's "impartiality might reasonably be questioned" (*Tennessee Cable Television Association* v. *Tennessee Public Service Commission* 1992), bringing the burden of proof closer to the common law standard.

In our view, recent controversies and research analyzing the impact of financial interests on the conduct and outcome of medical research show that financial interests can and do influence the behavior of those involved (Eichenwald and Kolata 1999a; 1999b; Reed and Camargo 1999; Stelfox, Chua, O'Rourke, et al. 1998; Lemmens and Singer 1998). These controversies understandably erode public trust. IRBs are supposed to counterbalance the concerns raised by these controversies and scandals by offering a system of independent, qualified, hands-off review. NIRBs and proprietary IRBs are financially dependent on the commercial actors they are supposed to control. It seems odd to hold as reasonable the presumption that financial interests can have a conscious or unconscious impact on these actors while ignoring that there is a serious risk of such impact on those who control them.

We hold that problems of conflict of interest in commercial IRBs are not adequately addressed through simple reliance upon the integrity of IRB members, or upon the fact that most IRB members are likely to adhere to high ethical standards. In a case concerning judicial bias one

century ago, Justice Lush pointed out: "The law, in laying down this strict rule [against bias] has regard, not so much perhaps to the motives which might . . . bias the judge as to the susceptibilities of the litigant parties" (*Serjeant* v. *Dale* 1877). Although, as stressed earlier, IRBs perhaps need not submit to the stringent conflict rules that courts ought to observe, the significant public interest in protecting trust and maintaining confidence in the system calls for the development of adequate conflict-of-interest rules. As we will discuss further, this is even more important in light of the nature of research ethics review.

Interestingly, the importance of establishing public trust in IRBs is recognized explicitly by the ICH GCP Guideline. In its definition of "independent ethics committee," the Guideline states that such committees not only have to ensure protection, but also have to *provide public assurance of that protection* (International Conference on Harmonisation 1996) (our emphasis).

What, then, are the conflicts that should be avoided? The law differentiates among bias as a result of (1) pecuniary interests, (2) personal involvement of the decision maker, and (3) alleged prejudgment of the merits of a particular case (Schwartz 1995; Flick 1984; Hewitt 1972). In general, the law regards financial interests much more severely than it does other interests or biases. There is a reason for that; as John Stuart Mill points out, "the love of money is one of the strongest moving forces of human life" (Mill 1988). In the context of the highly profitable pharmaceutical industry, is it unreasonable to anticipate that decisions can be influenced by the promise of financial gains? Moreover, as Thompson recognizes, the existence of other motives or conflicting interests does not mean that we should not address financial ones; financial interests are more tangible. Many factors that are qualified as "conflicting interests" are simply inherent to people's actions and are inevitable. Financial conflicts of interest, by contrast, are identifiable and avoidable (Thompson 1993).

In the case of a pecuniary conflict, a decision maker will be disqualified if the first two (under common law) or all three (under American law) conditions are fulfilled: (1) The "decision maker must stand to gain or lose personally as a result of his decision" (Flick 1984). (2) The interest is not remote or does not arise upon a purely speculative series of events. Interestingly, some English and Commonwealth courts have argued that interest as a shareholder or ratepayer is sufficient to disqualify a person on the basis of bias (Flick 1984). (3) Under American law, the interest

must also be substantial. The due process clause requires disqualification of a board member only if the interest is more than "*de minimis*." In contrast, English and Commonwealth common law prescribe that a minimal interest is sufficient to disqualify a person on the basis of bias. The position of the common law courts is ably summarized by Justice Blackburn, who declared that the interest "may be less than a farthing [historical quarter of a penny], but still it is an interest" (Flick 1984).

In contrast to financial interest, personal involvement in a case only leads to disqualification if there is a real likelihood that a hearing will not be fair. A paradigmatic example of this is when there is a close kinship between one of the parties and one of the judges or adjudicators. This type of bias might pose greater risk in academic IRBs, where colleagues have to review protocols of persons with whom they are closely related. Such personal conflicts are less likely to occur in NIRBs.

Prejudgment is an even more flexible concept. Courts recognize that adjudicators, particularly those who serve on specialized boards and have experience in the field, have often formulated opinions on cases or situations similar to the ones they have in front of them. In fact, oftentimes the very motivation for selecting these persons as adjudicators is based on their having expressed opinions on certain issues. In the IRB context, one would hope that special expertise of IRB members would not be in and of itself grounds for disqualification. The opinion of expert members is often invaluable in assessing the validity of a given protocol. These experts will often have expressed authoritative opinions on particular issues in research. Similarly, community members' statements about the need for better protection of subjects should not constitute grounds for disqualification, and previous decisions by an IRB should not be invoked to challenge a later decision on a similar study. One could compare the situation to that of judges: their earlier decisions, and the unavoidable interpretations of the law expressed in them, do not disqualify them from ruling on a similar case in the future.

In conclusion, when reviewers or judges have financial interests, they are disqualified if there is a clear potential for personal loss and if the financial interest is not too remote. Financial interests are identified as creating conflicts, and are more clearly subject to regulation than other types of interest. Scrutiny of financial interests, rather than of personal involvement and prejudgment, seems appropriate for IRB review, in particular when we are dealing with research undertaken entirely within a

commercial context. While some cases involving personal involvement and prejudgment may necessitate intervention, they do not require the same stringent regulations because they are often unavoidable and may be counterbalanced by the composition of the IRB. Personal involvement can only be decided on a case-by-case basis—for example, by looking at the specific relationship an IRB member has with a researcher who submits a protocol. We further believe that the public function of IRBs strengthens the need for stringent assessment of the impact of commercial interests on the review process. This public function emphasizes the need for a system that imposes public trust and thereby promotes participation in medical research.

The Role of Conflict-of-Interest Rules

We have argued that conflict-of-interest rules should provide an appropriate framework for review, and that they are essential to promote trust. Conflict-of-interest rules are particularly important when regulations allow much discretion and rely on the fairness and independence of individual decision makers. This is the case with research regulations. Two major types of rules are available for any type of regulation: procedural rules and substantive rules. Through procedural rules, legislators or regulatory agencies can establish a system of review and licensing. These procedural rules are ordinarily, if not always, accompanied by a set of substantive rules. Substantive rules specify what is allowed and what is forbidden. As applied to research ethics review, substantive rules specify *what* research is acceptable and procedural rules specify *how* one can decide and *who* can decide that a study is acceptable. Substantive rules describe the qualities the conduct of research itself needs to satisfy; procedural rules describe the qualities required of the decision-making process that validates the research project—including the ways in which substantive rules are applied and interpreted.

Research ethics codes and research regulations are characterized by the dominance of procedural rules. They typically provide details about the constitution and composition of IRBs, record keeping, and appeal procedures but are vague about how to weigh risks and benefits. IRB members are relied upon to make significant value judgments.

The FDA regulations, for example, contain concrete procedures but only general rules dealing with substantive issues. Issues such as IRB

membership, the functioning of the IRB, the keeping of minutes, notification procedures, and so on, are specifically regulated (21 CFR 56). Yet, not so much direction is provided as to what criteria IRBs should use in rejecting or approving protocols. Research procedure, for example, must be consistent with "sound research design" and should not "unnecessarily" expose subjects to risks. Risks have to be "reasonable in relation to anticipated benefits." Selection of subjects has to be "equitable." FDA rules expand on subject selection, but only to create more room for IRB interpretation. In assessing the equitable nature of the selection, "the IRB should take into account the purposes of the research and the setting in which the research will be conducted." And while "coercion" or "undue influence" is to be avoided, what such avoidance in fact entails remains unspecified.

Research regulations, in other words, provide no absolute standards upon which IRBs can rely. Appropriate protocol review requires a fair exercise of intelligence and discretion on the part of IRB members. As Harold Edgar and David J. Rothman point out, "there are very few provisions in the regulations that protect against bodies [IRBs] that might be sloppy, venal, or subservient to the institution. Put another way, the quality of an IRB's work depends to an inordinate degree on the conscience and commitment of its volunteer members" (Edgar and Rothman 1995). Procedural rules dealing with the membership and composition of IRBs, including conflict-of-interest rules, are important in research ethics review precisely because there is so much reliance on the fairness of IRB members. Members should be sufficiently detached that they can be trusted to weigh risks and benefits fairly. There should be no suspicion that objectives other than the protection of research subjects will prevail. Unfortunately, current provisions on conflict of interest, particularly regarding the way they are to be interpreted, are too vague to be helpful.

Conflict-of-Interest Rules in Research Codes and Regulations

The recently revised World Medical Association Declaration of Helsinki states in its principle 13 that all protocols for medical research involving humans have to be submitted to an "especially appointed ethical review committee which has to be independent of the investigator, the

sponsor or any other kind of undue influence" (World Medical Association 2000). It thus not only prohibits researchers from participating in the review of their own research, but also prescribes that reviewers should not be "dependent" on those who pay for the research. The reference to "any other kind of undue influence" was added under the last revisions to the Helsinki Declaration. It indicates that many potential sources of influence are recognized. While the notions of "dependence" and "undue influence" leave some room for interpretation, the provision clearly reflects the idea that reviewers should be kept at arm's length from investigators or sponsors.

Surprisingly, other research ethics codes and regulations totally fail to refer to this idea. The FDA rules point out that "No IRB may have a member . . . who has a conflicting interest," without providing further detail (21 CFR 56.107(e)). Data on FDA site visits to IRBs suggest that the FDA has identified conflicts of interest only when researchers participate in the review of their own research (Francis 1996). It is the duty of the local IRB to determine whether a situation gives rise to a conflict of interest. This seems to be a recipe for problems if the same rule applies to conflicts of interest within the IRB itself. If IRBs are supposed to decide what to do with conflicts of interest, what happens if its own members are in a conflict of interest?

The Office for the Protection from Research Risks' 1993 *Institutional Review Board Guidebook*, which provides further information on the rules of the federal policy, also avoids defining "conflict of interest" (Office for the Protection from Research Risks 1993). However, after stating that "[n]o IRB member may participate in the review of any project in which the member has a conflicting interest," the *Guidebook* mentions that a list of members must be kept by the IRB. This list must state "any employment or other relationship between each member and the institution (e.g., full-time employee, stockholder, unpaid consultant, or board member)." While both of these rules can be found under different sections of the federal policy (45 CFR 46.107(e); 45 CFR 46.103(b)(3)), the fact that they are lumped together in the *Guidebook* may indicate at least a recognition that these relationships can affect the functioning of the IRB.

Interestingly, while IRBs have to keep a list of the board members with the same details under the FDA Rules and Regulations as under the federal policy that applies to the funding agencies (21 CFR 56.115(a)(5)), the FDA does not itself keep records of the composition of these boards

and does not require the boards to report any changes in membership or in the status of the members.

The absence of stringent central oversight, the lack of clear conflict-of-interest rules, and the reliance on the individual integrity of IRB members are reminiscent of the emphasis on the professional integrity of medical practitioners. The traditional approach to ethical problems in medicine in general, and in medical research in particular, has been to emphasize personal and professional responsibility. Research and its review take place in a context that is highly permeated by this Hippocratic model of personal integrity and professional responsibility of the trusted healer. Only after the ethical pitfalls in several high-profile cases were exposed in the sixties and seventies—such as Tuskegee, Brooklyn Jewish Chronic Disease Hospital, and Willowbrook—did the medical community fully realize that many research practices have an impact on patient care and that there is a need for stringent review (Beecher 1966; President's Advisory Commission on the Human Radiation Experiments 1996). However, the research community preempted attempts to establish a more publicly accountable national regulatory structure of protection in the sixties by adopting a system of flexible control through federal funding agencies (President's Advisory Commission on the Human Radiation Experiments 1996; Edgar and Rothman 1995). Under this system, funding agencies are key participants in the establishment and enforcement of general research ethics rules, which are interpreted and implemented by local IRBs in light of the local context in which they operate. It is worth noting that, to this day, both the funding agencies and the local committees remain characterized by a strong representation if not dominance of medical professionals (McNeill 1993; 1998). In other words, IRB review has remained very akin to professional self-regulation, in which reliance on individual integrity is a core value. This may explain why oversight of medical research has often been restricted and has not led to a very stringent control of the IRB system.

Another reason Edgar and Rothman invoke to explain the local character of IRBs is worth mentioning here. Local review was set up at a time when research was expected to take place within academic institutions and teaching hospitals. In these places, it was presumed, there was "a shared commitment to the ideals of good science [which] would far outweigh any tendency for persons to trade favors or elevate concerns for the financial viability of the institutions above their loyalty to the integrity of science or the well-being of subjects" (Edgar and Rothman 1995).

The emphasis on localism and context-sensitive review of individual research projects still has many supporters, including Edgar and Rothman. As Jonathan Moreno points out, "local review does allow for familiarity with local conditions that could be relevant for human subjects research, and it provides a convenient source of cheap labor in the form of professors who feel obliged to serve" (Moreno 1998). However, these and other observers do recognize that there are serious problems. The circumstances of research review have changed from the time of the inception of the IRB system. Recent research scandals support this view. If local factors warrant local variations in review, different temporal circumstances also warrant different remedies. For one reason, commercial involvement in medical research has clearly changed the academic landscape and has led to IRBs that are set up as profit-making ventures. The drafters of the IRB system did not anticipate for-profit IRB review or the increasing commercialization of medical research. They envisioned a system grounded in review by a balanced in-house committee, consisting of dedicated members of the academic community and some other volunteers, who participated in IRB review out of pure altruism. Without suggesting that this ideal vision was ever fully realized, we argue that the changed circumstances make it more necessary than ever to analyze what types of conflicts may undermine the independence of IRBs.

Conflict of Interest in Commercial IRBs

The English and Commonwealth decisions holding that an interest as a shareholder or ratepayer is sufficient to create a disqualifying bias are very interesting in the context of discussing financial conflicts of IRBs and IRB members. When individual IRB members are paid by a commercial IRB, they have an interest in keeping their contractual relationship with this IRB. NIRBs, in turn, have an interest in obtaining as many contracts as possible from CROs. When NIRBs are financially dependent on their clients, they surely have an interest that is less remote than that of a shareholder or ratepayer. An NIRB's decision to reject protocols submitted by a CRO may affect its client–service provider relationship. This, in turn, could have an impact on the earnings of individual IRB members. American law softens the rule on conflict of interest, by suggesting that an interest must be "substantial." This could imply that one has to look in more detail at the salaries IRB members

receive, and what the percentage this amount is of their overall income. How do these rules apply to the two forms of commercial IRBs?

In the case of proprietary review, the company that establishes the IRB submits its own research protocols for review. Two situations are causes for concern here. First, individual IRB members may be recruited from among personnel of the company, which means they are employees of the institution submitting protocols for review. Consciously or inadvertently, directly or indirectly, pressure might exist to approve protocols or to be more flexible with respect to required modifications. While this situation also exists within academic IRBs, the pressure can be greater within private companies, whose practices are not subjected to the same level of public and academic scrutiny. Respect for superiors is part of the hierarchical corporate culture, and may be less prevalent in a university environment that values academic freedom. There might be fewer, or less reliable, means of protecting employee reviewers from corporate sanctions. In academic environments, where academic excellence and integrity should be core values, profit motives may be less likely to prevail. In a commercial context, profit is of the highest importance and the primary responsibility is to shareholders. By definition, CROs depend financially on the protocols that are submitted for review. Employees know very well that rejection of research protocols leads *de facto* to a loss for the company, since it means that lucrative research cannot be undertaken. They are also aware that when they insist on certain modifications to the protocol, research may be delayed or become more expensive. Moreover, systems of financial incentives within the company might increase the pecuniary consequences of rejecting protocols. Employees may receive shares in the company as part of their benefit package, in which case they have significant financial interests as shareholders in these companies. Every rejection of a protocol or any delay caused by the review process would have a negative impact on profit margins and thus on the value of the shares of the company.

Second, even if IRB members are attracted from outside the company, they are appointed by those in charge of the company. The latter have a primary interest in the profit margin of the company. They could easily terminate the appointments of IRB members whose decisions affect the profit margin of the company. Even if the board or president acts in good faith and respects the IRB's independence, the appearance of direct control over the IRB undermines the credibility of proprietary review. It is not unreasonable to expect that members may fear losing the financial

advantages linked to membership and thus act accordingly. Certainly, this is also a possibility within a university environment, where deans or hospital and departmental directors may feel the pressure of corporate investments. But as we have argued, academic scrutiny might be higher and other values prevail, or should prevail, in this setting. Within a commercial context, financial profit is clearly the driving force essential to corporate survival. This situation should encourage us to be even more vigilant about financial pressures. This appearance of conflict makes it crucial to require public scrutiny and access to information on how IRB members are protected from corporate sanction, whether they have secure positions (e.g., by long-term contracts), and whether they have any other financial interests in research undertaken by the company.

According to the American rules on bias, it is important to look at how much money IRB members receive from their work, to determine whether payment for this work is a significant part of their regular income. If the remuneration for review work is marginal, compared to a member's overall income, conflict of interest may be less of a problem under the American approach. Discussing NIRBs, Erica Heath suggests in the same vein that "the remuneration is probably not enough to make any member wealthy" (Heath 1998). It is hard to obtain information about payment of members, but in a survey undertaken for the Canadian National Council of Ethics in Human Research, respondents reported numbers varying between $50 and $200 per meeting. Other commercial IRBs pay per protocol reviewed. If one assumes that an IRB meets once a week, this can easily amount to $10,000 per year, not an insignificant amount and likely to be more than "*de minimis*." Some NIRBs meet even more frequently, up to twice a day (Kefalides 2000), which clearly means that IRB members can become financially dependent on their IRB work.

Presuming that some commercial IRBs pay their members less, which seems unlikely, IRB members who earn little income outside their work as reviewer may have a conflict of interest under the *de minimis* approach, while others who have another substantial source of income would have no conflict, even if they are paid more as members. The relatively small weight of the income they gain from participating in research review could be used to argue that external reviewers are more likely to be independent than, for example, a member of an academic IRB who is reviewing profit-oriented protocols submitted by the chair of her department.

Nevertheless, in the context of the commercial IRB structure, we feel more comfortable with the common law rules, which would see this as a situation in which conflicts of interest are inherent, regardless of the significance of IRB remuneration to a specific member. We have three reasons for holding this to be the case. First, it may not be practical to examine in detail how significant the remuneration is, with respect to the overall income of every individual IRB member. Second, the special role of IRBs within medical research demands that we err on the side of caution and develop policies that enhance public trust. This can only be done if rules on conflict of interest are clear and comprehensive. Third, IRB review requires, as we discussed, the exercise of much discretion. There is no clear standard to verify whether IRB members did perform their work without undue influence from their financial interests. Because of their particular work, strict detachment is required.

In the case of NIRBs, the financial interests are more remote. Much depends on the attitudes of the companies submitting the protocols for review. In an ideal world, NIRBs should not see their workload diminished by a thorough review of protocols. Serious review should be a marketable item. But CROs could cease to employ a NIRB that frequently rejects its protocols or requests substantial modifications if other IRBs, known to be more lenient, are also available. "Consistently unfriendly reviews," Leslie Francis points out, "might be thought to threaten ongoing relationships between IRBs and the institutions for which the studies are being reviewed" (Francis 1996). NIRBs may suffer if they frequently reject protocols, or request significant changes to protocols, which may result in delays for their clients. They may be dependent on a few very lucrative contracts with large CROs. In that case, their financial gains may be directly affected by performing a thorough, critical review. Outside the field of medical research, it is a general principle that reviewers or judges should not be directly paid by only one of the parties involved in the review. If this is such a fundamental rule elsewhere, why not in medical research?

Heath suggests that there is little difference between paying people to sit as professionals on IRBs or paying them to give their expert opinions as doctors or lawyers. They also "must occasionally deliver bad news to a client who seeks good news but also must pay regardless of the outcome" (Heath 1998). However, when doctors or lawyers give their expert opinion, the beneficiary of their opinion is the patient or client who is confronted with a medical problem or legal quandary. In the

case of IRBs, the primary responsibility of the reviewers is not toward the investigators or sponsor of a trial, but toward research subjects and the public. Moreover, when doctors or lawyers feel they must give bad news, it is not so much based on a somewhat discretionary weighing of risks and benefits, but results from an empirically based diagnosis or an appraisal of the current state of the law. The reason for their decision is their realistic assessment of what will happen to their clients, who remain free to follow or ignore their advice. The basis underlying their recommendation is measurable and more precise. Doctors or lawyers who give unprofessional advice are easily held liable for doing so. They have a professional duty to try to prevent harm to their individual clients. IRBs, however, can hinder a research project from going ahead, even if it would not necessarily have caused major problems to their clients. On the contrary, when IRBs give a negative review, their clients are stopped from conducting research and may be financially hampered by doing so. For example, when an IRB rejects a research protocol with a biased design, it may very well be that there was no likelihood of serious and immediate harm to subjects and thus no risk of liability or financial hardship to the company conducting the research. The positive results of a scientifically flawed study may boost the sale of a particular drug without identifiable physical harm to patients or research subjects that could result in legal liability.

Remedies against Conflict of Interest

Can these conflicts of interest be avoided? Several procedural remedies have been suggested to solve them. The most common suggestions are disclosure, removal of voting right, and prohibition from participating in the review.

The disclosure remedy is based on the idea that people can make truly informed decisions if they are aware of all factors that could influence their physicians' enthusiasm for the trial. If those who could be harmed by a conflict of interest are informed, the argument goes, they can then freely decide whether to take the risk. While this rings true in some circumstances, it ignores the fact that people are often in situations which make them vulnerable, and dependent upon others to protect them. When people or institutions offer special expertise to protect people against harm, "[t]hey must act in good faith to avoid conflict *per se*,

since resolution through disclosure may, in many cases, leave dependent parties without means of achieving further protection of independent aid" (Dickens 1995). Furthermore, the mere existence of a protective regime in the area of research, based on control by regulatory agencies and IRB review, indicates that reliance on informed consent is not sufficient. Mildred K. Cho and Paul Billings argue in favor of public disclosure rules because "research or review of review board activities may be facilitated by public disclosure of financial or other ties between review board members and investigators, or between funding sources and review board members or investigators" (Cho and Billings 1997). They thereby fail to distinguish between conflicts of interest of investigators and of IRB members. IRBs are themselves supposed to control conflict of interest among researchers. According to the latest revision to the Helsinki Declaration, for example, the IRB has an explicit duty to review financial relations between researchers and sponsors. It has to assess how financial interests could impact on the research process and on the recruitment of patients. Principle 13 states that "[t]he researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects" (World Medical Association 2000). A similar duty to scrutinize the research budgets for conflicts of interest is provided for by the Canadian Tri-Council Policy Statement (Medical Research Council, Social Sciences and Humanities Research Council, and Natural Sciences and Engineering Council 1998). When analyzing the potential conflicts, IRBs might consider that direct disclosure of a researcher's interest in a study is an appropriate remedy. But it seems odd to explain to research subjects that the committee protecting them against the negative impact of conflicts of interest is itself affected by such a conflict.

This is not to say that disclosure of financial conflicts is not a core requirement of conflict-of-interest policies. We support efforts by journals and academic centers to require disclosure of any financial ties with research sponsors. Disclosure of the financial interests of IRB members also seems appropriate to enhance public accountability if it is connected to a system of overview and authorization. It can be considered a minimum requirement and part of a larger system of public control to be exercised by other institutional authorities, funding agencies, or federal regulatory agencies. Disclosure of conflicts of interest to those within institutions and to regulators can be essential components of a third-party

assessment of the seriousness of the conflicts. This information could then allow decision makers to disqualify reviewers who have conflicts of interest. However, disclosure on its own, particularly the mere disclosure of institutional conflicts of interest to research participants, is insufficient as a remedy.

Would all problems be solved if those who are in an employment relationship with the IRB abstain from participation? We argue that even in that case, there is an inherent conflict of interest in the way commercial IRB review is currently organized. Depending on the payment IRB members receive, they may rely financially on these earnings, and may have a significant interest in keeping their status as a member. More important, conflict-of-interest rules are as much about perception of influence as they are about real influence, since they focus on establishing trust. Is there any way, then, to remedy conflicts of interest in NIRBs and proprietary IRBs?

First, it seems very difficult to avoid or correct conflicts of interest in proprietary IRBs or NIRBs when employees or full-time paid administrators of the IRB are involved. The perception that secondary interests (financial gain, promotion, employment) may affect the duty of IRB members to protect research subjects is serious. One way to decrease conflicts of interest in proprietary review would be to establish a system of accredited reviewers who would have to follow clear substantive guidelines and who would be held accountable for violations of their professional code. The paradigm for such a system is the accredited accountant, who is paid by the company but adheres to professional rules. Presently, neither the procedural rules nor the substantive rules of IRB review are appropriate for such a system of review. There are no real restrictions on membership of IRBs, and educational programs are very diverse and in need of improvement (Mastroianni and Kahn 1998). Above all, there is no single clear and reliable research code containing substantive rules that must be respected. In this context, it becomes very difficult to establish procedures for oversight and accountability in research review. One route would be to establish a professional code for research review.

In the absence of a professional code for IRB members, one could argue that when IRB review becomes a core aspect of professional practice, reviewers who participate as members of their profession can be held accountable according to their professional code. When they approve research protocols that contradict standard research and clinical practice,

they could be charged with professional misconduct. We are aware of one precedent of an IRB member being held accountable as reviewer by his professional organization. The New Zealand Medical Council found the chairman of an ethics committee, which approved a study in which women with cervical cancer died, guilty of professional misconduct for his role in inadequate review and monitoring of the trial (McNeill 1998). However, it may not be easy to establish whether those reviewers are participating as members of a profession, and what constitutes a violation of one's professional code in reviewing research, particularly in light of the vagueness of the rules of IRB review. Many members are clearly not bound by professional codes. Bioethicists, for example, who often play an important role in IRB review, have no professional code, and often have no training in research ethics when they start participating in the review of protocols. There is no agreement as to who qualifies as bioethicist and no generally recognized educational program and certification. Under the new Canadian Tri-Council Policy Statement, an IRB must have, among others, "at least one member knowledgeable in ethics" (Medical Research Council, Social Sciences and Humanities Research Council, and Natural Sciences and Engineering Research Council 1998). However, what "knowledgeable in ethics" means is undefined, and no specific training in research ethics is required. Consequently, it is naive to trust blindly in the appropriateness of the membership of IRBs and in their ability to always withstand secondary interests.

NIRBs differ in at least one interesting respect: they are, in theory, independent contractors. If they could be financially independent from large CROs, one would not necessarily fear conflicts of interest. But the only way to guarantee fully that they are not pressured to provide client-friendly review is to implement a system where forum shopping is avoided. In its report on independent boards, the Office of Inspector General stresses this concern. It mentions that several members of these boards support the idea of a federal requirement, obliging sponsors to inform the IRB of any prior review (Office of Inspector General 1998d). However, mere reporting seems insufficient to us, since it does not prevent an NIRB from approving a study that was rejected by a more exacting IRB.

If we want to have a credible system of research review, the possibility of forum shopping for friendly review should clearly be banned, with respect to not only NIRBs but also other IRBs. Forum shopping can be avoided by creating an administrative structure that involves

exclusive, mandatory jurisdiction, accreditation, and control. Under such a system, CROs and others involved in medical research would have to pay a licensing fee for submitting protocols. CROs should have no direct financial or other link with the IRB members and should not be able to exercise pressure—directly or indirectly—on decisions made by the IRB.

The disadvantage of separating reviewers from the research sponsor or from the research community where the research takes place is that it becomes even more difficult for the IRB to follow up and monitor research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended in 1978 against a system of regional or national review. It suggested that local review has "the advantage of greater familiarity with the actual conditions surrounding the conduct of research" and allows the IRBs to "work closely with investigators to assure that the rights and welfare of human subjects are protected" (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978). Influenced by this policy option, federal agencies involved in human subjects research consider the distance between the NIRBs and the place where research is undertaken as already problematic (Office of Inspector General 1998d). This is why the Department of Health and Human Services has problems recognizing research review by nonlocal or noninstitutional review boards. This concern will have to be addressed if our recommendations are accepted. However, off-site IRBs seem now to be widely accepted, by the Food and Drug Administration and by many other national regulatory agencies, without proper regulation to safeguard their independence. It is time to review this choice of local review and to think about a more structured review system.

The idea of a system of official authorization and exclusive jurisdiction is not new. In Canada, the province of Alberta has introduced a system of provincial board review through the College of Physicians and Surgeons, requiring approval from the College's IRB for studies undertaken by independent physicians who engage in research. In France, the Code of Public Health prescribes that any research on human subjects must be submitted to one of the regional committees set up under the authority of the Minister of Health. The Minister of Health has the power to issue permits for regional "advisory committees for the protection of humans in biomedical research" (Code de la Santé Public (France) 1994, article L.209-11, 12). These committees have exclusive and mandatory

jurisdiction in their territory, and the law specifies which committee has jurisdiction in case of multiregional trials. They are financed through statutory fees that are paid by research promoters for every protocol they submit. Members, who are selected from a list established by the regional authorities and appointed by the government, have to be fully independent and the minister may withdraw the committee's power if conditions of independence are no longer met (Hirtle, Lemmens, and Sprumont 2000; Mander 1996). In short, conflicts of interest are avoided while committees are assured of the financial means to do their work properly, without additional cost to the government.

In Denmark, research review is also undertaken by independent regional ethics committees in cooperation with a central committee. Members of the Danish regional scientific ethical committees are appointed by the Danish Medical Research Council, while the Minister of Education and Health appoints the members of the Central Scientific Ethical Committee (Law on the Scientific Ethics Committee System and the Examination of Biomedical Research Projects (Denmark) 1992). As under the French system, the financial independence of these committees is guaranteed through the levy of a fee and through governmental subsidies. Similar review committees with exclusive jurisdiction exist in other countries, including New Zealand and Sweden, and in several Swiss cantons (Hirtle, Lemmens, and Sprumont 2000).

In the absence of stringent rules on forum shopping, conflicts of interest can be reduced somewhat if the contractual relationships between the NIRBs and their clients, or the financing system of the proprietary IRBs, provide for long-term financial stability. For example, if an NIRB has a three-year contract with a CRO to review all its protocols, there is at least some financial guarantee. Similarly, if a proprietary IRB has received a guaranteed budget for several years, the IRB and its members cannot be put under constant pressure. However, this is not a guarantee of full independence. An NIRB can, as discussed earlier, be fully dependent on only a few large contracts. This dependence clearly constitutes a significant conflict of interest.

Under any system of IRB review, terms of appointment of IRB members should also be carefully determined. Short-term and contractual appointments place reviewers in a vulnerable position. In discussing administrative review, Geoffrey A. Flick points out: "[W]here the appointment of a staff employee is only for a short term of years or where there is a distinct flow of public officials into the industry they are

supposed to be controlling, there may be a temptation on the part of the decision maker not to needlessly offend potential future employers by controversial decisions" (Flick 1984). Long-term appointments are preferable, and authority over appointments should be regulated, to decrease the likelihood of pressure on IRB members. The Danish law, for example, stipulates that members are appointed for a four-year renewable term (Law on the Scientific Ethics Committee System and the Examination of Biomedical Research Projects (Denmark) 1992). Also, appeal procedures should be established. External audits by regulatory agencies should be required when IRB members' mandates are terminated. Regulatory agencies should be able to verify whether terminations were sufficiently motivated.

Independence is not the only issue. As Deputy Inspector General of the Department of Health and Human Services George Grob points out, specialized training programs to educate IRB members are urgently needed (Grob 1998). In a 1998 report, the Office of Inspector General recommends that all federally funded institutions should have a program for educating its investigators on human subjects protection (Office of Inspector General 1998c). While training and continuous education are important for members of all IRBs, Grob asserts that "this would be especially relevant for noninstitutional and nonscientific members" (Grob 1998). Training and continuing education should be required of all IRB members, and should be part of a formal system of accreditation. Adequate protection of research subjects requires more than the goodwill of volunteers.

In fact, over the last three years, significant efforts have been undertaken to set up educational programs and to implement systems of accreditation of programs and of certification of IRB members. For example, the American organization Public Responsibility in Medicine and Research (PRIM&R; http://www.primr.org/index.html), founded in 1974, now also offers through affiliated organizations an accreditation system for human research protection programs and a certification program for IRB professionals. Two organizations have been set up to deal with the accreditation and the certification processes: the Association for the Accreditation of Human Research Protection Programs (AAHRPP; http://www.primr.org/aahrpp.html) and the Council for Certification of IRB Professionals (CCIP; http://www.primr.org/certification.html) and a first certification examination has taken place. The National Institutes of Health (NIH) also took a significant step by requiring since

October 1, 2000 that all investigators who want to obtain research funding must describe what educational program on the protection of human research participants they have followed (National Institutes of Health 2000). The NIH also announced new programs to support research ethics education of researchers and to promote career development in research ethics. It remains to be seen whether these initiatives and new requirements will lead to the implementation of an all-encompassing, transparent, and sufficiently controlled official accreditation and certification system for IRBs and whether other countries will follow suit.

Lessons for Institutional IRBs

How does this discussion relate to academic IRBs? As we pointed out, some of the conflicts existing in academic review are very particular to the institutional context. Academic IRB members may feel inclined to accept studies of colleagues whom they trust, work with, and share other research interests with (Glass and Lemmens 1999; Cho and Billings 1997; Francis 1996). Issues of promotion, future co-authorship, and simple collegiality of the working environment may also create pressure. As Cho and Billings point out, scientist IRB members "rarely question their own or colleagues' competence publicly" and nonscientist members may be hesitant to enter the debate (Cho and Billings 1997). Comments of nonscientist members are easily qualified by the professionals dominating the IRB meeting as being uninformed.

More important, although many academic IRBs do function in an environment where profit motives are less immediate, IRBs and IRB members increasingly feel the pressure of corporate sponsorship (Glass and Lemmens 1999), particularly in light of the proportional decline of governmental funding (Reed and Camargo 1999). Even if no direct pressure is exercised on an IRB, most members are part of the institution in which research is undertaken and are well aware of the importance of attracting external funding. They may be tempted to accept studies that come with needed research dollars, which will help significantly to improve the research potential of their department or institute. When a lucrative study is rejected, some IRB members may have to return the department they just deprived of significant research funds. They may be challenged directly by the "rejected" colleague and may have to face

researchers whose employment at the institution depends in part upon their role in obtaining commercial funding.

Academic research centers are increasingly entering into institutional relationships with some major pharmaceutical companies and may become partly dependent on them (Bodenheimer 2000). This exacerbates pressure within the research centers to actively pursue research proposed by those companies. In other words, the fundamental difference between academic research units and CROs is diminishing and so, too, the difference between academic and proprietary IRBs. Thus, it is essential to introduce institutional policies that address the appropriate independence of IRBs and the need to protect IRB members when developing commercial partnerships. One way would be to reinforce some of the core aspects and values of academic scholarship that are increasingly under stress: academic integrity and independence, the public role of academic researchers, and tenure. The first two are values that require education and persuasion by role models. These values may also be strengthened by more stringent conflict-of-interest guidelines and a stricter control of these guidelines by academic institutions. Tenure seems particularly important to reinforce public trust in the independence of IRB members operating within the context of a corporate health care and research environment. Unfortunately, tenure appointments for physicians are the exception rather than the rule. And, although physicians may sometimes lack appropriate protection, they are still less financially vulnerable in light of their employability. Other traditional IRB members, such as bioethicists, are often hired by institutions contractually, either on a yearly renewal basis or on a fee-for-service basis. Independence is clearly jeopardized in this context, and an academic label attached to the job does not guarantee meaningful academic freedom.

Thus, academic IRBs need stricter conflict-of-interest rules, education, and accreditation of IRB members and greater public accountability as well. The conflicts of interest created by the increasing commercial pressures in academia add to other problems the academic IRB system is encountering.

Overall, George Annas's severe assessment that "Institutional Review Boards should be radically overhauled" does not seem to be an exaggeration (Annas 1996). The loopholes in the system of commercial IRB review are only part of a much larger problem. While Annas does not detail his proposals for change, his suggestions also seem to support the creation of a more accountable review structure. He proposes to set up

a national human research agency, that would "set the rules for research involving humans, monitor their enforcement, and punish those who fail to follow them" (Annas 1996). IRBs would be accountable to this agency, and no longer be supervised only by their own institution. We believe that an intermediary agency or institutional body, exercising a level of authority between that of a national or regional agency and the local IRB remains a valuable option. Greater local oversight of IRB function, combined with increased surveillance by federal agencies, seems a preferable model. However, this institutional supervision should be set up in a way that enhances the independence of IRBs and their public accountability.

One of us (Lemmens) was recently involved in the development of an ethics structure within a newly merged psychiatric institution. In order to strengthen the IRB's structural independence from commercial and other institutional interests, an umbrella ethics committee was set up at the level of the board of administrators. Members of this committee include members of the board of administrators, two bioethicists (one tenured), community representatives, chairs of the research and clinical ethics committees, and some members of senior management. The IRB's primary reporting relation is to this board committee, rather than to institutional players who may have a vested interest in attracting research funding. The function of this committee is to deal with organizational ethics issues, but it also serves to promote accountability of the IRB process and to strengthen its independence. IRB chairs and members, for example, are supposed to be formally appointed by this committee, which confirms their independence from hierarchical superiors. The central ethics committee also discusses issues that exceed the scope of IRB review, such as institutional conflicts of interest resulting from partnerships with industry. It remains to be seen whether this new type of structure will do the job and will strengthen the independence (real and perceived) of the IRB while also promoting open debate about issues of sponsorship and financial relations within the institution.

It should also be pointed out that new developments in research warrant the creation of specialized national review panels. Some novel types of genetic research, for instance, or research involving risks that transgress local boundaries or raise fundamental ethical concerns would benefit substantially from such national panels (Glass, Weijer, Cournoyer, et al. 1999; Edgar and Rothman 1995). A discussion of specialized review panels exceeds the scope of this paper, but it is notable that the recent

controversies in gene therapy trials in the United States and Canada have highlighted that conflict of interest is only one of the problems of IRB review. The need for specialized national review panels, or the expansion of the mandate of existing ones, should be on the table when discussing needed reforms of the research review system.

Conclusion

We believe that the credibility and integrity of research review are affected by inherent problems of conflict of interest in IRBs. While conflicts of interest are also a significant problem in academic IRBs, we have focused on conflicts affecting commercial IRBs for a number of reasons. We have argued that commercial IRBs are currently affected by a structural problem that affects their independence and undermines their credibility. In the eyes of the public, these IRBs may qualify more easily as the industry's partner than as the public's guardian. Considering the public role of IRBs, more appropriate governmental control and clear regulations are urgently needed than the ones currently in place. The integrity of IRB members and administrators is not sufficient to remedy the problem. Suggesting stricter conflict-of-interest rules ought not to be seen as a reflection of distrust of individual IRB members (Kassirer and Angell 1993). Nor does it mean that many commercial IRBs are currently doing a bad job. However, conflict-of-interest rules are essential to safeguard public trust. They target the perception of bias as much as they target actual bias. The aim of our argument is, to use Thompson's words, "to minimize conditions that would cause reasonable persons to believe that professional judgment has been improperly influenced, whether or not it has" (Thompson 1993).

While the financial context in which commercial IRB review takes place is a reason for particular and urgent concern, conflict of interest in academic IRBs should also be addressed when developing appropriate regulations. The conflicts we have identified in proprietary IRBs are relevant for academic IRBs. With increasing commercial involvement in academic centers, the financial impact of any decision will become a more prominent cause for tension in the decision-making process. This increases the need for major wide-ranging reform of the research review system. Such reform should work toward reinforcing public trust in

universities, in medical research, and in the institutions established to protect research participants.

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