Noninstitutional Commercial Review Boards in North America: A Critical Appraisal and Comparison with IRBs

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In line with an international trend, over the last two decades an increasing number of private research ethics boards or research review boards have been set up in the United States and Canada. Many countries now require prior research ethics review of all forms of research involving human subjects. Both international guidelines on medical research and national guidelines and regulations commonly stipulate that review by a duly constituted “independent ethics committee,” “institutional review board” (IRB), or a “research ethics board” (REB) is a precondition for any medical research involving human subjects. The Triparite Guideline for Good Clinical Practice of the International Conference on Harmonisation (ICH GCP Guideline) set up by the regulatory agencies of Europe, Japan, and the United States, also gives a central role to research ethics committees in the protection of human subjects. The International Conference on Harmonisation, on which the Canadian health authorities have observer status, aims at harmonizing different national regulatory requirements for clinical trials and medical research and its guidelines are likely to become the core international standards in clinical research. This growing regulatory demand for research review, combined with the increasing commercial involvement in research, has lead to a boom in the private review business. Since IRBs (or REBs) have traditionally been reluctant to review studies not undertaken within their institutions, private commercial review boards have become firmly established in the research market and have become particularly important for both contract research organizations and physicians in private practice who do not have access to the review boards set up within institutions.

SURVEY INFORMATION

To obtain more information on the functioning of private review boards, in 1997 the Canadian National Council on Ethics in Human Research provided funding to undertake a survey, the results of which we report here. The survey took place between May 1997 and June 1999. The original intent was to gather basic information on the functioning and role of both “proprietary” as well as “noninstitutional” review boards in the United States and Canada. Proprietary IRBs are review boards set up by contract research organizations or by pharmaceutical companies to review research designed to evaluate their own products. Noninstitutional review boards most often are commercial review boards that are set up as profit-making ventures. They are often described as “independent”...
review boards, to contrast them with institutional review boards. We prefer to use the term noninstitutional review boards (NIRBs), since we argue that there are inherent conflicts of interest in private, for-profit review that may affect the independence of these review boards. We also only discuss the NIRBs that function as commercial review boards. Due to a lack of adequate address lists and a lack of responses from "proprietary" review boards we contacted in a first phase of the project, it was decided to concentrate the survey on NIRBs. The exact response rate of NIRBs is difficult to assess. In the course of our research, we often found that what seemed to be a private NIB was in fact a contract research organization and that some NIRBs are actually carrying the name of an institution. Other NIRBs no longer existed. Several respondents indicated that they were not, or sometimes were no longer, a NIRB.

The problems we encountered in obtaining exact information as to the number of NIRBs in Canada and the United States points to a structural problem: Despite the role review boards are considered to play in safeguarding the welfare and rights of human subjects, and the fact that such boards are to be accountable to the public, there is no central registry. Thus detailed official information on the number of review boards (institutional or not) is hard to find. Even the U.S. Office of Inspector General, in its recent report on private review boards, had to satisfy itself with an estimate. It suggested that there are at least 15 NIRBs in the United States "and perhaps a few more." The website of the Health Industry Manufacturers Association contains a list of 22 U.S. and one Canadian NIRBs, an increase of 5 between September 1999 and May 2000, when the list was last updated. Although we did not have access to this list when conducting our survey, we otherwise identified 13 of the U.S. NIRBs cited on it. In Canada, we were aware of the existence of three NIRBs and have recently learned that there are at least two other private REBs. On the basis of the limited information we had, our response rate was 81.25% (13 respondents among the 16 NIRBs we identified at the time), comparable to that of the limited IG survey in the United States. Thus the survey gives a snapshot of the activities and functioning of 13 commercial NIRBs of a total of 25 known NIRBs in the United States and Canada. In discussing the results, we do not distinguish between Canadian and American NIRBs, since that would enable identification of the two Canadian REBs that responded. We also use "NIRB" to refer to both U.S.-based NIRBs and Canadian private, commercial REBs.

As the results discussed below indicate, there are some obvious limitations to the survey: It aims only at giving some basic information. The questionnaire was administered during a period of significant regulatory change in Canada, which is ongoing. The new Tri-Council Policy Statement existed only in draft format, and the 1987 Medical Research Council Guidelines on Research Involving Human Subjects were still in force. The ICH-GCP Guideline was also in the process of being adopted. Therefore it should not come as a surprise, for example, that the Tri-Council Policy Statement is identified by all but one of the NIRBs.

The survey was intended to give a general overview of the composition and functioning of the NIRBs. To facilitate comparison, the questions were largely based on a 1995 survey of institutional REBs conducted by the Canadian National Council on Bioethics in Human Research. The survey contains only general questions with respect, for example, to monitoring, and is not specific enough to catch some of the discrepancies among different responses. One participant pointed out, for example, that different NIRBs may have different ways of counting "numbers of protocols reviewed." The answer to the question "How many protocols are reviewed by your NIRB per year?" is therefore only an approximate indicator of their activities.

The survey was divided into three parts. The first part contained questions with respect to the structure and the membership of NIRBs. Questions focused on the existence of subcommittees within the NIRBs, the number of members, the duration of terms of office, the payment of members, and the requirements for becoming a member. The second part dealt with the procedural aspects of review. Questions in this section related to the number of protocols reviewed, the time spent discussing a protocol, the time between submission and decision, appeal procedures, and the frequency of meetings. In the third part, we tried to obtain some information on the content or the basis of decisionmaking, issues related to conflict of interest, and the extent of monitoring by the NIRBs.

SURVEY RESULTS

Structure and Membership

Of the 13 NIRBs that participated in the study, only one had a distinct subcommittee, which was formed in order to deal with adverse events. The average number of NIRB committee members, not including alternates, was 9.5, with the largest board being comprised of 16 members and the smallest of only five members. It must be admitted that some boards have a significant number of alternate members and that the average number of members at any given meeting could be higher than these figures suggest.

Disciplinary Background of Members. The question of who ought to sit on NIRBs has been much debated. Most agree that a balance should be struck among scientific expertise, sensitivity to the ethical issues involved in research, and representation of research participants and the public. Paul McNeil, for example, argues forcefully that if science is to be socially responsible, we should avoid having review boards that are dominated by scientists. As is the case for other review boards, medical expertise seems to be easier for the NIRB to come by than expertise in ethics. All NIRBs had physician members. According to some survey
respondents, members with specialized training in ethics are highly desirable but hard to find. Not more than 61% of the NlRls had a member of the clergy or an ethicist as member. Only slightly more than half of the responding boards had a member with legal expertise. The largest group represented on the committees surveyed was physicians. More than three quarters of the NlRls also had lay members who were not affiliated with the administration of the NlRL.

Surprisingly, other groups were also underrepresented on the NlRls: 61% of the boards had nurse members, and only 69% had experts in research design or biostatistics as members. These results are in line with surveys of institutional boards. A report on institutional review boards in the United States revealed that when it came to recruiting new members in order to strengthen IRB membership, chairs were more likely to place higher value on expertise in particular fields of science than on expertise in ethics.18 They too cited difficulties in locating individuals with desirable expertise as the main roadblock to adjusting IRB membership.

Most of the boards had a fairly balanced gender ratio among members, with the most unbalanced board being 75% male. On average, however, the balance was 52% male and 48% female. Of the 13 boards, nine had members belonging to a minority group. Members of minority ethnic groups comprise 3.4% of board membership overall. Eighty-three percent of the boards give special consideration to representation by women, patient groups, or members of special populations, depending on the type of protocol under review. This inclusion of members from particular groups or the inclusion of members with specific expertise is in keeping with the spirit of the U.S. federal regulations (22 CFR 95.107(a,b), and the Canadian Tri-Council Policy Statement.19 Some NlRLs ask consultants to attend board meetings, based on the need to have patient populations or therapeutic areas represented. This practice is also common for institutional IRB/REBs, which frequently use non-voting consultants with competence in specific areas that are not represented on the IRB/REB.20 In addition, some boards draw on alternate members when appropriate in order to ensure that patient values and viewpoints are represented as well as those of the broader community.

Membership Term. Over half the boards (62%) had no specific duration of term for members, while the remaining 38% had fixed term appointments. Only one NlRL provided a fixed term appointment of more than one year (two-year appointment).

Structure and membership thus closely resemble that of boards in academic health centers in terms of gender and ethnicity ratios, and in terms of policies regarding composition.21

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Unfortunately, NlRls encounter similar problems with respect to appropriate representation of members with ethics expertise and with expertise in research design and biostatistics. Nurses are also not represented in several boards.

In our view, the lack of specific duration of membership is the most problematic aspect of structure and membership, especially if it is linked with significant payment of members. It puts members in a vulnerable position and would allow the administration of the NlRL to dispose of members who are seen as being too critical. One could argue that regular review of members, such as annual performance appraisals, are a guarantee of quality. However, there would be other ways to deal with NlRL members who are not fulfilling their duty—for example, by stipulating clearly the duties incumbent on all members and the consequences of not fulfilling these duties. There should be a formal appointment procedure and regulatory safeguards against "dismissal without cause," and reasons for not complying with membership duties should be specified and filed. Members should be appointed for a significant period of time—for example, a minimum of three years.

Payments to Members. All but one of the 13 boards surveyed pays their members, which may indicate that this one board is not a traditional for-profit NlRL. Of those, 59% pay their members a fee per meeting, and the others pay their members per protocol reviewed. Even though we promised anonymity of the survey results, the fact that the amount paid to NlRL members is considered proprietary likely explains why there was a low response rate to the question of how much money members are paid. Only three of those who pay their members disclosed the amounts given per board member. Payments disclosed were $70, $140, and $200 per meeting. (All amounts, including Canadian, if any, are reported in U.S. dollars.) One board pays $200 for physicians and $125 for all other members per meeting. Some boards indicated that there was a fixed honorarium given per meeting of an undisclosed amount. Interestingly, only 42% of those who pay their members pay them equally for their services. There was no information as to who was paid more in these cases, but it seems fair to presume that physicians or people with particular expertise and training are paid higher than, say, lay members. Most members are not compensated for expenses above the amount they receive per meeting. Some review boards indicated that these expenses are covered under the compensation package.

The secrecy surrounding compensation and payment of board members is a concern. In the context of the growing attention to conflicts of interest in health care, disclosure of potential financial conflicts has become standard practice. Many scientific journals require authors to disclose financial interests that might affect, or
appear to affect, their independence. In the same vein, there are increasing calls for a more active review of conflicts of interest by review boards. This should involve, for example, review of the budget of clinical trials, disclosure of financial interest of investigators in conducting a trial, other financial links between a research sponsor and the investigator, and institutional conflicts. 12 The new Canadian Tri-Council Policy Statement explicitly requires REBs to review the budget of clinical trials. Article 7.3 states that “REBs shall examine the budgets of clinical trials to assure that ethical duties concerning conflict of interest are respected” (Art. 7.3).

We support this development. Since review boards have as one of their tasks the duty to determine whether a conflict of interest may affect or appear to affect the ethical conduct of a study, they should have a sense of the financial interests at stake. Financial interests in a study (e.g., finder’s fees and overall financial benefits for researchers or their institutions) may affect recruiting procedures and the informed consent process whether or not a researcher or institution is aware of that influence. Such interests can create significant pressure to go ahead with research and may lead to downplaying existing risks. Furthermore, truly informed consent requires disclosure of these interests to research subjects. If—as the Tri-Council Policy Statement acknowledges in a commentary on its conflict of interest rule (Art. 4.1)—the REB must require researchers to disclose this conflict to subjects, members must be able to verify what the potential conflicts are.

Since the review boards have a public role as well as a stringent obligation with respect to conflict of interest, the financial interests of members of the boards who conduct such a review should also be submitted to public scrutiny. At the least, regulatory agencies should know how members are compensated. It is worth mentioning that the Tri-Council Policy Statement explicitly refers to the risk that “undue or excessive honoraria” of members may lead to a conflict of interest (Art. 4.1). Surprisingly, it singles out “commercial REBs” as an example, while more fundamental issues with respect to conflict of interest of NIRBs and IRBs are not addressed. Clearly, if excessive honoraria can create a conflict of interest, they can do so in institutional boards as well. And the conflict created by excessive honoraria must be understood in the context of other factors, such as the overall independence of the board and the period of tenure of members.

Requirements for Membership.

The requirements for becoming a member of a NIRB vary somewhat. Only three NIRBs declared having set requirements for membership. Although most have no specific requirements, they preferred members to have prior experience serving on an IRB or REB, or to have some formal ethics training. In addition, those boards dealing with protocols pertaining to special research populations preferred members to be involved with that community in some way. One respondent said:

While having previously served on an IRB or having formal training in ethics are not stringent requirements, we ensure that some members meet these criteria. Members are trained internally to ensure comprehension of mandate, according to written standard operating procedures.

Another respondent explained that their needs cannot always be met:

[Members] must complete our training program and attend at least eight meetings before assuming voting status. Previous experience and formal research ethics training is highly valued but seldom available.

This is in contrast to the REBs surveyed by the National Council on Bioethics in Human Research, which found that only 17% of respondents felt there was inadequate scientific and ethics expertise available.34 That does not necessarily mean that institutional review boards are better in this respect, of course. It means that at least they are more confident about having sufficient scientific expertise. The fact that institutional boards are generally connected to academic institutions and can rely on a large pool of experts available in medical schools and academic hospitals explains why they may have easier access to scientific expertise.

Of the more practical considerations mentioned by our survey’s respondents, the ability to put time into the review of protocols and the person’s availability for meetings was also a consideration.

With respect to the problem of finding members with training in research ethics, private review boards do not seem to do worse than institutional review boards, where appropriate training is also often lacking.35 On the contrary, the organization of a training program by one of the NIRBs surveyed, and its requirement of attending eight meetings before assuming voting status, is an exemplary model that could be used by many institutional boards.

Procedural Aspects of Review by the NIRB.

Number of Protocols Reviewed.

The number of protocols reviewed in a year by the NIRBs varied greatly. One respondent suggested that the way that each board counts protocols may differ, thus calling into question the value of the information we obtained. Indeed, our question did not clearly distinguish initial review from other types of review, and some respondents may have included, for example, annual reviews in their answer. The greatest number of protocols reviewed in a single year was approximately 1,500 (reported by one respondent), while the least was 24. The report by the Inspector General of the U.S. Department of Health and Human Services claims that the number of protocols being reviewed by NIRBs is increasing. From 1996 to 1998, NIRBs reported an increase of approximately 36%.36 In 1997 the largest and oldest NIRB reviewed more initial protocols than did many IRBs in academic health centers.37

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Other research indicates that in 1995 an average number of 297 protocols was reviewed per year by IRBs of Category I universities in the United States (defined by the American Association of University Professors as an institution graduating at least 30 doctorally prepared individuals in three unrelated disciplines per year). Outcomes of Review. The outcome of the review process was not surprising. Sixty-seven percent of protocols were accepted outright per year, while 32% were accepted conditionally. Here our question ("accepted" and "accepted with revisions") was not specific enough to make an unambiguous analysis possible. The only clear conclusion is that on average, only 1% of protocols is rejected. Such a low rejection rate is not unusual in the research universe of the IRBs or REBs, given that provisional approval or deferral is commonplace.

Frequency of NRB Meetings. Most NIRBs meet more frequently than IRBs or REBs. The average number of meetings per year was 36, with five boards out of nine who responded to this question meeting 48 times or more. The other NIRBs met respectively 12, 15, 18, or 25 times a year. Most institutional IRB/REBs meet only monthly.

The average length of time that NIRBs spend discussing and voting on the average protocol is approximately 42 minutes. However, this is somewhat misleading, as there were significant differences in the times reported. Remarkably, one respondent indicated that the average time in which her or his NRB can speed through a protocol is five to ten minutes. At the other extreme, one respondent reported not discussing more than two protocols per meeting and spending two hours contemplating the ethical nature of each protocol. It has to be said that the chair of this NRB recently communicated that their average review time has been significantly reduced since answering the survey, and that the 1999 average was closer to 20 to 30 minutes per protocol. Three NIRBs indicated an average discussion time of one hour. Others spend between 15 and 25 minutes on each protocol.

Only one respondent did not answer this question. While these answers do not tell us very much about the depth of the discussion, in the absence of more information on the content of these protocols, it gives at least some indication that fairly lengthy debates are taking place in most NIRBs. The ongoing NRB reviewing the average protocol in 5 to 10 minutes seems to exclude any significant time for serious discussion. However, more detailed research should be undertaken to explain such a short review time. What are the protocols reviewed by this NRB? Are many of these reviews merely approvals of annual reports or fast track approvals of decisions by the chair of expedited reviews?

Short review times are considered to be one of the strengths of the private review system, and the review times seem indeed on average fairly short.

Several NIRBs responded to our question concerning the average time members spend on the preparation of review. Of those who responded, the average amount of time each board member spends preparing a protocol for review is about 70 minutes.

Turn-Around Time. The average length of time between the submission of the protocol and the decision of the NRB was 24 days, with the shortest being five days and the longest 55 days. Five out of ten NIRBs had review times of seven days or less. Other review times were 9, 12, 14, and 15 days. Short review times are considered to be one of the strengths of the private review system, and the review times seem indeed on average fairly short. Of the nine boards who responded to the question of whether the board guaranteed a time limit between submission and decision, 44% said yes, guaranteeing on average a turn-around time of six days.

According to the Inspector General's report on IRBs, on average it takes an academic health center approximately 37 days to provide decisions. The NCBHR report similarly found that the average time required to process an application from submission to approval was one month. This confirms the argument by proponents of the commercial review system that the NIRBs in Canada and the United States offer faster review times and that this may be desirable for industry. However, guaranteed review times are not necessarily exclusive to the NIRBs and regulators could think of imposing guaranteed review times for institutional review boards or for regional review boards. Several regulatory agencies have in fact come up with interesting alternatives, specifying by regulation maximum review times that must be respected by any review board, be it institutional or private.

Appeals. Despite the fact that 83% of the NIRBs claimed to have procedures for the appeal of their decisions, the vast majority had no standard procedures for doing so. Sixty-four percent of the boards that have a procedure of some sort in place have had cause to use it. There was some variation in the appeals procedure:

- The company would consult in writing experts in the field who would submit [a] written evaluation to the IRB. Then resubmitted to IRB who can accept or reject protocol.
- Contact chairman and offer an argument. Full board decides.

Formal written request to secretary/chairman outlining grounds for appeal and supporting documentation.

In a study of university IRBs, Hayes and colleagues found that 76% claimed to have a formal appeals process in place; 54% handled the complaints themselves; an outside committee was used 14% of the time.

The Review Process

There exists a longstanding controversy over whether the evaluation of
scientific merit falls within the purview of the IRB/REB review process. While the Nuremberg Code and the Helsinki Declaration point out that in order to be ethical an experiment must have scientific merit, it is not so clear how far the IRB's role extend.

As Robert Levine points out, the need for considering the scientific merits of a protocol does not mean that we can or should expect the boards themselves to undertake a very detailed assessment of the soundness of research design. IRBs often lack the expertise needed to conduct such a review. He points out that many IRBs rely on external assessment of the scientific validity of a protocol. This is particularly so when the research is being funded by a federal agency that generally submits the proposed research to a much more rigorous scientific review before making a funding decision. IRBs take into account the existence of more rigorous review by outside agencies in determining the extent to which they review the scientific merits of a protocol. Benjamin Freedman distinguishes two elements of scientific merit, validity and value, and agrees that the more technical aspects of scientific validity can often be assessed by a technical board, whereas the evaluation of the value of a study should be undertaken by the IRB itself.

Even in the United States, where there has been more hesitation to accept IRB responsibility for scientific review, authoritative sources such as the Belmont Report and the Final Report of the Advisory Committee on Human Radiation Experiments highlight that it is impossible to accurately weigh the risks and potential benefits without a scientific evaluation of the study. In our view, this does not mean that the IRB could never use an external review of the scientific validity of the protocol; nonetheless, IRB members should remain critical and be willing to ask questions to be reassured as to the scientific validity.

It is reassuring that most NRBs do consider that scientific merit plays a part in determining the ethical nature of the protocol under review. Considering the significant representation of scientific expertise on private review boards, minimal scientific review seems to be part of the review process. With the exception of some boards, most did acknowledge this explicitly: 83% of the boards believed that a scientific evaluation of the proposed study's value or validity was a task for the NRB. Of these boards, 30% had this evaluation done exclusively by outside experts, and the remaining 40% of boards had both inside and outside experts review the scientific merit of protocols, depending on the need for outside expertise. The National Council on Bioethics in Human Research found in its on-site visits of NRBs that 100% of respondents consider the scientific evaluation of the protocol to be the REB's responsibility.

We also asked boards to identify the guidelines they used, from a list provided, with an open category of "other guidelines" that they could indicate. U.S. regulations were obviously widely cited, but some U.S. boards also referred to Canadian guidelines. Four boards, two of them American, reported using the 1987 guidelines of the Canadian Medical Research Council. Only one Canadian NRB mentioned the—at that time draft—of the Tri-Council Policy Statement. All but one board noted that they followed FDA rules and regulations. Ten respondents referred to the Declaration of Helsinki, while nine stated that the ICH GCP guideline is one of their instruments. Seven NRBs indicated that they used the Nuremberg Code. Surprisingly, only two mentioned explicitly the Belmont Report. Then again, eight respondents said they consulted the Guidebook of the Office of Protection from Research Risks, which contains in its appendices the Belmont Report, the Nuremberg Code, and the Declaration of Helsinki. Finally, five respondents suggested that the WHO Guidelines for Good Clinical Practice is one of their sources. Surprisingly, the guidelines of the Council for International Organizations of Medical Sciences were not mentioned.

Conflict of Interest. In most cases (85%) board members of the NRBs receive and are expected to evaluate the entire protocol. It is surprising and inappropriate that two of the respondents indicated that only one person (the chairperson or the primary reviewer) receives the entire protocol, whereas members receive a summary and the informed consent form. All other boards indicated that all members receive a copy of the entire protocol. Of the 30 boards that responded to the question, all meet in person when reviewing a protocol. None of the 13 boards surveyed allow investigators to be present during voting on the protocol, despite the fact that 83% meet with investigators. Of these, 31% do so only when board members request it, while others indicated they "sometimes" meet with investigators. The remaining 35% never meet with investigators. This is in contrast to the result of a survey on institutional review boards, where 79% meet with investigators by request only. The disclosure of any potential conflicts of interest on the part of any board member is essential to establishing and maintaining an IRB/REB's credibility. One of the advantages claimed for NRBs is that they offer a source of expertise that is less likely to be colored by institutional or collegial bias than a proprietary board. However, as has been argued elsewhere, NRBs are caught in an inherent conflict of interest given that their commercial viability is at least partially contingent on the willingness of their clients to deal with them, which is not the case with other review boards.

The dependence on clientele, combined with the possibility for "forum shop-
ping—or, as the Office of Inspector General terms it, “IRB shopping”—is highly problematic for a review board that must operate independently. Indeed, nothing in the regulations or guidelines prohibits clients from picking and choosing whatever NIRB is willing to do the job. This is even more problematic in light of the lack of control and, particularly in Canada, the lack of accreditation and clear regulation of review boards. Review boards should be able to safeguard trust in the research enterprise. Even though most of them may be capable of exercising independent judgment and can resist commercial pressures, this does not necessarily translate into public trust. In the course of our survey, one NIRB member related that pressure by clients, though rare, does exist. The NIRB member mentioned the case of one client who originally refused to pay for review of a rejected protocol and then threatened never to do business again with the NIRB. The NIRB did not bend.

While we have been reassured both by this example of board integrity and by the integrity of many people involved in the private NIRB sector whom we met in the course of our research, the case highlights a serious problem. The research review system itself has been established to avoid relying solely on the integrity of individual researchers to safeguard the welfare and rights of research participants. If relying on individual integrity is judged to be insufficient when it comes to researchers, why would it be sufficient to rely on the individual integrity of committee members who review the research? These committee members are often much more removed from the possible suffering of research subjects and it may in theory even be easier for them to make detached, “calculated” judgments.

Moreover, as part of their job, review boards must weigh how conflicts of interest could affect the research endeavor. It seems illogical that the specific institutions that are supposed to assess conflicts of interest can themselves be in a situation of conflict. In light of the possibility of forum shopping, studies that would be deemed unacceptable by any other review board, private or institutional, can easily be channelled through a more lenient or more “corruptible” NIRB. It only takes one such NIRB to compromise the integrity of the entire protective regime. In the current system, nothing prevents companies or individual researchers from resubmitting a rejected protocol to one, two, or even five different NIRBs to obtain approval. Although they must disclose this resubmission to governmental agencies, it is unclear how these agencies will be able to discover such practices when they are not reported. In Canada, for example, researchers must disclose to the Therapeutic Products Program, the regulatory agency involved in the drug approval process, if a research protocol was rejected by a review board and must indicate the reasons for the rejection. However, it seems that there is no control over the truthfulness of this disclosure and it is unclear what the sanctions for noncompliance are. How can regulatory agencies in Canada find out, for example, that several American IRBs rejected a research proposal?

One way of avoiding this would be to mandate obligatory registration of every protocol submitted for IRB/REB review, and establish a national register of review decisions. While we do not suggest that this would solve other problems in the system, rules prohibiting forum shopping combined with control through a central register would at least alleviate these concerns. In the context of institutional IRBs, Levine argues that the notion that institutional IRBs are conflicted in conducting their duties needs correction:

This ... implies that IRBs regularly have the institutional interest at heart at the expense of those of research subjects. This sets up a false logic whereby the subjects’ interests are presumed to be in conflict with those of the institution, and the IRB somehow must choose between the two. The fact of the matter is that nothing could be more in the institutional interest than protecting the subjects of research.19

The same argument can be invoked in the context of NIRBs. That is, NIRBs have no interest in approving research in which subjects may be harmed since that may destroy their name and render them liable. However, we do not think that this argument is strong enough to justify the absence of detailed regulation with respect to conflicts of interest, for either private or institutional review boards. Whatever validity the argument may have for institutions, its relevance is diminished in the context of private, for-profit review boards.

First, even though research institutions have every interest in not exposing subjects to unethical research, it nevertheless happens—a short-sighted focus on research interests or financial interests has often been the underlying motive for unethical research. Research review has been introduced precisely because there is general agreement that harm to subjects should be avoided, not redressed after the fact. Research review is there to protect subjects from being enrolled in unacceptable studies. It expresses the idea that we should not solely rely on possible future liability or destruction of the good name of researchers or institutions as a safeguard against abuse. When it comes to the well-being of subjects, the remedy should be pre-emptive, rather than only corrective.

Moreover, the interests of well-established institutions, universities, and research centers are not limited to obtaining income for one well-defined
activity. Many people are attached to these institutions for different reasons, and many different interests are at stake. This is likely to create more of a balance. Lacking detailed regulations in the United States and Canada, NIRBs can be easily set up and do business for a short period of time. While most of them have very laudable motives, without regulation, little prevents others from entering the business solely as a means to make profit in a short period of time with only very limited concern for human subjects. Even with careful regulatory scrutiny, it remains easy to set up shop.

Second, there is also the question of how to deal with individual board members who find themselves in a conflict of interest. All boards surveyed recognized that conflicts of interest must be declared by board members and have therefore established specific guidelines on conflict of interests on the part of their members. All boards surveyed consider a member to be in a conflict of interest when he or she is involved in the study under review, or if he or she has a financial interest in performing the study. There was less of a consensus among respondents about whether other situations may create conflicts of interest for their members. However, the majority believed their members to be in conflicts of interest if they have a financial interest in the company for which the study is conducted (77%) or if they have a financial interest in the NIRB (67%). Some other circumstances under which NIRBs considered their members to be in a conflict of interest include having a personal relationship with the investigator, using the product in question, or having a financial interest of any kind in a company affiliated to the sponsor requesting review.

If members of the NIRBs find themselves in a conflict of interest, all boards demand that this conflict be disclosed, but most do not deem this disclosure to be sufficient. Sixty-nine percent of respondents require that the person in a conflict of interest withdraw from the NIRB for discussion of the relevant study, 46% specified further measures in cases of conflict of interest, which include deferral of voting privileges for that protocol and suspension or expulsion if the conflict of interest is intentionally not disclosed. Remarkably, some NIRBs allow members with a conflict of interest to participate in the discussion.

**Monitoring Approved Research.** It has become a standard provision in regulatory documents that the IRB’s role includes monitoring of approved research to ensure compliance, for example. While many different forms of monitoring are discussed and proposed in the literature, IRBs are rarely very active in this area and most limit their continuing review to periodic “paper-based” review. They often are already overburdened and see monitoring as an additional task for which they lack the necessary resources.

It may be even more difficult for the NIRBs to monitor approved research as they lack the inside knowledge about individual investigators and their research records that in situ ethics boards are more likely to possess, such as whether the researchers possess the skills needed to conduct the proposed research. IRB members may be aware that particular researchers tend to undertake any type of research, or that they have a history of being sloppy with consent procedures. At the other end of the spectrum, the IRB may be reassured when a researcher known for his diligence and caution is proposing a riskier study. NIRBs are certainly a part of the research landscape, but how much they know about a particular research community and its constituent members is sometimes questionable. Although this might be viewed as a virtue, in that the board may be more detached from internal institutional pressure, it is also puts the board at a disadvantage with respect to knowledge about the players. Thus it may be the NIRB must pursue continuing review and monitoring measures with extra vigilance. NIRBs as well as other IRBs should think about how to become more actively involved in monitoring ongoing research. One form of continuing review that recently has been shown to be feasible and highly effective for increasing subjects' understanding of the trial is very active monitoring of informed consent in high risk research. All the boards surveyed claim to monitor or follow up research that they have approved. However, not all pursue this endeavor with the same vigor. Some, but not all, adhere to U.S. FDA guidelines for follow-up. A variety of monitoring methods are employed by our respondents, including quarterly reports, annual reviews, adverse event reports, control of consent forms, spontaneous audits, site visits, and reports on completion of the research protocol. The answers provided by the different boards surveyed do not allow us to give further details about the appropriateness of the methods for continuing review, nor about the amount of time spent in monitoring approved research relative to other NIRB activities.

The methods described are consistent with those used for continuing/annual reviews conducted by institutionally based review boards. The NCBHR found that only 18% of responding REBs reported conducting ongoing review or audit of the research in progress, although 53% REBs required investigators to submit an annual report (which has now also become an explicit requirement under Article 3.3 of the Tri-Council Policy Statement), and 35% required an end-of-protocol report. Of those whom the NCBHR found did no monitoring, the reason given most commonly for not doing so was that the REB did not consider monitoring part of its mandate, or did not have the time or resources to take on that responsibility.

**International Research.** Finally, the boards were asked to identify the country of origin of the protocols they review. Forty-two percent of the boards surveyed review exclusively U.S. protocols. Considering the fact that 31 of the boards are located in the United States, this indicates that many of them are active internationally. In total, 80% of the protocols reviewed were considered of U.S. ori-
gin, 17% originated in Canada, 2% in Europe, and 1% elsewhere.

General Ethical Concerns Voiced by NIRBs

The last question of the survey was open. It allowed respondents to voice some general concerns, or to point out issues they considered crucial. There were a number of commonly held concerns raised by the NIRBs. These concerned issues around informed consent, privacy and confidentiality, and subject safety, as well as conflicts of interest, the scientific merit of studies, and questions relating to the qualifications of investigators and board members. (See Figure.)

Conclusion

From our survey, it becomes clear that commercial NIRBs are well established and are important participants in the context of medical research. In terms of composition and functioning, they seem to be comparable to (and in many respects better than) some institutional review boards. No conclusions can be drawn as to the quality of the review, but with respect to outcomes and process NIRBs do not differ substantially from other review boards. One major difference, often invoked to support private NIRBs, is the review time. NIRBs review the protocols much more quickly than the average institutional IRB/REB. It should not be argued that the ability to conduct fast review is exclusive to NIRBs, however, for as we pointed out, faster review times can be enforced by regulation of other review boards. Nonetheless, in the current context, NIRBs clearly can market themselves on that basis. The number of protocols reviewed by NIRBs is clearly significant and indicates that the drug approval system relies a great deal on them.

With respect to conflict of interest, most NIRBs have some form of conflict of interest policy. As with institutional review boards, these policies are often vague. Moreover, they cannot remedy the inherent conflict of interest embedded in the system of paid, commercial review. The problem of this conflict is even more poignant in light of the lack of adequate control over review boards, the vagueness of some rules, and the possibility for forum shopping. A more adequate system of accreditation of review boards and their members, prohibitions on forum-shopping, and stricter control of the work of NIRBs in general might alleviate some of the problems inherent in this structure.

New Initiatives. Recently, various agencies and organizations in the United States have undertaken new initiatives on the education and regulation of IRBs. Since October 2000, the NIH requires that all investigators interested in obtaining research funds must provide certification of ethics training in the protection of human research participants. The Department of Health and Human Services introduced for that purpose a web-based, continuing medical education tutorial: Human Participant Protections Education for Research Teams. The Office of Human Research Protection (OHRP, formerly OPPE) has developed a voluntary registration program for IRBs and NIRBs for the purposes of improving communication. It also plans to develop a computer-based education program for IRB administrators and institutional officials.

Outside government, several organizations have developed accreditation and education programs. Public Responsibility in Medicine and Research (PRIM&R) is developing an accreditation system for human research protection programs under the auspices of a new organization, the Association for the Accreditation

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Figure. General Ethical Concerns Expressed by NIRBs

INFORMED CONSENT
- Especially where children and other vulnerable subjects are concerned, and where subjects are paid to participate in protocols
- Inadequacies of many consent forms

PRIVACY AND CONFIDENTIALITY
- Ethical concerns regarding genetic research and access to sensitive information that results from it

SUBJECT SAFETY
- Full disclosure of risks and benefits
- Whether all drugs should be tested in both men and women
- Issues related to pregnancy and study participants, especially in AIDS studies
- Ethical issues of placebo-controlled studies or studies with lengthy washout periods
- Ethics regarding the use of vulnerable subjects in protocols

OTHER
- Conflict of interest of board members/investigators
- Scientific merit—"bad science is inherently unethical"
- Investigator qualifications to conduct the research
- Investigator compliance with NIRB requirements and follow-up monitoring
- Training of board members

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of Human Research Protection Programs (AAHRPP). Its aim is "to provide a process of voluntary peer review and education . . . in order to promote preservation of the rights and welfare of subjects in research and compliance with relevant ethical and regulatory standards." In addition, the Council for Certification for IRB Officials (CCIP), another PRIM&R affiliate, has launched an IRB professional certification program. While the funding agencies support these accreditation and certification efforts, there is no indication that they will assume the responsibility for these programs in the future or give them any official status.

In its draft report on "Ethical and Policy Issues in Research Involving Human Participants," the National Biosethics Advisory Commission (NBAC) recommends the development of a new, independent National Office of Human Research Oversight. One of the roles of this new office would be to "encourage" the development of certification programs for researchers and IRB members and accreditation programs for sponsors, institutions, and IRBs. Although these developments are certainly a significant step toward greater accountability, it remains to be seen whether voluntary compliance with such measures will be effective and can lead to an all-encompassing, transparent, and meaningful system of accreditation and certification of all IRBs and NRBs.

NBAC's draft recommendations would enhance in many respects the review system in the United States—for example, its proposals to increase the numbers of external and nonscientific members and to extend review requirements to all forms of research regardless of their funding source. The draft NBAC report further acknowledges that conflicts of interest may affect IRBs and mentions the potential conflict in the NRB structure. But it makes no substantive recommendation with respect to this type of conflict. It only suggests that "agreements that clearly described what the fee covers and not covers" could reduce conflicts in NRB review, adding the clarification that "the fee is for review and does not guarantee approval," as if such a self-evident explanation will be a sufficiently forceful argument to reduce potential pressure of clients and curb the structural conflict of interest imbedded in the NRB system.

The need for coherent and tight regulation of research ethics review is even more of an issue in Canada, which currently lacks clear regulations with respect to the constitution and functioning of review boards and has no governmental oversight and control. There is also no accreditation and certification system, although the National Council on Ethics in Human Research has been discussing some form of accreditation and has been involved in educational programs for REB members. The new Tri-Council Policy Statement and the implementation of the ICH-GCP guideline in Canada are only modest steps toward a more official recognition and regulation of the REB system. The latter has not yet led to the development of coherent and consistent federal and provincial regulations and adequate control by regulatory agencies, necessary to fill the explicit gaps in the ICH-GCP guideline.

Changes to the Canadian Food and Drugs Act? proposed in January 2000 by the Therapeutic Products Program (TPP) constituted a first attempt to provide clearer governmental recognition of REBs. Although the amendment was shelved as a result of elections, it is worth discussing here, since it represents a trend and could be reintroduced in one form or another.

Under the proposed regulations, a dual system of registration for trials in healthy subjects and a new 30-day default period for other trials would be introduced. This would have allowed drug companies to commence many drug trials (including studies of xenografts and prophylactic vaccines) if the TPP did not object within that time and if REB approval was obtained. For human dose tolerance studies in healthy subjects, a 48-hour review period by the TPP was targeted. Under such a system, it could be expected that many drug trials would go ahead without substantial review by the drug agency and that Canadian REBs would often be the sole body with a "public mandate" to appropriately review the protocol.

In a statement accompanying the proposed changes, the TPP explicitly recognized that "there is no accreditation system in Canada for REBs" and that "some Canadian REBs have limited resources and experience in the field." And yet, it merely "expected" "that those REB (sic) who are not able to undertake this responsibility would concentrate their efforts in other fields." This reliance on the work and integrity of REBs, combined with a modest "hope" that this regulatory amendment will draw attention to the need to have a formal accreditation system for REBs is remarkable and, in light of our findings, inappropriate. In effect, the proposal gave higher priority to the global competitiveness of the Canadian drug industry than to the development of clear accreditation and control mechanisms for the REBs that are supposed to protect the rights and welfare of human subjects.

As we argued, IRBs have to protect human subjects and also have to inspire trust in medical research. This requires not only that they act independently, but also that they are seen to be independent. One can doubt whether this is the case in the current system of private review, in which NRBs are service providers and depend on an inordinate degree on the goodwill of their clients. Their counterparts in institutions suffer from other problems of conflict of interest that may undermine their independence and credibility. The authority of both is undermined as a result of forum shopping. It is to be hoped that NBAC and the Canadian TPP will address these issues—which affect the core structure and credibility of IRB review—in a more satisfactory way in their final proposals.

In our view, changes to the research environment, in particular
the increasing commercialization and privatization of research, make it more necessary than ever to develop a tighter regulatory regime that deals with the potential for forum shopping and introduces publicly controlled certification and accreditation programs for IRBs and IRB members. Any movement toward deregulation and increased reliance on the private sector, particularly with respect to funding, conduct, and review of research, must be balanced by increased governmental surveillance, to make sure that growing private interests do not undermine the public good of research.

Governments and governmental organizations are ultimately accountable through our democratic systems, however imperfect these may be, private parties must be held accountable through regulation. Enhancing and expanding governmental control becomes all the more important as the government’s more substantive role in funding and conducting research diminishes.

The independence of IRBs is extremely important. Research regulations often set out detailed procedural rules, but are necessarily vague when it comes to describing substantive requirements. The process of research review requires good judgment and a careful weighing of risks and benefits. It will always have to rely to a large degree on the fairness and integrity of people who are disconnected from the research protocol and the interests others have in conducting the study. A solid independent IRB structure is a crucial component of any reliable review system.

Acknowledgment:
In the fall of 1996, the late Dr. Benjamin Freedman was asked by the National Council on Bioethics in Human Research (now the National Council on Ethics in Human Research) to analyze the phenomenon of the growth of private, noninstitutional review boards (NIRBs) in North America. With one of the authors of this survey, Trudo Lemmens, the decision was made to write a theoretical paper on the concept of conflict of interest in these boards and to assist with the development and analysis of a survey. Lemmens presented a first version of the theoretical paper to the III World Congress of Bioethics in San Francisco (21 November 1996). Shortly afterwards, in March 1997, Dr. Benjamin Freedman passed away unexpectedly. In tribute to Benjamin Freedman, the conflicts of interest paper was updated and recently published in the Milbank Quarterly (2000, 78: 547-84), and work on the survey was continued. The survey results are discussed in this paper, which we dedicate to him.

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References
9. Since the submission of this paper, the Office of Human Research Protection has changed its procedures. The revised procedure now includes registration of IRBs. However, this assurance program only binds IRBs that review research sponsored or regulated by a federal agency that follows the Common Rule.


36. E.g., Regulation of Medication in Clinical Trials of the Legislative Assembly of the Swiss Canton of Bern (Office Interministere de controle des medicaments, Reglement sur les medicaments au stade d’esai clinique), Doc. 230-1, 18 November 1993, Art. 8.1.


38. See ref. 5, Hertle et al. 2000.

39. See ref. 21, Hayes et al. 1995: 3.


42. See ref. 15, Levine 1986: 11.


47. See ref. 13, Medical Research Council 1987.


52. See ref. 15, Levine 1986: 541-57.


56. See ref. 23, Glass et al. 1999.


58. Levine RJ. Statement on institutional review boards presented to Subcommittee of Human Resources of the Committee on Government Reform and Oversight, United States House of Representatives, 11 June 1998.
