MONITORING CLINICAL RESEARCH: AN OBLIGATION UNFULFILLED

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Abstract • Résumé

The revelation that data obtained for the US-based National Surgical Adjuvant Breast and Bowel Project (NSABP) from subjects enrolled at Hôpital Saint-Luc in Montreal was falsified has eroded public trust in research. Institutions can educate researchers and help prevent unethical research practices by establishing procedures to monitor research involving human subjects. Research monitoring encompasses four categories of activity: annual reviews of continuing research, monitoring of informed consent, monitoring of adherence to approved protocols and monitoring of the integrity of data. The authors describe characteristics of research projects that may call for monitoring procedures in each category. The form taken by such monitoring depends on the nature of the protocol. Although appropriate research monitoring requires substantial investment of personnel and financial resources, it is required under guidelines regulating research involving human subjects in Canada. Research monitoring is a step forward in re-establishing public confidence in medical research.

La révélation selon laquelle les données obtenues pour le National Surgical Adjuvant Breast and Bowel Project (NSABP) des États-Unis, fournies par des sujets inscrits à l'Hôpital Saint-Luc de Montréal, ont été falsifiées à ébranlé la confiance de la population en la recherche. Les établissements peuvent éduquer les chercheurs et aider à prévenir les pratiques de recherche non éthiques en établissant des procédures de suivi des recherches sur des sujets humains. Le suivi des recherches comporte quatre catégories d'activités : examen annuel des recherches en cours, suivi du consentement éclairé, suivi de l'observation des protocoles approuvés et suivi de l'intégrité des données. Les auteurs décrivent des caractéristiques de projets de recherche qui peuvent nécessiter des procédures de suivi dans chaque catégorie. La forme de ces suivis dépend de la nature du protocole. Même si le suivi approprié des recherches nécessite un investissement important en ressources financières et humaines, il est nécessaire conformément aux lignes directrices qui régissent la recherche portant sur des sujets humains au Canada. Le suivi de la recherche est une étape à franchir pour redonner à la population confiance dans la recherche médicale.

Research in Canada received a clarion call on Mar. 13, 1994, in the form of newspaper headlines announcing the research fraud involving Hôpital Saint-Luc in Montreal.[1] A report by the US Office for Research Integrity (ORI) determined that Dr. Roger Poisson, a respected surgeon working in breast-cancer treatment at the hospital, had falsified data on 99 of the 1511 patients he had enrolled in the US-based National Surgical Adjuvant Breast and Bowel Project (NSABP) between 1977 and 1990.[2] Although in many cases Poisson had simply changed the dates of surgery and biopsy to make patients eligible for inclusion in the trial, other violations were more serious. The ORI found that the patients' levels of a hormone receptor had been fabricated in seven cases and that informed consent had not been obtained, or that such consent was questionable, in three cases. In a further three cases, Poisson had failed to record a history of cardiac disease that would have disqualified the patient from a clinical trial involving adjuvant therapy with doxorubicin, a cardiotoxic drug. As a result of this fraud, the US National Cancer Institute (NCI) barred Poisson from receiving federal US grants or contracts for 8 years.[3]

The effect of the research fraud has been widely felt. In its aftermath, Dr. Bernard Fisher resigned as the head of the NSABP cooperative group.[4] Although a reanalysis of the trial results showed that the fraud did not affect the main conclusions,[5–7] public trust in medical research was severely undermined.[8–10] To assuage public and congressional concerns, Dr. Samuel Broder, then director of the NCI, announced that the NCI would subject all tri-

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als it funded to stricter surveillance.[11,12] Nevertheless, the erosion of public trust may result in the reluctance of many patients to participate in clinical trials and in decreased funding for medical research generally.

This was not the first case of research fraud to be so well exposed.[13–18] Why does such fraud occur? Several factors are thought to motivate researchers to commit fraud: prestige, the high societal value placed on research,[19] and the competitive nature of biomedical research, which can be traced to medical school.[20]

Whatever the cause, the public will no longer tolerate what it perceives as a lax attitude on the part of medical researchers and research institutions.[8–10,21] Although a comprehensive solution to the problem necessitates a multifaceted approach involving government, funding agencies, cooperative groups, institutions, researchers and even subjects, local institutions must find meaningful ways to respond on their own.

Local institutions, through their research ethics boards (REBs), are obligated to ensure appropriate monitoring of research involving human subjects. A discussion of the need for local research monitoring and of the types of monitoring that need to be considered seems timely. At least two local institutions are considering establishing Offices for Research Audit. In this article we discuss the guidelines of the Medical Research Council of Canada (MRC), outline the arguments against and for monitoring and define four categories of research-monitoring activities. We hope that this conceptual framework will guide administrators and members of REBs in developing institutional policy on monitoring research. Furthermore, we hope that this article will trigger much-needed debate in the research community.

The duties of research ethics boards to monitor research

The guidelines of the MRC govern the conduct of all government-funded medical research as well as all pharmaceutical research undertaken during the drug-approval process in Canada.[22,23] Under the guidelines, research must be approved beforehand by an REB. The need for monitoring should be considered during the research-approval process, and "the procedures should be set by the REB as one of the conditions of approval."[22] If the REB believes that monitoring is not necessary for a particular trial (for example, a study involving a mail survey), "the reasons should be given."[22] The guidelines specify that, after approval of a protocol, the "REB . . . should ensure that the *actual implementation and conduct* of the project continue to meet the standards of ethics agreed to"[22] (emphasis added). Thus, REBs have an obligation to monitor continuing research. The guidelines indicate that an annual review in the form of a progress report by the investigator to the REB, although an acceptable form of monitoring for some studies, is a minimum requirement for continuing review.

> It is expected, however, that the institution's monitoring will be more active than simply seeking investigator's assurances. Research officers, or members cognizant of ethical concerns, may be required to maintain scrutiny by periodic review of the research and of the factors involved in the ethics approval. The actual form of this monitoring will vary with the specific research protocols. In certain cases, specialists from outside the institution might be asked to act as monitors.[22]

Therefore, REBs that employ only annual review do not fulfil the guidelines' monitoring requirements.

In fact, few if any Canadian REBs fulfil the guidelines. A study of Canadian REBs conducted in 1989 by the National Council on Bioethics in Human Research (NCBHR) found that very few committees did any monitoring beyond requiring annual reviews,[24] a finding that the NCBHR confirmed during a 1993 audit of Canadian REBs. Indeed, only 18% (8/44) of REBs surveyed reported that they audited continuing research.[25] However, the NCBHR noted that at least two of the REBs surveyed were considering monitoring programs.[25] Internationally as well, it seems that monitoring of research is the exception, not the rule.[26] A review of Australian committees showed that only 44% "always" or "usually" undertook postapproval review and that, in almost all (99%) cases, this involved only annual review.[27] A review of committees in Scotland showed that only 6 of 41 committees had formal procedures for monitoring and, in fact, 14 of 41 committees had no way of knowing if an approved protocol was ever implemented.[28] A landmark review of US committees showed similarly that 63% of committees had never "designated members or other representatives to observe the manner in which a research project is being conducted."[29,30]

Arguments against and for monitoring by REBs

Robert J. Levine has argued against routine monitoring by REBs on several grounds. First, routine monitoring would negatively affect the atmosphere of trust between the REB and the investigator.[31]

Second, Levine believes that monitoring procedures are unduly expensive. He points out that "presumptions of trust are much less costly, whether the costs are expressed in terms of dollars, human resources, or the quality of our social structures."[31] Finally, Levine does not see the use of a program that does not "seem to catch many wrongdoers anyhow,"[31] although he does seem to acknowledge the usefulness of review of research in certain cases.[32]

If the purpose of monitoring were to have REBs act as

a police force, they would surely be ill-prepared for the task. We believe, however, that the ultimate goal of any institutional commitment to monitoring of research must be the education of its research staff.[33] An effective institutional monitoring program should be coupled with an institution-wide program to educate researchers and other staff about the proper and ethical conduct of research. A monitoring program can help an institution develop an educational program that is responsive to its own needs, to "fill in the gaps." In the unusual case of an investigator with idiosyncratic research practices, a more clearly directed educational program may be appropriate.

In establishing monitoring programs, the perception that they reflect the REB's and institution's lack of trust in researchers is likely to be an important concern. This reaction is understandable, given that, in the past, such programs have been characterized as "police work." Therefore, such programs must be clearly identified as quality-assurance mechanisms. Medical audit is recognized as essential to improving the quality of medical care in an institution;[34,35] research audit is also an essential step to enhance the quality of research, a goal that researchers certainly endorse. Indeed, there is some indication that researchers may respond positively to such a program. A survey of Australian researchers found that, although many thought monitoring ensured the ethical conduct of research, those "who had their research monitored were more likely to strongly agree that monitoring and review ensures ethical conduct of research."[36]

Education and quality assurance are closely connected with another major goal of research monitoring, namely prevention. Poisson claimed in a letter to the ORI that he was at no point warned that what he was doing was wrong. He stated, "If I had a better understanding of the rules, I would not have been so lenient, nor would I have allowed exceptions to be made for . . . practical reasons."[2] It is tantalizing to speculate how an REB could have intervened if it had discovered Poisson's first instance of data falsification. The REB could have reminded Poisson of the importance of accurately reporting data and adhering to eligibility criteria. Furthermore, the REB (in cooperation with the NSABP) could have required close supervision of Poisson's enrolment and consent procedures to ensure compliance. Although this is speculation, the point is that prevention of a problem is always desirable; after the problem has occurred, damage control is the only option.[37]

In arguing that the cost of prevention is too great, the critics of monitoring have erred. The fraud involving breast-cancer research has shown how damaging a single case of research fraud can be. Schwarz[38] expresses the problem well.

> If integrity and credibility of the process is called into question, our ability to produce new methods for the diagnosis and treatment of disease will be compromised. The ultimate penalty will be paid in decreased benefits to public health. It's that simple, as well as that serious.

In portraying research audit as solely concerned with the detection of fraud, research monitoring's detractors have failed to recognize the role that monitoring can play in education and quality assurance in an institution.

Four categories of research monitoring

Heath[39] has suggested three useful categories of research review by REBs, to which we would like to add a fourth: (1) continuing (annual) review; (2) monitoring of the consent process; (3) monitoring for adherence to protocol; and (4) monitoring of data integrity. We do not intend to review each of these categories in detail, since much theoretic work is required in several of them. Instead, we will sketch the broad contours of each.

Table 1 summarizes our overview of the four categories of monitoring activities that are relevant to REBs. For each category, we list protocol characteristics that may indicate the need for such monitoring. A given protocol may, of course, have characteristics that trigger review activities in several categories. For example, a clinical trial of a novel and potentially toxic drug to treat subarachnoid hemorrhage may prompt an REB to consider continuing (annual) review, consent monitoring and perhaps monitoring of adherence to protocol. In Table 1, avenues of intervention are outlined for each category. Because review by an REB must respond to local standards, it is impossible to dictate which interventions a given committee should recommend for a given protocol. However, in considering the protocol for a new therapy for subarachnoid hemorrhage, a hypothetical committee could, for example, ensure that a committee to monitor data and safety exists and that the investigator reports to the REB biannually. Furthermore, the REB may insist that the competence of potential subjects be assessed by a physician who is not involved in the clinical trial. Finally, the REB may ask the investigators to develop and submit for approval an audit program for treatment procedures to ensure that the study protocol is followed scrupulously.

In the following discussion we provide additional detail concerning each of the monitoring categories. Because few committees monitor research adequately and because we had to rely on published reports, many of the circumstances that prompted committees to monitor research are exceptional and dramatic (e.g., the first implantation of an artificial heart). As REBs begin to fulfil the requirements of the MRC guidelines, however, monitoring will become more commonplace.

Annual review

Most Canadian REBs (53% of those surveyed by the NCBHR) require that investigators submit a report to the REB each calendar year after the approval of a protocol.[25] A report may also be required (by 36% of REBs) at the conclusion of the study.[25] As we have seen, this is the minimum standard for continuing review in the MRC guidelines,[22] which require that annual reviews include at least "any changes that may have occurred in scientific knowledge or in the design of the study, as well as the progress of the study."[22] Thus, the investigator should report the number of patients accrued, his or her assessment of the outcome or progress of these subjects and any adverse drug reactions.[39] Furthermore, the investigator must report any new information, generated outside the trial, that may disturb clinical equipoise (i.e., the uncertainty within the community of experts concerning the relative superiority of one of the treatments involved in the trial).[40]

In research studies involving possible serious adverse drug reactions, mortality or serious morbidity, the REB may recommend the establishment of a committee to monitor data and safety (if no such committee exists) or more frequent reports from the researcher.[22] Similarly, more frequent review may be needed because results of other relevant clinical trials in the field are anticipated. If clinical equipoise is disturbed by the publication of results of a closely related research study, the REB may decide to halt a trial.[40]

Consent monitoring

External audits of research studies have often found that informed consent and its proper documentation are deficient. The US Food and Drug Administration (FDA) documented deficiencies in informed consent in 51% of audits conducted from 1977 to 1988.[41,42] The NCI found that, at 12% of the cooperative-group sites audited, there were deficiencies in the consent obtained from more than 30% of trial participants.[43] Audit programs may help to rectify these shortcomings. A recent report from the Cancer and Leukemia Group B (CALGB) trial demonstrated the success of an aggressive audit and education program, which reduced the incidence of inadequacies in consent obtained from 18.5% to 3.9% of trial participants.[44]

Since the MRC guidelines charge REBs with ensuring that informed consent is properly obtained and documented, they are empowered to monitor consent procedures by at least two means.

> The plan may provide for inspection of the means by which information is given to prospective subjects, or for an independent assessment of how much informed subjects understand of what they have been told.[22]

Robertson states succinctly, "Monitoring could be as simple as checking that signed consent forms exist or as complicated as interviewing subjects or observing the investigator recruit subjects."[45] Periodic monitoring of consent documents is a straightforward first step to ensure

Table 1: Characteristics that indicate the need for monitoring and avenues of intervention by research ethics boards (REBs) in four categories of research monitoring

Category of monitoring	Characteristics that indicate the need for monitoring	Avenues of intervention
Annual review	• Expected adverse drug reactions • Other concurrent research on the treatment	• More frequent review by the REB • Recommendation of the formation of a committee to monitor data and safety
Consent monitoring	• Greater than minimal risk to the subjects • Enrolment of members of a vulnerable population (e.g., prisoners or patients with advanced cancer) • Inclusion of incompetent (or potentially incompetent) subjects	• Periodic review of consent documents • Involvement of a third party to assess competence • Involvement of a subject advocate in consent negotiations • Periodic post hoc review of subjects • Periodic assessment, in person, of consent negotiations • Presence of a member of the REB at all consent negotiations

Monitoring of adherence to protocol	• Complex treatment regimen
	• Safety interventions to prevent serious toxic effects, required by
	  • the protocol or
	  • the REB
		• Review of management plan prepared by researchers
		• Involvement of a third-party expert
		• Periodic review of documents (e.g., patient charts or pharmacy records)

Monitoring of data integrity	• Generation of research in which the integrity of data is not monitored by an outside agency	• Requirement that data integrity be guaranteed • Periodic in-house data monitoring • Periodic external monitoring

that the requirements for written informed consent have been fulfilled. Faden, Lewis and Rimer[46] have shown the feasibility of such a review; they reviewed the following information from the consent documents for 214 research subjects: the protocol number, who solicited consent, where and when consent was obtained, whether the consent form was witnessed and, if so, by whom. The study required 160 person-hours to complete.

Certain studies — those that involve greater than minimal dedicated research risk (i.e., the risk of interventions done to answer the research question that are not associated with therapy),[47,48] draw subjects from vulnerable patient populations (e.g., patients with advanced cancer) or include incompetent or potentially incompetent subjects — may require more intensive monitoring by the REB. In the case of studies involving incompetent or potentially incompetent research subjects, the REB may require that a third party assess the patients' competence to consent.[45] Shannon and Ockene[49] describe the deliberations of the REB in their institution concerning the first Thrombolysis in Myocardial Ischemia trial (TIMI-1), for which only patients suffering the first hours of an acute myocardial infarction were eligible. Concerns about voluntary participation and comprehension of consent information led the REB to require that family members be present during the consent negotiation and that they also agree with the subject's decision to enter the trial. The involvement of family members in consent is a creative solution that merits consideration in studies like this one that involve seriously ill patients and immediate treatment. In other studies in which the competence or voluntary participation of subjects are issues, the REB may appoint an advocate for the subjects, who must be present during consent negotiations. McGrath and Briscoe[50] describe a research centre that employs a full-time patient advocate. In the extreme case of novel research that poses serious risks for vulnerable subjects, the REB may require that a member of the REB supervise, in person, the consent negotiations for all patients enrolled in a trial. In the first implantation of an artificial human heart[51] and in the first case of heart transplantation with a nonhuman heart[52,53] the REB had a member present during the consent process.

As a means of quality control, REBs may wish to observe consent negotiations in order to monitor prospectively the adequacy of information given to potential research subjects. They may also wish to assess subjects' comprehension of consent information by testing subjects immediately after the informed consent has been given.[54–56] The results of such testing may lead to efforts to improve comprehension; such efforts may include a 24-hour delay before subjects sign the consent form,[57] audiovisual presentations about the research[58,59] or a policy requiring subjects to complete a multiple-choice test satisfactorily before enrolment.[60,61] Testing of subjects' comprehension should be immediate; although testing subjects some time after the informed-consent process may be more practical, difficulties with recollection confound the significance of data obtained in this fashion.[62,63] Theoretic work is needed to define standards for the recollection of consent information.

Monitoring for adherence to protocol

Empiric research shows that it is relatively common for investigators to deviate from REB-approved protocols. A survey of researchers showed that half thought that researchers deviated "at least sometimes" from the original research plan without the approval of the REB.[36] Of 92 researchers, 13 (14%) said that they had deviated from their own proposals without approval by making changes to the overall study design, the defined subject samples or the participation required of subjects.[36]

Data from the external audits discussed earlier seem to confirm this finding. During 26% of the audits conducted between 1977 and 1988, the FDA discovered major problems with nonadherence to protocol.[41,42] The NCI uncovered deviations from drug dosages or other protocol regimens in 12% of the study sites audited; in 19% of the sites monitored, more than 30% of the cases had had such deviations.[43] The CALGB audits revealed "major protocol deviations in drug dosing" in 10.8% of cases audited.[44]

If protocols involve complex treatment regimens or require critically timed safety interventions to prevent serious toxic effects, REBs may wish to institute monitoring to ensure that approved procedures are being followed. (Pharmaceutical companies, as a rule, aggressively audit adherence to protocols in all studies.) The optimal approach is for REBs to encourage researchers to develop self-monitoring mechanisms, which may involve other experts within or outside the institution. In exceptional cases, procedures may be monitored directly by a member of the REB. Perhaps as a response to procedural violations by Cooley and Liotta in the first mechanical-heart transplantation,[64] the University of Utah Institutional Review Board appointed a member to ensure that procedures were followed in the subsequent implantation of an artificial heart in Barney Clark.[65]

In conjunction with a monitoring program and as part of a quality-control program, REBs may wish to audit relevant pharmacy and medical records directly to ensure that procedures have been followed.

Monitoring the integrity of data

Capturing data of the highest quality is central to the validity of subsequent inference.[66] The pharmaceutical in-

dustry has taken great strides, undoubtedly as a result of the FDA approval process, to ensure that all data in clinical trials are independently audited.[67] Pharmaceutical companies typically monitor each site every 6 to 10 weeks during the course of a study.[67] Clinical-trial cooperative groups also have procedures for monitoring data quality and integrity. The NCI, for example, requires that each site in its 14 cooperative oncology groups be audited at least once every 3 years.[67] These mechanisms proved insufficient to prevent the fraud that occurred during the NSABP trial. As mentioned earlier, the NCI is initiating mechanisms for more stringent research surveillance.

Despite the fact that pharmaceutical companies and cooperative groups audit data integrity, REBs have a role to play. To fulfil their obligation to monitor data integrity, REBs most often must simply review the audit procedures proposed by the pharmaceutical company or clinical-trial cooperative group. Therefore, REBs' greatest concern is any research generated in the institution that is not subject to external audit. In these cases, REBs may wish routinely to require investigators to sign guarantees of data integrity, as suggested by DeMets and Meinert.[37] In addition, the institution may wish to establish a program to conduct periodic in-house or external audits of data. To develop such programs, institutions may draw on the substantial body of published articles on data-quality control in clinical trials.[68–71]

Administration of reviews and financial issues

An institution that establishes a program to monitor research should consider carefully how the program will be administered and funded. Although a detailed review of administrative models is beyond the scope of this article, Fig. 1 shows three possible administrative models. These models are not mutually exclusive, and can be used in combination. As the institution's agent in the review of experimentation involving human beings, an REB must play a central role in such a program. Certain aspects of routine review, such as periodic monitoring of consent documents, periodic observation of consent negotiations, testing subjects for comprehension, periodic document checks for adherence to procedures and data-audit programs for in-house research, may best be handled by an office for research audit (Model C in Fig. 1). Such an office, established by the institution in collaboration with the REB, could handle continuing reviews and coordinate institutional education programs to respond to problems discovered through the reviews. However, it must be directly responsible to the REB, which would ultimately deal with any difficulties encountered.

In some cases the REB may wish to monitor research projects directly (Model A). This model may be most appropriate in novel research that presents a serious risk to subjects. In most cases of continuing review, however, good research practice dictates that the investigators develop a monitoring program (Model B). Such a program could involve a system of checks and procedures within the project or third-party supervision of procedures (e.g., third-party assessments of subject competence). Self-

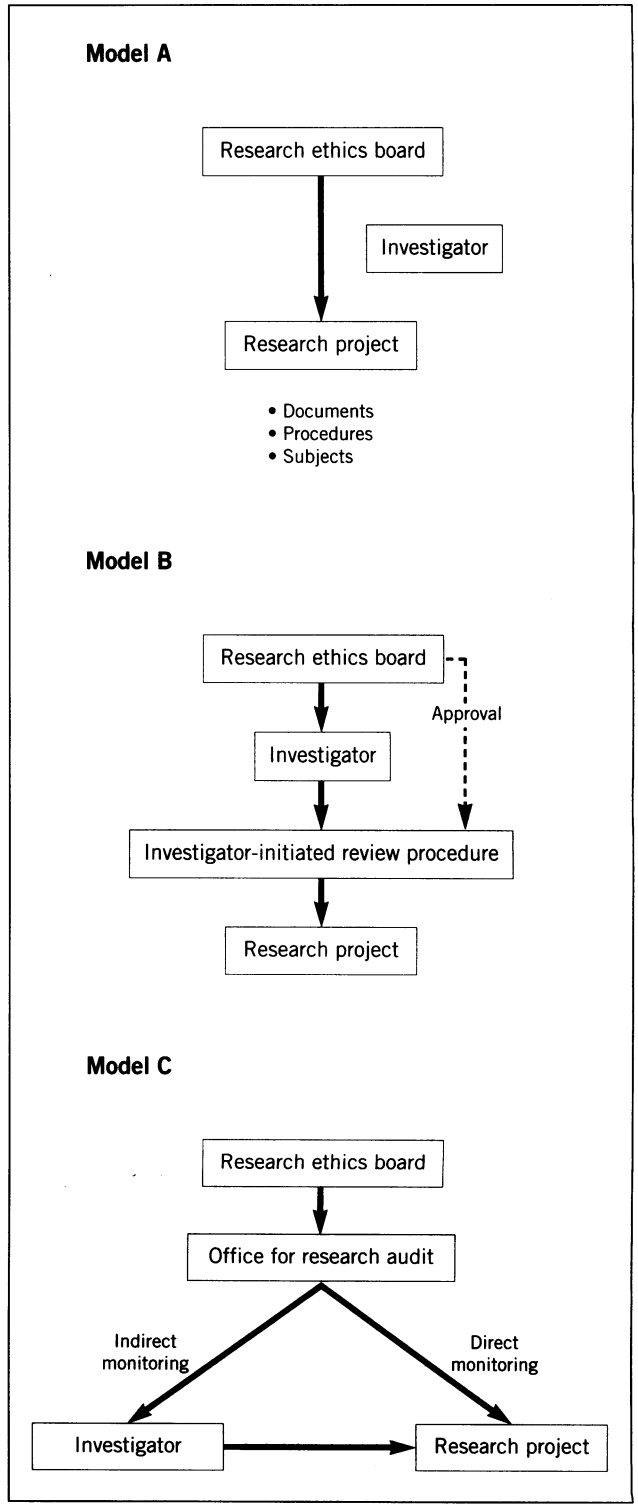

Fig. 1: Three models for the administration of research monitoring.

monitoring by researchers is the model most consonant with the prime goal of continuing review: education.

Continuing review requires institutions to commit substantial financial resources and personnel to the process. The MRC guidelines state that "researchers and institutions should bear the cost of this day-to-day monitoring, which is largely similar to monitoring practices already accepted in health professions and commercially funded research."[22] However, pharmaceutical companies and government funding agencies should take into account the additional costs entailed by review when they fund research involving human subjects. Discussions among researchers, institutions and funding agencies are needed to define specific arrangements.

Conclusion

The monitoring of continuing research provides institutions with the chance to affirm publicly their commitment to the ethical conduct of experimentation involving humans. When combined with educational programs, monitoring offers the opportunity to prevent problems in the conduct of research. In many cases investigators will develop their own monitoring programs. However, the establishment of institutional programs to review clinical research will play an essential role in regaining the public's trust in research.

It is not enough to ask society for unquestioning trust, nor can it be assumed that scientists are different from other human beings and totally incapable of error, deceit, misrepresentation, or bias. The scientific community must be vigilant for this, since nothing less than the viability of the biomedical science enterprise is at stake.[38]

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