Should IRBs Monitor Research More Strictly?

by Nicholas A. Christakis

IRBs were established to protect the rights and welfare of human subjects of research.[1] This duty has usually been fulfilled by reviewing the research protocol and the informed consent document to ensure an acceptable level of risk and a complete process of informed consent. Ensuring subject well-being, however, may at times require a contact with the investigator and the project beyond reviewing paperwork. Protection of the subjects of research may occasionally require the IRB to monitor the adherence to its decisions and assess the adequacy of the entire informed consent process.[2]

The federal regulations regarding IRBs anticipated the necessity of monitoring activity. They provided for the IRB to "have authority to observe or have a third party observe the consent process and the research."[3] Moreover, the IRB is supposed to "suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects"[4] and inform the Secretary of HHS. Obviously, to make a determination of this kind requires some form of ongoing surveillance or, at a minimum, some ongoing personal contact with the research and not just a perfunctory annual review.

Yet few IRBs maintain such an ongoing contact. In a study conducted for the U.S. government and published in 1978, 63% of IRBs surveyed never designated representatives to observe the manner in which a research project is being conducted. Only 47% reported that their institution had a policy by which investigators could report harm to subjects arising from the research.[5] More recent anecdotal evidence is consonant with this study.[6] For example, in one report, only 2-3 percent of IRB members reported direct participation by their IRBs in the consent process or review of adherence to committee decisions.

Diverging Views of Monitoring

IRB function is based on the ethical principles of respect for persons, beneficence and justice.[7] Suggestions that IRBs monitor compliance with their recommendations arise from the recognition that despite IRB intentions, these precepts are often incompletely respected. What often ensues, as law professor John Robertson of the University of Texas argues, is "an elaborate charade—hours of IRB time invested in cosmetic surgery on consent forms to mask the ugly ethical fact that subjects often enter research without fully understanding what they are doing."[8]

For this reason, some have supported stricter supervision of the implementation of IRB decisions. Indeed, this expectation of ongoing monitoring by IRBs was articulated early in the development of IRBs. Robertson maintained that an "IRB should monitor the consent process, test subject understanding, and modify its requirements accordingly."[9] Elsewhere, he argued that IRBs should "take steps to monitor investigator compliance with consent requirements, on a sample or comprehensive basis, and hold accountable investigators who do not comply."[10]

Arthur Caplan, a medical ethicist, also advocated monitoring. He recognized that "the primary problem with the present system of IRB review...is that it devotes too much time to the production of paper promises and almost no time to the enforcement, investigation, or general assurance that the promises will be kept."[11] Basically, Caplan would prefer to have IRBs review fewer protocols (through a method of random sampling), and spend more time on enforcement.

On the other side of the debate were those who feared that such monitoring of IRB decisions could rapidly result in the transformation of the IRB from a review and advisory body into a police force. The adverse outcomes of such a transformation have been well summarized by Robert Levine of the Yale School of Medicine. Arguing that IRBs must remain credible in order to function well, Levine maintains that

> IRBs must resist any efforts to turn the IRB into a police force....If the IRB is obliged to function as a police force, it can only indicate to the community of investigators that it is operating from a presumption of mistrust. Presumptions of mistrust cost a lot in time and energy of IRB members, most of whom have no training in police work in the first place....[T]he basic presumption of trust...is fundamental to the existence of the academic community. Further, if the IRB is perceived as a police force by members of the institution, it is likely to lose...its "informal monitoring system," that is, unsolicited reports by students, nurses, physicians, and so on.[12]

Thus, Levine feels that IRBs do not have the time, training, or inclination to do police work and that even if they did, such activity would lead to a loss of both IRB credibility and any informal monitoring extant in the community.[13]

Erica Heath, formerly of the University of California at San Francisco, similarly argues that "IRB activity to ensure adherence to an approved protocol would invade the trust established between the IRB and an investigator. An adherence audit could be done most thoroughly through on-site inspection. The IRB members seem ill-suited for this job."[14] Heath favors such active monitoring only in cases of demonstrated breach of rulings.

A Workshop on Whistleblowing in Biomedical Research conducted in Washington, D.C. in 1981 reached the same conclusion, against active monitoring or investigative functions for IRBs.[15] Instead, a passive system involving an office designated to receive and investigate complaints was advocated. Such an office would presumably field complaints from an "informal monitoring system." Alternatively, a single staff person affiliated with the IRB could field such complaints.[16]

Monitoring in Practice

How, then, have IRBs dealt with these conflicting expectations regarding their monitoring duties? The literature reveals a few occasions when an IRB has established a review or follow-up procedure. IRB members seem to have resolved their anxiety about how much monitoring they should do by occasionally adopting a more active role in two types of protocols: (1) research that is especially risky; and (2) research that is likely to come under scrutiny by outsiders—such as the press. However, even in these types of protocols, monitoring is conducted only sporadically.

Some have specifically advocated the riskiness of the protocol as a standard for IRB monitoring. Levine maintains

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that "the need for monitoring systems is likely to arise from considerations of some aspects of risks and benefits...."[17] Presumably, higher risk would warrant greater IRB surveillance. For example, in a case involving cardiac catheterization, one IRB "required its own oversight process....It was felt that the IRB would be able to assure itself continuously of the ongoing safety of the project and appropriateness of the consent process."[18] And, indeed, the federal regulations recognized the importance of more supervision when the stakes are higher, as in the case of pregnant subjects.[19]

With respect to protocols subject to outsider scrutiny, more active IRB surveillance likely results both from the IRB's increased feeling of responsibility, and from the IRB's increased feeling of exposure. It is probably no coincidence that the dramatic, path-breaking protocols that are likely to receive press coverage are subjected to especially stringent IRB oversight to begin with: they are probably more risky. However, higher IRB surveillance of the research in question may also be in reaction to the likelihood that the IRB itself may come under scrunity and be held to a higher standard of responsibility. For example, a committee at the University of Utah established to select a patient for the implantation of the artificial heart included as a nonvoting participant a member of the IRB whose job it was to "ensure that all the review procedures outlined in the protocol (were) followed."[20] Similarly, in the case of the xenotransplantation of Baby Fae at Loma Linda Medical Center, an IRB member monitored the informed consent process as a participant.[21] In both of these cases, the IRBs came under considerable media scrutiny as a by-product of the coverage of the novel procedure in question.[22]

The argument against monitoring by IRBs is based in part on the belief that such activity would compromise trust. Proponents of this argument, however, may unjustifiably assume that investigators with good faith will implement IRB recommendations entirely. Problems may arise even aside from the admittedly rare case of an unscrupulous investigator. Some investigators may fail to implement IRB requirements not through bad faith, but rather through administrative negligence. Simple examples of this involve using outdated consent forms instead of IRB approved revised versions,[23] or obtaining biased or inappropriate witnessing for consent documents.[24] Errors of this kind make a sham of the whole deliberative IRB review intended to assure a good informed consent process and an appropriate informed consent form. Truly some type of follow-up would be necessary to avoid such errors.

Moreover, if IRB credibility rests on a presumption of trust, then why, in some cases, do IRBs nevertheless institute their own oversight process? It must be because they feel, in the types of situations outlined above, that their responsibility extends beyond reviewing paperwork. IRBs do not, and arguably cannot, perform this monitoring function all the time. It is therefore presumably the rarity of such activity—and the attendant small IRB time input—that prevents the undermining of investigator trust. But this is a dubious supposition; indeed, investigators may feel relatively more mistrusted if they are subject to *ad hoc* spot checks than if they were uniformly scrutinized under some specified guidelines.

We should be aware that we are letting issues of practicality (*e.g.*, monetary and time constaints) and credibility (*e.g.*, loss of investigator trust) get in the way of a uniform application of our obligation and of our mandate. This trade-off may be necessary, but it is only necessary if we believe that any kind of monitoring would result in the loss of investigator good will, would thus undermine the whole IRB process, and hence ultimately adversely affect subjects even more. Thus, a compromise has evolved between ensuring true informed consent and appropriate risk in all protocols on the one hand and preserving investigator trust on the other hand. It is important to acknowledge this compromise openly.

Where Increased Vigilance May be Needed

There may be more appropriate circumstances than those outlined above to subject research to IRB monitoring. That is, given that it is impossible to monitor all research, but also given that some informal monitoring is indeed going on, more appropriate, formal guidelines could be established that would better protect the subjects of research. While increased vigilance in cases of outsider scrutiny may well be cynical and self-serving, increased vigilance in cases of greater risk does seem sensible and serves to protect subjects adequately. There is ample precedent for increased attention to ethical precepts such as subject autonomy and justice when more is at stake, when the research is riskier.[25]

But beyond research where subjects are at special risk, we should monitor research where consent itself is at special risk. There are two types of situations where this obtains and where IRB monitoring is therefore appropriate. One type of situation arises when the study population itself is vulnerable. Such populations include the incarcerated, the mentally infirm, the young, and so forth. These groups are often relatively less able to give informed consent.

Alternatively, certain kinds of researchers are especially prone to take risks and neglect appropriate consent procedures. Such "permissive" researchers, admittedly a minority, have been described by Bernard Barber of Columbia University as falling within one of the following groups: (1) the "relatively unsuccessful scientist striving for recognition;" (2) the "extreme mass producer" researcher; (3) the "underrecognized," presumably disaffected, faculty member; and (4) the investigator in an especially competitive field.[26] In sum, ambitious, isolated investigators are more prone to neglect subject rights. In addition, researchers previously identified as practicing inadequate informed consent would also constitute a suspect group.[27]

Stricter IRB oversight and monitoring is therefore necessary in studies where: (1) the research is especially risky; (2) the research population is vulnerable to poor consent; and (3) the researcher is prone to obtain poor consent. A mechanism for identifying which protocols fall within these categories should be established within each institution. IRBs should expend some systematic effort in monitoring such protocols and thus properly protect human subjects of research.

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[1]As per National Research Act, Public Law 93-348, Sec. 474.

[2]Monitoring may also involve investigation to identify unapproved activities going on at the institution. This type of monitoring will not be considered here. For a detailed description, see Heath, E.J.: The IRB's monitoring function: Four concepts of monitoring, *IRB: A Review of Human Subjects Research, 1(5): 1-3, 12 (1979).*

[3]45 CFR 46.109e.

[4]45 CFR 46.113. See also 46.108c.

[5]Cooke, R.A. and Tannenbaum, A.S.: A Survey of Institutional Review Boards and Research Involving Human Subjects, an Appendix to *Report and Recommendations re Institutional Review Boards* by The National Commision for the Protection of Human Subjects of Biomedical Research, DHEW publication No. (OS) 78-0009, Washington, D.C., 1978, pgs. 1.1-1.310, especially pgs. 1.205 and 1.207.

[6]See: Robertson, J.A.: Taking consent seriously: IRB intervention in the consent process, *IRB: A*

Review of Human Subjects Research, 4(5): 1-5 (1982) at pg. 1 re conference of IRB members where only 2-3 percent reported monitoring of informed consent; Faden, R.R. Rimer, B. and Lewis, C.: Monitoring informed consent procedures: An exploratory record review, *IRB: A Review of Human Subjects Research*, 2(8): 9-10 (1980) at pg. 9 stating that "most IRBs have no mechanism for monitoring the consent procedures . . . ."; and, Heath op. cit., at pg. 2 re "informal survey."

[7]See, e.g., National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, DHEW publication No. (OS) 79-12065, Washington, D.C., 1979.

[8]Robertson, op.cit., pg. 1.

[9]Robertson, J.A.: Ten ways to improve IRBs, *Hastings Center Report*, 9(1): 29-33 (1979), pg. 31; see also pg. 30.

[10]Robertson, Taking consent seriously, op.cit., pg. 2.

[11]Caplan, A.L.: Random sampling: A modest proposal for reforming IRB review, *IRB: A Review of Human Subjects Research*, 4(6): 8 (1982).

[12]Levine, R.J., The impact of Institutional Review Boards on clinical research, *Perspectives in Biology and Medicine*, 23:S98-S114 (1980), p.S99-S100.

[13]Regarding informal monitoring, see also Levine, R.J., The Institutional Review Board, in the Appendix to *Report and Recommendations re Institutional Review Boards* by the National Commision for the Protection of Human Subjects of Biomedical Research, DHEW publication No. (OS) 78-0009, Washington, D.C., 1978, pgs. 4.1-4.73, at pgs. 4.46-4.47.

[14]Heath, op. cit., pg. 3.

[15]Mishkin, B.: "Whistleblowing in biomedical research: Report from a workshop, *IRB: A Review of Human Subjects Research*, 4(2): 8-9 (1982). Regarding IRB involvement in whistleblowing, see also Shannon, T. A. "Whistle blowing and countersuits: The President's Commissions and fraudulent research, *IRB: A Review of Human Subjects Research*, 3(7): 6-7 (1981), and Scher, S.R.: "IRBs and the falsification of research data," *IRB: A Review of Human Subjects Research*, 3(7): 8 (1981).

[16]Cohen, J.M: The Benefits of professional staff for IRBs, *IRB: A Review of Human Subjects Research*, 3(6): 8-9 (1981). Indeed, IRBs could have professional staff to perform investigative functions, though this would be costly. It is noteworthy that a recently published protocol review guide for IRBs altogether omits mention of the possibility of *active* IRB monitoring of the research or of the informed consent process; see, Prentice, E.D.; and Antonson, D.L.: A protocol review guide to reduce IRB inconsistency, *IRB: A Review of Human Subjects Research*, 9(1): 9-11 (1987).

[17]Levine, The Institutional Review Board, op. cit., pg. 4.53.

[18]Shannon, T.A. and Ockene, I.S. Approving High Risk, Rejecting Low Risk: The Case of Two Cases, *IRB: A Review of Human Subjects Research*, 7(1): 6-8 (1985).

[19]In 45 CFR 46.205(a)(2), informed consent monitoring and site visits by the IRB are specifically raised in the case of pregnant subjects.

[20]Woolley, F.R. Ethical issues in the implantation of the total artificial heart, *New England Journal of Medicine*, 310: 292-296 (1984), pg. 294.

[21]R. Sheldon, the chairman of the Loma Linda IRB, described the participation of his IRB at a conference sponsored by PRIMR (Public Responsibility in Medicine and Research), held in Boston, MA in February 1986. For more details on media coverage of this IRB, see Christakis N., and Panner, M.: Baby Fae and the media: How the law allows appropriate access, *IRB: A Review of Human Subjects Research*, 8(2): 5-7 (1986).

[22]It should be noted, however, that media coverage may result in some selection bias; that is, that the existence of IRB monitoring is made known precisely because the research receives publicity in the first place.

[23]Adkinson, N.F. Starklauf, B.L. and Blake, D.A.: How can an IRB avoid the use of obsolete consent forms? *IRB: A Review of Human Subjects Research*, 5(1): 10 (1983).

[24]Faden, et. al., op. cit, at pg. 9.

[25]See, for example, *The Belmont Report*, op. cit., especially at pg. 7.

[26]Barber, B.: The ethics of experimentation with human subjects, *Scientific American*, 234(2): 25-31 (1976).

[27]See, for example, Levine, R., The IRB and the virtuous investigator, *IRB: A Review of Human Subjects Research*, 7(1): 8 (1985).

Should I Enroll in a Randomized Clinical Trial? Excerpts from A Patient's Guide

When a randomized clinical trial is designed to compare two standard forms of therapy for a serious disease, how does one convey to prospective subjects an adequate sense of what is at stake as they weigh the three (or more) alternatives with which they are presented? This, I believe, is one of the greatest challenges to those who would be effective in negotiating informed consent. The best effort I have seen to meet this challenge is in A Guide for Patients *prepared by the Collaborative Ocular Melanoma Study Group.* While the entire booklet is commendable for the lucidity of both its expository prose and its illustrations, space permits reprinting only the following passage from the last three of its 20 pages.*

—Robert J. Levine

Now you have read a great deal about choroidal melanoma including how it is diagnosed and how it can be treated. You also have read much about clinical trials and how they provide treatment alternatives for patients. But you may well be wondering how to decide whether or not to participate in a clinical trial. Perhaps it would be helpful to listen in, so to speak, on an imaginary conversation among three patients, each of whom has a medium-sized melanoma and has been told about the treatment options available and about the Collaborative Ocular Melanoma Study:

Patient A:—I've decided to have my eye removed. If the cancer has not already spread, I know that enucleation will rid my body of cancer. What's more, I've tried patching that eye and seeing how well I can get along with just one eye. I really can do everything, including reading the newspaper and driving my car. It's true that I have noticed some loss of depth perception and some loss of vision off to the far side, so I'll have to be extra careful when I pour milk into my coffee and when I change lanes while driving. But apart from that, I don't see any problem. So that's why I've decided on enucleation. It's simple and straightforward, and it's been the accepted treatment for 100 years or longer.

Patient B: I've decided to have my tumor treated with a radioactive plaque. From what I understand, the patients treated with radiation so far have about the same life expectancy as those patients treated with enucleation. So what's the point of having my eye taken out if there is no guarantee that it's going to let me live longer?

Patient A: Well, that's a good point, except that my doctor told me that not many patients treated with radiation have actually been observed for more than three to five years. I'd sure be a lot more interested in radiation if I knew how long all these patients treated with radiation are going to live. And anyway, enucleation doesn't sound as bad as radiation. You are going to have to have at least two operations, one to put the plaque in place and a second to remove it, and you may still have to have your eye removed later if the tumor continues to grow.

Patient B: But at least I'll have some vision in the eye—at least for a period

*For further information on the Collaborative Ocular Melanoma Study and its *A Guide for Patients*, contact Barbara S. Hawkins, Director, at the Wilmer Ophthalmological Institute, The Johns Hopkins Medical Institutions, 550 North Broadway, Suite 301, Baltimore, Maryland, 21205.