

CASE STUDY

Approving High Risk, Rejecting Low Risk: The Case of Two Cases

by Thomas A. Shannon and Ira S. Ockene

In private conversation, business meetings of IRBs, and workshops on human subject research, concern is often expressed over the apparent lack of consistency in the way in which IRBs evaluate protocols. Conclusions are sometimes perceived as arbitrary and capricious. We have observed that protocols with high-risk elements are often quickly approved, while other protocols that present apparently lower risks run into great difficulty during the evaluation process. We will use two recent cases, not to provide solutions to the problems, but rather to indicate the dynamics that led to different outcomes.

The Two Protocols

The first case was a study of the relationship between muscle swelling and delayed onset of muscle soreness. The hypothesis under investigation was that muscle damage associated with delayed onset of muscle soreness results in localized inflammation of the affected area and increases pressure on the nerve endings of the muscle proprioceptors, thereby producing a sore sensation. Thirty college-age females were to be recruited from a college 50 miles away from the medical center and were to be placed in three groups: one control group and two different exercise groups. They would be offered academic credit for participating in the study. After three testing sessions to determine the subjects' maximal strength and muscle discomfort threshold, the subjects were to report to the radiology laboratory for a CAT scan of the upper aspect of the nondominant arm. Six days after this CAT scan, subjects would fill out a questionnaire on muscle soreness. Then the two exercise groups would perform different exercises; and at 8, 24, 30, and 48 hours following exercise the subjects would report back to the laboratory for blood samples, evaluation of muscle soreness, a measurement of muscle discomfort threshold, strength testing, and

another CAT scan at 30 hours. Changes in muscle size, as determined by the CAT scan, would be evaluated to determine whether there was an association with delayed-onset muscle soreness.

The second case was a study of thrombolysis in myocardial infarction (TIMI). This study attempts to determine which of two drugs, streptokinase or R-tPA (Recombinant tissue-type Plasminogen Activator), is more effective in acutely dissolving the coronary artery blood clot causing a person's heart attack and thereby restoring blood flow to the heart. Basically, this protocol requested that the person, when admitted for a heart attack, give consent to be randomized into either of the treatment arms, which would be carried out in a double-blind fashion. The patient would be taken to the cardiac catheterization laboratory, catheters placed in the heart, and x-rays of the coronary arteries and left ventricle would be obtained. If the artery causing the heart attack is blocked, one of the two drugs would be injected to dissolve the clot. X-rays would be taken during the time of the drug administration. After the procedure the patient would be transferred to the coronary care unit and treated in standard fashion, including the administration of heparin to prevent a new clot from forming in the coronary artery. Prior to discharge, the patient would be asked to undergo a second cardiac catheterization to assess the results of the treatment. He or she would also be asked to return to the hospital for a follow-up exam in six weeks and at six months after entering the study.

Even a superficial examination reveals great differences between the two studies with respect to risk-benefit ratios, as well as the level of invasive procedures that the subjects are required to undergo. Yet, the first protocol was rejected by the IRB after two reviews and the second was promptly approved. These decisions, occurring close in time, raised concerns among the IRB members as to why the IRB acted as it did. It is instructive to examine each of these cases in turn.

Rejecting Low Risk

The protocol testing muscle soreness offered no benefits whatsoever to the

students who would be involved in the procedure. This was clearly stated by the researchers and was understood by the IRB. The concern, then, became determining the level of risk that is low enough to allow subjects to enter into research that is of no benefit to them. Four blood samples were to be drawn and the consensus was that this presented minimal risk, if any risk at all. The students would experience muscle fatigue, but there was consensus that this was not a risk worth considering. Some members of the IRB raised the question of the risk presented by the 100-mile round trip to the medical center from the university where the students would be recruited. The IRB determined that, since this risk was routinely undertaken by many people, it did not present a major problem for the research protocol. The major risk problem was presented by the administration of two CAT scans. The risk of radiation localized to one small area of the body (in this case the upper arm) is difficult to quantify. The x-ray equivalent of two CAT scans that the IRB accepted was that of three sets of kidney x-rays. Although this dosage is within acceptable diagnostic levels, an argument was made that because these were women of childbearing age, the risk exposure for a nondiagnostic procedure of no personal benefit was a problem. Even though the body was well shielded and the radiologist skilled, nonetheless it was argued that the risk, however small, was unwarranted because no benefits were to be derived.

Still another issue was the possible coercion of students who would be offered academic credit for participation in the research. Even though students would be recruited for the protocol through advertisements outside the class, many IRB members felt that offering academic credit for participation was unduly coercive. Another concern was the cost of the experiment in terms of the resource allocation of the CAT scan for research not directed toward a clinical end. This perception about costs related to questions raised by some IRB members about the value of the research in terms of the overall cost of time, personnel, and equipment required to generate the results. Also issues relating to the supervision of the

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research and the monitoring of the students were raised as problems resulting from the logistics of using two widely separated geographical sites.

Finally, there was the issue of the relationship between the investigator and the IRB. This was the first time the investigator had appeared before the IRB and, obviously, this was the first protocol he had prepared for the committee. Differences in style between the investigator and members of the IRB surfaced quickly and appeared to present several issues that provided a context in which problems other than the risk-benefit ratio were evaluated.

The committee spent two sessions reviewing this protocol and discussing the various concerns, especially the CAT scan, and talked about the structure of the protocol and the net benefits to be gained in terms of the hypothesis. A majority of the IRB remained unconvinced that the risks were justified by what could be learned and voted to reject the protocol.

Approving High Risk

The second project was very different. The TIMI protocol obviously presented several major risks to the subject. These included: the possible delay of therapy during the heart attack while the investigator negotiated consent with the subject, the risks of cardiac catheterization during a heart attack, extra x-rays that would be taken during the process of cardiac catheterization, the use of a genetically engineered medication that has had very limited use in human subjects, and a second cardiac catheterization that was not clinically indicated.

The risks presented by the first cardiac catheterization and the extra x-rays, although high, were perceived as acceptable because of its diagnostic and therapeutic value. The patient would be given a new medication (no placebo group) felt to represent a significant advance in the treatment of myocardial infarction. The main problems had to do with the negotiation of consent and the second cardiac catheterization. At the time when consent was to be negotiated, the subject would be suffering a heart attack, would probably be under the influence of an analgesic or narcotic, and perhaps would be of questionable competence. The investigator recognized these problems and stressed the role of the research team in attempting to explain efficiently, but thoroughly, the value and the risks of the proposed research to the subject and family of the subject. Because of the potential bene-

fit of the research to the subject, the IRB was willing to allow the family to participate in the consent process if the patient was perceived to be competent, although in pain or moderately sedated. Consent from the family alone was not felt adequate.

The second cardiac catheterization presented a problem because the catheterization was not therapeutically necessary and put the subject at risk of both mortality and morbidity. However, the catheterization was necessary to examine the structure of the heart vessels in order to make a further evaluation of the effectiveness of this innovative therapy. Structured into the design of the protocol was a separate consent process for the second catheterization. Thus, the subject would not have to make that decision at the time of being entered into the protocol. The IRB basically argued that the risk-benefit ratio for the second catheterization was acceptable and that, if a subject so chose, at a time when the consent process would be more orderly, he or she could undergo the second catheterization. The potential value of the study influenced this evaluation.

The IRB had worked extensively with this investigator in the past. The

NOTES FOR CONTRIBUTORS

Case Studies are analyses of decisions reached by IRBs in actual cases. The institutions involved in IRB decisions in case studies may be identified or may be given pseudonyms. In either event, case studies may be published only with the approval of both the investigator whose protocol is the subject of the case study and the IRB that reviewed the protocol. Such approval should be in the form of letters from the investigator and the IRB chairperson. If the investigator does not wish to be identified to the editorial staff, the IRB chairperson should indicate that he or she has a letter from the investigator approving publication of the case study but expressing a desire to remain anonymous. Investigators and IRB chairpersons should be offered the option of reviewing the final manuscript.

investigator had presented multiple invasive studies of various cardiac medications and had, in the IRB's perception, an excellent track record in terms of trustworthiness, exemplified by his willingness to report immediately any problems in research by notifying the appropriate people. The investigator also had great experience with various cardiac medications and had worked closely with many other individuals in different laboratories within the medical center where he was perceived to be skilled and trustworthy.

In presenting the protocol, the investigator noted the ethical problems within the protocol and responded to them by presenting various solutions and alternatives. Thus, the investigator, in terms of his own presentation, helped the IRB think through the various problems.

Finally, the protocol was part of a thirteen-center, NIH-supported trial, with exceptionally careful controls and monitoring requirements. The protocol, although containing significant risk, was approved by the committee on the basis of its design and because of the conviction that the investigator was aware of the dilemmas and difficulties of the project and would take all possible steps to resolve these problems. In addition, the committee required its own oversight process, with a pre-discharge interview of each patient enrolled in the trial by the administrative coordinator of the committee. Thus, 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.

Questions for IRBs

Given the nature of the two studies, one could easily argue that opposite conclusions could or should have been reached by the IRB. It may be helpful for other IRBs to consider several issues as they evaluate various protocols. First is the difficulty of evaluating the risk of x-rays and trying to find appropriate language with which to express the level of exposure to radiation. Some individuals are highly concerned about exposure to x-rays; others are willing to accept higher levels of exposure. Familiarity may breed contempt. X-rays are accepted as routine procedures within many areas of health care. Some may think it is not the task of the IRB to worry about the risk of three extra x-rays 30 years from now. Although several articles have been written on this topic, our perception is that this will continue to be a major problem for

IRB members. What one can press for, however, is a greater precision in the articulation of risk and the level of x-ray exposure that is appropriate.

Second, one may question the practice of having the investigator present the protocol in person. Our IRB has the investigator present the protocol so that questions can be answered by the investigator when necessary. Our experience has been that we obtain more complete and adequate explanations of many of the factors that go into the development of a particular protocol, as well as the way in which it will be carried out, by having the researcher present. However, the researcher's presence also presents problems. It is possible for the personality of the researcher to conflict with the personality of members of the IRB, and the

protocol can be evaluated in terms other than risk-benefit ratio. Some investigators may be more or less articulate or diplomatic than others, and this may cause the protocol to be seen in a different fashion.

Third, the question of the relationship between design and acceptability of risks continues to present itself. A research protocol that is both poorly designed and presents a high level of risk is inappropriate. On the other hand, there are many protocols that suffer from design problems but present low-level risk. Frequently the major harm that will be suffered by subjects is the loss of time. While one can argue that the design of a protocol can be improved and the level of risk decreased, nonetheless, one still has to contend with the fact that some subjects are

going to be exposed to risk for a moderately small gain of knowledge.

Issues other than risk-benefit analysis come into play here. Our perception is that it is appropriate for members of IRBs to examine themselves and their own attitudes toward research in general. Excessive or unjustified paternalism may lead to intervention into areas that are not particularly problematic. It may be best left to the discretion of the individual subject as to whether or not he or she wishes to invest time in a research protocol that carries modest risk with it, but also does not provide very many personal benefits. Paternalism will remain a problem within IRBs, and it is our sense that members of IRBs need to be alert to the way in which paternalism can function within the dynamics of a meeting.

COMMENTARY:

The IRB and the Virtuous Investigator¹ by Robert J. Levine

Beecher's Code, written in 1966, contains the following statement:¹ at p. 289

An even greater safeguard for the patient than consent is the presence of an informed, able, conscientious, compassionate, responsible investigator, for it is recognized that patients can, when imperfectly informed, be induced to agree, unwisely, to many things.

Henry Beecher was telling us that certain characteristics of investigators are of vital importance to the well-being of research subjects. These characteristics are moral virtues, acquired habits or dispositions to do what is morally right or praiseworthy. Moral virtues are traits of character that dispose their possessors to act in accord with moral principles, rules, or ideals.² at p. 261

Was Beecher also telling us that the IRB ought to take such characteristics into account in considering whether or not to approve protocols? I think that he was. In this regard it is worth noting that in 1967, a slightly modified version of Beecher's Code became the Code of the Massachusetts General Hospital's Committee on Research and the Individual.¹ at p. 289

In this issue of *IRB*, Shannon and Ockene report that their IRB—at least occasionally—considers the moral vir-

tues of investigators at their institution. In their decision to approve a "high-risk" protocol, one important factor was that the investigator had "an excellent track record in terms of trustworthiness, exemplified by his willingness to report immediately any problem in research by notifying the appropriate people." Moreover, "within the medical center . . . he was perceived to be skilled and trustworthy."

When such considerations contribute to a decision to disapprove, however, the authors experience some anxiety. "Differences in style between the investigator and members of the IRB surfaced quickly and appeared to present several issues that provided a context in which problems other than the risk-benefit ratio were evaluated." They worry that this might be improper and suggest that as a remedy, IRBs should consider excluding investigators from their meetings. (Parenthetically, I think that strategy is unlikely to be effective. In most institutions, most of the investigators are known by one or more IRB members who have had ample opportunity to form opinions about their proclivities to act in accord with moral principles, rules, or ideals.)

I believe that most IRBs do consider the reputations of investigators as they are reviewing their protocols. While such considerations are not usually decisive in approval or disapproval decisions, I commonly hear statements like

this: "Yes, Dr. Roe forgot to specify that she will get the approval of the responsible physician before she contacts any particular patient with an invitation to participate in her protocol. But we all know that Dr. Roe always does this so let's not quibble over the documentation." On the other hand, "We have had several complaints that Dr. Doe recruits patients as research subjects without discussing his plans with their personal physicians. We should postpone approving his protocol until we have a clear account of his plans for communications with the responsible physicians. Perhaps we should require him to put in writing exactly what he plans to tell them."

IRBs also seem to consider moral virtues—particularly trustworthiness—when deciding upon the necessity for monitors and consent auditors. Some investigators—in the view of some IRBs—just need to be watched.

To say that IRBs do consider the reputations of investigators as they review their protocols is not the same as saying that they should. Careful analysis of this issue is needed. I hope readers will send papers and letters on this topic for consideration for publication in *IRB*.

REFERENCES

- ¹Beecher, H.K.: *Research and the Individual: Human Studies*. Little, Brown and Co., Boston, 1970.
- ²Beauchamp, T.L. and Childress, J.F.: *Principles of Biomedical Ethics*. Oxford University Press, Second Edition, New York, 1983.

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