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THE ROLE OF INSTITUTIONAL REVIEW BOARDS IN FACILITATING RESEARCH, MARKETING OF DRUGS AND DEVICES, AND PROTECTING HUMAN SUBJECTS

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ABSTRACT

Concern for outside review of medical research involving human subjects has been documented as far back as the early Nineteenth Century. It was not until 1966, however, when applicants for Public Health Service grant funding were subjected to such a requirement, that researchers were required to undergo review. Institutional Review Boards (IRB) are the bodies charged with performing the mandated screening functions by the Department of Health and Human Services (HHS) for federally funded projects and by the Food and Drug Administration (FDA) in the drug and device approval process.

This paper explores an IRB's responsibilities under the HHS and FDA regulations generally, and emphasizes several critical attendant issues including: the manufacturer's IRB; IRB members' individual

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liability; compensation for research injuries; civil rights protections afforded subjects; impact upon academic and health practitioner research; and effect upon drug and device approvals.

BACKGROUND

Concern for outside review of medical research involving human subjects has been documented as far back as the early Nineteenth Century. Levine considers the idea's origination to be a statement by Thomas Percival in 1803 that no innovative therapy should be instituted without peer consultation.[1] The federal government maintained no policy relative to this issue until 1966, when review was mandated for those applying for Public Health Service research grants.[2] Prior consideration of "the risks and potential medical benefits of the investigation" was the first imposition of a risk-benefit criterion being met before permission to conduct federally funded research would be granted.[3]

This policy of the Surgeon General has been deemed by one observor as "the seed of the most significant development of decentralized administrative decision making in the past twenty years."[4] The National Research Act[5] was passed by Congress in 1974, establishing the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research, granting the Commission powers to "conduct a comprehensive investigation and study to identify basic ethical principles"[6] to underlie the conduct of human subjects research. The Commission was empowered to develop guidelines and procedures to reach established goals and to recommend policy to the Secretary of the then Department of Health, Education, and Welfare (HEW) with respect to human subjects research supported by HEW.

A key requirement of the Act was the establishment of Institutional Review Boards (IRBs) at those institutions conducting research under HEW contract. These IRBs were charged with reviewing biomedical and behavioral research employing human subjects "in order to protect the rights of the human subjects of such research."[7]

HEW's Policy for the Protection of Human Research Subjects[8] was promulgated in 1975. Universities, hospitals conducting research and medical schools all sought to establish an IRB at their respective institutions to comply. Then and today, there exists confusion in the research community relative to the dual role of the IRB as both a federal administrative agency while functioning as a local board. Substantial revision of the original regulations was undertaken by the Department of Health and Human Services (HHS) in 1981.[9] The Food and Drug Administration (FDA) also published new regulations governing IRBs that same year.[10]

The 1981 regulations served to narrow the scope of IRBs to an extent, by establishing categorical exemptions from coverage under the Act. These include broad categories of research which ordinarily present little or no risk of harm to subjects. Specifically exempted are research protocols using only survey or interview procedures, observation of public behavior, or study of data, documents, records, and specimens. The need for a broadly based IRB and a sensitivity to risks of certain special populations who might be less able to give truly informed, uncoerced consent, seem also to be embodied in the revision.

Both the 1975 and 1981 regulations make it clear that IRBs are charged to determine if "risks to subjects are reasonable in relation of anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result."[11]

IRB RESPONSIBILITIES

IRBs are required to consist of a minimum of five (5) members. These members must represent both sexes, more than one profession, and diverse cultural and racial backgrounds. At least one member must be a non-scientist, and there must be another member who maintains no other affiliation with the institution. Though only five (5) members are required, many Boards consist of a larger group from the following representative disciplines - medicine, pharmacy, nursing, law, philosophy, psychology, social and behavioral sciences, and members of the public.

The general function of an IRB is to review, approve or deny, and serve as an on-going monitor of all research on human subjects that takes place within the institution. The IRB is responsible for assuring compliance with all applicable federal, state and institutional regulations. The rules and regulations of HHS and the FDA cited above establish the guidelines for IRB review of human subjects research. The scope of the regulations promulgated by these two federal agencies, while having similar goals, must be distinguished. The HHS regulations apply to proposed research funded in whole or in part by that Department. Such research need not involve drugs and/or devices to fall within the ambit of the HHS regulations. The FDA regulations, on the other hand, apply specifically to studies involving investigational drugs and devices, whether funded by HHS or not. Thus, according to FDA regulations, all research with investigational drugs, including research done to investigate a new claim or indication for a marketed drug, requires IRB approval. This distinction results in some differences in the structure and functional requirements for the operation of an IRB. Some specific differences which will impact on drug

and device research are as follows:

a. HHS provides that an IRB may waive the requirement for signed informed consent when the principal risk of the research to be conducted is a breach of confidentiality. FDA makes no such provision, as the research regulated by that agency would not fall into such a category.[12]

b. The FDA, unlike HHS, does not require the IRB to report changes in membership. However, the FDA states that it may refuse to consider a study in support of an application for a research or marketing permit if the institution refuses to allow the FDA to inspect IRB records.[13] Since HHS does not issue research or marketing permits, it has no such provision.[14]

c. Because the FDA has undertaken a substantial surveillance program, the FDA explicitly requires that research subjects be informed of the inspection of the records of the study.[15] While HHS maintains the right to inspect such records, it does so infrequently, and does not require the same informed consent.[16]

d. HHS provides for waiving or altering elements of informed consent under certain conditions entailing minimal risk to the subjects involved.[17] The FDA provides explicit guidelines for exemption from the informed consent requirements in emergency situations only.[18]

Both regulations provide for extensive record keeping. These records include all research proposals, consent forms, minutes of all meetings, records of continuing review, copies of all correspondence, listing of IRB members, and written policies and procedures. These

records must be kept for three years from the completion of a given study.

One of the functions of the IRB is to approve or deny proposed research protocols. This decision making process involves a balancing of the risks benefits, and costs from the perspective of both the individual and society at large. The IRB's assessment of risks and anticipated benefits involves a series of steps. The IRB must:

1. identify the risks associated with the research, as distinguished from the risks of therapies the subject would receive even if not participating in research;
2. determine that the risks will be minimized to the extent possible;
3. identify the probable benefits to be derived from the research;
4. determine that the risks are reasonable in relation to the benefits to subjects, if any, and to the importance of the knowledge to be gained;
5. assure that potential subjects will be provided with accurate and fair description of the risks or discomforts and the anticipated benefits; and
6. determine intervals of periodic review and, where appropriate, determine that adequate provisions are in place for monitoring and data collected.

Steps 1 - 4 of this process involve a risk/benefit analysis. Risks are classified and should be evaluated as physical, psychological, social and economic. Benefits are likewise classified as physical, psychosocial, and derivative, and are considered relative to both the immediate subject and society as a whole.[19] The IRB must make its

evaluation as compared with the absence of the proposed research. It cannot compare the research protocol with "the next best alternative course of action." In this way, the IRB cannot deny a research protocol because it believes the effort could be better spent.[20]

Once these risks and benefits have been identified, Step 5 ensures that all research participants give informed consent to their participation. The basic elements of an informed consent form are:

1. A statement that the study involves research and an explanation of the purposes, duration, and procedures of the research, specifying which procedures are experimental
2. A description of any reasonably forseeable risks or discomfort
3. A description of any benefits to the subject or to others that may reasonably be expected from the research
4. A disclosure of appropriate alternative procedures or courses of action
5. A statement describing the extent, if any, to which confidentiality of records identifying the subjects will be maintained
6. For research involving more than minimal risk, an explanation as to whether any compensation or medical treatments are available if injury occurs and, if so, of what they consist and/or where further information can be obtained
7. An explanation of who to contact for answers to pertinent questions about the research and the research subject's rights, and who to contact in the event of a research-related injury
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits,

and that the subject can discontinue participation at any time without penalty or loss of benefits.[21]

It is important for the IRB to consider the characteristics of the prospective subjects that may affect their ability to give informed consent. The seriously ill, children, or mentally retarded individuals may not be able to comprehend the required information, while prisoners or other institutionalized individuals are so situated that the voluntariness of their consent may be in doubt.[22]

Finally, as identified in Step 6, the investigators must remain accountable to the IRB throughout the term of the research protocol. Periodic review of the research activity is necessary to determine whether the risk/benefit ratio has shifted, whether there are unanticipated findings involving risks to subjects, and whether any new information regarding risks and benefits should be provided to the subjects. Any unanticipated side effects and/or adverse reactions must be reported to the IRB. An evaluation must then be made whether the research should be modified or discontinued.

EMERGING ISSUES

Several issues and matters of concern arise from such a review of the status of the IRB in research monitoring. Some will be considered here by way of a caveat for future Board members and researchers as well as pharmacy and other health practitioners upon whom human subjects research impacts.

Of growing concern is the possible liability of individual IRB members. Research subjects who have been injured as a result of a research protocol, as well as investigators who are denied permission to proceed with submitted protocols, may seek redress through litiga-

tion. The threat, however real or unreal, may keep potential IRB members from agreeing to serve in this capacity.[23] Where the institution will be ultimately liable under the doctrine of Respondeat Superior for the acts of the IRB that are within the scope of their employment and authority, the individual members will be held to a standard of care commensurate with individual areas of expertise.

A significant burden to be met by the prospective plaintiff in such a case is the establishment of causation. A plaintiff must show that the act of approving (or disapproving) the research protocol in question was the direct and proximate cause of the plaintiff's injuries. Such a burden will be exceedingly difficult to bear, particularly when the research subject has given informed consent to participation. An IRB may want to consider the establishment of a separate fund for compensation and treatment of research-related injuries.

Another area for IRB consideration concerns the patient requiring emergency experimental treatment. Special problems of informed consent are raised here which are not dissimilar to some alluded to above. When analyzing a proposed research protocol with a potential application for emergency situations, the IRB should establish criteria for follow-up documentation and review once the emergency is over. If the research protocol calls for continued participation, informed consent must be re-established, and the patient provided the opportunity to withdraw from the study.[24] Other persons who require special consideration as well are prisoners, mentally incompetent, pregnant women and the terminally ill.

Additional considerations raised include the ethical matter of payment of human subjects for their participation. Generally, this

practice is considered acceptable to the extent that the compensation does not serve to induce participation in spite of informed consent reservations a subject might have.

Entrepreneurs have emerged in recent years who sell IRB services to institutions which do not have the resources to establish their own Boards. One could argue that the expertise provided and the frequency of review by these panels would hone the necessary skills, thus benefiting the process. One must consider the question also of how frequently an institution would use a paid IRB if that body continually responded negatively to protocol proposals. The potential legal implications could be enormous.

One further concern is the issue of IRBs established by pharmaceutical companies to review their drug or device research protocols. Many of the questions raised immediately above need consideration as well.

CONCLUSIONS

The time frame still is relatively short for the proliferation of definitive case law arising from the existing statutory and regulatory requirements. Given the nature of such research and the capacity of plaintiffs' counsel, such activity is a reasonable expectation.

We look forward to further study of this issue.

REFERENCES

1. R. Levine, Ethics and Regulation of Clinical Research, 208 (1981).
2. W. Curran, Governmental Regulation of the Use of Human Subjects Research; The Approach of Two Federal Agencies, in Experimentation With Human Subjects, 402 (P. Fruend ed. 1970).
3. R. Levine, op. cit., 209.

4. R. Schwartz, "Institutional Review of Medical Research," The Journal of Legal Medicine, Vol. 4, No. 2, 1983, 143.
5. Public Law No. 93-348 (1974).
6. Ibid, §202 (a) (1) (A) (i).
7. Ibid, §212 (A).
8. 45 C.F.R. pt. 46 (1975).
9. 45 C.F.R. pt. 46 (1981).
10. Ibid, §46.111(a) (2).
11. 21 C.F.R. §56.111(a) (2) (1981).
12. 21 C.F.R. §56.109.
13. Ibid, §56.115.
14. 45 C.F.R. §46.115.
15. 21 C.F.R. §50.25(a)(5).
16. 45 C.F.R. §46.116(a) (5).
17. Ibid, §46.116(c) and (d).
18. 21 C.F.R. §50.23.
19. R. Levine, "The Role of Assessment of Risk Benefit Criteria in the Determination of the Appropriateness of Risk involving Human Subjects," 1 Appendix to the Belmont Report, DHEW Pub. No.(05) 78-0013, 2-1-2-59 (1978).
20. Schwartz, op. cit., 143.
21. J. Basso, "The Role of the Institutional Review Board in Research Involving Human Subjects," Drug Intelligence and Clinical Pharmacy, 17:828, November 1983.
22. L. Roth, C. Lidz, A. Meisel, P. Soloff, K. Kaufman, D. Spiker and F. Foster, "Competency to Decide About Treatment or Research An Overview of Some Empirical Data," International Journal of Law and Psychiatry, Vol. 5, 29-50, 1982.

23. W. Woodward, "An Investigator/Defendant Corrects the Record," IRB 1:5:10 (1979).

24. N. Abramson, A. Meiseland, P. Safar, "Informed Consent in Resuscitation Research," 246 JAMA 24(1981).