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Office of the Secretary

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PROTECTION OF HUMAN SUBJECTS

Institutional Review Board; Report and Recommendations of National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

[4110–08–M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

PROTECTION OF HUMAN SUBJECTS

Institutional Review Boards: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

AGENCY: Department of Health, Education, and Welfare.

SUMMARY: Basic regulations governing the protection of human subjects involved in research, development, and related activities supported or conducted by the Department through grants and contracts were published in the FEDERAL REGISTER on May 30, 1974 (39 FR 18914). At that time it was indicated that notices of proposed rulemaking would be developed to provide additional protection for subjects of research.

On July 12, 1974, the National Research Act (Pub. L. 93–348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to study the Institutional Review Board mechanism. The Commission was further required to make such recommendations to the Secretary as it determined appropriate to assure that biomedical and behavioral research conducted or supported under programs administered by him met the requirements respecting informed consent identified by the Commission. Pursuant to Section 202(a)(2) of that Act, the Commission has transmitted its Report and Recommendations regarding IRBs to the Secretary. Pursuant to Section 205 of the Act, the Secretary is required to publish the Report and Recommendations as received from the Commission and is taking that action in this issue of the FEDERAL REGISTER. The Department has not yet completed its final review of this report. The Department will be evaluating the Report during the comment period.

Written comments, data, views, arguments and inquiries concerning the Recommendations of the Commisson may be sent to the Office for Protection from Research Risks, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. To facilitate analysis of the comments, it would be appreciated if they were arranged by Recommendation number. Additional copies of this notice may be obtained by writing to the same address. All comments received will be available for inspection at Room 303, Westwood Building, 5333 Westbard Avenue, Bethesda, Maryland, weekdays (Federal holidays excepted) between the hours of 9 a.m. and 4:30 p.m. To assure full consideration, all comments should be submitted on or before January 29, 1979. After receipt and review of such comments, it is the intent of the Department to issue final rules, taking into consideration this Report and Recommendations and relevant comments submitted.

Dated: November 7, 1978.

JULIUS B. RICHMOND,
Assistant Secretary for Health.

Approved: November 20, 1978.

HALE CHAMPION,
Acting Secretary.

THE NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH

INSTITUTIONAL REVIEW BOARDS: REPORT AND RECOMMENDATIONS

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NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH

SEPTEMBER 1, 1978.

REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS

TABLE OF CONTENTS

INTRODUCTION

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established under Pub. L. 93–348 to develop ethical guidelines for the conduct of research involving human subjects. To date, the Commission has issued reports with recommendations for the protection of several categories of research subjects, including the human fetus, prisoners, children, and those institutionalized as mentally infirm. These recommendations have been directed to the Secretary of Health, Education and Welfare with respect to research conducted, supported or regulated by DHEW, and to Congress with respect to research not subject to regulation by DHEW.

In the present report, the Commission considers the performance of Institutional Review Boards (IRBs), which are required to review all research involving human subjects that is conducted at institutions receiving funds for such research from DHEW under the Public Health Service Act. IRBs or similar bodies are required also to review research regulated by DHEW under the Federal Food, Drug, and Cosmetic Act, and most research involving human subjects that is conducted or supported by other departments and agencies. This review of proposed research by IRBs is the primary mechanism for assuring that the rights of human subjects are protected. Thus, the Commission's previous recommendations regarding particular categories of research subjects are intended ultimately to be carried out by IRBs, by establishing conditions and requirements that IRBs should determine to have been satisfied before approving research. The Commission now turns its attention to the IRB mechanism itself, to evaluate its performance and recommend steps to improve the review process.

The legislative mandate to study IRBs is set forth in the charge to the Commission to consider "[m]ech-

anisms for evaluating and monitoring the performance of Institutional Review Boards * * * and appropriate enforcement mechanisms for carrying out their decisions" (section 202(a)(1)(B)(v) of Pub. L. 93–348). In addition, the Commission is directed "to determine the need for a mechanism to assure that human subjects in * * * research not subject to regulation by [DHEW] are protected" (section 202(a)(3)). (Following its study of IRBs, the Commission has recommended that IRBs be employed as the mechanism to assure protection of human subjects in non-DHEW research.)

Although IRBs were not required by law until the passage of Pub. L. 93–348 in 1974, they had already been in existence for many years at most of the 500 institutions where they now operate. However, there was little current, systematic information about IRBs when the Commission began its consideration of their performance. The Commission therefore undertook a substantial effort to develop information about the performance of IRBs, the research they review, and the strengths and weaknesses of this mechanism.

The Commission supported an extensive survey of IRB members, investigators and research subjects at a sample of 61 institutions, including medical schools, hospitals, universities, prisons, institutions for the mentally ill and retarded, and research organizations. The background, development and administration of the present DHEW regulations governing IRBs were examined. Three public hearings were held at which federal officials, representatives of IRBs, investigators and other concerned persons presented their views on IRBs. The National Minority Conference on Human Experimentation, convoked by the Commission to assure that viewpoints of minorities would be heard, made recommendations to the Commission that pertained to IRBs. The Commission also reviewed several papers prepared under contract on such topics as informed consent, evaluation of risks and benefits, issues that arise in particular kinds of research (such as social experimentation or deception research), and the legal aspects of IRB operation. A substantial amount of correspondence on IRBs was received and reviewed by the Commission. In addition, a survey was made of the standards and procedures for the protection of human subjects in research conducted or supported by federal departments and agencies. Finally, the Commission conducted public deliberations to develop its recommendations on IRBs.

Following the recommendations on IRBs set forth at the outset of this report are chapters on the existing regulatory system at DHEW, the Commission-sponsored survey of IRBs and the research reviewed by them, legal aspects of IRB operation, and the Commission-conducted survey of standards and procedures for the protection of human subjects in research conducted or supported by federal departments and agencies. An appendix to this report contains the final report of the survey of IRBs, which was conducted by the Survey Research Center at the University of Michigan; summaries of all testimony presented to the Commission at its three hearings on IRBs; descriptions of the protective standards and procedures at federal departments and agencies; and a contracted paper on the operation of IRBs. Other relevant papers, on such topics as informed consent and risk-benefit assessment, will be included in the appendix to the Commission's forthcoming report on the basic ethical principles that should underlie the conduct of research involving human subjects.

* * * * *

Definitions. For purposes of this report:

1. *Scientific research* is a formal investigation designed to develop or contribute to generalizable knowledge.

Comment: A research project generally is described in a protocol that sets forth explicit objectives and formal procedures designed to reach those objectives. The protocol may include therapeutic and other activities intended to benefit the subjects, as well as procedures to evaluate such activities. Research objectives range from understanding normal and abnormal physiological or psychological functions or social phenomena, to evaluating diagnostic, therapeutic or preventive interventions and variations in services or practices. The activities or procedures involved in research may be invasive or noninvasive and include surgical interventions; removal of body tissues or fluids; administration of chemical substances or forms of energy; modification of diet, daily routine or service delivery; alteration of environment; observation; administration of questionnaires or tests; randomization; review of records, etc.

2. *Human subject* is a person about whom an investigator (professional or, student) conducting scientific research obtains (1) data through intervention or interaction with the person, or (2) identifiable private information.

Comment: "Intervention" includes both physical procedures by which data are gathered (e.g., venipuncture), and manipulations of the subject the subject's environment that are performed for research purposes. "Interaction" includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

RECOMMENDATIONS

The ethical conduct of research involving human subjects requires a balancing of society's interests in protecting the rights of the subjects and in developing knowledge that can benefit the subjects or society as a whole. The elements that must be considered in this balancing of interests are identified and analyzed in the Commission's separate report on the basic ethical principles that should underlie the conduct of research involving human subjects. In the recommendations that follow, the Commission expresses its judgment about the ways in which those elements ought to be brought to bear on research practices., so that a reasonable and ethical balance of society's interests may be attained.

The Commission's deliberations begin with the premise that investigators should not have sole responsibility for determining whether research involving human subjects fulfills ethical standards. Others, who are independent of the research, must share this responsibility, because investigators are always in positions of potential conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of the human subjects of their research.

The Commission believes that the rights of subjects should be protected by local review committees operating pursuant to federal regulations and located in institutions where research involving human subjects is conducted. Compared to the possible alternatives of a regional or national review process, local committees have the advantage of greater familiarity with the actual conditions surrounding the conduct of research. Such committees can work closely with investigator to assure that the rights and welfare of human subjects are protected and, at the same time, that the application of policies is fair to the investigators. They can contribute to the education of the research community and the public regarding the ethical conduct of

research. The committees can become resource centers for information concerning ethical standards and federal requirements and can communicate with federal officials and with other local committees about matters of common concern.

The Commission further believes that institutions receiving federal support for the conduct of research involving human subjects should be governed by uniform federal regulations applicable to the review of all such research, whether it is supported by one federal department or another, or is not federally supported. The regulations should also apply to research conducted intramurally by federal departments and to research conducted by private organizations that is otherwise subject to federal regulations (e.g., research conducted to meet the regulatory requirements of the Food and Drug Administration).

The Institutional Review Boards (IRBs) that have existed for some years at institutions that conduct research involving human subjects have been closely examined by the Commission. The Commission finds on the basis of its study that IRBs play an essential role in the protection of human subjects. However, the existing system may be improved. The following recommendations are made to strengthen, simplify and broaden the coverage of this system.

Recommendation (1) (A) Federal law should be enacted or amended to authorize the Secretary of Health, Education, and Welfare to promulgate regulations governing ethical review of all research involving human subjects that is subject to federal regulation.

(B) Federal law should be enacted or amended to provide that each institution which sponsors or conducts research involving human subjects that is supported by any federal department or agency or otherwise subject to federal regulations, and each federal department or agency which itself conducts research involving human subjects, shall give assurances satisfactory to the Secretary of Health, Education, and Welfare that all research involving human subjects sponsored or conducted by such institution, or conducted by such department or agency, will be reviewed by and conducted in accordance with the determinations of a review board established and operated in accordance with the regulations promulgated by the Secretary under the authority recommended in paragraph (A) of this recommendation.

(C) Federal law should be enacted or amended to provide that all research involving human subjects sponsored or conducted by an institution that receives funds from any federal department or agency to provide health care or conduct health-related research shall be subject to federal regulation regarding the review and conduct of such research, as provided under paragraphs (A) and (B) of this recommendation.

(D) Federal Law should be enacted or amended to authorize and approriate funds to support the operation of institutional Review Boards by direct cost funding.

Comment: (A) Recommendation (1)(A) would establish DHEW as the single cognizant agency for the promulgation of regulations relating to the protection of human research subjects. Such regulations, dealing with the composition, functions and procedures of IRBS, would apply to all entities that receive financial support from the federal government to conduct research involving human subjects. Entities conducting such research to fulfill federal regulatory requirements (*e.g.,* of the Food and Drug Administration or the Environmental Protection Agency) would be covered by the same regulations. Thus, all entities under federal jurisdiction would be subject to a single set of regulations relating to review of research invloving human subjects, without regard to the particular federal department(s) that support or regulate their research. An alternative to the enactment of federal law might be the issuance by the President of an executive order establishing DHEW as the single cognizant agency for the promulgation of regulations to protect human subjects.

Implementation of Recommendation (1)(A), by law or executive order, is necessary to assure government-wide uniformity in the review requirements that are imposed on entities subject to federal regulation. A survey by the Commission has shown that virtually all federal agencies with policies for the protection of human subjects currently adopt DHEW standards and procedures to a substantial degree. However, there are many variations arising out of differences in wording, imposition of additional requirements, introduction of minor changes, etc. Establishing DHEW as the sole authority for the issuance of reglations in this area would not substantially change current practice but would reduce the burden on IRBs to interpret and apply the regulations to which they are subject. Moreover, uniformity would assure a minimum level of protection to human subjects of research, no matter which federal agency is supporting the research or which entity is conducting it.

Recommendation (1)(A) accords with Recommendation No. 9 (Education) of the Commission on Federal Paperwork, which reads as follows:

> Cognizance for regulations in the specific area of the protection of human subjects should be assigned to the Department of Health, Education, and Welfare, acting with the advice and consent of an appropriate interagency committee.
>
> No agency other than HEW should be permitted to paraphrase, interpret or particularize these regulations * * * [I]n the regulations for a controversial subject of this nature there should be a mechanism for the Federal Government to speak with one voice.

As the Paperwork Commission noted, DHEW has been preeminent and has served as the lead agency in the field of protecting human subjects. Establishing sole, government-wide responsibility in DHEW for the promulgation of regulations in this area will prevent unnecessary duplication of effort within the government and by the regulated entities as well.

(B) Recommendation (1)(B) would establish DHEW as the single cognizant agency for the accreditation of all IRBs, including IRBs established by nonfederal entities and IRBs that are established within federal departments and agencies. DHEW would also carryout compliance and educational activities to assure that the quality of performance of all IRBs is high. Although some nonfederal entities may receive support for research involving human subjects from federal departments other than DHEW, the Commission recommends centralization of accreditation and compliance responsibility in DHEW as a means of promoting uniform treatment and administrative efficiency. Similarly, the Commission recommends that DHEW accredit and review the compliance of IRBs established by other federal intities, to assure uniform review, throughout government, of proposed research involving human subjects. As an alternative to enactment of law, recommendation (1)(B) might be accomplished by the issuance of an executive order.

Establishment of DHEW as the sole authority for accreditation and compliance activities would recognize that department's initiation of the requirements of IRBs and its extensive experience in supervising their operation. As with the promulgation of regulations (Recommendation (1)(A)), centralizing authority to conduct these activities would also assist in standardizing the review of research with human subjects and reducing the burden on nonfederal IRBs that is imposed by federal enforcement activities.

If such centralization is not accomplished by law or executive order, the Commission suggests that other federal departments and agencies recognize DHEW accreditation and compliance activities, and that DHEW accept such responsibility whether or not it supports research at the same entities. It should be noted that accreditation and compliance are structural matters, re-

lating to the composition, functions and procedures of IRBs (see the following recommendations); DHEW does not regulate substantive decisionmaking, which is the responsibility of the IRBs alone. Thus, centralization in DHEW should not be considered an intrusion of that department into the proper jurisdiction of other federal agencies.

Should it prove unfeasible to centralize in DHEW accreditation and compliance activities for IRBs established within other federal departments and agencies, the Commission favors centralization of such activities in DHEW at least with respect to all IRBs that are established by nonfederal entities, notwithstanding their federal sources of support for research involving human subjects. This would accomplish the goal of reducing the burden on such IRB that is imposed by multiple-agency enforcement activities, and would at least partially accomplish the goal of assuring uniform review of human subjects research in which the government is involved.

Recommendation (1)(B) does not require that each entity establish a single IRB. An entity may establish more than one IRB to meet special needs; however, each IRB must satisfy the regulatory requirements.

Research need not be reviewed, in some instances, by an IRB located in the entity where the research is to be conducted. While it is generally desirable for an entity at which research involving human subjects is conducted to establish an IRB, it may be appropriate for several small institutions in close proximity to establish a single IRB to serve those institutions. Similarly, it may be appropriate for an institution at which only a small amount of research involving human subjects is conducted to arrange for review of all such research by an IRB at a neighboring institution. Where an investigator is associated with more than one entity or the research will be conducted at more than one entity, review by one IRB (generally at the entity most substantially involved with the research) should satisfy statutory and regulatory requirements. Other entities that are involved with the research may also require review by their IRBs, however. In such instances, IRBs should give priority to consideration of protocols that are receiving multiple review, in order to reduce the extended time period that such review may otherwise entail.

Recommendation (1)(B) also does not require that IRB review precede application for a grant or contract, although such review should always precede the initiation of research involving human subjects. Since many proposals submitted to the government are never funded or conducted, a requirement that IRB review and approval precede any consideration for funding by the government may place an unnecessary burden on IRBs and subject them to undesirable time pressures. On the other hand, IRB review prior to application for funding may resolve or eliminate problems that could jeopardize funding, and being asked to review projects that have already been approved for funding also may place IRBs under inappropriate pressures. On balance, review prior to or within a specified time after submission of applications, as is presently required by DHEW, appears most appropriate.

(C) Recommendation (1)(C) would extend the requirement of IRB review to entities conducting human subjects research that is not federally supported or otherwise subject to federal regulation at present, if the entities receive federal support to provide health care or conduct health-related research.

(D) Recommendation (1)(D) would require that at least a portion of the funds necessary to support the operation of IRBs be directly provided rather than reimbursed through the indirect cost mechanism. Direct cost funding would help to assure that IRBs are adequately supported to carry out their responsibilities and, in addition, would highlight the significant role played by IRBs. It would be appropriate for such funding to provide at least a portion of the salary of the IRB chairman or of the cost of administrative support for the IRB. Recognition of IRBs by providing earmarked funds for their operation would complement the compliance and education activities of DHEW in promoting quality performance by IRBs. Direct cost funding should not, however, be accomplished by reducing the amount of funds appropriated for the conduct of research.

The Commission does not take a position on the question of whether federal support should be provided for all review activities of IRBs or only the review of research for which support is being sought from the government. Since an institution is required by federal law to assure the review of all research involving human subjects if the institution applies for federal support to conduct any such research, it may be argued that all review activities should be the financial responsibility of the government. It may also be argued, however, that the review of nonfederally funded research is the proper obligation of the institution to the prospective subjects, and hence the financial responsibility of the institution.

Recommendation (2) (A) Federal law should be enacted or amended to authorize the Secretary of Health, Education, and Welfare to establish a single office to carry out the following duties:

(i) Accreditation of Institutional Review Boards based upon the submission of assurances containing descriptions of their membership, authority, staff, meeting facilities, review and monitoring procedures and provisions for recordkeeping;

(ii) Compliance activities, including site visits and audits of Institutional Review Board records, to examine the performance of the Boards and their fulfillment of institutional assurances and regulatory requirements; and

(iii) Educational activities to assist members of Institutional Review Boards in recognizing and considering the ethical issues that are presented by research involving human subjects.

(B) Federal law should be enacted or amended to authorize an appropriate funds to support the duties described in paragraph (A) of this recommendation.

Comment: Recommendation (2) requires that DHEW consolidate and expand its accreditation and compliance activities to provide within the federal government a single supervising authority for all IRBs that are required under Recommendation (1) to review research involving human subjects. In addition, this DHEW office should conduct educational activities to assist IRB members in discharging their review responsibilities. The Commission suggests that the office be established outside of any subdivision of DHEW and that funds be appropriated to support its operation.

Institutions should be required to submit information such as the following to enable accreditation determinations to be made:

* The names and qualifications of members of the IRB and the process by which members are selected;

* The resources (e.g. meeting room, staff, office facilities, release of IRB members from other responsibilities) that will be devoted to the review function;

* The general operating procedures of the IRB, and the number and types of proposals that are expected to be reviewed by it;

* Expedited review procedures, if any, and the categories of research for which such procedures will be used; and

* Procedures to assure that all research involving human subjects conducted by or at the institution will be reviewed by an IRB and, if approved, will be conducted in accordance with any restrictions or conditions imposed by the IRB.

Site visits, audits of IRB records, and other compliance activities should be conducted routinely to assure continuing quality control of the perform-

ance of IRBs. The compliance effort should be aimed at educating, improving performance of IRBs, and providing needed advice. Where necessary, however, failure by investigators, institutions or IRBs to meet their responsibilities should be subject to sanctions ranging from warnings to loss of IRB accreditation and consequent ineligibility to receive federal funds for research involving human subjects or refusal by a regulatory agency to accept data.

DHEW should develop materials to assist in the orientation of new members of IRBs and mechanisms for dissemination of information about ethical issues and key IRB decisions to promote uniform treatment of similar protocols. Caution should be exercised, however, to avoid usurping the IRBs' decision-making authority. The accreditation and compliance, as well as the educational, functions of DHEW should be aimed at assuring and promoting the effective operation of IRBs, but not as a forum or mechanism for questioning the substantive decisions of IRBs. DHEW should assure that IRBs have appropriate authorities, membership, and rules and standards of operation, and that useful materials are provided for the information of IRB members; these functions should not include any activities intended directly to influence or alter IRB decisions.

The generation of information about the various topics in its mandate has been essential to the operation of the Commission. Similarly, a program of research in the ethical issues that arise in research involving human subjects would greatly assist the compliance and educational activities of DHEW in this area.

Recommendation (3) The Secretary of Health, Education, and Welfare should require by regulation that an Institutional Review Board:

(A) Consist of at least five men and women of diverse backgrounds and sufficient maturity, experience and competence to assure that the Board will be able to discharge its responsibilities and that its determinations will be accorded respect by investigators and the community served by the institution or in which it is located;

(B) Include at least one member who is not otherwise affiliated with the institution;

(C) Have the authority to review and approve, require modifications in, or disapprove all research involving human subjects conducted at the institution;

(D) Have the authority to conduct continuing review of research involving human subjects and to suspend approval of research that is not being conducted in accordance with the determinations of the Board or in which there is unexpected serious harm to subjects;

(E) Maintain appropriate records, including copies of proposals reviewed, approved consent forms, minutes of Board meetings, progress reports submitted by investigators, reports of injuries to subjects, and records of continuing review activities;

(F) Be provided with meeting space and sufficient staff to support its review and recordkeeping duties;

(G) Be authorized and directed to report to institutional authorities and the Secretary any serious or continuing noncompliance by investigators with the requirements and determinations of the Board;

(H) Be provided with protection for members in connection with any liability arising out of their performance of duties on the Board.

Comment: (A) IRB members should be appointed by a governing body or chief executive officer of the institution, who should consult widely to find persons who will serve on the IRB with distinction and commitment. The IRB should include persons who are familiar with the ethical issues in research involving human subjects. The IRB should also include persons with the scientific competence necessary to analyze accurately and thoroughly the risks and benefits of the types of proposals generally reviewed by the IRB, since this analysis is essential to the review process. To assure the IRB's access to such expertise, yet guard against self-interest influencing or appearing to influence IRB determinations, at least one-third but no more than two-thirds of the IRB members should be scientists, including members of the disciplines in which research is customarily reviewed by the IRB. The expertise of IRB members should be supplemented, when necessary, by the use of consultants.

In its deliberations, it is desirable that the IRB show awareness and appreciation of the various qualities, values and needs of the diverse elements of the community served by the institution or in which it is located. A diverse membership will enhance the IRB's credibility as well as the likelihood that its determinations will be sensitive to the concerns of those who conduct or participate in the research and other interested parties.

If an IRB regularly reviews research that has an impact on a broad category of vulnerable subjects (*e.g.,* residents of an institution for the retarded), the IRB should include persons who are primarily concerned with the welfare of those subjects (*e.g.,* parents of retarded children). The IRB should establish formal or informal consultation with community and other bodies that have interests in areas affected by or involved in the conduct of proposed research.

The institution should provide suitable orientation to new IRB members, in order to familiarize them with the purpose and authority of the IRB, the standards it applies, the ethical and legal principles that apply to research involving human subjects, and the main ethical dilemmas that arise in research. IRB members should be appointed for a fixed term of at least a year and should not be removed during this term except for good cause. An IRB's membership should be relatively stable from year to year in order to enhance the experience of the IRB and to introduce stability into standards applied by the IRB. Some degree of turnover of members and chairman is desirable, however, as a way both of exposing more members of the institution to the issues considered by the IRB and of introducing into the IRB a variety of viewpoints.

The institution should encourage service on the IRB and indicate the importance of such service by giving IRB members appropriate relief from other duties, by giving recognition for service on the IRB (*e.g.,* in decisions regarding promotions) and by providing remuneration to nonemployees.

(B) A member of the immediate family of a person who is affiliated with the institution should not be appointed to serve as the unaffiliated member of an IRB.

(C) Institutional support is necessary for the successful operation of an IRB and can be expressed most directly in rules, procedures, etc. that are formally adopted by the institution to assure that the IRB is lawfully established and that all research involving human subjects will be reviewed and conducted in accordance with its determinations.

(D) The IRB should adopt procedures for the continuing review of approved research, such as examination of records, requiring reports from investigators, soliciting information from subjects, and observing the recruitment of subjects and conduct of the research. As a basic requirement, all investigators should be directed to report immediately to the IRB any substantial changes in the research activity, unanticipated problems, or adverse reactions by subjects. In research that presents more than minimal risk to subjects (*i.e.,* more than the risk of harm or discomfort that is normally encountered in the daily lives, or in the routine medical or psychological examination, of normal persons) or involves vulnerable subjects (*e.g.,* children, institutionalized or hospitalized persons), investigators should be required, in addition, to make periodic reports to the IRB on the progress of the research. The frequency of

such periodic reports should depend upon the degree of risk presented to subjects, but at a minimum should be on an annual basis.

The justification for undertaking some studies rests, in part, on uncertainty about the relative safety and efficacy of alternative therapies. New knowlege, however, is continually being developed, and uncertainties that play a role in prompting a study may be reduced over time as new information is developed in the study or elsewhere. Subjects should not be excluded from known benefits simply because those benefits were unknown or uncertain at the time the research began. An important aspect of the continuing review of research, particularly in studies that involve the evaluation of a therapeutic procedure for a chronic condition, is to assure that subjects are not excluded from the benefits of newly developed knowledge by continuing in a protocol after the superiority of a particular therapy for their condition has been demonstrated.

At the discretion of the IRB, the consent process or the research itself may be observed on a sample or routine basis, subjects may be interviewed about their experience in research, and research records (including consent forms) may be reviewed. Also at the discretion of the IRB, investigators may be required to provide subjects with a form on which they can report to the IRB their experiences in research. The form could be given to subjects at the time consent is obtained and be completed by subjects who wish to do so during or after their participation.

Observation of the consent process or conduct of research is both a difficult and delicate task. The designation of staff or members of the IRB to observe research activities can impose a substantial strain on the limited resources of the IRB. Further, such observation may intrude on confidential relationships or the privacy of individual subjects. IRBs should take these factors into account when determining appropriate means for continuing review of a protocol, and alternatives such as investigator reporting requirements should be considered. However, certain research will warrant observation to assure the protection of subjects, and in such cases IRBs have an obligation to take suitable measures.

In cases in which the investigator is responsible for the care of the subjects, the IRB may require that a neutral person, not otherwise associated with research or the investigator, be present when consent is sought, to explain the research to prospective subjects, or to observe the conduct of the research. The involvement of a physician or therapist as an investigator may have significant advantages for patients and make, available to them new forms of therapy. However, research interests may compromise the therapist's sound judgments regarding therapeutic goals. The involvement of a neutral third party may reduce the possibility of such a conflict of interest occurring, particularly in research that presents more than minimal risk. Such a person may be designated to play a role in informing subjects of their rights and the details of protocols, assuring that there is continuing assent to participation, determining the advisability of continued participation, receiving complaints from subjects, and bringing grievances to the attention of the IRB as part of its continuing review of research.

(E) Records regarding research protocols reviewed by IRBs should be retained for five years after completion of the research. Minutes should be in sufficient detail to show the basis of actions taken by the IRB.

(F) An IRB should have an identifiable meeting space and designated staff to support its function. Although the staff may be part-time, their effort should be identified and placed on a continuing basis.

(G) Any knowledge of serious or continuing noncompliance by investigators with the requirements and determinations of the IRB should be transmitted by the IRB to institutional authorities and to the Secretary of Health, Education, and Welfare. Institutions should take such steps as are necessary and appropriate to assure compliance by all investigators with IRB requirements and determinations.

(H) Protection against liability arising out of their performance of duties on the IRB may be provided to members in any of several ways, including sovereign immunity, insurance, indemnification by the institution, or specific provisions of state law. The Institution should assure that such protection is provided either by law or by means of institutional arrangements.

Recommmendation (4) The Secretary of Health, Education, and Welfare should require by regulation that all research involving human subjects that is subject to federal regulation shall be reviewed by an Institutional Review Board and that the approval of such research shall be based upon affirmative determinations by the Board that:

(A) The research methods are appropriate to the objectives of the research and the field of study;

(B) Selection of subjects is equitable;

(C) Risks to subjects are minimized by using the safest procedures consistent with sound research design whenever appropriate, by using procedures being performed for diagnostic or treatment purposes;

(D) Risks to subjects are reasonable in relation to anticipated benefits to subjects and importance of the knowledge to be gained;

(E) Informed consent will be sought under circumstances that provide sufficient opportunity for subjects to consider whether or not to participate and that minimize the possibility of coercion or undue influence;

(F) Informed consent will be based upon communicating to subjects, in language they can understand, information that the subjects may reasonably be expected to desire in considering whether or not to participate, generally including:

(I) That an Institutional Review Board has approved the solicitation of subjects to participate in the research, that such participation is voluntary, that refusal to participate will involve no penalties or loss of benefits to which subjects are otherwise entitled, that participation can be terminated at any time, and that the conditions of such termination are stated;

(II) The aims and specific purposes of the research, whether it includes procedures designed to provide direct benefit to subjects, and available alternative ways to pursue any such benefit;

(III) What will happen to subjects in the research, and what they will be exected to do;

(IV) Any reasonably foreseeable risks to subjects, and whether treatment or compensation is available if harm occurs;

(V) Who is conducting the study, who is funding it, and who should be contacted if harm occurs or there are complaints; and

(VI) Any additional costs to subjects or third parties that may result from participation;

(G) Informed consent will be appropriately documented, unless the Board determines that written consent is not necessary or appropriate because (I) the existence of signed consent forms would place subjects at risk, or (II) the research presents no more than minimal risk and involves no procedures for which written consent is normally required;

(H) Notwithstanding the requirements of paragraphs (E), (F) and (G) above, informed consent is unnecessary (I) where the subjects' interests are determined to be adequately protected in studies of documents, records or pathological specimens and the importance of the research justifies such invasion of the subjects' privacy, or (II) in studies of public behavior where the research presents no more than minimal risk, is unlikely to cause embarrassment, and has scientific merit;

(I) There are adequate provisions to protect the privacy of subjects and to

maintain the confidentiality of data; and

(J) Applicable regulatory provisions for the protection of fetuses, pregnant women, prisoners, children and those institutionalized as mentally infirm will be fulfilled.

Comment: (A) Subjects should not be exposed to risk in research that is so inadequately designed that its stated purpose cannot be achieved. It must be recognized, however, that equally rigorous standards of scientific methodology are not suitable in all disciplines or necessarily appropriate for all research purposes. Not all research is intended to provide a definitive test of a hypothesis, and much research, such as research done by students, has modest aims. The Commission's statements in previous reports that all research should be scientifically sound should be interpreted as requiring that the proposed methods be suited to the discipline and the objectives of the research.

(B) The proposed involvement of hospitalized patients, other institutionalized persons, or disporportionate numbers of racial or ethnic minorities or persons of low socioeconomic status should be justified.

(C) Materials or information that are obtained for diagnostic or therapeutic purposes should be used whenever possible: *Provided,* Such use will not unjustifiably increase the burdens of the ill. Where appropriate, screening should be employed to eliminate from participation in research persons who would be at particularly high risk. The number of subjects exposed to risk in research should be no larger than required by considerations of scientific soundness.

(D) The possible harms and benefits from proposed research involving human subjects may not be quantifiable but should be evaluated systematically to assure a reasonable relation between the harms that are risked and the benefits that may be anticipated for the subjects or the gains in knowledge that may result from the research. This evaluation should include an arrayal of alternatives to the procedures under review and the harms and benefits associated with each alternative.

The evaluation of possible harms in relation to expected benefits or gains in knowledge may provide sufficient grounds on which to disapprove proposed research, when this relation is found to be unreasonable. This would be the case, for example, where research includes an intervention that presents a high degree of risk to subjects and no great likelihood of producing direct benefit to them, or where an alternative to the intervention would present less risk but the same likelihood of benefit. Even when, as in most cases the relation between possible harms and benefits or gains in knowledge is not found to be unreasonable, the evaluation will serve an important purpose of exposing fully the ethical and other issues that may be involved and thereby aiding in decision making by all parties concerned. The evaluation aids the IRB not only in judging whether it is reasonable to invite the participation of subjects in the research, but also in determining whether the information that will be given to subjects is sufficient for their own determination whether or not to participate.

In evaluating risks and benefits to subjects, an IRB should consider only those risks and benefits that may result from the conduct of the research. For example, the risks and benefits of therapies that subjects would receive even if not participating in the research should not be considered as risks and benefits of the research. (However, the risks and benefits of established therapies provide a point of comparison for the risks and benefits of new therapies that are the object of research.) The possible long-range effects of applying knowledge gained in the research (*e.g.,* the possible effects of the research on public policy affecting a segment of the population) should not be considered as among those research risks falling within the purview of the IRB, although such consequences may be relevant to a policy decision by an institution as to the desirability of approving the research at that institution. The IRB may advise institutional authorities in such cases.

As risk increases and, similarly, as the vulnerability of patients increases (by virtue of illness, institutionalization, etc.), it becomes more important to evaluate risks of harm and possible benefits and to require a reasonable relation between them. In effect, the IRB should assume more of the burden of determining whether subjects ultimately should be allowed to participate. In research that does not present significant risk to subjects, however, an IRB should not prevent an investigator from inviting subjects to participate in research because of its judgment that the research appears to be of marginal scientific importance or does not include an intervention that may benefit the subjects. Also, if the prospective subjects are normal adults, the primary responsibility of the IRB should be to assure that sufficient information will be disclosed in the informed consent process, provided the research does not present an extreme case of unreasonable risk.

(E) Circumstances in which prospective subjects might be coerced or unduly influenced should be avoided in the consent process. The need for concern about coercion or undue influence will depend upon the nature of the particular studies and the amount of risk they present. Protective steps may include the following:

* Providing subjects with an interval of time (consistent with the nature of the protocol) in which to weigh risks and benefits, consider alternatives, and ask questions or consult with others;

* Avoiding, whenever possible, seeking consent in physical settings in which subjects may feel coerced or unduly influenced to participate;

* Avoiding, whenever possible, seeking consent when subjects are in a vulnerable emotional state;

* Limiting remuneration to payment for the time and inconvenience of participation and compensation for any injury resulting from participation; and

* If students in a course will be requested to participate in research, assuring that this is understood at the outset and that reasonable alternatives are offered.

(F) Informed consent requires that all information relevant to a decision regarding participation be properly communicated to subjects. The information must be presented in a manner likely to result in its being understood. Thus, for example, medical or technical terms should be explained in lay language when they must be used. Written statements should be straightforward and easily readable. The specific information to be communicated should include those items that it is reasonable to expect that the subjects would want to know in making a decision regarding particpation in the research. While Recommendation (4)(F) contains a list of topics about which it can generally be presumed that subjects would want to be informed, it should be recognized that no such list is wholly adequate for this purpose. Thus, there may be research in which it is not reasonable to expect that subjects would want to be informed of some item on the list (*e.g.,* 1who is funding the research). More frequently, it can be expected that research will involve an element that is not on the list but about which it can be expected that subjects would want to be informed. Such information should, of course, be communicated to subjects. In addition, the investigator should indicate to subjects that questions are appropriate and be prepared to answer such questions. The investigator should also indicate whether the results of the research will be made available to subjects.

In some research there is concern that disclosure to subjects or providing an accurate description of certain information, such as the purpose of the

research or the procedures to be used, would affect the data and the validity of the research. The IRB can approve withholding or altering such information provided it determines that the incomplete disclosure or deception is not likely to be harmful in and of itself and that sufficient information will be disclosed to give subjects a fair opportunity to decide whether they want to participate in the research. The IRB should also consider whether the research could be done without incomplete disclosure or deception. If the procedures involved in the study present risk of harm or discomfort, this must always be disclosed to subjects. In seeking consent, information should not be withheld for the purpose of eliciting the cooperation of subjects, and investigators should always give truthful answers to questions, even if this means that a prospective subject thereby becomes unsuitable for participation. In general, where participants have been deceived in the course of research, it is desirable that they be debriefed after their participation.

(G) As a rule it is desirable that there be documentation of consent to provide the investigator with evidence thereof and the subjects with a readily available source of information about the research. However, consent forms should not be considered the only method by which information about the research is communicated to subjects. Usually an oral presentation will be an effective method of communicating with subjects. The documentation of consent (*i.e.,* the consent form) should never be confused with the substance of informed consent.

Because a consent form documents an agreement between two parties, both the subject and the investigator should retain a copy. The form should contain the address and phone number of the investigator and indicate how to contact the IRB.

In some studies of illegal or stigmatizing characteristics or behavior, subjects would be placed at risk by the creation of documents linking them with the research. The most secure method of protecting confidentiality of subjects in such studies is to create no written record of their identity, since such records may be vulnerable to subpoena. Confidentiality assurances are available from the Department of Justice and the Department of Health, Education, and Welfare that may effectively protect such documents from subpoena in certain studies of illegal behavior or drug abuse. When such protection is not available in studies in which a breach of confidentiality may be harmful to subjects, and subjects might prefer that ther be no documentation linking them with the research, the IRB may waive the requirement for documentation of consent in the interest of protecting the subjects.

In other studies, the requirement for documentation may place an undue burden on the research while adding little protection to the subjects. Such burdens might include a negative impact on the validity of a survey sample or introduction of an element that is incongruent with the social relationships involved in the research, (*e.g.,* in anthropological research). For research that would be burdened by a requirement of written documentation of consent, such documentation may be waived: *Provided,* That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. (For example, a physical intrusion into the body may generally require written consent, whether or not the intrusion is performed for purposes of research.) In many cases (*e.g.,* a survey using mailed questionnaires) it would be appropriate for the investigator to provide subjects with a written statement regarding the research, but not to request their signature. In other cases (*e.g.,* a telephone survey) an oral explanation might be sufficient, because subjects can readily terminate their involvement in the research.

In all research, but particularly when a short form or no written consent will be used, it is important for the IRB to review the investigator's plans regarding information that is to be provided orally.

(H) In studies of documents, records or pathological specimens, where the subjects are identified, informed consent may be deemed unnecessary but the IRB must assure that subjects' interests are protected. (If the subjects are not identified or identifiable, the research need not be considered to involve human subjects.) The Privacy Protection Study Commission concluded that medical records can legitimately be used for biomedical or epidemiological research, without the individual's explicit authorization.

"Provided, That the medical-care provider maintaining the medical record:

"(i) Determines that such use or disclosure does not violate any limitations under which the record or information was collected;

"(ii) Ascertains that use of disclosure individually identifiable form is necessary to accomplish the research or statistical purpose for which use of disclosure is to be made;

"(iii) Determines that the importance of the research or statistical purpose for which any use of disclosure is to be made is such as to warrant the risk to the individual from additional exposure of the record or information contained therein;

"(iv) Requires that adequate safeguards to protect the record or information from unauthorized disclosure be established and maintained, by the user or recipient, including a program for removal or destruction of identifiers; and

"(v) Consents in writing before any further use of redisclosure of the record or information in individually identifiable form is permitted."

The IRB should assure that such conditions exist before approving proposed research in which documents, records or pathology specimens are used for research purposes without explicit consent, and that the importance of the research justifies such use.

When the conduct of research using documents, records or pathology specimens without explicit consent is anticipated, incoming patients or other potential subjects should be informed of the potential use of such materials upon admission into the institution or program in which the materials will be developed, and given an opportunity to provide a general consent or to object to such research. The IRB should scrutinize with care any proposal to isolate and use materials about persons with particular problems or conditions, to assure compliance with the foregoing provisions regarding the use of private information.

Other situations in which informed consent might not be necessary arise in field research in the social sciences. Sometimes in such research, purely observational methods are supplemented by interaction with the persons being studied and therefore come within the Commission's definition of research involving human subjects. An IRB may waive the informed consent requirement in such research when it finds a number of factors to be present. The behavior to be studied must in some sense be public, *e.g.,* responses of businesses or institutions to members of the public, or social behavior in public places. Nondisclosure must be essential to the methodological soundness of the research, and must be justified by the importance or scientific merit of the research. Further, the research must present no more than minimal risk and be unlikely to cause embarrassment to the subjects.

(I) When proposed research involves the collection of data that might be harmful to subjects if disclosed to third parties in an individually identifiable form, the IRB should be particularly attentive to the adequacy of provisions to protect the confidentiality of the data. Depending upon the degree of sensitivity of the data, appropriate methods for protecting the confidentiality of the data may include the coding or removal of identifiers as soon as possible, limitation of access to the data, or the use of locked file cabinets. IRBs should be aware of the general vulnerability of research data to subpoena, particularly in stud-

ies that collect data that would put subjects in legal jeopardy if disclosed. When the identity of subjects who may have committed crimes or abused drugs is to be recorded in a research investigation, the IRB should see that the study, if it is eligible, is conducted under the appropriate assurances of confidentiality available from the Department of Health, Education, and Welfare and the Department of Justice.

(J) The Commission has transmitted recommendations for regulatory guidelines governing the conduct of research involving various subject populations with reduced capacity to give informed consent. IRBs should assure that research involving these populations complies with the guidelines that are adopted by DHEW.

Recommendation (5) The Secretary of Health, Education, and Welfare should require by regulation that an Institutional Review Board shall review proposed research at convened meetings at which a majority of the members of the Board are present and that approval of such research shall be reached by a majority of those members who are present at the meeting; *Provided, however,* That the Secretary may specifically approve expedited review procedures adopted by an Institutional Review Board for carefully defined categories of research that present no more than minimal risk. The Secretary should require, futher, that an Institutional Review Board inform investigators of the basis of decisions to disapprove or require the modification of proposed research and give investigators an opportunity to respond in person or in writing.

Comment: To require that IRB determinations be made by unanimous vote might result in a serious retardation of the review process, would place excessive power in the hands of single members. and would create an incentive for mitigating the diversity of viewpoints represented on the IRB.

Since discussion among IRB members is an important element in the successful functioning of an IRB, all members of the IRB should receive a copy of each research protocol and IRB determinations should be made in convened meetings of a respresentative quorum of the members. However, IRBs that review large amounts of research may find that certain categories of research recur with some regularity, present no more than minimal risk to subjects, and present no serious ethical issue requiring IRB deliberation. The IRB should be permitted to define categories of such research that would receive expedited, rather than full review, thereby enabling it to concentrate its attention on research that presents more serious issues. These categories should be subject to DHEW approval before the expedited procedure can be used.

Expedited review should be carried out by the IRB chairman or by an experienced reviewer designated by the chairman. The review should assure that the research in fact falls into a defined category of research not requiring full IRB review and that the research involves no violation of the basic ethical principles governing research involving human subjects. The reviewer should have authority to approve the research if it meets the conditions specified by the IRB, to request that the investigator bring the research into conformity with the specified conditions, or to refer the proposal to the IRB for full review. When there is any problem regarding informed consent, reduction of risk, etc., the research should be referred to the IRB for full review. Investigators should always be able to request full IRB review. Records of each expedited review, including the protocol, should be maintained as part of the IRB's records and be available for inspection by any member of the IRB. All members of the IRB should receive prompt notice of protocols approved by expedited review, and any member should be able to demand that the research be reviewed by the full IRB.

The following list provides some examples of research procedures for which expedited review procedures may be appropriate. It should always be remembered, however, that a study may entail more than minimal risk to subjects even though it involves procedures that ordinarily present no more than minimal risk. For example, a minimal risk procedure may be used in combination with more serious interventions, the subjects may be particularly vulnerable to harm from ordinarily harmless procedures, or data may be collected that could be harmful to the subjects if disclosed. For these reasons, care should be taken in defining and using categories of research for expedited review, and the reviewer should be alert for elements in particular proposals that require full review.

Among the procedures for which expedited review (subject to the caveats described) may be appropriate are:

(A) Collection (in a nondisfiguring manner) of hair, nail clippings and deciduous teeth;

(B) Collection for analysis of excreta and external secretions including sweat, saliva, placenta expelled at delivery, umbilical cord blood after the cord is clamped at delivery, and amniotic fluid at the time of artificial rupture of the membranes prior to or during labor;

(C) Recording of data from adults through the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amount of energy into the subject or an invasion of the subject's privacy. Such procedures include weighing, electrocdardiogram, electroencephalogram, thermography, detection of natural occurring radioactivity, diagnostic echography, and electroretinography;

(D) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in a six-week period, from subjects 18 years of age and over who are not anemic, pregnant or in a seriously weakened condition;

(E) Collection of both supra- and subgingival plaque. *Provided,* The procedure is no more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

(F) Voice recordings made for research purposes such as investigations of speech deficits;

(G) Moderate exercise by healthy volunteers;

(H) The use of survey research instruments (interviews or questionnaires) and psychological tests, interviews and procedures that are part of the standard battery of assessments used by psychologists in diagnostic studies and in the evaluation of judgmental, perceptual, learning and psychomotor processes: *Provided,* That the subjects are normal volunteers and that the data will be gathered anonymously or that confidentiality will be protected by procedures appropriate to the sensitivity of the data;

(I) Program evaluation projects that entail no deviation for subjects from the normal requirements of their involvement in the program being evaluated or benefits related to their participation in such program; and

(J) Research using standard protocols or noninvasive procedures generaccepted as presenting no more than minimal risk, even when done by students.

Expedited review procedures may also be used to review minor changes in previously approved research.

The expedited review procedures to be used and the specific categories of research to which they will be applied must be adopted by the IRB and specifically approved by the accreditation office established by the Secretary of Health, Education, and Welfare. The IRB's authority to use such expedited review procedures should be revoked if an audit shows a pattern or improper application of such procedures.

Although the Commission has not recommended that IRBs be required to meet in public, it supports the principle of open meetings. The public generally should have access to IRB meetings, limited only by local law or

a decision of the IRB to close a meeting in order to discuss personal or proprietary information. Public access to meetings should not necessarily extend to the documents that will be discussed at the meetings. IRBs should make provision to consider requests by investigators to close meetings or portions of meetings at which their research proposals will be discussed.

The Commission has not recommended a mechanism for appeal from IRB determinations, since it believes that an IRB should have the final word at its institution regarding the ethical acceptability of proposed research involving human subjects. When there is disagreement in an area that may be outside the expertise of an IRB, however, the use of outside consultants is to be encouraged. Also, when there is disagreement over the application of regulations or guidelines issued by the Department of Health, Education, and Welfare, the accreditation and compliance office described in Recommendation (2) should provide expeditious clarification or interpretation upon request by an IRB. Should an institution wish to establish an appeals process, the Commission suggests that it be restricted to investigation of prejudice or unfairness and that the appeals board not be given authority to conduct a secondary review of the protocol or to reverse the IRB decision.

CHAPTER 1. EXISTING MECHANISMS FOR APPLYING ETHICAL GUIDELINES TO RESEARCH INVOLVING HUMAN SUBJECTS

The problem of applying general rules and guidelines to specific cases, and the use of groups to make such decisions when questions of public interest or societal values are at stake, has a very long history. A system of a "multidisciplinary" nature can be found as early as the sixth century B.C., when Solon replaced the old Athenian court system with one in which all citizens—including the lowest class—could participate. *(1)* They were chosen by lot to sit in panels as judges and preside over what amounted to both the lower courts and the court of appeal. In Anglo-American law, the jury is a prototypic body for deciding how broad rules apply to individual cases. Both Solon's court system and the jury are extensions of political democracy to questions of criminal and civil responsibility.

A jury of peers, picked at random from the citizenry, is of course not the sole means available for applying rules to situations. A quite different approach, though also stated in terms of "peers," has characterized the history of some professions. The medical profession, for example, has traditionally professed concern with assuring that individual practitioners deliver care which is both necessary and of high quality. The origin of the professionally-controlled licensure mechanism in 19th century American medicine can be seen in these terms, although it has also been interpreted as part of the effort to establish professional monopoly. *(2)* Thus, it is widely held that a defining characteristic of a profession is a high degree of control over its own work. *(3)* The actual performance of professionals has also been subject to the review of peers, at least under some circumstances. Examples range from editorial boards of professional journals to tissue review or medical audit committees in hospitals to DREW study sections. In recent years, the actual performance of physicians has come under the broader scrutiny of Professional Standards Review Organizations (PSROs), established in connection with the federal government's payments under the Medicare, Medicaid, and Maternal and Child Health programs. *(4)* None of these review procedures, however, was established for the express purpose of making decisions in the face of ambiguous or conflicting social values.

Human Subjects Review Procedures. Any useful set of ethical principles, guidelines or rules will require interpretation when applied to particular situations. In research involving human subjects, the desirability of bringing to bear on such interpretations the judgment of individuals other than the research investigator has come to be widely recognized and is the basis of present regulatory approaches to the protection of human subjects.

The first formal review procedures for protection of subjects apparently were established in 1953, when a document called "Group Consideration of Clinical Research Procedures Deviating from Accepted Medical Practice or Involving Unusual Hazard" was issued in connection with the opening of the Clinical Center at the National Institutes of Health. *(5)* This document showed particular concern with the issues of how much risk to subjects was justifiable and what aspects of a study must be disclosed to subjects. More importantly it introduced the idea that the resolution of such issues on any particular project should be subjected to group consideration, although primary responsibility was seen as remaining with the investigator. *(6)* These original guidelines have undergone several revisions and continue to pertain to the "intramural programs" at NIH.

The Development of the Institutional Review System. The use of the Institutional Review Board (IRB) as a regulatory mechanism for research supported by DHEW derives from the Public Health Service (PHS) review requirements initiate in 1966 by the Surgeon General. *(7)* (Two surveys conducted in the early 1950s showed that some institutions had some type of review procedure prior to the Surgeon General's requirements, although such procedures were hardly uniform or universal. *(8)*) In his memorandum establishing the institutional review requirement, the Surgeon General issued the following statement of general policy:

> Public Health Service support of clinical research and investigation involving human beings should be provided only if the judgment of the investigator is subject to prior review by his institutional associates to assure an independent determination of the protection of the rights and welfare of the individual or individuals involved, of the appropriateness of the methods used to secure informed consent, and of the riskes and potential medical benefits of the investigation. *(9)*

This statement, it can be noted, explicitly assumed that the requirement pertained to biomedical research, although a "clarification" issued by the Surgeon General later in the same year extended applicability to behavioral research. The initial requirement was limited to PHS-supported research, and was seen as supplementing the internal review system that had evolved since 1947 for evaluating the scientific quality of research proposals.

A number of administrative changes in the PHS review requirements were made in the years following the Surgeon General's memorandum. The most significant change was a shift from the initial procedure under which a description of the review procedure was submitted with each proposal to a system of general assurances of institution compliance with the requirements, under which an institution sought one approval for procedures that would be applied to the review of any proposal within the IRB's jurisdiction. In 1971, the well-known *Institutional Guide to DHEW Policy on Protection of Human Subjects (10)* was published, establishing the PHS requirements as DHEW policy. Applicability was confined to studies "in which subjects may be at risk," and, though no longer limited to PHS, remained confined to research supported by DHEW. However, the *Institutional Guide* stated that if the Secretary judges that an institution has failed to discharge its responsibilities for the protection of "individuals in its care," whether or not DHEW funds are involved, the Secretary "may question whether the institution and the individuals concerned should remain eligible to receive future DHEW funds for activities involving human subjects." Administration of

the policy remained in the Institutional Relations Section of the Division of Research Grants, NIH. Throughout, the *Institutional Guide* provided more detail and direction than had earlier PHS statements.

DHEW REGULATIONS FOR PROTECTION OF HUMAN SUBJECTS (45 CFR PART 46)

Regulations for protection of human subjects were issued by DHEW on May 30, 1974 (45 CFR Part 46). *(11)* These regulations, as subsequently amended (March 13, 1975 and August 8, 1975), *(12)* currently govern the system of Institutional Review Boards. The applicability of the regulations is stated to be "to all Department of Health, Education, and Welfare grants and contracts supporting research, development, and related activities in which human subjects are involved" (sec. 46.101). Elsewhere, the regulations quote section 212(a) of the National Research Act (Pub. L. 93–348), which provides:

> The Secretary shall by regulation require that each entity which applies for a grant or contract under this Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant or contract assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an 'Institutional Review Board') to review biomedical and behavioral research involving human subjects conducted at or sponsored by such entity in order to protect the rights of the human subjects of such research.

The regulations provide no clarification of the apparent inconsistency between this statement and the regulations' own statement of "applicability."

The regulations indicate that safeguarding the rights and welfare of "subjects at risk" is primarily the responsibility of an institution that receives DHEW support for such research. To this end, the following DHEW policy is stated:

> [N]o activity involving human subjects to be supported by DHEW grants and contracts shall be undertaken unless an Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval * * * (§ 46.102(a)).

Specifically, the regulations require IRB review of proposed research to determine whether "subjects will be placed at risk," and, if so, whether:

> (1) [t]he risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;
> (2) The rights and welfare of any such subjects will be adequately protected;
> (3) Legally effective informed consent will be obtained by adequate and appropriate methods in accordance with the provisions of this part. (Sec. 46.102(b)).

When an IRB finds that risk is involved in research, the regulations also require that it "review the conduct of the activity at timely intervals" (§ 46.102(d)). Amendments published August 8, 1975, gave IRBs additional responsibilities in the review of research involving fetuses, pregnant women of human *in vitro* fertilization. *(13)* These amendments were issued to incorporate the recommendations of the National Commission for the Protection of Human Subjects.

With regard to the composition of IRBs, the regulations require the following:

> The Board must be composed of not less than five persons with varying backgrounds to assure complete and adequate review of activities commonly conducted by the institution. The Board must be sufficiently qualified through the maturity, experience, and expertise of its members and diversity of its membership to insure respect for its advice and counsel for safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the Board must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The Board must therefore include persons whose concerns are in these areas (Sec. 46.106(b)).

The regulations also specify that no member shall be involved in the review of an activity in which he has a conflicting interest, except to provide information; that no Board shall consist entirely of persons associated with the institution; and that no Board shall consist entirely of members of a single professional group.

General and Special Assurances. Recipients or prospective recipients of DHEW support research involving "subjects at risk" must provide "written assurance acceptable to DHEW that they will comply with DHEW policy." This assurance "shall embody a statement of compliance with DHEW requirements for initial and continuing Institutional Review Board review of the supported activities" and "a set of implementing guidelines, including identification of the Board and a description of its review procedures * * *" (§ 46.104(a)). No grant or contract involving human subjects at risk can be made unless the investigator is affiliated with or sponsored by an institution which assumes such responsibility.

Research may be conducted under two types of assurances—general and special. A general assurance describes the "review and implementation procedures applicable to all DHEW-supported activities conducted by an institution" (§ 46.105(a)). That is, the general assurance describes established procedures that will be brought into play repeatedly, and thus is typically submitted by institutions in which DHEW-supported research involving human subjects is recurrent. A special assurance, on the other hand, is the mechanism used when a proposal is submitted by an institution that does not have an approved general assurance, and describes the "review and implementation procedures applicable to a single activity or project" for which support is sought (§ 46.105(b)).

For general assurances, the "implementing guidelines" submitted by the institution must contain a "statement of principles which will govern the institution in the discharge of its responsbilities for protecting the rights and welfare of subjects. This may include appropriate existing codes or declarations, or statements formulated by the institution itself" (§ 46.105(a)). This statement is consistent with DHEW's view of the regulations as specifying procedures but not constituting an ethical code.

As of August 1, 1977, 534 institutions had an acceptable general assurance on file with DHEW. A substantial minority of these institutions were restricted in the types of studies that they were approved to review, most of these institutions were restricted from reviewing either medical or "Investigational New Drug" studies, or "behavioral" studies. Approximately 350 special assurances annually are approved. Since many projects run for several years, as many as 1,000 special assurances may be in effect at one time.

The regulations state that failure to comply with the regulations may result in early termination of awards or may affect the evaluation of subsequent applications or proposals (§ 46.121). The sanction of terminating a grant or contract due to noncompliance with the DHEW policy has not been used since the DHEW regulations were issued in May 1974.

A Note on Regulations for Education Research. DHEW regulations for protection of human subjects (45 CFR Part 46) do not apply to the National Institute of Education (NIE) and the U.S. Office of Education (OE). *(15)* The General Education Provisions Act gives to the Director of NIE and the Commissioner of Education authority to issue their own regulations, subject to the approval of Congress. *(16)* 45 CFR Part 46 has not been adopted for education research because some of the provisions therein are seen by the Education Division as inappropriate to the research conducted under its auspices. *(17)* NIE regulations do prohibit the use of data collection instruments "which constitute unnecessary or offensive intrusion of privacy through inquiries regarding such matters as re-

ligion, sex, race, or politics." *(18)* They also require parental consent of each respondent prior to the use of such instruments, although the Director of NIE may grant a waiver of this requirement. *(19)* NIE also requires that subjects be protected "from physical, psychological, or sociological harm, in accordance with the specific provisions of the Department's policy on the treatment of human subjects." *(20)* The provisions cited therein refer in turn to provisions of the DHEW Grants Administration Manual. *(21)* Similarly, OE grant and contract regulations also incorporate the DHEW Grants Administration Manual. *(22)* This Manual, in turn, requires approved assurances, IRB review, and informed consent procedures that are nearly identical to those of the DHEW regulations (45 CFR Part 46). Thus, though the citations are circuituous, a system similar to that of the rest of DHEW appears to be required within the Education Division. *(23)*

DHEW IMPLEMENTATION OF REGULATIONS FOR PROTECTION OF HUMAN SUBJECTS

Responsibility for monitoring the composition and function of IRBs is assigned to the Office for Protection from Research Risks (OPRR) in the Office of the Director, NIH. This office reviews both general and special assurances as they are submitted, and either approves or disapproves them or requires modifications of the composition or procedures of the IRBs.

Negotiations for approval of an assurance are initiated with the submission by an institution of a statement of compliance and implementing procedures. The assurance may be submitted voluntarily by the institution or requested by OPRR. For a special assurance, OPRR's review is generally limited to the composition of the IRB and its findings with respect to the proposal involved. For a general assurance, OPRR determines whether the composition of the IRB is proper, whether the procedures for meetings and review are adequate, and whether there is an appropriate statement of adherence to an ethical code. In making these judgments, OPRR determines whether the members of the IRB are properly diverse with respect to background, affiliation, training and academic rank, as the regulations require. There is no specific regulatory requirement for including racial or ethnic minorities or women, but OPRR attempts to see that they are included. OPRR also reviews the applicant institution's statement regarding the manner of appointment of members to the IRB, the quorum requirement and voting procedures, and whether the IRB has regularly scheduled meetings. In addition, OPRR reviews the proposed methods for monitoring ongoing research projects and procedures for record-keeping and for notifying the responsible parties in case of unexpected complications.

Staff members of OPRR make approximately 30–40 site visits per year in the process of negotiating assurances. At such visits, they review the operating procedures of the IRBs and examine the IRBs' files.

REVIEW OF RESEARCH PROPOSALS

DHEW regulations provide that "[n]otwithstanding any prior review, approval, and certification" by an applicant institution, all applications and proposals "involving human subjects at risk" submitted to DHEW shall be evaluated by the Secretary for compliance with the regulations. Both partmental employees and outside experts or consultants may be used. This evaluation "may take into account, among other pertinent factors, the apparent risks to subjects, the adequacy of protection against these risks, the potential benefits of the activity to the subjects and to others, and the importance of the knowledge to be gained" (45 CFR 46.115(a)). The means by which this is done varies within the department, and differs for grants and contracts.

Review of Grant Proposals. All applications received by NIH or ADAMHA are reviewed by DHEW staff to determine whether or not human subjects are involved, regardless of the initial determination by the applicant's IRB. (When errors of omission are identified, OPRR is advised and the responsible IRB is then requested to take appropriate action.) Grant applications are then reviewed by an Initial Review Group (generally called a "study section"), which provides scientific review of the research design and the competence and experience of the principal investigator. The study sections are composed of recognized authorities in specialized areas of research. Statutory and administrative guidelines require selection from various geographic areas, rotation of membership and the inclusion of women and other minority representatives.

The DHEW Grants Administration Manual (Chapter 1–40–20–B) stipulates that:

> Review groups may (a) recommend disapproval if the hazards are so grave as to be unacceptable; (b) recommend approval without restrictions when the subject's rights and welfare are not infringed; (c) recommend approval but record expressions of concern to be communicated to the institution sponsoring the project or activity; or (d) recommend approval contingent on limitation of the scope of the work or the elimination of objectionable procedures involving human subjects.

Any decision short of unqualified approval must be communicated to the official of the sponsoring institution who signed the proposal and to the principal investigator. In addition, if the review group finds undue hazards to subjects or if it questions the ethical probity of a research proposal, the matter is referred to OPRR for further review. In most cases, OPRR writes to the IRB involved to call attention to the objections raised by the reviewers.

OPRR does not require that consent forms be submitted to DHEW with research proposals. (In fact, the present Director of that office has discouraged the practice on the grounds that study sections have no legal staff competent to assess consent forms and procedures, and there is insufficient staff at OPRR and the Office of the General Counsel to perform this job.) By contrast, ADAMHA requires its review groups to assure that the consent procedures for each project are adequate; thus, in many cases, the ADAMHA study sections review consent forms as part of the review process.

Once a grant application has been recommended for approval by a study section, it must undergo final review and approval by one of 14 National Advisory Councils. Each institute of the NIH and ADAMHA has such a council, which is required by law to include lay and public members in addition to scientific members with the appropriate expertise for the areas served by the council. The councils receive a summary of findings and the recommendations of the study sections and, on the basis of their own review and discussion, advise the appropriate departmental official whether or not the research should be supported. (The official is not required to follow the advice of the council and may in fact be unable to support all the proposals which have been approved; however, no project may be funded following disapproval of the Advisory Council.)*

DHEW components other than NIH and ADAMHA have procedures which are similar, if not identical to, those outlined above. Some rely primarily on staff review supplemented by "outside opinions" of consultants, reviewers or "field readers." Others rely on in-house committees, particularly for review and approval of contracts.

Thus, the present system involves several reviews of a research grant supported by DHEW: first by an IRB, next by DHEW staff, study section and Advisory Council, and finally continuing review by the IRB. These reviews are intended to complement each other.

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* Some institutes permit funding of small grants (with direct costs under $35,000) without the review and approval of a National Advisory Council or Board.

Review of Contract Proposals. The DHEW regulations for protection of human subjects also apply to research conducted under contract. Under DHEW procurement regulations (41 CFR 3–4.55) the judgment as to the need for IRB review is to be made by the agency supporting the research and specified in the Request for Proposal. The diversity within DHEW regarding review procedures for contract proposals probably exceeds that of grant review procedures. Within NIH, all contracts involving human subjects in "nontherapeutic research" must be reviewed and approved by the Medical Board of the NIH Clinical Center. Projects involving "therapeutic research" are reviewed by committees of varying composition within the various institutes.

FOOTNOTES

1. J. Bury, *A Histroy of Greece,* 1900, pp. 184–185, cited in Barbara Mishkin, "Multidisciplinary Review for the Protection of Human Subjects in Biomedical Research: Present and Prospective HEW Policy," 54 *Boston University Law Review* 1974, p. 278.
2. Richard H. Shryock, *Medical Licensing in America, 1650–1965,* Baltimore: Johns Hopkins Press, 1975; Jeffrey L. Berlant, *Profession and Monopoly: A Study of Medicine in the United States and Great Britain,* Berkeley: University of California Press, 1966, particularly Chapter 5.
3. Eliot Freidson, *Profession of Medicine: A Study in the Sociology of Applied Knowledge,* New York: Dodd, Mead, 1970.
4. P.L. 92–603, Title XI, Part B, Section 1151. More generally see Richard H. Egdahl and Paul M. Gertman (eds.), *Quality Assurance in Health Care,* Germantown, Md.: Aspen Systems, 1976.
5. Mark Frankel, *The Public Health Service Guidelines Governing Research Involving Human Subjects: An Analysis of the Policy-Making Process,* Washington, D.C.: George Washington University Program of Policy Studies in Science and Technology, 1972, p. 9.
6. *Ibid.,* p. 11.
7. The background of this development is described in Frankel, *op. cit.,* and in William J. Curran, "Government Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," *Daedalus,* Vol. 98, 1969, pp. 542–594.
8. The first was done by Louis G. Welt, "Reflections on the Problems of Human Experimentation, *"Connecticut Medicine,* Vol. 25, 1961, pp. 75–79. The second, conducted by the Boston University Law-Medicine Research Institute, is described by Curran, *op. cit.,* pp. 546–548.
9. Surgeon-General, "Memo to Heads of Institutions Conducting Research with Public Health Service Grants," February 8, 1966.
10. DHEW, *The Institutional Guide to DHEW Policy on Protection of Human Subjects,* DHEW Publication No. (NIH) 72–102, December 2, 1972.
11. DHEW, Protection of Human Subjects, 45 CFR Part 46, 39 FR 18917, May 30, 1974.
12. DHEW, Protection of Human Subjects: Technical Amendments, 45 CFR Part 46, 40 FR 11854, March 13, 1975.
13. DHEW, Protection of Human Subjects Fetuses, Pregnant Women, and *In Vitro* Fertilization, 45 CFR Part 46, 40 FR 33526, August 8, 1975.
14. The National Commisiion for the Protection of Human Subjects of Biomedical and Behavioral Research, Research on the Fetus: Report and Recommendations, Washington, D.C.: DHEW, 1975. (DHEW Publication No. (OS) 76–127).
15. Caspar W. Weinberger, Secretary, DHEW, in introduction to DHEW Regulations for Protection of Human Subjects, 45 CFR Part 46, 39 FR 18917, May 30, 1974.
16. General Education Provisions Act, secs. 408(a)(6)(c) and 431.
17. Thomas K. Glennan, Jr., Director, National Institute of Education, in introductory comments to the Institute's General Provisions for Research and Development Grants, 45 CFR Part 74, published as regulations in 39 FR 38992, November 4, 1974.
18. 45 CFR Part 74, § 1410.1(c), 39 FR 39006, November 4, 1974.
19. 45 CFR Part 74, § 1410.1(f), 39 FR 39006, November 4, 1974.
20. 45 CFR Part 74, § 1410.2 39 FR 39006, November 4, 1974, citing Title 41, Subpart 3, § 4.55 of the Code of Federal Regulations.
21. Chapter 1–40, DHEW Grants Administration Manual.
22. Memorandum from Mary Moore, Office of the Assistant Secretary for Education, June 7, 1976.
23. *Ibid.*

CHAPTER 2. A STUDY OF THE PERFORMANCE OF INSTITUTIONAL REVIEW BOARDS

In preparation for its deliberations on mechanisms forr protecting human subjects, the Commission recognized the importance of developing systematic information about the performance of Institutional Review Boards (IRBs). Although IRBs play a key role in the existing system for protecting human subjects, only superficial information about IRBs was available from DHEW, and existing studies were either dated, of limited depth, or based on the experience of single, selected IRBs.* The Commission therefore contracted with the Survey Research Center of the University of Michigan for a systematic survey of a representative sample of IRBs.

This study focused on review procedures and research projects at a probability sample of 61 institutions drawn from the more than 420 institutions with general assurances approved by DHEW. The study covered research reviewed by IRBs at these institutions between July 1, 1974 and June 30, 1975. Approximately 3,900 persons were interviewed, including more than 2,00 research investigators whose proposals had been reviewed, over 800 members or persons especially knowledgable about the IRBs in the sample, and almost 1,000 subjects or third persons who consented on their behalf.**

IRBs exist in a number of distinctive institutional environments. Medical schools (and universities that share IRBs with medical schools) accounted for 59 percent of the research reviewed by IRBs in the sample. Universities (with IRBs separate from those for medical schools) and hospitals accounted for 18 percent and 15 percent, respectively. Most of the remaining research was conducted in institutions for the mentally infirm, although some was conducted in research institutions or in dental or nursing schools.

Approximately 60 percent of the studies reviewed by IRBs was biomedical, most frequently involving the administration of drugs or the study of samples of bodily fluids or tissues. Investigators in many of these studies reported that the major intervention (e.g., the administration of a drug) would have occurred even if the patient had not been involved in the study. Behavioral research—most frequently using interviews, questionnaires, testing or observation—accounted for about one-third of the research reviewed by IRBs; about a fifth of the behaviooral research entailed the study of an intervention such as social or psychological therapy, behavior modification techniques or educational innovations. The remaining small fraction of the research reviewed by IRBs (about six percent) involved secondary analyses of data or the study of bodily fluids or tissues that had been obtained for other purposes.

IRBs face greatly varying work loads. An IRB at a small institution may not receive even a single proposal in a given year, while IRBs in major medical schools or universities receive hundreds of proposals for review. The average IRB reviews 43 proposals per year. The number of members on IRBs in the sample ranged from 5 to 55, with an average of 14. IRBs in the

*Bernard Barber *et al., Research on Human Subjects: Problems of Control in Medical Experimentation,* Russell Sage Foundation, New York, 1973; Dale H. Cowan, Human Experimentation: The Review Process in Practice, *Case Western Reserve Law Review,* Vol. 25, No. 3, 1975, pp. 533–564; Bradford H. Gray, An Assessment of Institutional Review Committees in Human Experimentation, *Medical Care,* Vol. 13, No. 4, 1975, pp. 318-328; Sherry E. Marcy, *A Systems Study of a University Committee for Protection of Human Subjects of Experimentation,* Unpublished Master's Thesis, Yale University School of Public Health, 1974; Kenneth Melmon et al., Emerging Assets and Liabilities of a Committee on Human Welfare and Experimentation, *New England Journal of Medicine,* Vol. 282, No. 8, 1970, pp. 427–431; Eugene J. Millstein, *The DHEW Requirements for the Protection of Human Subjects: Analysis and Impact at the University of California,* Research Management Improvement Project, University of California, Berkeley, 1974.

**In addition to its reports on the performance of IRBs, the Survey Research Center made separate reports on research involving prisoners, research involving children, and research involving those institutionalized as mentally infirm. Those reports are summarized in the Commission reports on those respective topics.

sample met as few as two and as many as 51 times per year, with an average of 10 meetings per year. The average IRB expended 760 member-hours per year on IRB work; this figure ranged as high as 5,000 member-hours for one IRB. IRBs spend an average of almost one hour per proposal in meetings, and the total number of member-hours per proposal (including time spent outside of meetings) averaged 38 hours and ranged as high as 270 hours at one IRB.

Composition of IRBs. The majority of IRB members in the sample were biomedical scientists (50 percent) or behavioral scientists (21 percent); about 90 percent did not identify themselves as biomedical or behavioral scientists. This latter group included administrators, lawyers, nurses, members of the clergy and others. Biomedical researchers, behavioral researchers, full-time administrators and "community representatives" were each found on approximately 90 percent of the IRBs. About three-fourths of the IRBs included a lawyer; this was particularly characteristic of IRBs in medical schools and occurred least frequently (in fewer than one-third of the IRBs) at institutions for the mentally infirm. All IRBs included at least one member who was not otherwise affiliated with the institution. The membership of half of the IRBs was reported to include racial or ethnic minorities. Eighty-eight percent of the IRBs included women. Three-fourths of IRB members were asked to serve (only five percent said they sought membership), and fewer than five percent said that they had had any special training for their role, although most said they had received a briefing or some written instructions (e.g., the DHEW regulations).

A diversity in attitudes and concerns is associated with the diversity of membership on IRBs. There were differences among biomedical scientists, behavioral and social scientists, and other IRB members regarding the issues that they reported raising for discussion, the matters about which they believed that other members perceived them to be expert, and the emphasis that they reported placing on different aspects of research proposals. Nonscientists generally reported themselves to be less active and less influential than other IRB members, Nevertheless, almost all IRB members indicated that viewpoints of all members were sought and considered in IRB decisions, and almost 90 percent of IRB members expressed satisfaction with their accomplishments on the IRB.

Policies and Procedures of IRBs. Although there are a few common denominators among IRBs—almost all reported discussing proposals in convened meetings and most review all research, regardless of funding source—the diversity of their policies and procedures is striking. About two-thirds of the IRBs had a procedure to screen out proposals that did not need attention from the IRB. About half of the IRBs assigned proposals to individual members for intensive review, and about one-fourth of the IRBs reported delegating some responsibility to subcommittees for similar purposes. Half of the IRBs required that proposals be submitted on standard forms, and most of the others provided investigators with some instructions regarding the submission of proposals. About half of the IRBs took formal votes on all proposals, and almost all took formal votes on at least some occasions. Two-thirds of the IRBs accepted majority approval as satisfactory; one-fourth required unanimity. More than half of the IRBs said that their meetings were open to nonmembers. More than one-fourth of the IRBs said that investigators always attend the meetings at which their porposals are discussed, and more than 80 percent of the IRBs reported that this happened at least occasionally.

One-fifth of the IRBs reported that approved proposals are routinely subjected to further review. Thirteen percent of the IRBs reported that rejected proposals were automatically reviewed a second time, half of the IRBs had provisions for investigators to appeal IRB dicisions.

IRB Involvement After Final Review. Most IRBs approved some projects with the stipulation that they be reviewed again after periods ranging from one month to three years, but usually after one year. When an ongoing project was submitted for review, four-fifths of the boards required that information be provided concerning such matters as the progress of the research, changes in the original protocol, tentative results, the number of active subjects and refusals to participate, consent forms and subject-related problems. Only half of the boards reported having either a formal or informal policy regarding the reporting of injuries to subjects. In most of these IRBs, investigators were supposed to notify the IRB in the event of injuries to subjects; a few IRBs reported that research was to be halted or reviewed again if injuries occured. Forty percent of the Boards had a policy regarding treatment of or compensation for injuries to subjects.

More than one-third of the Boards had, at some time, designated someone to observe the manner in which projects were conducted; half of these Boards said that this was done routinely, and the others reported that projects were observed only under certain circumstances, such as when there was particular risk, when children were involved or when there had been problems in the past.

Over 80 percent of the IRB members felt that it was likely or certain that their IRB would learn of the existence of research involving human subjects that had not been reviewed or that was being conducted in way that was substantially different from the manner approved by the IRB. Respondents from universities felt least certain of this. One-fourth of the IRBs had become aware of the conduct of such research in the previous year. In such situations, IRBs were reported to have intervened to require research to be reviewed or to have called the matter to the attention of institutional authorities.

IRB Modifications of Research Proposals. Information provided by investigators indicated that more than half of the proposals reviewed by IRBs were modified, either by requests for additional information or by substantive modifications. Most modifications occurred as a result of the formal review process, although some projects were modified as a result of informal contacts between investigators and IRB members. IRBs sought more information about almost one-third of the proposals submitted for review, and they required modifications regarding informed consent in one-fourth of the proposals. Modifications regarding scientific design, subject selection, risks and discomforts, and confidentiality were each made in three to four percent of proposals.

IRBs varied markedly in the percentage of proposals that they modify. Modifications in every proposal were reported for 14 percent of the IRBs, while at 22 percent of the IRBs no more than one-third of the investigators reported that the IRB had required modification in their proposals. IRBs also varied in the variety of modifications they make. For 19 percent of the IRBs, only one type of modification in proposals was reported, while seven percent of IRBs made all six types identified in the survey (*i.e.,* modifications regarding consent, risks, scientific design, subject selection, confidentiality and "other" modifications). The median number of types of modifications by IRBs was 2.5.

Risks and Benefits of Research Approved by IRBs. More than half (55 percent) of the projects for which information was available were expected by the investigators to be of benefit to the research subjects. There was little difference in this regard between biomedical projects and projects that involved a behavioral intervention, although the nature (medical or psychological) of the benefits differed. Fewer than one-third of the behavioral pro-

jects that did not involve the study of an intervention were expected to benefit subjects.

Estimates of the probability and magnitude of the possible harms to subjects were also provided by investigators. One-fourth of the investigators judged their projects to be without risk, and another fourth judged their research to have no more than a "very low" probability of "minor" complications. About half of the research involved more risk—at least a "low" probability of minor complications or a "very low" probability of serious complications. Table 1 shows that as the assessed risk of projects increased, so did the likelihood that the projects would benefit subjects; provisions for treatment of injuries to subjects and the actual occurence of injuries to subjects also were most likely to be found in studies in which the investigator's assessment of risk was relatively high.

These estimates of risk should not be treated as objective assessments of the degree of risk present in research. The assessment of independent raters would undoubtedly differ in some cases from the assessment of investigators themselves. That is, after all, one rationale for the review process. Nevertheless, the validity in the aggregate of the investigators' estimates of the riskiness of their research receives some confirmation from the fact that injuries to subjects were more likely to be reported in studies in which risks were assessed as relatively high (see Table 1). Table 1 also shows that as the risk of projects increased, so did the likelihood that the projects would benefit the subjects. Only about one-third of the "no risk" projects were expected to benefit subjects, while at the other end of the risk scale, 80 percent of the projects were expected by the investigators to benefit subjects.

TABLE 1.— *Risk, Benefit, and Availability of Treatment for Harmful Effects*

[Percent of projects]

Relative risk level*	Expected by investigator to benefit subjects	Harmful effects reported	Treatment reported available
No risk (N=710)	34	0	14
Very low risk (N=446)	52	1	31
Low risk (N=459)	63	3	52
Moderate risk (N=483)	80	12	81

*As assessed by investigators

Overall, harm to subjects was reported in three percent of the projects. These harms were generally considered trivial or only temporarily disabling. Three investigators reported fatal effects; in each of two projects one subject died and in one project three subjects died. Each of these projects involved cancer research, and in two of the projects some subjects were in near terminal condition at the time of their participation in the research.

In three projects, the investigator reported that a breach of confidentiality had occurred which had harmed or embarrassed a subject; most investigators reported having some procedure to protect subjects' confidentiality, but in more than ten percent of the projects no such procedures were reported.

There were some indications that IRBs which review relatively risky research are more careful in their reviews. For example, a more comprehensive set of issues was reportedly discussed during the review of proposals, and the rate of modification of proposals was greater, in IRBs that review more relatively high risk research. This correspondence between risk and performance occurs in medical schools and hospitals, but not in universities. Thus, it appears that in some IRBs the allocation of energy may not be related to the degree of risk in the projects under review.

Selection of Subjects in Projects Approved by IRBs. By and large, IRBs accepted investigators' plans for selection of subjects. However, changes were required in three percent of the projects, usually by limiting or restricting the sample in some way. "Patients" served as subjects in 76 percent of the projects approved by IRBs in medical schools and in 86 percent of projects in hospitals. In almost half of these projects, the subjects were the investigator's own patients. Patients were subjects in only 17 percent of the projects in universities (and 66 percent of projects in other institutions). University projects most frequently involved college students (37 percent) as subjects. Subjects in most research were selected because of a specific condition or characteristic. For patients, their disease was usually a selection criterion; in research in universities, the most common selection criteria were demographic characteristics such as age or educational situation. Persons identified as patients served as subjects in three-fourths of the projects expected to benefit subjects and in half of the other studies. Persons selected from the general population were more likely to be participants in projects not expected to benefit subjects than in projects expected to provide such benefits.

Projects in which investigators reported relatively high proportions of (1) males, (2) persons between 41 and 64 years of age, and (3) high or middle income persons were more likely than other projects to be above average in risk. Overall, although more investigators described their subjects as "low income" persons than as "high income" persons, there was no evidence that low income persons were particularly likely to be selected either for relatively risky research or for research that was not expected to benefit subjects. Projects involving substantial proportions of children or older people were more likely to be expected to benefit the subjects than were projects that drew more heavily on 19 to 40-year-olds.

Informed Consent. Informed consent is the focus of considerable activity by IRBs; yet it clearly remains a problem. According to investigators, IRBs required changes regarding the obtaining of consent in one-fourth of the projects they approved. Virtually all of these changes pertained to the content of consent forms—most commonly through the addition of materials—rather than the way in which consent was obtained; in fewer than one percent of the studies did IRBs require changes regarding the timing of the consent process, who obtained consent, the setting in which consent would be obtained, or the presence of a witness.

Investigators reported that informed consent was obtained in almost 90 percent of the projects. Usually such consent was obtained in writing. The major reasons cited for not obtaining consent were that the return of questionnaries implied consent, that only routine procedures or treatments were being used, or that the study was based exclusively upon existing records, data or materials gathered for other purposes.

Principal investigators had either exclusive or shared responsibility for obtaining consent in 70 percent of projects, and someone other than the persons seeking and giving consent was present when consent was sought in about half of the projects. In two-thirds of the studies expected to benefit subjects directly, investigators reported that the benefits to others in the future or to scientific knowledge

were mentioned in about half of the projects. In projects not expected to benefit subjects directly, benefits to others and benefits to scientific knowledge were each reportedly emphasized in the consent process in about half of the studies; direct benefits to subjects were reportedly given emphasis in about one-fifth of these studies. Principal investigators generally reported that the participation of subjects was requested when consent was obtained. Investigators recommended participation in 35 percent of the projects expected to benefit subjects, and in seven percent of the projects not expected to benefit subjects.

In 15 percent of the studies, investigators reported that some information was withheld from subjects. This occurred most frequently (29 percent) in studies conducted in universities and least frequently (12 percent) in projects conducted in medical schools, and as often in projects expected to benefit subjects as in other studies. The reason given for withholding information was usually to eliminate sources of bias in the study or because it was believe that the subject would not understand the information. The information not disclosed usually pertained to the purpose of specific procedures in the study or to the identity of the medication or treatment being used with particular subjects (as in double-blind research designs). In a few projects (two percent) investigators reported that subjects were given information that was untrue. Most of these projects were conducted in universities. The false information usually concerned the purpose of the procedures used in the study, and the reasons again pertained to the avoidance of bias in the data.

Subjects were paid in a few studies (seven percent of the studies expected to benefit subjects and 20 percent of other studies). These payments tended to be small—usually under ten dollars—but ranged as high as one or two hundred dollars in rare instances.

Despite the general use of consent forms and the evidence of IRB concern regarding such forms, concent forms tended to be inadequate, according to an analysis of the content and readability of the actual forms used in the research. On an index composed on six consent elements mentioned in DHEW regulations (45 CFR 46.103(c))—the purpose of the research, the procedures involved, the risks, the benefits, a statement that subjects are free to withdraw from the research, and an invitation to ask questions—only 18 percent of the forms were complete or nearly complete. Twenty-one percent of the forms from hospitals and medical schools were complete or nearly so, while this was true of less than 10 percent of the forms from universities and other institutions. Descriptions by investigators of the topics covered in oral explanations added only negligibly to the information that was transmitted to subjects.

Some elements received more coverage than others in consent forms. The procedures of the research were not mentioned in 10 percent of the forms; the purpose was not mentioned in 23 percent; neither the presence nor the absence of benefits to the subjects was mentioned in 45 percent. Risk was not mentioned in 30 percent of the forms, and 70 percent of these forms were in studies that were described by investigators as entailing at least a very low probability of minor harm to subjects. Even in consent forms in which these various elements were mentioned, fewer than half of the forms provided a detailed description. In some cases, these topics were mentioned only in statements saying "I certify that I have been informed of the purpose, procedures, and risks and benefits of this study." A statement regarding withdrawal from the study was not present in 22 percent of the consent forms; however, many of these may have been from studies in which the active participation of subjects ended quickly. An offer to answer questions appeared in more than half of the consent forms. A description of alternative treatments might have been expected in studies that were expected to be of benefit to subjects; however, this occurred in fewer than 20 Percent of the cases. Similarly, consent forms from projects described by investigators as including an "experimental" element might have been expected to mention this. About 60 percent of the consent forms from such projects, however, did not call attention to the experimental nature of the project through the use of words such as "experiment," "research," or "investigation."

A "reading ease score" was computed for each consent form, using a standard measure, the Flesch Readability Yardstick.* Consent forms tended to be written in academic or scientific language that may be difficult for the layman to understand. Descriptions of the procedures used in the research tended to be somewhat more readable than descriptions of the purpose or risks of the research; but overall, no more than 15 percent of the consent forms were in language as simple as is found, for example, in *Time* magazine. In more than three-fourths of the consent forms, fewer than ten percent of the technical or medical terms were explained in lay language. It is questionable whether many subjects would find most consent forms very useful to them in making decisions regarding participation in research. No information is available on the degree to which the difficult language of the consent forms is mitigated by oral explanations in simpler terms.

No relationship was found between the completeness and readability of consent forms. There was no tendency for the more complete consent forms to be either more or less difficult to read than were the less complete consent forms.

Comparisons were made of the pre- and post-review versions of consent forms from the same projects to attempt to elucidate why IRBs required many modifications in consent forms, yet approved forms that were frequently incomplete and difficult to read. No significant difference was found on the average reabability or completeness scores between consent forms as submitted to the IRBs and the consent forms as approved by the IRBs. This was true even on consent forms changed by the IRBs. Furthermore, an examination of forms as submitted for review showed no significant differences (in the expected direction) between those for which modification was requested by the IRBs and those for which no modification was requested. That is, the less readable and less complete forms were no more likely to elicit a request for modification than were the relatively readable and complete forms.

The performance of Institutional Review Boards. The present study included examination of differences among IRBs in the extent to which each (a) is comprehensive in its discussions of proposals, (b) has procedures to monitor the progress of research, (c) makes modifications in proposals to improve the protection of the rights and welfare of human subjects, (d) approves readable and complete consent forms, (e) is judged by IRB members to do a good job, and (f) is viewed positively by investigators.

Although a high score on any particular measure may not indicate an effective IRB, one that scores high on all of these aspects could presumably be judged to be effective, and an IRB that scores low on all of these aspects is presumably ineffective. However, no such patterns among the criteria emerged in the analysis of the data. Instead, it was found that an IRB's score on one of the measures tended to be unrelated to its score on the other measures. Thus, for example, there was no relationship between evaluations of an IRB by its members and by evaluations by the investigators whose research it reviews. Overall, four-fifths

* Rudolf Flesch, A New Readability Yardstick, Journal of Applied Psychology, Vol. 18, No. 3, June 1948, pp. 221-233. The "reading-ease score" is based on word length, i.e., the average number of syllables per 100 words, and sentence length, i.e., the average number of words per sentence.

of the specific indicators of performance showed no relationship to each other; of the few relationships found, almost as many were negative as were positive.

There were, however, some findings of interest regarding the relationship of the measures of performance. IRBs that most frequently made modifications in consent forms tended to approve the most complete consent forms. However, this appears to be an indirect effect of the IRBs' attention to consent forms, because the consent forms submitted to these IRBs were also more complete than those submitted to other IRBs. No similar effect regarding readability was found, nor was there any evidence of improvement (regarding readability or completeness) on consent forms as a direct result of changes required by the IRB.

There was also evidence that the Boards which make the most common types of modifications in proposals tend to receive lower evaluations from investigators. Thus, IRBs that made frequent requests for more information from investigators were evaluated in less positive terms by investigators. Similarly, at institutions where IRBs made relatively frequent modifications concerning consent, investigators more frequently disagreed with the statement that the IRB protects the rights and welfare of human subjects. These findings suggest that there may be a trade-off between IRB activity and investigator acceptance, particularly when investigators do not see a link between the IRBs' actions and the protection of subjects. Clear trade-offs among the measures of performance occurred infrequently, however.

IRBs whose work load included a large proportion of biomedical research tended to rank relatively high on many (though not all) criteria of performance. For example, they tended to make more modifications regarding consent and risk in proposals, they more often monitored projects, and they reported their discussions as relatively more comprehensive. On the other hand, they were more likely to approve research in which no provisions were made to protect the confidentiality of the data and to approve less readable, though more complete, consent forms.

In general, the procedures, policies and composition of IRBs showed relatively little relationship to the various measures of performance. Again, no consistent pattern emerged. Thus, for example, IRBs that assigned proposals to individuals or subcommittees for intensive review tended to make a greater variety of modifications in the proposals they reviewed. However, they did not make more frequent modifications, nor did they rank high on any other measure of performanced. IRBS for which approved proposals were subject to a subsequent review made more modifications regarding risk and scientific design than did other Boards, but they were no more likely than others to make other modifications in proposals (e.g., regarding consent) and they were less likely to monitor the actual conduct of the research.

The various measures of performance showed almost no relationship to either the presence of particular types of persons on the IRB or the overall heterogeneity of membership.

The operation of the review process was viewed more favorably than unfavorably by most research investigators and IRB members (see Table 2). However, a substantial minority, particularly of the investigators, felt that the review procedure is an unwarranted intrusion on the investigator's autonomy, that the IRB gets into inappropriate areas, that it makes judgments it is not qualified to make, and that it has impeded research. The problem (from a list of ten problems) most frequently indicated by Board Members was getting members together for meetings. More than one-fourth of the IRB members indicated as problems the need for rapid action to meet deadlines imposed by funding agencies, the lack of precise DHEW guidelines, and the time spent unnecessarily reviewing research with little risk.

Attitudes of Research Subjects. Investigators who found it appropriate to cooperate in this aspect of the research sent letters to their subjects indicating that the Survey Research Center wished to interview them about their experience in research. Only those subjects who returned a post card indicating willingness to be interviewed were contacted. This procedure was employed to protect the privacy of the subjects of the research under study, and it complicated the inherent difficulties of contacting such a sample. Thus, a true probability sample of research subjects was not obtained, and the sample cannot be considered representative. Furthermore, periods of up to a year had elapsed since some subjects' participation. These data, therefore, must be interperted with caution.

Most subjects or third parties recalled giving consent for participation, but one out of ten indicated that it was not understood that they were to be involved in "research." The majority, however, felt that they had been given clear, sufficient and accurate information about the project in which they participated. The single most prevalent reason for subjects' participation was the expectation of medical, psychological or educational benefits. Almost all of the respondents (98 percent) felt that participation was voluntary; most felt positively about the experience; and two-thirds felt that they (or the subject) benefited directly. Thirteen percent, however, said that they had experienced unexpected difficulties. About 70 percent said they would be very willing to participate in a similar study again.

Subjects and third parties who consented on their behalf offered a number of suggestions and comments. including the desirability (expressed by 19 percent) for additional information about the research and the need (expressed by 11 percent) for more care or courtesy on part of investigators in their treatment of subjects.

Summary. To summarize briefly the study's findings, IRBs are quite active in the review of proposed research. They modify over half the proposals reviewed. They are very concerned with informed consent and require modifications regarding informed consent in one-fourth of the proposals reviewed. There is a clear tendency for IRBs to approve research in which risk is related to benefits to subjects. On the negative side, IRBs' attention to the issue of informed consent is almost exclusively confined to consent forms, with IRBs having little other impact on the process by which consent is obtained. Nevertheless, consent forms were frequently deficient in content and tended to be difficult for the average layman to understand. Furthermore, no evidence was found that IRBs help to improve consent forms. Forms that are difficult to understand when first submitted to IRBs are no more understandable after they pass the review. Neither are they more complete.

IRB members and investigators were virtually unanimous in agreeing that the IRBs at their institutions help to protect the rights and welfare of human subjects, and most agreed that the procedures are reasonably efficient and even that they have had the effect of improving the scientific quality of research. There are some serious criticisms of IRBs as well, particularly from among social and behavioral researchers. Nonetheless, researchers as well as IRB members seem to recognize the need for the review of research, to accept the legitimacy of IRBs, and to be prepared to play a role in supporting the work of IRBs.

[4110–08–C]

Table 2

Attitudes of Different Types of Investigators and Review Committee Members Toward the Review Procedure and Committees

	Percent Agreeing with Each Statement					
	Review Board Members			Research Investigators		
	Biomedical Sciences (N=370)*	Behavioral & Social Sci. (N=135)*	Other (N=220)*	Biomedical Sciences (N=940)*	Behavioral & Social Sci. (N=395)	Other (N=180)
The human subjects review procedure has protected the rights and welfare of human subjects——atleast to some extent.	99%	99%	99%	99%	96%	98%
The review procedure has improved the quality of scientific research done at this institution——atleast to some extent.	78	62	70	69	83	83
The review procedure runs with reasonable efficiency——atleast to some extent.	99	96	99	96	94	94
The review procedure is an unwarranted intrusion on an investigator's autonomy——at least to some extent.	13	11	6	25	38	23
The review committee gets into areas which are not appropriate to its function——at least to some extent.	39	24	27	50	49	39
The review committee makes judgments that it is not qualified to make--at least to some extent.	28	21	20	43	49	25
The review procedure' has impeded the progress of research done at this institution——at least to some extent	26	30	22	43	54	36

* N's are approximate since non—response varied from item to item.

CHAPTER 3. LEGAL ASPECTS OF INSTITUTIONAL REVIEW BOARDS

While the courts have not been directly involved, a number of legal issues—including questions related to federal spending power, academic freedom, due process, tort liability, and open meetings and records—are relevant to the operation of IRBs.

Federal Spending Power. An IRB is created by the institution in which it operates. The institution selects the members and invests the IRB with authority to review research according to standards adopted by the institution. To obtain federal research funds, however, the institution must conform the composition, structure and duties of its IRB to DHEW regulations issued pursuant to the National Research Act (1974), *(1)* which directed DHEW to require that any institution receiving support must establish an IRB to review "research involving subjects conducted at or sponsored by the institution." Despite some ambiguity in the Act and in regulations implementing this directive, *(2)* DHEW requires IRB review of all research involving human subjects, whether or not federally funded. Although the power of Congress to regulate nonfunded activities through the funding power has been challenged in other contexts, it has not yet been definitively settled. *(3)* If the courts restrict Congress' power to regulate nonfunded activities as a condition of federal funding, however, it is likely that they will permit regulation of nonfunded activities when reasonably related to the purpose of the federal spending. *(4)*

If the purpose of research support by DHEW is to promote ethically conducted research involving human subjects, it could be argued that application of the regulations to all such research, whatever the funding source, reasonably advances protection of subjects in the DHEW-funded research. Requiring the same rules for all research in a given category might make the institution generally more aware of problems in protecting subjects and overseeing research, and might induce greater awareness, commitment and consistency in ethical concerns among investigators, all of which would enhance ethical conduct of federally funded research. While it could also be argued that review of all research is not essential to the protection of subjects in funded research and in some cases might even undermine that goal, *(5)* the condition appears closely enough related to the purpose of assuring ethically conducted research in the funded program to satisfy a rational relation test. *(6)*

Academic Freedom and Free Inquiry. Some have argued that the requirement of prior review and approval by an IRB violates constitutional rights of academic freedom and free inquiry. This question has not been specifically addressed by the courts, nor has a constitutional right to do research been recognized. Yet there is good reason to believe that if a case arose, the Supreme Court would recognize a First Amendment "right to research." *(7)* Such constitutional protection would not be precluded because research contains elements of conduct. *(8)* It would be anomalous if the publication and reading of a scientific article could not be prohibited, but the research that must occur before it were published could be.

If research is within the ambit of the First Amendment, then the government cannot regulate or restrict it on the basis of the ideas or knowledge sought (its "content"), but only on the basis of the manner in which the research is carried out. Thus, the state may not interfere with the researcher's choice of the end or topic of research, but may regulate only the methods used in the research, in order to protect interests in health, order and safety with which unrestricted research might conflict. Such restrictions are valid if they are reasonably related to protection of nonspeech interests and are not so vague and overbroad that they chill the exercise of protected speech. Thus, the state may restrict research methods to protect the health or autonomy of subjects, or the safety of the surrounding community, even if, in some instances, the restrictions prevent the research altogether. It could not, however, ban a study on the ground that the knowledge sought was undesirable unless it presented a clear and present danger of substantive harm within the state's power to prevent. Moreover, the clear and present danger test is a strict one, and requires that the harm from the knowledge sought be both imminent and substantial; *(9)* public offense or dislike for particular knowledge would not satisfy the test.

The IRB review process is essentially a system regulating the manner of conducting research in order to protect the interests of subject—interests which are independent of the knowledge sought or the uses to which it will be put. The researcher remains free to investigate the topic, as long as he uses methods that will not harm subject interests that the state or institution may validly protect.

Where the IRB system is imposed on researchers as a condition of employment, matriculation or receipt of research funds, the same constitutional limitations will not apply. Neither the government nor a university has a legal obligation to support research of any particular kind, nor hire researchers in any particular area. *(10)* Research allocation decisions may be based on an assessment that the research is important, acceptable to the community, or meets some other reasonable purpose of public spending. Thus, an institution may empower the IRB to apply both content and manner restrictions to research that it funds, whether or not such a system would be constitutional if directly imposed by the state on nonfunded research.

However, in imposing restrictions, the institution may restrict research only if it follows its own goverance procedures, which are usually incorporated into the investigator's contract of employment with the institution. Failure to follow those procedures may bar the institution from imposing sanctions on an investigator who fails to comply with IRB requirements. It may also technically invalidate institutional assurances, because the IRB would lack authority to do what it is assuring it will do. *(11)*

The need to observe governance procedures incorporated in employment contracts also applies to research in nonacademic settings, such as hospitals and private firms. Hospitals and health care institutions may regulate research conducted by their staff and on their premises, within the limits of the contractual relationship with research staff. If hospital by-laws allocate authority over these decisions to the medical staff or board of directors, then regulation can occur only if formally voted by these bodies. Private research firms or organizations may also be bound by contractual arrangements with staff.

Due Process. When an IRB modifies or disapproves research protocols, the liberty or property interests of investigators may be sufficiently affected to bring to bear the procedural due process rights developed by the Supreme Court in recent years for persons adversely affected by governmental decisions. *(12)* Since these rights attach only when there is "state action," they bind only those IRBs located in public institutions. *(13)* Unlike First Amendment rights, they probably cannot be withheld or waived as a condition of funding. *(l4)* IRBs in private institutions are not presently required to recognize these rights unless they are independently a part of their rules, regulations or by-laws and hence part of a researcher's contract with the institution, or required by state law. *(15)*

Once the threshold of governmental action affecting a liberty or property interest is crossed, the question then arises of what process is due the investigator. The IRB must of course act reasonably in applying criteria for protection of subjects, and it ordinarily cannot impose conditions or act on considerations not reasonably related to subject protection or other valid in-

stitutional concerns. Beyond a right to nonarbitrary action, the courts repeatedly emphasize the flexible or contextually relative nature of due process, finding different elements required in the particular circumstances of different decision-making contexts. However, the minimum required in any context is "some kind of notice and some kind of hearing"—notice that adverse action may be taken and its basis, and a chance to respond before a deprivation occurs. *(16)*

In the ordinary case of initial or continuing review, it should be constitutionally adequate if an IRB that plans to disapprove or require modifications in research informs the investigator of this possibility, with reasons, and of the opportunity to request reconsideration and personally appear before the IRB at its next meeting. In fact a recent case involving academic dismissal from medical school *(17)* suggests as long as the investigator has had the opportunity to present a written response to the IRB's decision, no formal hearing may be required. Such procedural safeguards as a right to counsel, cross-examination of adverse witnesses, burden of proof, and other elements of due process might be required in particular cases where an institution is imposing sanctions for unethical conduct or noncompliance with IRB conditions, but they probably are not required of IRBs in the ordinary course of initial and continuing review. Nothing, of course, prevents an institution or DHEW from requiring the IRB to extend procedural safeguards beyond the legal minimum. Due Process has never been held to include a right to appeal from an adverse governmental decision, civil or criminal.

Tort Liability. IRB members may be personally liable to subjects and investigators for "malpractice" or negligence in discharging their IRB functions. At the present time, few IRB members have been sued, though members of other medical peer review committees occasionally have been. *(18)* However, the possibility may affect the recruitment of IRB members, the scope of review, and the need to develop other systems of accountability.

On the principle that one who undertakes to protect others must act responsibly, IRB members could be liable if they did not exercise reasonable care in carrying out review. This might occur if their approval led to a research activity and injuries that would not have occurred if a reasonable person, confronted with the same information, would have placed conditions on the research that would have prevented the injury. Thus, an injured subject could allege negligence by IRB members in assessing the risks and benefits of proposed research, or in approving consent procedures not reasonably likely to assure legally effective consent. Negligence may also exist if continuing review of research is so perfunctory that subjects suffer preventable injuries or if the IRB knowingly permits evasion or noncompliance with the review process.

An investigator may also sue individual IRB members for negligent or malicious review that damages the investigator's legally protected interests. For example, if an investigator lost a research grant or otherwise suffered damages as a result of IRB decisions not taken in good faith, in timely fashion or with reasonable care, the investigator could claim tortious interference with business or contractural relations, though recovery would probably depend upon establishing malice or gross negligence. An investigator might also claim defamation against persons reporting incorrect information about his or her qualifications or conduct of research to an IRB, or against IRB members who convey such information to other IRB members.

In all these situations the law will probably hold IRB members to a standard of due care in assessing the risks, benefits and procedures for protecting the rights and welfare of subjects and interests of investigators. If failure to exercise due care in reviewing or monitoring research is causally related to a subject's or an investigator's injuries, then personal liability may be found. An IRB member will, of course, have the ordinary defenses of lack of negligence and causation. If the use of ordinary, reasonable care in decision-making can be established, there would be no liability. Even a lack of ordinary care will not lead to liability unless the plaintiff can establish that it proximately caused the injury; if the injury would have occurred even though the IRB had taken proper action, there is no liability. In jurisdictions where the doctrines of sovereign or charitable immunity protect the institution from the liability for actions of its IRB, IRB members could escape personal liability if they were deemed to be working as institutional officers in their IRB roles.

In some states IRB members may also have a defense based on statutes *(19)* that provide immunity for the decisions of medical peer review committees. These statutes were enacted to encourage thorough peer review by protecting members from suit. While they do not appear intended to include IRBs, their language in some instances may be broad enough to justify an argument that IRBs functioning as official hospital or medical staff committees are covered. But even if IRBs functioning in hospitals were held to be within such statutes, the immunity conferred may have little significance. Nonhospital based IRBs (the vast majority), and in many cases lay members of such committees, are not covered. Moreover, they generally provide immunity only against strict liability and may offer little protection against suits based on negligence. While it is conceivable that some courts would apply these statutes to claims of negligence against IRB members, the limited scope of protection they provide and the uncertainty of their coverage suggest that they will have little impact on the potential liability of IRB members.

In most jurisdictions, an IRB member or other person sued by an investigator for defamation may also have a defense of qualified privilege for statements made to the IRB in good faith without malice. *(20)* Since the purpose of the privilege is to encourage socially useful information, it would probably apply to statements relevant to the IRB's function of protection subjects. A qualified privilege may also be established by having the investigator agree as a condition of employment to waive any claim against persons who provide the IRB information about the investigator's qualifications or conduct of research, a procedure often used in applications for hospital staff privileges. *(21)*

Although liability for negligent IRB activities may be justified as a means to encourage IRB members to act responsibly, the possibility of liability may pose problems. While suits by investigators or subjects against IRBs have been extremely rare, some people may not serve on an IRB if they know that they risk suit. This fear could be minimized if institutions insured IRB members against liability. Where institutional employee status is necessary for insurance coverage, nonemployee IRB members, such as community members, could be made employees or agents of the institution for that purpose (this would not change their community status for purposes of meeting the DHEW membership requirements). *(22)* Since insurance against personal liability should eliminate reluctance to serve on IRBs, it may be unnecessary to provide immunity from all suits.

Compliance with IRB review requirements could possibly affect the tort liability of investigators who injure subjects in research that is unreviewed or not in compliance with IRB restrictions. In negligence *per se* jurisdictions, violation of IRB rules could be taken as evidence of negligence. In other jurisdictions, the widespread use of IRBs in the research community may create a standard of care for the conduct of all research. In both cases an injured subject would have to establish causation—that IRB

review would have averted the injury of lead to a different decision on consent.

Compliance with IRB review and approval conditions, however, will not necessarily shield researchers from liability. Approved procedures may be negligently carried out. In addition, while IRB approval may indicate whether research itself, in light of risks to subjects, is negligent, it would not foreclose a subject's claim that both the IRB and research have been negligent in reviewing and conducting the research at all. Nor is an IRB's view of adequate disclosure in the consent process determinative if state law requires more complete disclosure.

Public Access to IRB Meetings. Institutions vary in the openness of their IRB meetings. Although federal open meeting laws are not applicable, IRBs functioning in state, county or municipal institutions may not be legally free to decide whether their meetings shall be open or closed. State "sunshine" laws may require public access to IRB meetings, since IRBs may be considered public or governmental bodies within these statutes. *(23)* They are created by and function as instrumentalities of public institutions, such as state universities and hospitals, to which open meeting laws clearly apply. As subunits of governmental agencies, these IRBs would appear to be covered in some states. Whether they qualify depends on the wording of particular statutes and how courts confronted with the question will interpret them.

An IRB that is covered by a state open-meeting law must provide access to meetings to all members of the public, including investigators, subjects, subject representatives, and the press. As a corollary, the IRB must also give prior public notice of the time and place of its meetings. However, IRBs may generally hold closed sessions for certain matters, usually of a disciplinary or personnel nature. *(24)* An IRB, for example, could meet in executive session to decide whether to hire a particular staff person, recommend new members, or discuss an investigation or disciplinary action against a particular investigator. There might also be an exception if open consideration of a protocol involved discussion of the investigator's competence or jeopardized proprietary or patent interests.

Retention and Confidentiality of IRB Records. IRB review of research generates a variety of documents, including research protocols, consent forms, conditions of approval, requests for reapproval or changes in protocols, reports of adverse effects and continuing review, minutes of meetings, correspondence with investigators, and the like. Section 46.119(a) of the DHEW regulations requires retention of "copies of all documents presented or required for initial and continuing review" by the IRB. State laws requiring maintenance and retention of patient records for varying lenghts of time are not applicable to IRB records. even when the IRB functions in a hospital or medical school, for these laws pertain only to the patient's medical record and not the the records of hospital governance or peer review committees. *(25)* Thus, research activities carried out on hospital patients must be made part of the patient's chart and retained in this form as long as hospital records in that jurisdiction are retained.

In general, IRB records are not confidential unless they identify individual subjects who are patients; however, § 46.119(b) of the DHEW regulations prohibits disclosure of IRB records that identify particular subjects. Beyond these limitations, the institution of IRB may choose to make IRB records available to the public, the press or other investigators, except possibly where researchers could claim a confidential relation. *(26)* A more common practice is for institutions to treat IRB records as nonpublic documents. However, an institution's authority to withhold IRB records may be limited. IRBs in public institutions may, under open meeting and public records statutes, be required to make their records available, even though federal policy may permit the same protocol to be withheld until a project is funded. *(27)* Open-meeting laws generally require public access to the minutes of meetings as well as the meetings themselves. It is unclear, however, whether access to the minutes includes access to all written materials provided to IRB members, such as protocols and reports of monitoring, or merely the record of formal votes.

Whether or not a public IRB is covered by a state open meeting law, it may have an obligation to disclose protocols and other IRB materials under public records or state freedom of information statutes, which are often different in origin and coverage than sunshine laws. An IRB might not be a "state agency" or "governing body" for open meeting purposes, but may be a "public agency" or "local agency" for public records laws. If covered by these statutes, the IRB would also probably have to disclose protocols and other reports used or recieved by an IRB in the course of its business. While some "public records" may be exempted from disclosure if they meet statutory exemptions, as might occur with IRB monitoring of particular investigators or if patent or proprietary rights would be threatened, protocols of proposed research will probably not fit those exceptions and would have to be revealed.

Records of IRBs located in both public and private institutions may be subpoenaed in suits brought by subjects against investigators or by injured research subject who is suing the investigator (but not the IRB) would be able to discover and admit into evidence IRB records pertaining to conditions or restrictions which the IRB placed on proposed research. If the material sought from the IRB concerns its evaluation or assessment of how an investigator has carried out authorized research, however, the records probably would be held to be privileged. *(28)* Most states exempt such records from disclosure in order to encourage full and candid discussion of activities reviewed, a privilege likely to extend to IRB records as well.

FOOTNOTES

1. 42 U.S.C. 289L–3(a). The regulations now contained in 45 CFR Part 46 were first issued on May 30, 1974, 39 FR 18917, before passage of the act, and have been supplemented with provisions for research with pregnant women and fetuses. 45 CFR § 46.201–46.211.40 FR 33528, August 8, 1975.

2. *See, e.g.,* 45 CFR 46.10l(a), 46.102(a), 46.105(2).

3. For a discussion of this question and the Buckley Amendment, *see* Comment, "The Federal Conditional Spending Power: A Search for Limits," 70 *Northwest L. Rev.* 293, 310–321 (1975). It has also been raised in connection with Title IX of the Education Amendments of 1972, 20 U.S.C. 1232g.

4. *Id.* at 298–302. *See also United States v. Butler,* 297 U.S. 1 (1936); *Steward Machine Co. v. Davis,* 301 U.S. 548 (1937).

5. It might undermine that goal if review of nonfederally funded research was so time-consuming that the IRB could not give proper attention to federally funded research. Or the hostility engendered in investigators by such a requirement could undermine the efficacy of review of DHEW-funded research.

6. Since the facilities, devices, and even ideas used in non-funded research may have at some point been in interstate commerce, and the results of the research, if published or disseminated to others, might enter commerce, an alternative basis for upholding Section 212(a) would be as an exercise of the commerce power. (This justification would not apply if an investigator or institution could show that nonfederally funded research had no contact at all with interstate commerce.) Given the judicial tendency to interpret broadly interstate commerce, it would be difficult to show that the regulation did not affect interstate commerce. *See, e.g., Heart of Atlanta Motel, Inc. v. United States,* 379 U.S. 241 (1964); *Fry v. United States,* 421 U.S. 542 (1975).

7. *See* Robertson, "The Scientists' Right to Research: A 'Constitutional Analysis,' " *Univ. So. Calif. L. Rev.* (1978) (in press).

8. *United States v. O'Brien.* 391 US. 367 (1968).

9. *See generally, Schenck v. United States,* 249 U.S. 47 (1919); *Brandenburg v. Ohio,* 395 U.S. 444 (1969).

10. *Stewart Machine Co. v. Davis,* 301 U.S. 548 (1937); *Maryland Public Interest Re-*

search v. Elkins, 565 F.2d 864 (4th Cir. 1978).

45 CFR 46.104(b).

Board of Regents v. Roth, 408 U.S. 564 (1972); *Goldberg v. Kelley,* 397 U.S. 254 (1970); *Goss v. Lopez,* 419 U.S. 565 (1975). *See also, Board of Regents v. Horowitz,* 98 S.Ct. 948 (1978).

13. Unless there were a sufficient nexus between the state and the private entity to constitute state action under recent Supreme Court decisions. *See Moose Lodge No. 1070 V. Irvis,* 407 U.S. 163 (1972); *Jackson v. Metropolitan Edison Co.,* 419 U.S. 345 (1975).

14. Otherwise the state could eliminate all procedural due process protections in hiring and other contexts by making waiver of due process a condition of the grant or benefit. *See Arnett v. Kennedy,* 416 U.S. 134 (1974); *Bishop v. Wood,* 426 US. 341 (1976).

15. *See, e.g., Greisman v. Newcomb Memorial Hospital,* 192 A.2d 817 (N.J., 1963).

16. *Mathews v. Eldridge,* 424 U.S. 319 (1976); *Dixon v. Love,* 428 U.S. 406 (1977); Mashaw, "The Supreme Court's Due Process Calculus for Administrative Adjudicating in *Mathews v. Eldridge:* Three Factors in Search of a Theory." 44 *U. Chi. L. Rev.* 28 (1976).

17. *Board of Curators v. Horowitz,* 98 S.Ct. 948 (1978). *See also Mathews v. Eldridge,* 424 U.S. 319 (1976), in which a personal hearing prior to termination of social security disability benefits was not required. The value of that additional protection, given the narrowness of the issue and the opprotunity of the applicant to present his case in writing, was held not to justify the cost of providing the hearing.

18. *See, e.g., Purcell v. Zimbelman,* 500 P.2d 335 (Ariz. (1972). The chairman of the University of Maryland Medical School's IRB has been sued for approving research projects with jail inmates that did not provide for adequate informed consent. *Baily v. Mandel,* Civil Action No. K–74–110 (D.C. Md. 1974). *See also Nielsen v. Regents of the University of California,* Civil No. 665–049 (Superior Court of California, County of San Francisco, filed September 11, 1973), where an IRB member sued other IRB members to enjoin them from "approving, aiding, or abetting" a research project involving children.

19. For a general account of these statutes; *see* Reed Hall, "Hospital Committee Proceedings and Reports: Their Legal Status." 1 *Amer. J. Law and Med.* 245 (1975).

20 *Id.* at 254–258 and cases cited.

21. The standard disclaimer in many applications for hospital privileges is most likely immune from attack as unconscionable. *See* Hall, note 19 *supra; cf. Tunkl v. Regents of University of California,* 60 Cal.2d 92, 383 P.2d 441 (1963).

22. 45 CFR 46.106(b)(2).

23. *See generally,* D. Wickman, "Let the Sun Shine In," 68 *Northwestern L. Rev.* 480 (1973); *McLarty v. Board of Regents,* 200 S.E.2d 118 (Ga. 1973); *Cathcart v. Anderson,* 630 P.2d 313 (Wash. 1975).

24. *See generally,* Wickman, note 23 *supra* at 483–486. Not all state statutes provide for exceptions. *See, e.g.,* Fla. Stat. § 286.011 (1975).

25. Aspen Systems Corporation, *Hospital Law Manual,* pp. 2–5, 1977. Since an exhaustive survey of hospital record requirements in every state has not been made and individual states might now or in the future require retention of hospital peer review committee records, individual hospital-based IRBs should consult regulations applicable to them.

26. It is not clear whether under state law such a right would exist.

27. *See* National Commission for the Protection of Human Subjects, *Disclosure of Research Information Under the Freedom of Information Act,* DHEW Publication No. (OS) 77–0003, April 1977, pp. 7–15.

28. *See generally* on immunity of hospital committee records from discovery and admissibility, Hall, note 19 *supra;* Jacobs *et al.,* "Objection Overruled: The Fear That Quality Review Documents are Discoverable or Admissible in Court is Unfounded," *Quality Review Bulletin,* Jan./Feb. 1976. p. 28; *Bredice v. Doctors' Hospital, Inc.,* 50 F.R.D. (D.C. 1970).

CHAPTER 4, FEDERAL POLICIES FOR THE PROTECTION OF HUMAN SUBJECTS

Introduction. A survey of the policies, regulations, etc. for the protection of human research subjects at the various departments and agencies of the Federal government was conducted by the Commission's staff in 1975 and updated at the end of 1977. In the first phase, 61 federal departments and agencies* were queried to determine whether they conduct or support research involving human subjects and, if so, what policies or regulations are in force to protect the subjects. Twenty departments and agencies other than DHEW reported that they conduct or support research involving human subjects.** Four of these have components that operate under their own policies for the protection of human subjects, and, accordingly, the survey reports on 28 federal entities that conduct or support research involving human subjects outside the regulatory authority of DHEW.

As a result of the update, in which agencies were given the opportunity to comment on summaries of their original responses and to provide any revised materials it is believed that the survey covers all federal policies and regulations for the protection of human research subjects in effect on January 1, 1978.

Summary. It is clear that DHEW has been preeminent in the area of protection of human subjects of research. Almost all the other agencies that have formal policies or regulations governing such research follow (to a greater or lesser extent) the standards and procedures of DHEW; roughly half or these agencies impose additional requirements. The degree to which the other federal agencies monitor implementation and compliance varies, however; and nine agencies conducting or supporting research with human subjects have no formal policies to assure the protection of human subjects. Thus, the degree of protection afforded subjects of federally funded research varies from nonexistent to standards that exceed those imposed by DHEW. The norm, however, is substantial conformity with present DHEW regulations.

Of the 19 federal entities other than DHEW that have formal policies or regulations governing research with human subjects. 17 adopt DHEW standards and procedures to a substantial degree, and most of these cite DHEW regulations or policy as a reference. Among these 17 are four that follow DHEW regulations strictly, eight that follow DHEW regulations but impose some additional requirements (regarding composition of review boards, standards of review, or provisions for selection of subjects or informed consent) and five that have policies similar to those of DHEW without adopting DHEW regulations specifically and in their entirety. In a few instances, there is a different standard for triggering the provisions of the regulations.

Approximately one-third of the government entities that support or conduct research with human subjects have no formal policies or procedures to protect such subjects; however, most of the research supported by those agencies consists of questionnaires and surveys (activities about which there is presently no uniform understanding with respect to the nature and extent of protective mechanisms that should be applied). Only two agencies—the Law Enforcement Assistance Administration (LEAA) and the Department of Housing and Urban Development (HUD)—support research involving active intervention in the lives or behavior of subjects and have no formal policies or procedures for reviewing the ethical acceptability of such research or for assuring the adequacy of informed consent.

Findings. Twenty federal departments or agencies, other than DHEW, reported that they conduct or support biomedical or behavioral research with human subjects. Four of these (the departments of Commerce, Defense, Justice and Transportation) have separate subsidiary components that operate under their own policies or regulations for the protection of human subjects. Thus, there are a total of 28 federal entities that regulate the conduct or support of research with human

*Of the 77 federal agencies listed in the U.S. Government Manual, 16 were excluded as highly unlikely to conduct or support research with human subjects. Such agencies included, for example, the Federal Property Council, the American Revolution Bicentennial Commission, the Farm Credit Administration, and the Overseas Private Investment Corporation.

**In 1975, 21 agencies reported that they conduct or support research with human subjects; however, two of these were subsequently combined in the Department of Energy, reducing the number of agencies that conduct such research to 20.

subjects outside the authority of DHEW.

Of the 28 federal entities, nine have no formal policies or regulations for the protection of human subjects. Three of these are within the Department of Transportation, which is in the process of developing departmental regulations in this area. Four others are involved primarily in survey research entailing no intervention in the lives or activities of the subjects: the Civil Service Commission, the Commission on Civil Rights, the Internal Revenue Service and the United States Information Agency. Although their activities fall within the Commission's definition of research with human subjects, it should be noted that data gathering, in and of itself, has not universally been considered "research with human subjects." Since the Privacy Act of 1974 sets forth conditions for maintaining confidentiality of data and the Office of Management and Budget reviews the appropriateness of all questionnaires sent out by federal agencies, there would appear to be minimal risk presented to respondents of such surveys. Real concern is raised only with respect to the remaining two agencies that lack formal policies, LEAA and HUD. Both of these agencies support behavioral or social research involving systematic changes or interventions in people's lives for the purpose of determining the effects of an intervention or comparing the effects of one intervention with those of another. This clearly constitutes research with human subjects. LEAA states on the record that it does support behavioral research involving human subjects***; HUD states that it does not. This problem is explored more fully, below.

Three departments have review procedures designed to assure technological soundness of the research and safety of the subjects, but have no review of ethical acceptability of research *per se.* The National Oceanic and Atmospheric Administration and the Federal Aviation Administration require technical review, safety provisions, fitness standards and medical supervision. *(1)* Similarly, although the Navy adopts DHEW standards and procedures for its intramural research, it requires of contractors only that they make adequate safety provisions and conform to the ethical standards of the American Medical Association. *(2)*

Five agencies have formal policies or regulations that are substantially similar to, but not entirely consistent with, those of DHEW. For example, the Bureau of Prisons requires local review by a board composed of two prison officials, a research analyst, a psychologist, an inmate, a representative of the employees union and a representative of the community. Although the consent provisions adopted by the Bureau are those of DHEW, the review standards differ. Proposals are reviewed for relevance to the mission of the Bureau, potential benefits to mankind, professional standing of the investigator, and assurance that the research will not adversely affect ongoing programs. The Bureau also requires all research involving inmates to be approved by the Director of Prisons, and it absolutely prohibits medical experimentation and drug testing. The Bureau is "guided by" the Nuremberg Code and states that it relies on the investigators to protect the rights and lives of subjects. *(3)* Similarly, the National Aeronautics and Space Administration (NASA) adopts the review standards and consent provisions of DHEW, but the IRBs that review research consist entirely of NASA personnel, primarily staff physicians and scientists. In one research center, a representative from the office of general counsel is also included; in the other research center, a personnel officer is included. Following review by the IRB, all research proposals must receive the approval of the installation's medical officer, general counsel and safety officer before being forwarded to the director of the installation for final review and approval. *(4)* Other agencies that follow DHEW standards or procedures with some variation include: the clinical investigation program of the Air Force, the Bureau of Standards, and the Agency for International Development.

Four agencies adopt DHEW regulations by reference, with no additions or modifications: The Consumer Product Safety Commission, the Department of Energy, the National Academy of Sciences, and the National Science Foundation. Eight agencies adopt DHEW provisions br reference but add various other provisions relating to applicability, IRB composition, review standards, consent procedures and selection of subjects. For example, the Environmental Protection Agency (EPA) exempts from its regulations opinion polls and questionnaires, projects involving merely collection of blood, urine, mothers' milk or nonviable fetal tissue, and medical observations that are not preceded by purposeful exposure to chemcials or environmental conditions under investigation. (EPA is developing a different set of regulations to govern such activities.) EPA also prohibits testing for possible carcinogenic effects on human subjects.

With regard to IRB composition, the Army and the Air Force require that the IRB include a lawyer and a clergyman; the Air Force adds that there should be three lay members of the IRB but that the chairman should be a physician. The draft Intelligence Community Directive contains the provision that no more than one-half of the members of an IRB may be members of the Intelligence Community.

Some agencies impose review standards additional to those of DHEW, including: prior animal studies, use of minimal number of subjects and avoidance of unnecessary physical and mental discomfort (Army, Navy and Air Force); performance of adequate physical and psychological examinations before, during and after participation in research, and provision of compensation that will be commensurate with the risk involved but not so excessive as to constitute undue inducement (National Highway Traffic Safety Administration). With respect to informed consent, the Army, Navy and Air Force require the consent procedure to be witnessed in all cases, and the Red Cross requires investigators to inform subjects of any abnormalities discovered during the conduct of the research but to keep such information confidential unless specifically released from that requirement by the donor (subject) or the donor's legal representative. The Army, Navy and Air Force also have special consent provisions for children and the mentally disabled.

In addition, the Department of Agriculture requires that selection of subjects be made without regard to sex, race, color, religion or national origin unless these characteristics are factors to be studied, and it specifically excludes pregnant and lactating women from studies involving food additives or chemicals not recognized as safe by the Food and Drug Administration (FDA), EPA or the Animal and Plant Health Inspection Service. Similarly, the Army and Navy (but not the Air Force clinical investigation program) exclude prisoners from participation in research; the Navy also excludes the institutionalized mentally infirm. The Air Force aerospace research program excludes children, prisoners, the mentally incompetent and females (unless there is resonable assurance that there is no concomitant pregnancy and methods adopted for contraception assure against increased risk).

Miscellaneous provisions include requirements that investigators conform to the provisions of the Privacy Act of 1974 and, in some instances, that such fact be disclosed on the consent form. Several agencies require debriefing fol-

***LEAA specifically prohibits the use of its funds for biomedical research except for projects generally recognized and accepted as not involving physical or psychological risk to subjects, and specifically approved by the Office of Administration after consultation with DHEW.

lowing research involving incomplete disclosure, the Veterans Administration provides a mechanism for appeal from an IRB's decision, and the Army, Navy and Air Force specifically provide for treatment of injuries arising as a consequence of participation in research. Finally, a number of agencies specifically apply their regulations to research conducted outside the United States and require that such research conform, in addition, to the legal and ethical standards of the country in which the research will be conducted.

Problems Identified. As the preceding discussion makes clear, the protection of human subjects in federally funded research is far from uniform despite the great number of agencies that substantially follow the standards and procedures of DHEW. The extent of protection ranges from nonexistent to a plethora of requirments imposed in addition to those of DHEW regulations. Just as the lack of formal policies and regulations is a serious problem, so too is the confusion that may result from the many variations presented by agencies that have imposed manifestly reasonable but diverse additions or modifications to the DHEW standards. An IRB that reviews projects funded by different agencies must face the difficult task of satisfying multiple (and perhaps incompatible) requirements regarding applicability of the regulations, IRB composition, review standards, consent procedures, selection of subjects and so forth. To do so requires referral to the funding agency's particular provisions after first identifying the source of support for each proposed project. The administrative burden imposed thereby can be immense; and the problem is compounded by the fact that some projects receive support from two or more federal agencies.

Another problem arises from the lack of a uniform definition of "research with human subjects." Thus, when federal agencies conduct or support social experimentation, they may not consider it necessary to apply procedures for the protection of human subjects. For example, HUD submitted a number of printed materials to the Commission describing its housing allowance "experiments" in which subjects are selected according to predetermined criteria, assigned to different "treatment groups" according to the research "design," and followed for a period of years through periodic interviews and inspections to determine the different effects on the recipients' behavior of the various housing allowance schemes under study. *(5)* Nevertheless, despite the fact that HUD describes the "experiments" in terms of a systematic intervention into people's lives in order to gather data by which to answer specific questions, the department: stated in response to the Commission's inquiry that HUD has "never sponsored any human subject or biomedical studies." *(6)*

Similarly, in 1975 Medicaid recipients successfully challenged an experiment (supported by DHEW) designed to assess the effects of requiring a copayment for medical care, on the grounds that it had not been reviewed by an IRB *(Crane v. Mathews (7)).* The Secretary of Health, Education, and Welfare argued that the project was not "research with human subjects" and that therefore the review requirements were not applicable. the court disagreed and stopped the project pending review and approval by an IRB.*

These examples suggest that the term "research with human subjects" is not uniformly understood. A uniform definition would be helpful to Federal agencies that may be unsure as to whether certain programs which they support fall within the category of activities to which procedures for the protection of human subjects should apply.

Another problem is the lack of central coordination of research activities in some departments, and the absence of high-level staff sufficiently knowledgeable to supervise the protection of human subjects in projects conducted or supported by various components of the department. For example, EPA reported in 1975 that "it is the policy of the Environmental Protection Agency to comply fully with the policies and practices established by the Department of Health, Education, and Welfare to protect human subjects in our research program." *(9)* This statement, however, apparently referred only to research conducted under the auspices of EPA's Environmental Research Center at Research Triangle Park, North Carolina. It appears that other components of EPA also supported research involving human subjects, but without the constraints imposed upon the research conducted at Triangle Park. It was recently revealed *(10)* that a contract with a Mexican gynecological hospital to study the effects of ingesting a massive amount of fungicide narrowly missed being put into effect. The original plan had been to conduct the tests in the U.S., but the IRB that reviewed the protocol found the risks excessive. It was reported that EPA staff therefore agreed with the contractor to conduct the tests in a Mexican gynecological hospital, but a fortuitous review prevented approval of the contract. EPA has since forbidden the testing of carcinogens on human subjects under its auspices and has required that all future EPA research comply with DHEW regulations for the protection of human subjects. *(11)*

Similarly, although DHEW regulations "are applicable to all Department of Health, Education, and Welfare grants and contracts supporting research, development, and related activities in which human subjects are involved," *(12)* implementation of the regulations is not uniform within the Department. For example, the Education Division (which includes the National Institute of Education (NIE), the Office of Education (OE) and the National Center for Education Statistics) takes the position that it is not subject to the Department's regulations because it has statutory authority to write its own regulations. *(13)* Therefore, present NIE and OE regulations require that research conducted or supported by the components of the Education Division comply with the DHEW *Grants Administration Manual* Chapter 1–40 and the DHEW Procurement Rules. *(14)* These both require IRB review only when the investigator determines that the research subjects will be at risk (as was the case in earlier DHEW policy). The Center for Disease Control (CDC) also follows the old Institutional Guide to DHEW Policy, in which IRB review is not triggered unless the investigator determines that the subjects of his or her research will be at risk. (The Commission has been advised that CDC's policies will be updated "in the near future" to incorporate the provisions of current DHEW regulations and the Commission's recommendations on research involving children. *(15)*

The regulations of FDA governing research regulated by that agency in the course of approving applications for new drug investigations and licensing, differ from the regulations governing research supported by DHEW in that IRB review is required by FDA only when the subjects of the research are institutionalized, or when the investigator already is "affiliated with an institution which agrees to assume responsibility for the study." *(16)* Investigators lacking such affiliation apparently may conduct research with human subjects without such review. (The Commission has been informed that FDA is drafting proposed regulations that would extend the requirement for IRB review to all human experimentation under its regulatory jurisdiction, thus conforming to regu-

*An IRB subsequently reviewed the project and determined that the subjects would be at risk of physical harm as a result of being required to pay for necessary medical care. The IRB further determined that the benefits of the proposed research did not weigh the risks and that the research design was "so seriously inadequate that it would be very unlikely to provide any accurate or reliable information upon which to base policy decisions regarding Medicaid copayments." It therefore disapproved the project.

lations governing research conducted or supported by DHEW.) FDA regulations also permit a waiver of the consent requirement if the investigators "deem it not feasible or in their professional judgment contrary to the best interests" of the subjects. *(17)* This is explained as applying to cases in which (1) the communication of information to obtain consent would seriously affect the patient's well-being or (2) the patient is in a coma or is otherwise incapable of giving consent. his representative cannot be reached, and it is imperative to administer a drug without delay. *(18)*

In summary, most of the departments and agencies of the federal government that have formal policies or regulations governing research with human subjects follow the standards and procedures of DHEW, at least to some extent. However, the nature and extent of the deviations from the DHEW regulations are such that the protection of human subjects in federally funded research is far from uniform, and the administrative burden of implementing diverse sets of standards is unnecessarily great. Further, some agencies have no policies or regulations governing such research because, in large measure, there is confusion regarding the kinds of activities to which such regulations should apply.

FOOTNOTES

1. National Oceanic and Atmospheric Administration, Department of Commerce, NOAA Diving Regulations, *NOAA Diving Manual,* Appendix C, U.S. Government Printing Office, Washington, D.C., 1976; Federal Aviation Administration Order 9950.3A (December 8, 1974).

2. Office of Naval Research, Code 600 Memorandum No. 97A (27 March 1974).

3. Bureau of Prisons, Draft revision of October 1967 Policy Statement 6110.1, to be published in Spring 1978; Policy Statement 3700.3 (June 10, 1977).

4. NASA, Management Instruction 7100.8 (February 2, 1972); Ames Management Manual 7170–1 (as revised March 19, 1969); Ames Memorandum 74/200 (December 11, 1974); Johnson Space Center Management Instruction 7100.8A (March 29, 1977).

5. Department of Housing and Urban Development, *The Experimental Housing Allowance Program* (1974); *Second Annual Report of the Experimental Housing Allowance Program* (1974); and *Experimental Housing Allowance Program Initial Impressions and Findings* (1975).

6. Letter (Nov. 18, 1977) to the Commission's Staff Director from Patricia M. Worthy, Deputy Assistant Secretary for Regulatory Functions, Department of Housing and Urban Development.

7. 417 F. Supp. 532 (N.D. Ga. 1976).

8. Clarification Statement Regarding the Georgia Department of Human Resources Human Research Review Boards Review of the Proposal Entitled "Recipient Cast-Participation in Medicaid Reform," Russell J. Bent, Chair.

9. Letter (Oct. 20, 1975) from Roy E. Albert, M.D., Acting Deputy Assistant Administrator for Health and Ecological Affairs, Environmental Protection Agency.

10. Bob Wyrick, "EPA Officials Devised Cancer Tests on People," *Washington Post* June 22, 1977.

11. Environmental Protection Agency, Order 1000.17, October 25, 1977.

12. 45 CFR 46.101.

13. General Education Provisions Act, 20 U.S.C. 1221e(3).

14. 45 CFR 100a.263; 45 CFR Part 1400.

15. Letter (Feb. 6, 1976) from David J. Sencer, M.D., then Director, CDC; telephone communication (Nov. 14, 1977) from Bruce Dull, M.D., Assistant Director of Program, CDC.

16. 21 CFR 312.1(a)(2) 10C; FDA *Compliance Program Guidance Manual,* transmittal 77–39, March 15, 1977.

17. 21 CFR 310.102(a).

18. *Id.,* subsections (f) and (g).

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