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Human Experimentation: The Review Process in Practice

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Human Experimentation: The Review Process in Practice

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Institutional peer review is now a firmly established mechanism for the oversight and control of the use of human subjects in medical experimentation. Dr. Cowan describes in detail the structure and operation of two institutional review boards with which he is familiar. The author also outlines some of the difficulties that these procedures and existing federal regulations pose for both researchers and policymakers.

> For we must not deceive ourselves, morals do not forbid making experiments on one's neighbor or on one's self; in everyday life men do nothing but experiment on one another. Christian morals forbid only one thing, doing ill to one's neighbor. So, among the experiments that may be tried on man, those that can only harm are forbidden, those that are innocent are permissible, and those that may do good are obligatory.[1]

I. BACKGROUND

SINCE 1966, all research and research training grants involving human beings and supported by the United States Public Health Service (PHS) have been subject to peer review by local institutional committees on human investigation. This review was mandated by the Surgeon General for all recipients of PHS grants.[2] Since the vast majority of investigators engaged in human experimentation received some or all of their support from the PHS, the promulgation of the policy requiring prior review of proposed projects involving humans was followed by the establishment of review committees in all institutions sponsoring such activities in the United States.

The original PHS guidelines required that institutional peer review "should assure an independent determination of (1) the rights and welfare of the individual or individuals involved, (2) the ap-

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1. C. BERNARD, AN INTRODUCTION TO THE STUDY OF EXPERIMENTAL MEDICINE 101-02 (2d ed. H.C. Greene transl. 1949).

2. Memorandum from Surgeon General, Public Health Service, to the Heads of Institutions Conducting Research with Public Health Service Grants, Feb. 8, 1966, on file at *Case Western Reserve Law Review*.

propriateness of the methods used to secure informed consent, and (3) the risks and potential medical benefits of the investigation."[3] The review was to be done by a "committee . . . made up of staff of, or consultants to, [each] institution who [were] at the same time acquainted with the investigator under review, free to assess his judgment without placing in jeopardy their own goals, and sufficiently mature and competent to make the necessary assessment."[4] It was considered "important that some of the members be drawn from different disciplines or interests that do not overlap those of the investigator under review."[5]

Impetus for the establishment of some guidelines for the regulation of human research was initially provided by the revelations at the Nuremberg trials of the Nazi atrocities committed in the name of medical science during World War II. The first set of guidelines established was the Nuremberg Code,[6] which had as its central tenet the voluntary consent of the subject involved. The rapid expansion of medical research after World War II required the involvement as subjects of increasing numbers of individuals. There arose a multiplicity of complex moral and ethical problems requiring discussion and clarification. In 1964, the World Medical Association issued a code of ethics on human experimentation known as the Declaration of Helsinki.[7] The Declaration of Helsinki emphasized the rights of the individual subject, the principle of informed consent, and the concept that the "importance of the objective [be] in proportion to the inherent risk to the subject."[8] Additionally the Declaration of Helsinki drew attention to the "fundamental distinction . . . between clinical research in which the aim is essentially therapeutic for a patient, and clinical research the essential object of which is purely scientific and without therapeutic value to the person subjected to the research."[9] The Declaration also enunciated the principles that clinical research should be based on adequate scientific background

3. *Id.* at 1.
4. *Id.* at 2.
5. *Id.*
6. United States v. Brandt, 2 Trials of War Criminals Before the Nuremberg Military Tribunals (The Medical Case) 181-82 (Military Tribunal I, 1947).
7. World Medical Ass'n, *Human Experimentation: Code of Ethics of the World Medical Association, Declaration of Helsinki*, 2 BRIT. MED. J. 177 (1964).
8. *Id.*
9. *Id.*

and experimental design and that responsible investigators should be "scientifically qualified persons."[10]

The Declaration of Helsinki was officially endorsed by the major organizations concerned with clinical investigation and the major medical societies in the United States.[11] Thus, despite some earlier reservations on the part of university departments of medicine regarding the value of a procedural document dealing with human investigation and the value of review committees,[12] the major thrust of the PHS directive of 1966 was in accord with the announced consensus of the biomedical research community. It is pertinent to add that the Surgeon General's directive was also, in part, a response to a new public mood regarding human experimentation. The new public concern was based on an awareness of reported abuses of individuals such as the well-publicized episode at the Jewish Chronic Disease Hospital in Brooklyn, wherein live cancer cells were injected into human subjects apparently without their consent.[13]

In 1971, the PHS revised and expanded its earlier policy statement regarding human experimentation.[14] The revised policy incorporated comments and suggestions by representatives of grantee and contractor institutions and reflected the experience gained from implementation for several years of the earlier policy. The policy is applicable to "all grants or contracts which support activities in which subjects may be at risk."[15] An individual is considered to be "at risk" if he may be exposed to the possibility of harm—physical, psychological, sociological, or other—as a consequence of any activity which goes beyond the application of those established and accepted methods necessary to meet his needs.[16] In essence, the policy applies to any investigative study involving humans which goes

10. *Id.*

11. A listing of endorsing organizations is contained in World Medical Ass'n, *Human Experimentation: Declaration of Helsinki*, 65 ANNALS OF INTERNAL MED. 367, 368 (1966).

12. *See* Welt, *Reflections on the Problems of Human Experimentation*, 25 CONN. MED. 75 (1961).

13. *See* Langer, *Human Experimentation: New York Verdict Affirms Patient's Rights*, 151 SCIENCE 663 (1966); *cf.* Hyman v. Jewish Chronic Disease Hosp., 15 N.Y.2d 317, 206 N.E.2d 338, 258 N.Y.S.2d 397 (1965).

14. NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U.S. DEP'T OF HEALTH, EDUCATION AND WELFARE, THE INSTITUTIONAL GUIDE TO DHEW POLICY ON PROTECTION OF HUMAN SUBJECTS (U.S. Dep't of Health, Education, and Welfare Pub. No. [NIH] 72-102, 1971) [hereinafter cited as THE INSTITUTIONAL GUIDE].

15. *Id.* at 1.

16. *Id.* at 2.

beyond currently accepted diagnostic or therapeutic procedures.

The revised basic policy, now reflected in regulations[17] promulgated by the Department of Health, Education, and Welfare (HEW) in May 1974,[18] has the following essential elements: (1) The institution receiving HEW funds or accountable to HEW for funds awarded for the support of research involving human subjects shall be responsible for safeguarding the rights and welfare of those subjects.[19] (2) All requests for grants and contracts must be reviewed and approved by an appropriate institutional committee to assure adequate discharge of this institutional responsibility before the grants or contracts will be made by HEW.[20] (3) The review by the institutional committee shall determine that the rights and the welfare of the subjects are adequately protected,[21] that the risks to an individual are outweighted by the potential benefits to him or by the importance of the knowledge to be gained,[22] and that informed consent is to be obtained by methods that are adequate and appropriate.[23] (4) There must be continuing review of research activity involving human subjects by the institutional committee.[24] (5) The institution must submit for HEW review, approval, and official acceptance, an assurance of its compliance with this policy.[25] Additionally each proposal involving human subjects must be accompanied by a certificate provided by the institution stating that the proposal has been or will be reviewed in accordance with the institution's assurance.[26] (6) Grants or contracts for research involving

17. 45 C.F.R. §§ 46.1-.22 (1974). These regulations in effect formalized the guidelines set forth in THE INSTITUTIONAL GUIDE.

18. The Public Health Service Act has been amended by the National Research Service Award Act of 1974, Pub. L. No. 94-348, 88 Stat. 342. In accordance with the new Act, the Secretary of HEW has promulgated new regulations. 40 Fed. Reg. 11854 (1975).

These most recent amendments are technical in nature and were promulgated as this issue went to press. The amendments substitute the words "institutions" and "Institutional Review Board" for existing references to "organizations" and "committees" respectively. The amendments eliminate the inconsistent terminology between the National Research Service Award Act of 1974 and HEW regulations. Other changes are minor and may be found by consulting 40 Fed. Reg. 11854 (1975).

19. 45 C.F.R. § 46.2(a) (1974).

20. *Id.*

21. *Id.* § 46.2(b)(2).

22. *Id.* § 46.2(b)(1).

23. *Id.* § 46.2(b)(3).

24. *Id.* § 46.6(b).

25. *Id.* § 46.4(a).

26. *Id.* § 46.11(a).

human subjects will only be made to individuals who are affiliated with or sponsored by an institution which can and does assume responsibility for the protection of the subjects.[27] (7) No grant or contract involving human subjects shall be made unless the proposal for such support has been reviewed and approved by an appropriate professional committee within the responsible component of HEW.[28]

II. THE REVIEW PROCEDURE IN PRACTICE

Within this general framework, institutions are free to devise the policies and procedures which they determine to be applicable to the local situation. The PHS has thus charged the local institutional committees with the tasks of formulating policies, administering those policies, and evaluating the consequences of the policies. The extent and manner in which different institutions have responded to the Surgeon General's directive varies.[29] The manner in which Case Western Reserve University (CWRU) has developed and currently implements and evaluates policy on human experimentation illustrates one approach taken in response to the PHS directive. Fundamental to the development and implementation of policy in this area by CWRU was and is the concept that human experimentation is a cooperative venture between the investigator and the subject whereby "the rights of society and the rights of individual subjects are protected at the same time that faculty investigators are privileged to carry out the mandate to advance knowledge."[30]

A. *The Procedure at University Hospitals of Cleveland*

After the announcement of the federal policy in 1966, CWRU organized and identified for administrative purposes seven jurisdictional areas. These areas are the School of Medicine, three affiliated teaching hospitals (University Hospitals of Cleveland, the Veterans

27. *Id.* § 46.2(c).

28. *Id.* § 46.2(a).

29. For a review of the policy of the University of California at San Francisco, see Melmon, Grossman & Morris, *Emerging Assets and Liabilities of a Committee on Human Welfare and Experimentation*, 282 NEW ENG. J. MED. 427 (1970).

30. Case Western Reserve University Council on Research Involving Human Subjects, University Policy on the Involvement of Human Participants in Research, Training, Demonstration and Related Activities, Nov. 30, 1972, at 1 [hereinafter cited as University Policy], on file at *Case Western Reserve Law Review.*

Administration Hospital, and Cleveland Metropolitan General Hospital), the School of Dentistry, the School of Nursing, and all other schools combined (including basic, social, and behavioral sciences). Within each area an essentially independent review group was established. The practice of protocol review was not new to University Hospitals. This institution had been actively reviewing protocols involving human subjects since the establishment, with PHS support, of its Clinical Research Center in 1960.

The activities of each of the independent review groups within the University are guided by the regulations laid down by HEW[31] and by the policy adopted by CWRU[32] in conformity with the HEW regulations. The policy of CWRU goes beyond the spirit and letter of the recommendations and requirements formulated by the PHS and is on file with the National Institutes of Health (NIH) as required by the regulations.[33]

Each review committee has approached its assigned responsibilities differently. These differences have included the size and composition of the committees, the duration of service for the members, the frequency of meetings, the procedure for handling protocols, and the manner of communication with project directors. Necessarily, the policies, procedures, and activities of the committees have reflected the size, interests, and diversity of the staffs of the institutions. The differences may be illustrated by a description of the committee structure and the route a protocol travels at two of the institutions, University Hospitals (UH) and Cleveland Metropolitan General Hospital (CMGH). The protocols reviewed by the institutional committees are not the detailed grant applications or contract proposals that are submitted to the NIH (or other agency) for funding. Rather, they are separate protocols, which include a capsule summary of the research project and detailed considerations of all factors pertinent to the use of human subjects in the proposed project.

Because of its geographical proximity and unique administrative relationship to the School of Medicine, the Clinical Review Committee of University Hospitals reviews protocols from the School of Medicine and the School of Nursing, as well as protocols from University Hospitals. Initially, the Dean of the School of Medicine served as chairman of the committee, which was comprised of the departmental chairmen. Since the Dean occupied a position outside of and

31. *See* note 17 *supra.*
32. University Policy, *supra* note 30.
33. 45 C.F.R. § 46.7 (1974).

superior to the departmental chairmen, this provided a means for resolving differences between different departments. Because of the burden this placed on an individual who already had a substantial number of duties and responsibilities, it was felt appropriate after several years to relieve the Dean of this particular task. Accordingly, the Chief of Staff of UH became the chairman of the committee with the same perquisites as the Dean.

As noted, the committee initially was comprised of the chairmen of the different departments. It was found, however, that the chairmen were not necessarily the most knowledgeable individuals to review diverse proposals and that their time commitments often prevented them from devoting adequate attention to the tasks of the committee. The chairmen were therefore permitted to designate departmental representatives, subject to approval by the Chief of Staff. The Clinical Review Committee of UH now includes a faculty member from the Department of Pharmacology and each of the clinical departments—including radiology, pathology, and anesthesiology—and two representatives from the School of Nursing. A community representative, presently the Director of Health of Cuyahoga County, and an attorney complete the committee membership. The Secretary of the Clinical Research Center serves as secretary of the committee. The tenure of each member of the committee is indefinite, being determined primarily by the willingness of the member to serve and the discretion of the departmental and committee chairmen. Responsibility for the overall activity and effectiveness of the committee resides in the chairman.

All persons with appointments at CWRU are subject to the University regulations, which apply to those conducting human experimentation whether or not research undertaken by them is supported by the PHS.[34] When an investigator proposes to undertake a research project involving human subjects, he must first prepare a summary of the contemplated investigation. The summary must include a description of the purposes of the study, the methods to be used, the nature and number of human subjects involved (*e.g.*, normal controls, patients with specific diseases), the manner in which prospective subjects will be solicited and selected for study, the risks to the subjects and the potential benefits to be derived, the precau-

34. A small but very significant amount of biomedical research is funded by private groups or corporations such as the American Cancer Society, the American Heart Association, and local groups such as the Cleveland Kidney Foundation.

tions that will be taken to prevent or deal with complications resulting from the investigation, the manner in which informed consent will be obtained, and copy of the consent form to be used. In experiments involving the use of investigational new drugs, the manner of procuring consent must conform to Food and Drug Administration (FDA) policy.[35]

The proposal is first sent to a departmental committee, which reviews the protocol before forwarding it with recommendations to the departmental chairman for approval. The departmental review screens out poorly conceived or inadequately documented protocols. The responsibility for departmental action and approval lies with the departmental chairman. After obtaining departmental approval, any protocol having special features, such as those involving the use of radioisotopes or experimental drugs, is forwarded to the appropriate committee (*e.g.*, Isotope Committee) for review of the special procedures. All protocols dealing with cancer projects are reviewed in a similar manner by the Cancer Coordinating Committee of UH. Once a protocol has been approved by appropriate special review committees, it is submitted to the full Clinical Review Committee. Each of the members of the general committee is expected to review and familiarize himself or herself with each protocol. In addition, each protocol is assigned to two members of the committee who review it in detail. The members responsible for the detailed review present the protocol to the committee for discussion and outline any deficiencies or aspects of the protocol that require clarification or revision. If the committee members feel they lack the expertise to evaluate a given protocol they may enlist the opinion of an outside consultant. The consultant need not be a member of the staff of University Hospitals or CWRU School of Medicine. Following thorough discussion of the protocol, the committee may vote to approve, disapprove, or defer action on a protocol. Often further clarification is needed regarding research methods to be used, the risks or expected benefits, or the manner of obtaining informed consent. The need for further information can be communicated either verbally or in writing to the project director by the chairman of the committee, another committee member, or the secretary to the committee. If the project director wishes, he or she may request to appear personally before the committee to answer questions or provide more detailed explanations of the proposed study. It is also open to the chairman of the committee to request that the project director discuss

35. 21 C.F.R. § 130.37 (1973).

the project with the committee. In accordance with university policy, all projects involving definite risks to the participants receive final review and approval through an assembled quorum of the committee.[36] In general, the chairman tries to develop a consensus for approval. Thus, it is unlikely that the chairman will accept a protocol for approval if there is a closely split vote. The results of the review are communicated to the project director, the appropriate departmental chairman, and the Office of Research Administration of the University by the chairman or his designee.

In the event an unanticipated opportunity arises to perform a unique study and rapid approval is required, the chairman of the committee is authorized to give administrative approval for the performance of one experiment upon written request of the investigator and after consultations with at least two other members of the committee. The proposal must then be submitted for formal review via the usual procedures. Further studies may not be done until approval has been given by the full committee.

From 1969 through 1972, 261 new protocols were submitted to the Clinical Review Committee of University Hospitals. Thirty-five percent required some revision before gaining final approval. Five protocols were disapproved. In each case, the basis for disapproval was an unfavorable risk-benefit ratio. In 1972 alone, 85 new protocols were submitted for review. In addition, 47 protocols previously approved were presented for annual review as required by HEW.[37] To accomplish this task, the general hospital committee at UH met biweekly.

B. *The Procedure at Cleveland Metropolitan General Hospital*

At Cleveland Metropolitan General Hospital a Committee on Investigation in Humans (CIH) was established in 1966 by the hospital's Executive Medical Staff in accordance with the directive of the Surgeon General. Initially the committee was composed of the chairman of each of the clinical departments plus Pathology and Radiology, the President of the Medical Staff, and the Medical Director of the Outpatient Clinics. As constituted, the membership of the CIH was virtually identical with that of the Executive Medical Staff. An additional senior physician with considerable experience

36. University Policy, *supra* note 30, at 5.

37. THE INSTITUTIONAL GUIDE 11. Such an annual review would be necessitated by a delay in excess of 12 months between the initial proposal submission date and the actual commencement of the experiment.

in clinical investigation was selected as chairman. In contrast to UH, CMGH has no Chief of Staff. Also, unlike the committee at UH, the committee at CMGH did not include a member of the hospital administration. After being in existence several years, a representative of the Nursing Service and an attorney from outside the hospital (Professor of Legal Medicine, Director of the Law-Medicine Center, CWRU) joined the committee as full members. Within the past year a representative of the community who is not affiliated with CWRU was appointed to the committee as mandated by the recent regulations.[38] In parallel with the situation at UH, the seven departmental chairmen now recommend representatives from their departments to serve on the committee. These individuals are nominated by the committee and appointed by the hospital Board of Trustees at their discretion. According to the bylaws of CMGH, the CIH is a standing committee of the Medical Executive Committee. The Medical Executive Committee has the final responsibility for the appointment of qualified professionals to the CIH. The responsibilities of the Chairman of the CIH and the charge to the committee are similar to those described above for University Hospitals.

An investigator wishing to undertake research involving humans at CMGH must submit a written protocol to the appropriate hospital departmental chief for approval. The protocol must contain essentially the same information as that required at UH. Similarly, all investigative studies involving humans must be submitted to the same process whether or not they require additional inside or outside support or funding, whether supported by public or private funds. After approval of the departmental chief has been secured, the protocol is forwarded to the chairman of the CIH, who distributes it to the committee members. Each committee member is expected to review each protocol thoroughly prior to the next regular meeting of the committee. Adverse comments on points requiring clarification are requested from the members prior to the meeting. If any are communicated to the chairman, he relays them to the principal investigator for immediate action prior to the committee meeting if possible. If the chairman deems it necessary, a consultant from outside the staff of the committee or the hospital may be employed to review the merits of a specific protocol.

A principal investigator may, at his own request or that of the committee, appear in person before the committee to present addi-

38. 45 C.F.R. § 46.6 (1974).

tional information or to respond to questions. In the event a specific protocol directly involves a member of the review committee, or if there is a possibility of conflict of interest involving a member of the review committee, that individual does not participate in the committee's discussion of the protocol apart from supplying information and responding to questions if so requested by the committee. He or she plays no role in the decisionmaking process and must abstain from voting or leave the room during the vote. The minutes of the meeting record the fact that the member left the room or otherwise did not vote on the protocol.

After the general discussion, the chairman informally polls the committee members to obtain a consensus of the committee regarding approval of a protocol. If no consensus for approval exists, the committee suggests changes in the protocol and asks that it be resubmitted. If a consensus exists, there is a formal motion for approval. Two votes are taken. The first vote is on the risk involved and whether the benefit to the subject and the importance of the knowledge so outweigh the risk as to warrant allowing the subject to accept it. The second vote is for approval of the protocol. The committee may vote approval with no amendment, approval with amendment (requiring no further action by the committee), or conditional approval. Protocols approved conditionally must be revised by the investigator in accordance with the suggestions and requirements of the committee. The protocol is then resubmitted to the chairman, who is charged by the committee to ensure compliance with the recommended changes.

Approval for a project on an "emergency" basis may be obtained by an investigator upon submission of a written summary of the protocol to the appropriate departmental chief and to the Chairman of the CIH. The approval given by these individuals is provisional. A complete protocol must be submitted immediately thereafter to the full committee for formal approval. Emergency approval ordinarily allows performance of only one experiment and is given only for beneficial (therapeutic) research. In such a case a special meeting of the entire committee is convened if possible.

CMGH has a Perinatal Unit supported in part by the Public Health Service in which investigations of special societal concern that affect both mother and child are conducted. All studies done on the Perinatal Unit must be approved by a separate Perinatal Scientific Review Committee. Studies which receive approval are then forwarded to the hospital CIH where approval is required as for other

protocols before the project can be activated.

Reviews of all approved protocols are conducted at least annually by a subcommittee of the CIH, which contains one representative each from the Departments of Medicine, Surgery, and Obstetrics-Gynecology. The annual review must state: (1) whether the protocol is active, inactive, or discontinued; (2) any change in investigators with identification of additional or deleted investigators; (3) any change in procedures outlined in the original protocol, with appropriate details; (4) the place where the study is being conducted; (5) the type of consent (verbal or written) obtained; (6) whether a consent form was obtained from each subject, and, if not, the reason for any exceptions; (7) the location where the consent forms are kept; (8) the names and hospital numbers of all patients studied the previous year; (9) a brief summary of the rationale, methods of study, and general plan of investigation as described in the original protocol; (10) a summary of the significant results that have accrued from the study; (11) the nature of all side effects or untoward reactions that occurred, major or minor, expected or unexpected; and (12) an estimate of the number of additional subjects to be studied in the forthcoming year. Additionally a copy of the currently approved consent form used by the investigator must be provided to conform with current guidelines. New regulations require that adverse reactions be reported promptly.[39]

In 1972, 40 new protocols, 2 amendments, and 4 addenda to active, approved protocols were submitted to the CIH at CMGH. Seventeen required modification or resubmission after committee discussion prior to final approval. A total of 149 protocols were subjected to annual review, of which 58 were reported to be completed, inactive, or discontinued. To accomplish this task, the committee met once each month. Five protocols were approved by mail vote. Notification of approval is reported to the project director, the departmental chief, and the Office of Research Administration of CWRU.

Proposals involving human subjects which emanate from a jurisdictional area outside the School of Medicine must receive approval by the appropriate institutional committee. After receiving local institutional approval, each grant application or contract proposal is subject to review by the Dean of the School of Medicine (or Dentistry, Nursing, etc., as appropriate) or his or her designee. The Dean

39. 45 C.F.R. §§ 46.6, .7 (1974).

does not review the protocols submitted to the institutional committees on human investigation, but rather the full grant applications or contract proposals. The Office of the Dean then forwards the grant application or contract proposal to the University Office of Research Administration (ORA). The Director of the ORA must certify that the proposal has the approval of the appropriate local institutional committee on human experimentation. All research projects receiving financial support must be administered through the hospital where the work is to be conducted or through the ORA.

In addition to certifying that a research proposal has gained the necessary institutional approval, the ORA has two other functions. One is to assist faculty members and members of the University administration in the acquisition and administration of grants and contracts. The other is to participate in the formulation of University policy through membership of the director on the University Council.

C. *Review at the National Level*

After receiving approval by the local institution and the University,[40] all projects involving human subjects which are submitted to the Public Health Service for funding are again reviewed by an appropriate study section of the National Institutes of Health. These study sections are comprised of individuals from around the country who have expertise in a field of biomedical research. Members of study sections are appointed for terms of two to four years and are primarily charged with evaluating the scientific merit of the project proposals for which financial support is sought. Although their primary concern is not necessarily the ethics or propriety of the proposed research, they have a duty to review the ethical considerations in each project and to disapprove any project which, in their estimation, lacks satisfactory ethical safeguards.

Decisions of the study sections are subject to review by the National Advisory Councils (NAC's). Each Institute of the NIH has one NAC whose members include both scientists and laymen from

40. It is University policy that all research proposals involving human subjects which are submitted to the PHS for funding be approved by the appropriate institutional committee on human investigation prior to submission to the federal government. In general, no proposals are forwarded by the University's Office of Research Administration which have not received local approval. Occasionally, however, because of deadline limitations, a proposal has been forwarded to the PHS for which approval has been sought from the local committee but not yet received. Financial support of such proposals is not provided by the PHS until local approval has been given.

various geographical areas. Among the responsibilities charged to the National Advisory Councils is that of again reviewing the ethical considerations attending projects approved by the study sections. Although virtually all project proposals which are unacceptable on ethical grounds are screened out at the prior levels of review, NAC's occasionally disapprove projects because of ethical considerations. The NIH now has made fully active a group that reviews for ethical considerations every protocol submitted to it involving human experimentation. This review is the responsibility of the Chief of the Institutional Relations Section of the Division of Research Grants, NIH, HEW.

A decision by a study section or a National Advisory Council of the National Institutes of Health that a particular project does not comply with the guidelines of the Department of Health, Education, and Welfare supersedes the approval given the project by the local institutional committee. Differences of this nature may be, and usually are, resolved by further communication between the HEW and the local institutional committee via the Office of Research Administration. These communications generally take the form of forwarding to the study section or National Advisory Council information that was provided by the project director to the local institutional review committee, either spontaneously or in response to specific questions, and that was not included in the protocol as written in the grant application. They may also include copies of the minutes of the committee concerned with the proposal and copies of communications passed back and forth between the committee and the project director.

D. *Criteria Used for Evaluation of Protocols*

The criteria used by the Clinical Review Committee of University Hospitals and the Committee on Investigation in Humans at Cleveland Metropolitan General Hospital (as well as the other independent review committees at CWRU) to evaluate the ethical propriety of a research proposal are based on the guidelines laid down by HEW.[41] There are three basic criteria: (1) protection of the rights and welfare of the subjects, (2) weighing of the risks against the benefits, and (3) determination that informed consent is to be obtained by methods that are adequate, appropriate, and consistent with local regulations. In addition, the committee will demand evi-

41. THE INSTITUTIONAL GUIDE; *see* note 17 *supra.*

dence from the investigator that proper confidentiality will be maintained for all data collected from each individual.

Implementation of the three criteria stated above constitutes the greatest challenge for the committees. The precise manner in which a given committee implements these guidelines to assess a specific protocol varies according to the particulars of the proposal. Moreover, the application of these criteria varies with the personal backgrounds, experiences, and biases of the members of the review committee. Situations arise, for example, in which a specific protocol is approved by the CIH at CMGH but not approved by the committee at UH. Attempts to resolve differences between separate committees at CWRU are made on an ad hoc basis by subcommittees of the two parent committees meeting together. The subcommittees try to achieve a consensus. The consensus must, however, be ratified by each parent committee. In the last analysis, each committee makes its own rules and sets its own priorities. Certain general considerations are utilized by the members to establish policies and precedents which are rational and consistent with the responsibilities of the committees towards both the subjects and investigators.

1. *Protecting the Subject—The Adversary System*

To assure that the rights and welfare of the subjects are protected, the committees give consideration to the role of the individual undertaking the research as an investigator as distinguished from his or her role as a physician. There is a distinct contrast between the relationship of a physician to a patient and that of an investigator to a subject.[42] Beecher has paraphrased Ladimer in saying that "the physician accepts patients and is mainly concerned with their welfare; the investigator selects subjects (problems as well as individuals) and, while responsive to the patient's interest, is bent on solving the scientific problem."[43] Bondy observed that

> the double role which the clinical investigator plays as both the physician and the scientist . . . is a very touchy point because most of the experimental subjects come into your hands because they are patients. . . . [Y]ou have a special rapport which hinges on the fact that you are a physician. The attitude of a subject toward you is strongly conditioned

42. Blumgart, *The Medical Framework for Viewing the Problem of Human Experimentation*, 98 DAEDALUS 248, 255-62 (1969).

43. Beecher, *Experimentation in Man*, 169 J.A.M.A. 461, 465 (1959), *paraphrasing* Ladimer, *Human Experimentation: Medicolegal Aspects*, 257 NEW ENG. J. MED. 18, 21 (1957).

> by the fact that you are a doctor of medicine. This frequently produces a conflict because the experiment very often requires manipulations that are not properly in line with what a physician does. The object is not to improve people but to learn from them. . . . This is just the opposite of a physician's usual practice. The objectives of the experiments are excellent, but the experiments themselves are anti-medical. They are useful; they may be justified; but the physician who is in charge of these experiments is in a very difficult position.[44]

Indeed, Guttentag suggested that the "physician-friend" and "physician-experimenter" should be two separate individuals.[45] Recognizing that "the presence of an intelligent, informed, conscientious, compassionate, responsible investigator" is a prerequisite for the safeguarding of an ethical approach to experimentation,[46] a leading medical journal proposed editorially that a patient advocate system be instituted "to preserve the rights of the individual in the quest for the right to health for society."[47] The physician-friend, to use Guttentag's term, or patient advocate would protect the welfare of the subject and the physician-investigator would be responsible for the integrity of the experiment.

In fact, this type of "adversary" system is utilized by review committees today in certain circumstances. For example, at Cleveland Metropolitan General Hospital, all patients who are potential subjects for one of the studies involving newborn infants or very young children must be cared for by one or more physicians who are not engaged in the experiment. These physicians are responsible solely for the medical care of their young patients and act as advocates for their patients vis-à-vis the investigators. They have the authority to stop a study or withdraw a particular patient-subject from a study if they deem it appropriate to do so. This protection is chiefly applied to nontherapeutic research. Similarly, in dealing with the examination of tissues removed at surgery, experimenters are not permitted to participate in the decisions which lead to the performance of the biopsy or operation in question. These medical decisions may be made

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44. Beeson, Bondy, Donnelly & Smith, *Panel Discussion: Moral Issues in Clinical Research*, 36 YALE J. BIOL. & MED. 455, 467 (1964).

45. Guttentag, *The Problem of Experimentation on Human Beings: The Physician's Point of View*, 117 SCIENCE 207, 210 (1953).

46. Beecher, *Ethics and Clinical Research*, 274 NEW ENG. J. MED. 1354, 1360 (1966).

47. Editorial, *Friendly Adversaries and Human Experimentation*, 275 NEW ENG. J. MED. 785, 786 (1966).

only by the patient's physician and only on the basis of criteria that would ordinarily be used in the particular situation.

On the other hand, the committees have recognized that there are situations where insistence upon an adversary system is either not feasible or is counterproductive. Examples of the former situation are studies, such as therapeutic trials, which will be of immediate benefit to the patient-subject (as well as to society). In the evaluation of alternative chemotherapy regimens for the treatment of specific cancers, for example, the physician supervising the administration of the different chemotherapeutic agents and the results thereof is often also the physician with primary responsibility for the care of the patient. The reason for the physician's dual role is that there is no one else with the same degree of expertise both in the care of patients with the particular neoplasm (cancer) in question and in the pharmacology and use of the different anticancer agents. In this situation, greater reliance is placed on the integrity of the physician to discharge his or her responsibility to his or her patients honorably than is usually the case in projects that are without immediate benefit to the subject.

Occasionally, cases arise where an investigator simply refuses to allow a third party to intercede between him or her and the patient-subjects. This may be because confidentiality between the physician-investigator and the patient-subject is essential to the performance of the study, because unpredictable availability of suitable subjects precludes ready availability of appropriate patient advocates, or because the investigator indicates that it is a matter of his or her own honor, integrity, and judgment that the work should proceed without outside interference. The situations are highly individualistic and the committees make their decisions on an individual basis.

2. *The Risk-Benefit Ratio*

A number of general considerations affect the manner in which committees evaluate the risk-benefit ratio in studies involving human subjects. The observation has been repeatedly made that whenever a physician treats a patient he or she is, in a sense, performing an experiment since one can never be absolutely certain what the result of treatment will be. Freund quotes F.M. Cornford's statement:

> The principle of the dangerous precedent is that you should not do an admittedly right action for fear that you or your equally timid successors should not have the courage to do right in some future time, which ex hypothesi is substantially

> different but superficially resembles the present one. Every public action which is not customary either is wrong or, if it is right, is a dangerous precedent. It follows that nothing should ever be done for the first time.[48]

To provide the independent institutional committees with some guidance regarding what constitutes an experiment, the CWRU policy statement states that an experiment includes "every project which includes procedures that go beyond the diagnostic and therapeutic needs of the patient or subject or may serve as a source of potential inconvenience, embarrassment or abridgement of rights of privacy to a participant."[49] Included are "procedures that may induce or result in a potentially harmful altered state or condition" such as "surgical procedures; the removal of organs or tissues for biopsy, transplantation, or banking; the administration of drugs or radiation; the use of indwelling catheters or electrodes; the requirement of, or potentiality for, strenuous physicial exertion; [and] subjection to deceit."[50]

All experiments involve some risk.[51] A cardinal principle that guides all committees is that the risk must be commensurate with the benefit expected from the experiment. The heavier the risk, the greater must be the benefit. The approach taken by committees has gone beyond the thinking reflected in the quotation from Claude Bernard at the beginning of this article, that "those [experiments] that are innocent are permissible . . . ."[52] Initially, some reviewers did not feel it was a valid concern of review committees whether or not a proposed project might produce useful information if the project posed minimal or no risks to the subjects. Now, however, all agree with Rutstein that a study "that could not possibly yield scientific facts . . . is by definition unethical" and "[a] worthless study cannot possibly benefit anyone . . . ."[53] Reviewers now have a more activist view of their role and will suggest alterations in the design of experiments that they believe will reduce the risks or improve the quality of the data generated.

In addition to the evaluation of the overall design of experiments,

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48. Freund, *Ethical Problems in Human Experimentation*, 273 NEW ENG. J. MED. 687, 688 (1965).

49. University Policy, *supra* note 30, at 2.

50. *Id.* at 2-3.

51. McCance, *The Practice of Experimental Medicine*, 44 PROCEEDINGS OF ROYAL SOC'Y MED. 189, 192 (1951).

52. C. BERNARD, *supra* note 1, at 101-02.

53. Rutstein, *The Ethical Design of Human Experiments*, 98 DAEDALUS 523, 524 (1969).

criteria used to assess risk include (1) whether the experiment is the very first one in a series or one which has been done somewhere previously, (2) whether the investigator knows that he or she will at all times retain control of the situation, (3) whether the investigator has had experience both in the general field in which he or she is working and with respect to the procedures to be undertaken, and (4) whether safeguards or antidotes are available to counteract an untoward event that might occur in the course of the study. In situations where the research is concerned solely with discarded human materials obtained at surgery or in the course of diagnosis or treatment, and the use of these materials involves no possible risk to the subject, the committees concern themselves only with the circumstances under which the materials are to be procured.

The major consideration that attends the evaluation of the benefit of an experiment is whether the results will be of immediate benefit to the individual subjects or whether, instead, the results are intended to benefit society at large. In studies that may be termed therapeutic (beneficial to the patient-subject) the review committees assess the experimental design of the study and the state of knowledge upon which the design is based. For example, in a clinical trial in which the possible efficacy of treatment with one drug is compared to no treatment or to an alternative drug, the investigator must supply the committee with pertinent background information indicating (1) the current mode of therapy for the condition in question, (2) the basis (or lack thereof) of the current therapy, and (3) the evidence in support of the treatment procedures to be studied. Particularly in situations where an agent is to be compared with a placebo, the investigator must demonstrate that evidence is currently lacking regarding the utility of any form of specific therapy. The committee members, armed with this information, appropriately referenced, will then often go to the library to familiarize themselves further regarding the condition to be studied and the proposed treatment regimens. Their main concerns are that subjects in at least one of the study groups will benefit appreciably from the treatment, that the subjects in the other groups will be no worse off than if they were treated by conventional means, and that the experiment is properly designed to yield valid data.

Evaluating the benefits of experiments which are nontherapeutic, but which are intended to advance our knowledge generally to the benefit of mankind, is infinitely more complex. The crucial issue here is the fundamental conflict between the rights of the individual and the rights of society. Although this conflict has been debated

at length in the context of medical research and human investigation,[54] no ready formula exists to guide the members of a review committee. The basis for determining the expected benefits of a project that is not directly beneficial to the patient-subject derives from the collective medical wisdom and experience of the committee members. In a sense, the committees have avoided confrontation with such global issues as the individual versus society and have focused more narrowly on the specific medical issues that are immediately pertinent to the individual proposals. The willingness of the investigator himself to undergo the proposed procedure has not generally been accepted as a measure of the benefit of the procedure relative to the risk involved. Such willingness may be a sign of good faith, but it is recognized that the investigator may have an obsession with his idea or, at the least, substantial emotional and intellectual commitment to it. Hence, he or she may not be the best person to assess dispassionately the risks and benefits and his or her self-experimentation may be nothing more than a zealous act.

In general, review committees have taken the position that it is justifiable to use human subjects for nonbeneficial research if they are satisfied that the project is scientifically wise, that the benefits to be gained exceed the risks to any one subject, that subjects will be fully apprised of their participation in an experiment, and that the participant-subjects will be studied only after giving informed consent. The involvement of human subjects in research is viewed by the committees as a cooperative venture between investigator and subject. Although members of the review committees at CWRU have acknowledged the right of individuals, be they normal or patients, to volunteer for hazardous procedures where the risks may exceed the benefits, they have not sanctioned any such studies. They are guided by and have been faithful to the one overriding principle: *primum non nocere*—first of all, do not harm.

3. *Informed Consent*

The third criterion used to evaluate the acceptability of a proposed protocol, that of the quality and manner of obtaining informed consent, has been equally difficult to implement. Consent is viewed as serving several functions: (1) It protects the personal integrity and dignity of the individual; (2) it protects the individual's health

54. *See, e.g.*, Beecher, *supra* note 43; Blumgart, *supra* note 42; Freund, *supra* note 48; Jonas, *Philosophical Reflections on Experimenting With Human Subjects*, 98 DAEDALUS 219 (1969).

and bodily integrity;[55] and (3) it causes the investigator to reflect on the manner in which the experiment itself is conducted.[56] In their deliberations the committees have used as a reference the basic elements of informed consent outlined by HEW:

> (1) A fair explanation of the procedures to be followed, including an identification of those which are experimental; (2) A description of the attendant discomforts and risks; (3) A description of the benefits to be expected; (4) A disclosure of appropriate alternative procedures that would be advantageous for the subject; (5) An offer to answer any inquiries concerning the procedures; and (6) An instruction that the subject is free to withdraw his consent and to discontinue participation in the project or activity at any time.[57]

This last point has been amended by many investigators, including this writer, to include the stipulation that the investigator is also free to terminate participation of the subject if the investigator deems it advisable for appropriate social, ethical, medical, or other reasons. At a minimum, however, the six basic elements of informed consent must be listed on the consent form each prospective subject is asked to sign. The HEW guidelines, as well as the present regulations, also direct that the consent agreement may not contain exculpatory language whereby the subject waives, or appears to waive, his legal rights or releases the investigator or the sponsoring institution from liability for negligence.[58] Indeed, exculpatory clauses in consent agreements have been disallowed in courts of law.[59]

In addition to these considerations, a number of other factors are weighed by the reviewers when they are relevant to particular protocols. These include whether the research is beneficial or nonbeneficial to the individual subject, the ability of the potential subjects to comprehend the information supplied by the investigator, the physical circumstances in which solicitation for participation in the study will occur, and the magnitude of any inducements, financial or otherwise, that may be used to obtain subject cooperation. The review committees at CWRU have, until now, agreed that the signed consent

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55. *See* Jaffe, *Law as a System of Control*, 98 DAEDALUS 406, 423 (1969).

56. *See* Freund, *Legal Frameworks for Human Experimentation*, 98 DAEDALUS 314, 323 (1969).

57. THE INSTITUTIONAL GUIDE at 7. These elements are substantially the same elements that appear in the HEW regulations promulgated in May of 1974. 45 C.F.R. § 46.3(c) (1974).

58. 45 C.F.R. § 46.9 (1974).

59. *See, e.g.*, Tunki v. Regents of Univ. of California, 60 Cal. 2d 92, 383 P.2d 441, 32 Cal. Rptr. 33 (1963).

given by parents or legal guardians for the participation of their children in medical research is acceptable provided the method for obtaining consent is appropriate, *i.e.*, is in accordance with the above-stated guidelines. There is now, however, considerable controversy on this matter and the issue is presently unresolved, particularly with respect to nonbeneficial research.

The committees have on occasion required that a third party, such as a family member, be present to witness the obtaining of consent, in order to provide another opinion to the subject being solicited, or to ensure that the explanation provided is understood by the subject. The extent to which the various elements that comprise informed consent enter into the equation by which the committees assess the adequacy and appropriateness of the consent varies with and is unique to each proposal. There is no all-embracing formula. Both investigators and reviewers recognize that the definition of truly informed consent defies description, that "[i]f suitably approached, patients will accede, on the basis of trust, to about any request their physician may make,"[60] and "[a] far more dependable safeguard than consent is the presence of a truly responsible investigator."[61]

III. PROBLEMS RELATED TO THE REVIEW PROCESS

What problems attend the implementation of the review process for the investigator and for the review committee? The major problems from the viewpoint of the investigator are (1) the paperwork involved in providing adequate documentation for the safety, benefits, and risks of the proposed research, (2) difficulties that may arise in communicating effectively to a subject the nature and risks of the study so that the subject can make an informed decision regarding his or her participation; (3) the lack of any mechanism whereby a decision of a review committee can be appealed; and (4) the lack of any legal safeguards for the performance of human experimentation that has received peer review and approval by a legitimate review committee.

The problem of informed consent for some investigators is based in part on the fact that they prefer not to state explicitly what they intend to do or why. For others, full explanation of the procedures may directly impair the study. For example, in studies designed to evaluate the relative efficacies of two drugs, it is often important that

60. Beecher, *supra* note 46, at 1355.
61. *Id.*

neither the subjects nor the investigators know which drug is being given and to whom—the so-called double-blind trial. In these situations it may not be feasible to provide the subjects with the information they would ordinarily need to determine whether to participate. Rather, full disclosure is made to the subject of all the possible side effects or risks that either regimen may entail and the fact that neither he or she nor the investigator knows which regimen will be given. Despite these problems, the review process provides the investigator with the opportunity of having his research plans evaluated by an impartial, disinterested group of his peers. The review committees seek to be constructive and to help the investigator and, to the extent they do, are an advantage for the investigator. Investigators have been uniformly appreciative when the interchange occasioned by the review process has resulted in improvement in experimental design or an increase in the potential for obtaining decisive results.

The problems that attend the review process for the review committees are multiple and complex. They have yet to be resolved and one can do little more than list them.

(1) The local institutional committees have been charged with the dual responsibility of both formulating and implementing policy. They have often had little guidance in performing these roles in the myriad diverse situations that have arisen and have had to establish precedents where none existed previously. Simply stated, the law is silent on these matters. In an attempt to solve this problem, the CWRU Faculty Senate Committee on Research and Scholarship established a coordinating committee consisting of the chairmen of the seven institutional review committees within CWRU. In 1971 this group was redesignated the University Council on Research Involving Human Subjects and was charged with responsibilities to initiate or modify policies or procedures, to communicate experience, problems or practices between the seven committees, to monitor implementation of University policy, to report periodically to the Officers and Administration of the University on issues or problems in the area of human experimentation and to serve as a vehicle for communicating with the Committee on Research and Scholarship and with the faculty.[62]

(2) In almost every case, the committees have had to maintain a fine balance between acquiring adequate documentation for making a decision and imposing an excessive amount of paperwork upon

62. University Policy, *supra* note 30, at 6.

the investigator. The committees must balance the need to protect the patients' rights and welfare against the privilege of the investigator to undertake research. In a more general sense, the committees must balance the need to protect the individual against the mandate that exists in medicine to improve patient care.

(3) There is an increasing volume of paperwork for the members of the review committees. All of the members have other responsibilities for teaching, research, and patient care. As the workload increases, the time and commitment each member can devote to other responsibilities is inevitably reduced.

(4) Proper evaluation of some protocols is too complex for local institutional committees. For example, CMGH is a member of a cooperative cancer chemotherapy group that embraces over 30 other institutions nationwide. An increasing number of protocols devised to evaluate treatment regimens are being introduced to determine optimal therapy for various neoplasms. These protocols have been designed by a national committee and have received scientific approval by the National Cancer Institute, a component of the National Institutes of Health; nevertheless, they must be approved locally before they can be used locally. The protocols involve so many different tumors and drugs and so many combinations of drugs and other therapeutic modalities, many of which are still investigational, that it is not feasible for the CIH at CMGH to make a truly informed decision on each one. Consequently, the committee has adopted the procedure of delegating a subcommittee to review each protocol, chiefly to determine the adequacy of consent. The scientific merits of each protocol are reviewed on the basis of published material and experience. Since no one institution can have enough experience to have compiled its own definitive data, however, cooperative multi-institutional studies are necessary. The most complete data are available only to a central group, which evaluates composite results on which new protocols are based.

(5) Projects involving special groups raise special problems. Foremost among these are projects involving children, particularly newborn infants, and women during pregnancy. An additional problem surrounds research done on aborted fetuses and products of conception. Stringent federal regulations exist which essentially prohibit certain types of investigation, often with unfortunate and unintended consequences. For example, FDA regulations require that the labeling of a drug prescribe, recommend or suggest its use only under the

conditions for which it was tested and approved.[63] Because children are generally agreed to be incapable of giving consent and because controversy exists whether their parents or guardians can legally give consent for their participation in research,[64] particularly where the research is not of therapeutic benefit to the child, investigators are becoming progressively more reluctant to test new drugs in children. Consequently, manufacturers indicate on the drug labels that clinical studies have been insufficient to establish recommendations for use in infants and children. Stated simply, one cannot use new drugs in children unless they have been certified for use in children. But one cannot get the new drugs certified for use in children because it is nonbeneficial research and one cannot do nonbeneficial research in children. Hence, either the pediatricians practice illegally or the children become therapeutic orphans.

(6) There is no readily available mechanism for exchanging information with review committees at other universities and no mechanism for resolving differences between committees. Each review committee builds "a body of general principles over a period of time on a case-by-case basis."[65] Since the viewpoints and biases of committees may differ, the possibility exists that two committees might evaluate a particular protocol quite differently. The University Council, as mentioned above, is primarily a policy making group and is not equipped to resolve such differences. Presently, these problems are resolved by discussions between ad hoc subcommittees of each parent institutional committee. The compromise agreed upon by the subcommittees must be ratified by each parent committee. A number of suggestions have been made regarding the establishment of a clearinghouse whereby the deliberations and decisions pertaining to difficult problems would be available for dissemination and discussion for the purpose of achieving through dialogue some degree of national consensus. The merits of these proposals have been discussed by Curran.[66]

(7) It is difficult to monitor compliance with decisions of the institutional review committees. The annual review is retrospective

63. 21 C.F.R. § 1.106(a)(1) (1973).

64. *See* Capron, *Legal Considerations Affecting Clinical Pharmacological Studies in Children*, 21 CLINICAL RESEARCH 141-42 (1973); Chalkley, *Developing Guidelines*, 21 CLINICAL RESEARCH 777, 779 (1973).

65. Curran, *Governmental Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies*, 98 DAEDALUS 542, 584 (1969).

66. *See id.* at 586.

and does not include any provisions or mechanism for supervising ongoing research. Consequently, there is no way to determine, for example, whether a surgical procedure is being done for a valid diagnostic or therapeutic reason or simply for research purposes. Similarly, it is not possible to ascertain in every single instance in which drugs are being administered whether they are being administered only for approved purposes. The logistics and manpower demands make anything beyond initial approval and annual review impossible.

(8) The perspectives of the committees are relatively limited. In recognition of a need to broaden the scope of the committee deliberations, there has been some movement to include on committees more members from outside of medicine, including the consumer. This has been done in part to improve the public image of human experimentation and to reduce the suspicions of the outside world. Inclusion of nonphysicians raises further problems, however, since, as these individuals admit frankly, they often do not comprehend the medical issues involved and thus are obliged to defer to the physicians' judgment with respect to matters requiring scientific competence.

Two additional problems with which committees are becoming increasingly concerned are those dealing with the legal status of review and with compensation for subjects injured during participation in experiments. There have been few lawsuits resulting from human experimentation,[67] and thus there is little case law to guide review committees or policymaking councils. Similarly, the legal status of the investigator and his insurability for professional liability are wholly undetermined.[68] This writer vividly recalls being officially informed, at the start of a 2-year term as a Clinical Associate at the NIH, that no insurance carrier would underwrite a professional liability policy protecting individuals who were engaged in clinical investigation. It is highly doubtful now whether professional liability insurance obtained by someone engaged in the practice of medicine would protect that individual in the event he or she undertook human experimentation and a lawsuit were filed because of some injury alleged to have arisen from the research. Calabresi[69] and Havighurst[70] have pointed out that little attention has been paid to the

67. Jaffe, *supra* note 55, at 408.

68. Beecher, *Human Studies,* 164 SCIENCE 1256, 1257 (1969).

69. Calabresi, *Reflections on Medical Experimentation in Humans,* 98 DAEDALUS 387, 391-99 (1969).

70. Havighurst, *Compensating Persons Injured in Human Experimentation,* 169 SCIENCE 153 (1970).

problem of compensation for subjects injured in human experimentation and discuss possible solutions to this problem.[71]

IV. General Comments on Federal Regulation

Despite these problems, the consensus among investigators and members of review committees, who are often themselves investigators, is that on balance the current method of operation is a reasonable one. Objective evidence to support the effectiveness of the review procedures as applied nationwide is provided by the fact that the percentage of problem projects (proposals presenting possible hazards to subjects and judged unacceptable) among the total projects involving human subjects declined from 7.4 percent in 1966 (the last year projects were submitted to NIH before the ethical guidelines were instituted) to 1.7 percent in 1968.[72] Nonetheless, the feeling that more must be done has enjoyed considerable support.[73]

The impetus for drafting new law or new regulations affecting the conduct of human investigation has generally resulted from incidents of flagrant abuse of human rights and extensive publicity of these incidents. For example, the Nuremberg Code was produced in response to the horror stories that were revealed at the Nuremberg war crime trials. The promulgation of the HEW guidelines[74] was in substantial part a result of the New York case in which live cancer cells were injected into elderly individuals without their knowledge.[75] Most recently, revelations of the Tuskegee syphilis study have inspired a new series of laws and regulations.[76] The present regulations,[77] which in substantial measure codify the prior HEW guide-

71. For a general discussion of this problem see Adams & Shea-Stonum, *Toward a Theory of Control of Medical Experimentation With Human Subjects: The Role of Compensation*, 25 Case W. Res. L. Rev. 604 (1975).

72. Curran, *supra* note 65, at 579.

73. Congress has recently passed the National Research Service Award Act of 1974, Pub. L. No. 94-348, 88 Stat. 342. Two examples of other legislative proposals that have been introduced are S. 2072, 93d Cong., 1st Sess. (1973), introduced by Senator Kennedy, and H.R. 10403, 93d Cong., 1st Sess. (1973), introduced by Representative Rogers. In addition to this legislation, HEW has promulgated new regulations, 45 C.F.R. §§ 46.1-.22 (1974), which were recently amended. *See* note 18 *supra*. *See also Hearings on S. 2071, S. 2072, and H.R. 7724 Before the Subcomm. on Health of the Senate Comm. on Labor and Public Welfare*, 93d Cong., 1st Sess., pt. 4, at 1207-53 (1973).

74. The Institutional Guide.

75. *See* note 13 *supra* and accompanying text.

76. *See* note 73 *supra*.

77. 45 C.F.R. §§ 46.1-.22 (1974).

lines, merit some general observations. These comments are made from the viewpoint of one investigator who will be subject to the regulations.

The general tone of the public debate over the regulations confirms Edsall's observation that a well-publicized abuse of human rights leads to an overall reaction that "tends to spiral more and more tightly into a set of concepts and terms that give emphasis to only one view of the total situation."[78] A component of this "one view" is the idea that investigators are using human beings.

> Whenever this *use* appears to have been improper, the investigator is considered to have violated the *rights* of the individual. . . .
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> . . . All of these words, phrases, and concepts—even though they are in themselves totally correct and admirable—tend to narrow the framework of thinking in this field and to force it into a somewhat rigid moralistic-legalistic structure based largely upon the risk of individual "violations" of a code and upon enforcement of the code by an essentially legalistic system of controls. Such a structure . . . tends to create and perpetuate a situation in which the investigator finds himself working in an atmosphere of supervision and suspicion.[79]

Most investigators are already acutely aware that times have changed and that there has occurred "an abrupt change in public trust and confidence in the conduct of medical research."[80] A major concern of investigators is that the emphasis on adversary procedures, in which the investigators are placed in the position of potential wrongdoers whose every move must be closely monitored and regulated, will legitimize the erosion of trust that has occurred. They feel that there is a need to stress instead the harmonious relationship that must prevail between researchers and subjects if the public is to continue to benefit from discoveries in biomedical science.

Closely related to this concern is a widespread feeling that the development and implementation of greater restrictions and guidelines will adversely affect or indeed stifle the remarkable inventiveness that has been the pride and accomplishment of the biomedical research effort in the United States. There are several features of

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78. Edsall, *A Positive Approach to the Problem of Human Experimentation*, 98 DAEDALUS 463, 464 (1969).

79. *Id.* at 464-65.

80. Chalkley, *supra* note 64, at 779.

the regulations that promote this concern. One is the sheer weight of the bureaucracy which has been proposed to regulate human experimentation. Many investigators and review committees are already of the opinion that the paperwork involved in preparing and approving acceptable protocols is extensive and taxing. To compound this with even more reports, memoranda, and the like will so overburden those wishing to undertake research that some, perhaps many, will conclude that it is simply not worth the trouble to prepare the required documentation. The consequence of this contraction of effort will be a marked slowing of the pace of improvement in medical practice. This result may well be as objectionable to the general public as their unease with the use of human subjects in research.

Apart from the administrative burdens that inevitably flow from the implementation of the regulations, the interposition of two or three more layers of bureaucracy at both the national and the local levels is unlikely to improve the review process.[81] Rather, like all other bureaucracies and regulatory agencies, the staffs of the advisory committees and groups will feel a need to justify their existence and demonstrate their effectiveness. The result will be some degree of harrassment of investigators who are seeking to comply with the law and a slowing down of the review process so that the time required to secure approval will increase from one or two months to upwards of four months. Since the number of identified abuses in clinical research is so small, especially when considered in relation to the number of investigators pursuing human experimentation, it will be difficult if not impossible to demonstrate that the added controls have produced a detectable decrease in abuses.

Under the provisions of the National Research Service Award Act of 1974,[82] "each entity which applies for a grant or contract under [the] Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects" must establish an institutional review board.[83] Although the Act does not specify the required composition of such boards, existing regulations require that the board shall not consist entirely of members of a single profession or persons affiliated with the parent organization.[84]

81. Ratnoff, *Who Shall Decide When Doctors Disagree? A Review of the Legal Development of Informed Consent and the Implications of Proposed Lay Review of Human Experimentation*, 25 CASE W. RES. L. REV. 472 (1975).

82. *See* National Research Service Award Act of 1974, Pub. L. No. 94-348, 88 Stat. 342.

83. *Id.* § 474.

84. 45 C.F.R. §§ 46.6(b)(4), (5) (1974).

Such requirements could lead to reduction in the number of physician members. Already nonphysicians on the committees express a sense of inadequacy regarding their ability to evaluate intelligently some of the more complex scientific problems submitted for review. The effect of any restriction on physician membership would be to place a greater responsibility for scientific review on fewer individuals. The physician members would either have to spend considerable time giving their nonmedical colleagues short courses in medicine, or the latter would simply defer to the physicians and confine their attention to such issues as the quality of informed consent.

Hitherto, physicians serving on institutional review committees have done so recognizing that such service is a necessary function of their positions on the staffs of the sponsoring institutions. They have never received monetary or other recompense for their time and effort. It is unrealistic to expect that nonphysicians who are asked to serve on one or another institutional advisory group and who by law must have no prior affiliation with the institution will donate their time. Yet scant attention has been paid to the question of how the involvement of the representatives of the community will be financed. If strict limitations are placed on physician membership, the costs for maintaining these advisory groups may become very great.

In response to recommendations put forward by Katz and others for the establishment of a National Human Investigation Board,[85] a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established under the National Research Service Award Act.[86] The Commission is designed to provide overall direction in the area of policy formulation and to relieve local institutional committees of the burden of policy formulation in certain critical and sensitive areas.[87] Nevertheless, the purpose and

85. *See Hearings on S. 974, S. 878, and S.J. Res. 71 Before the Subcomm. on Health of the Senate Comm. on Labor and Public Welfare*, 93d Cong., 1st Sess. 1053 (1973).

86. National Research Service Award Act of 1974, tit. II, pt. A, § 201(a), Pub. L. No. 94-348, 88 Stat. 342.

87. The purpose of the Commission is to conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research, evaluate existing guidelines for the protection of human subjects, and make appropriate recommendations to the Secretary of HEW concerning further steps, if any, to be taken. *Id.* § 202(a)(1)(A). The duties of the Commission are (1) to identify the requirements of informed consent for participation by children, prisoners, and the institutionalized mentally infirm, *id.* § 202(a)(1)(C)(2); (2) to determine the need for a mechanism to assure that human subjects not reg-

function of the Commission are not designed to usurp the responsibilities of the local institutional committees in the implementation of policy, *i.e.*, in the actual review of protocols. It is important that local committees retain responsibility for implementation of policy since local committees (1) have the advantage of being most sensitive to local problems and responsive to local conditions, (2) can be made more readily aware of any violations and can more effectively monitor continuing compliance with committee decisions, and (3) provide a mechanism whereby the investigator may become involved in the problems of ethical research.

Plans for disseminating decisions of local committees, particularly those made in relation to especially difficult problems, have considerable merit.[88] A system for exchanging information would provide committee members in one area the benefit of experience gained by committees in other areas and would promote uniformity in decision-making. Plans for a scheme to compensate subjects injured in the course of human experimentation also answer a need to provide greater safeguards for these individuals.[89] In relation to these, it is important that laws and regulations make determinations regarding the legal status of the decisions of review committees and of the protocols that have been approved through proper application of review procedures. The liability of both investigators and review committees has to be defined. Presently, researchers, members of review

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ulated by the Secretary are protected, *id.* § 202(a)(1)(C)(3); (3) to investigate the nature and extent of research involving living fetuses, the purposes for which such research has been undertaken, and alternative means for achieving such purposes, *id.* § 202(b); (4) to investigate the use of psychosurgery during the 5-year period ending December 31, 1972, *id.* § 202(c); and (5) to undertake a comprehensive study of ethical, social, and legal implications of advances in biomedical and behavioral research and study, *id.* § 203.

The last of these functions is to include an analysis and evaluation of (1) scientific and technological advances in past, present, and projected biomedical and behavioral research and services; (2) implications of such advances, both for individuals and for society; (3) laws and moral and ethical principles governing the use of technology in medical practice; (4) public understanding of and attitudes toward such implications and laws and principles; and (5) implications for public policy of such findings as are made by the Commission with respect to advances in biomedical and behavioral research and technology and public attitudes towards such advances. *Id.* §§ 203(1)-(5). The life of the Commission ends in 1976, *id.* § 204(d), when it will be succeeded by the National Advisory Council for the Protection of Subjects of Biomedical and Behavioral Research. *Id.* § 211(a), *amending* 42 U.S.C. § 217(f)(1).

88. Such a proposal is contained in S. 2072, 93d Cong., 1st Sess., § 1208 (1973).

89. Such a plan is advocated in Havighurst, *Compensating Persons Injured in Human Experimentation*, 169 SCIENCE 153 (1970).

committees, patient advocates, and institutions are subject to civil liability arising out of injuries sustained in the course of research projects even though they may have complied faithfully with current regulations.[90] In evaluating claims of injury, courts are free to decide the issues with the benefit of hindsight. That is, they may apply standards of practice which may not have existed at the inception of the project and which indeed may have resulted from the findings of the project.

V. CONCLUSION

It is reasonable that efforts designed to improve the ethical climate of human experimentation should redound to the benefit of the investigator as well as his subjects. Progress in medical science depends on research, much of which requires human experimentation. Consequently, human experimentation is necessary and proper, and the researcher involved in such endeavors should not be placed in jeopardy or penalized for attempting to aid society.[91] The goal of the physician engaged in human experimentation, therefore, must be to proceed in the way that will maximize the benefits to society while protecting the rights and welfare of the human subjects. By ensuring that every project is properly designed and executed, a smoothly functioning institutional review committee can assist the investigator in achieving this goal.

90. Cady, *Forensic Medicine, Medical Malpractice: What About Experimentation*, 6 ANNALS OF W. MED. & SURGERY 164 (1952). *See* Adams & Shea-Stonum, *supra* note 71, for a discussion of the liability of a physician for injury resulting from experimentation.

91. Beecher, *supra* note 43, at 470.