able to all those concerned. This, I am sure you will agree, will serve the public interest better than a piecemeal and possibly distorted release through newspaper articles. For that reason, I believe it would serve a useful purpose to insert the report in the *Congressional Record*. A formal endorsement by the Secretary of the Department would add to the positive influence of this very important report.

With kindest wishes.

Sincerely yours,

SAM J. ERVIN, JR., *Chairman.*

[Item I.A.25]

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., July 29, 1974.

HON. SAM J. ERVIN, JR.,
Chairman, Subcommittee on Constitutional Rights, Committee on the Judiciary, U.S. Senate, Washington, D.C.

DEAR SENATOR ERVIN: Thank you for your letter of July 12 about issues of individual rights and psychosurgery, referring to an article which appeared in the *Washington Post* on June 5.

First, let me tell you how the study came to be made. There are two reports, not one. In 1972, then Assistant Secretary for Health Merlin K. DuVal asked the Director, National Institute of Mental Health (NIMH) and the Director, National Institute of Neurological Diseases and Strokes (NINDS), to jointly provide him with their professional advice concerning brain surgery and socially undesirable behavior. As a result of this request and of discussions with the National Academy of Sciences, two groups were established to provide that advice. The major task of the groups was similar, i.e., to study the many issues involved in therapeutic approaches to abnormal behavior with a view to laying the scientific framework as a basis for recommendations and policy formation. There were differences between the groups in specific focus or intensity of analysis. The NIMH group focused more on the clinical and psychological issues on brain surgery and behavior, while the NINDS group emphasized our current state of knowledge regarding brain function as related to human clinical applications. It should be stressed, however, that these are not mutually exclusive concerns and cannot be considered in isolation from each other.

The NINDS report was submitted to the Office of the Assistant Secretary on October 5, 1973; the NIMH report was submitted on January 21, 1974. Each report has been reviewed officially by the other Institute, and comments have been received. I am enclosing copies of both reports with this letter for your use. Part I of the NINDS report has been published as a supplement to the *Archives of Neurology*, January 1, 1974. We have been providing copies of both reports to the public on request.

Let me stress again that these reports were prepared at the request of, and to provide advice to, the Assistant Secretary. They do not, at this time, have my endorsement of all their details. As you clearly point out, they raise a number of medical, legal, ethical, and administrative issues and provide recommendations concerning those issues. However, the Department does not now nor will we in the foreseeable future support research efforts involving surgery on the human brain solely for the treatment of psychiatric or behavioral problems.

P.L. 93-348, "The National Research Act," provides for a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the duties of that Commission is to consider the use of psychosurgery, evaluate the need for it, and recommend to me policies defining the circumstances (if any) under which its use may be appropriate. We anticipate that the Commission will use these reports and other proposals we may develop during the course of its deliberations. We will, of course, work closely with the Commission during its lifetime to consider and propose policies for the broad range of issues involved in the protection of human subjects of biomedical and behavioral research.

I greatly appreciate the support you have given us in earlier letters. Let me assure you that the Department will continue to provide leadership on these issues.

Sincerely,

CASPAR W. WEINBERGER,
Secretary.

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[Item I.A.26]

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., July 25, 1974.

Hon. SAM J. ERVIN, Jr.,
Chairman, Subcommittee on Constitutional Rights, Committee on the Judiciary, U.S. Senate, Washington, D.C.

DEAR SENATOR ERVIN: This is in further response to your letter of February 22 requesting information about Departmental research programs aimed at altering human behavior.

A canvass of non-health-related agencies of the Department has identified ten projects to which your request is applicable. One project is supported by the National Institute of Education (NIE), one by the Office of Child Development (OCD), and eight by the Social and Rehabilitation Service (SRS).

All programs under the responsibility of the Office of Education and the National Institute of Education (NIE) have been reviewed, and biomedical and behavioral research designed to alter the behavior of human subjects is not being supported. One project supported by NIE may be a possible exception; I am enclosing a description of it for your use. [See Item I.C.1.]

Broadly interpreted, your request could include all education programs since all attempt, through a learning environment, to modify human behavior. As was the case in my reply of May 10, 1974, however, we are using the following operational definition of behavioral modification: the systematic application of psychological and social principles to bring about desired changes in or to prevent development of certain "problematic" behaviors and responses. Thus, descriptions of a number of types of research have not been included in our inventory. Such research covers development of new knowledge and improved materials and techniques; studies observing and analyzing human behavior; improving the components of the educational process (structure, dynamics, materials, teaching techniques, etc.); interventions (e.g., new curriculum materials, specialized environments) to examine freely expressed and untreated behaviors in response to interventions that lead to the development of educational interactions and environments most encouraging to the fullest development of natural (and socially approved) behaviors; and research focused upon a defined subset of human behavior—that specifically delineated area of cognitive skills and social competencies expected to be developed during the school years. NIE is also currently supporting a small number of research projects dealing with problematic or handicapped behavior. These projects are designed to monitor and analyze the characteristics and effects of such behavior upon the learning abilities of the individuals involved; neither the design nor the effect of the projects is to alter the behavior of the individuals under study.

Here too, if our operational definition omits projects of major interest to you, we would, of course, be happy to provide information on additional categories of projects should you so desire.

The OCD project is focused upon "Modification of Children's Racial Attitudes." This project is investigating some of the attitudinal and behavioral components of racial prejudice in elementary school children, and assessing the relative efficacy of various modification procedures upon these attitudes and intergroup behavior at different age levels.

The SRS projects are entitled as follows:

1. "Evaluation of Automated Training System for Wheelchair Pushups."
2. "Contingency Management Systems in Medical Rehabilitation."
3. "Operant Conditioning Methods in the Management of Chronic Pain."
4. "Testing of an Automated Training System for Wheelchair Pushups."
5. "Shaping Self-Care Behaviors in Children with Chronic Disabilities."
6. "Management of Behavior in Extended Living Facilities for the Retarded."
7. "Functional Skill Remediation in Hemiplegia; Behavioral Learning Approach Applied to Physical Therapy."
8. "Development and Evaluation of Self Help Groups of Mothers of Children with Birth Defects."

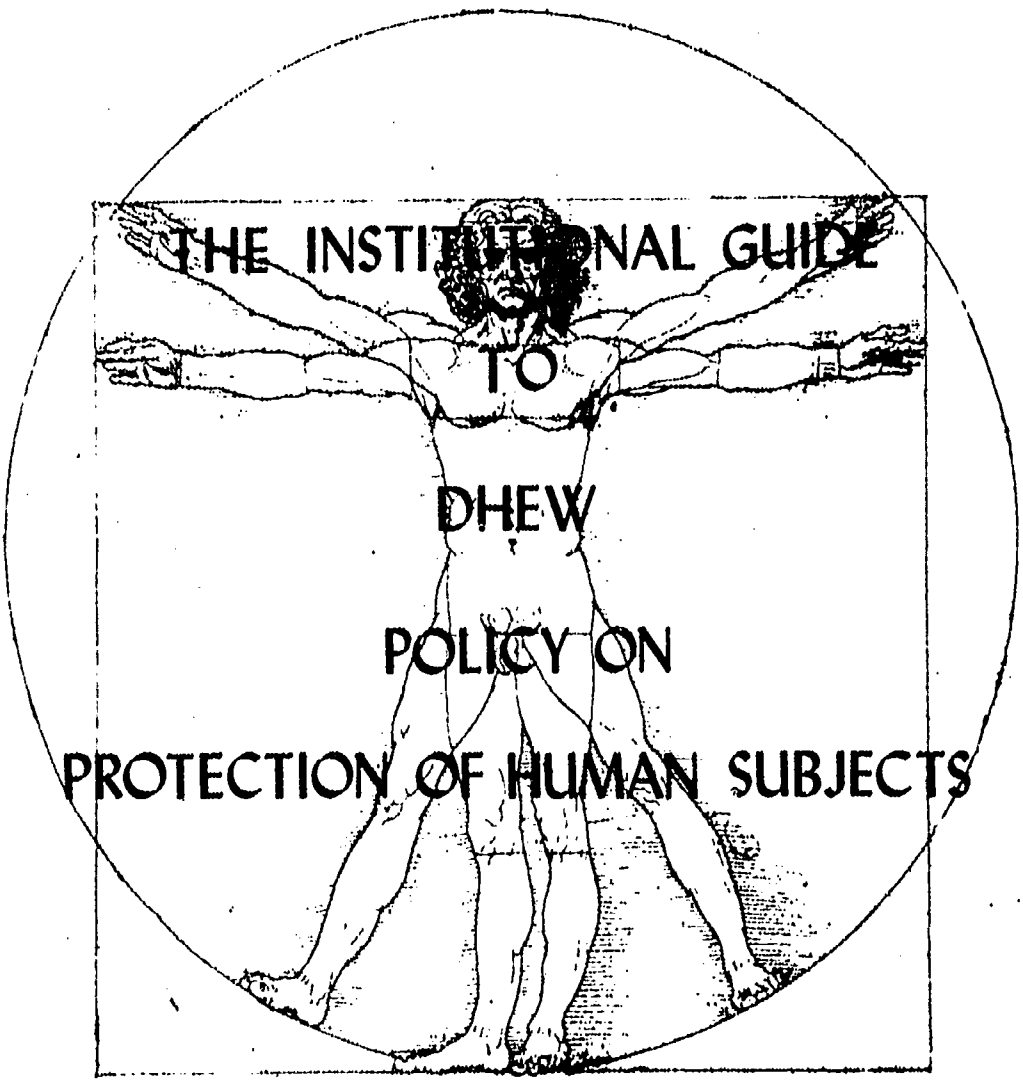
I understand that Dr. Edwards has recently sent you copies of the document published in the *Federal Register* of May 30 which sets forth procedures governing the protection of those human subjects who participate in research projects sponsored by the Department. This then represents the current listing of Department projects pursuant to your request.

Sincerely,

FRANK CARLUCCI,
Acting Secretary.

B. Materials Relating to HEW Guidelines

[ITEM. I.B.1]



U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service — National Institutes of Health

DHEW Publication No. (NIH) 72-102

December 1, 1971

FOREWORD

The Department's basic policy, quoted in the first few paragraphs of this Guide, is simple in concept. However, simplicity in conception is not always easily translated into simplicity in application. Many of the basic terms of the policy, such as subject, risk, and informed consent, are differently understood in the several professions that participate in the varied grant and contract programs supported by the Department. This Guide provides working definitions of the policy's more critical terms, and outlines flexible operating procedures which can be adapted to a variety of grant and contract mechanisms.

A flexible policy is essential. Research, development, and the roduction to practice of new ideas are not carried out in a practical, ethical, or legal vacuum. The public interest obviously would not be served by an inflexible approach to what can or should be done. Ultimately, the decisions required by this policy must depend upon the common sense and sound professional judgment of reasonable men. The Department's policy and the Guide are intended to provide room for the exercise of this judgment.

In its present form, the Guide reflects several years' experience with an earlier Public Health Service policy. It incorporates many comments and suggestions by representatives of grantee and contractor institutions, and by consultants and staff of the operating agencies of the Department. Future experience in the application of the policy in the fields of health, education, and welfare will simultaneously raise questions and suggest changes. Correspondence should be addressed to the Chief, Institutional Relations Branch, Division of Research Grants, National Institutes of Health, Bethesda, Md. 20014.

D. T. Chalkley, Ph. D.
Chief, Institutional Relations Branch
Division of Research Grants, NIH, DHEW

CONTENTS

NOTE

Bold face indicates policy as stated in DHEW Grant Administration Manual Chapter 1-40.

Light face indicates interpretation of DHEW policy.

POLICY

Safeguarding the rights and welfare of human subjects involved in activities supported by grants or contracts from the Department of Health, Education, and Welfare is the responsibility of the institution which receives or is accountable to the DHEW for the funds awarded for the support of the activity.

In order to provide for the adequate discharge of this institutional responsibility, it is the policy of the Department that no grant or contract for an activity involving human subjects shall be made unless the application for such support has been reviewed and approved by an appropriate institutional committee.

This review shall determine that the rights and welfare of the subjects involved are adequately protected, that the risks to an individual are outweighed by the potential benefits to him or by the importance of the knowledge to be gained, and that informed consent is to be obtained by methods that are adequate and appropriate.

In addition the committee must establish a basis for continuing review of the activity in keeping with these determinations.

The institution must submit to the DHEW, for its review, approval, and official acceptance, an assurance of its compliance with this policy. The institution must also provide with each proposal involving human subjects a certification that it has been or will be reviewed in accordance with the institution's assurance.

No grant or contract involving human subjects at risk will be made to an individual unless he is affiliated with or sponsored by an institution which can and does assume responsibility for the protection of the subjects involved.

Since the welfare of subjects is a matter of concern to the Department of Health, Education, and Welfare as well as to the institution, 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 the Department. As a result of this review, the committee may recommend to the operating agency, and the operating agency may require, the imposition of specific grant or contract terms providing for the protection of human subjects, including requirements for informed consent.

APPLICABILITY

A. *General*

This policy applies to all grants and contracts which support activities in which subjects may be at risk.

B. *Subject*

This term describes any individual who may be at risk as a conse-

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quence of participation as a subject in research, development, demonstration, or other activities supported by DHEW funds.

This may include patients; outpatients; donors of organs, tissues, and services; informants; and normal volunteers, including students who are placed at risk during training in medical, psychological, sociological, educational, and other types of activities supported by DHEW.

Of particular concern are those subjects in groups with limited civil freedom. These include prisoners, residents or clients of institutions for the mentally ill and mentally retarded, and persons subject to military discipline.

The unborn and the dead should be considered subjects to the extent that they have rights which can be exercised by their next of kin or legally authorized representatives.

C. *At Risk*

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. The determination of when an individual is at risk is a matter of the application of common sense and sound professional judgment to the circumstances of the activity in question. Responsibility for this determination resides at all levels of institutional and departmental review. Definitive determination will be made by the operating agency.

D. *Types of Risks and Applicability of the Policy*

1. Certain risks are inherent in life itself, at the time and in the places where life runs its course. This policy is not concerned with the ordinary risks of public or private living, or those risks associated with admission to a school or hospital. It is not concerned with the risks inherent in professional practice as long as these do not exceed the bounds of established and accepted procedures, including innovative practices applied in the interest of the individual patient, student or client.

Risk and the applicability of this policy are most obvious in medical and behavioral science research projects involving procedures that may induce a potentially harmful altered physical state or condition. Surgical and biopsy procedures; the removal of organs or tissues for study, reference, transplantation, or banking; the administration of drugs or radiation; the use of indwelling catheters or electrodes; the requirement of strenuous physical exertion; subjection to deceit, public embarrassment, and humiliation are all examples of procedures which require thorough scrutiny by both the Department of Health, Education, and Welfare and institutional committees. In general those projects which involve risk of physical or psychological injury require prior written consent.

2. There is a wide range of medical, social, and behavioral projects and activities in which no immediate physical risk to the subject is involved; e.g., those utilizing personality inventories, interviews, questionnaires, or the use of observation, photographs, taped records, or stored data. However, some of these procedures may involve varying degrees of discomfort, harassment, invasion of privacy, or may constitute a threat to the

subject's dignity through the imposition of demeaning or dehumanizing conditions.

3. There are also medical and biomedical projects concerned solely with organs, tissues, body fluids, and other materials obtained in the course of the routine performance of medical services such as diagnosis, treatment and care, or at autopsy. The use of these materials obviously involves no element of physical risk to the subject. However, their use for many research, training, and service purposes may present psychological, sociological, or legal risks to the subject or his authorized representatives. In these instances, application of the policy requires review to determine that the circumstances under which the materials were procured were appropriate and that adequate and appropriate consent was, or can be, obtained for the use of these materials for project purposes.

4. Similarly, some studies depend upon stored data or information which was often obtained for quite different purposes. Here, the reviews should also determine whether the use of these materials is within the scope of the original consent, or whether consent can be obtained.

E. *Established and Accepted Methods*

Some methods become established through rigorous standardization procedures prescribed, as in the case of drugs or biologicals, by law or, as in the case of many educational tests, through the aegis of professional societies or nonprofit agencies. Acceptance is a matter of professional response, and determination as to when a method passes from the experimental stage and becomes "established and accepted" is a matter of judgment.

In determining what constitutes an established and accepted method, consideration should be given to both national and local standards of practice. A management procedure may become temporarily established in the routine of a local institution but still fail to win acceptance at the national level. A psychological inventory may be accepted nationally, but still contain questions which are disturbing or offensive to a local population. Surgical procedures which are established and accepted in one part of the country may be considered experimental in another, not due to inherent deficiencies, but because of the lack of proper facilities and trained personnel. Diagnostic procedures which are routine in the United States may pose serious hazards to an undernourished, heavily infected, overseas population.

If doubt exists as to whether the procedures to be employed are established and accepted, the activity should be subject to review and approval by the institutional committee.

F. *Necessity to Meet Needs*

Even if considered established and accepted, the method may place the subject at risk if it is being employed for purposes other than to meet the needs of the subject. Determination by an attending professional that a particular treatment, test, regimen, or curriculum is appropriate for a particular subject to meet his needs limits the attendant risks to those inherent in the delivery of services, or in training.

On the other hand, arbitrary, random, or other assignment of subjects

to differing treatment or study groups in the interests of a DHEW supported activity, rather than in the strict interests of the subject, introduces the possibility of exposing him to additional risk. Even comparisons of two or more established and accepted methods may potentially involve exposure of at least some of the subjects to additional risks. Any alteration of the choice, scope, or timing of an otherwise established and accepted method, primarily in the interests of a DHEW activity, also raises the issue of additional risk.

If doubt exists as to whether the procedures are intended solely to meet the needs of the subject, the activity should be subject to review and approval by the institutional committee.

INSTITUTIONAL REVIEW

A. *Initial Review of Projects*

1. Review must be carried out by an appropriate institutional committee. The committee may be an existing one, such as a board of trustees, medical staff committee, utilization committee, or research committee, or it may be specially constituted for the purpose of this review. Institutions may utilize subcommittees to represent major administrative or subordinate components in those instances where establishment of a single committee is impracticable or inadvisable. The institution may utilize staff, consultants, or both.

The committee must be composed of sufficient members with varying backgrounds to assure complete and adequate review of projects and activities commonly conducted by the institution. The committee's membership, maturity, experience, and expertise should be such as to justify respect for its advice and counsel. No member of an institutional committee shall be involved in either the initial or continuing review of an activity in which he has a professional responsibility, except to provide information requested by the committee. In addition to possessing the professional competence to review specific activities, the committee should be able to determine acceptability of the proposal in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes.[1] The committee may therefore need to include persons whose primary concerns lie in these areas rather than in the conduct of research, development, and service programs of the types supported by the DHEW.

If an institution is so small that it cannot appoint a suitable committee from its own staff, it should appoint members from outside the institution.

Committee members shall be identified by name, occupation or position, and by other pertinent indications of experience and competence in areas pertinent to the areas of review such as earned degrees, board certifications, licensures, memberships, etc.

Temporary replacement of a committee member by an alternate of comparable experience and competence is permitted in the event a mem-

[1] In the United States, the regulations of the Food and Drug Administration (21 CFR 130) provide that the committee *must* possess competencies to determine acceptability of the project in these terms in order to review proposals for investigational new drug (IND) studies.

ber is momentarily unable to fulfill committee responsibility. The DHEW should be notified of any permanent replacement or additions.

2. The institution should adopt a statement of principles that will assist it in the discharge of its responsibilities for protecting the rights and welfare of subjects. This may be an appropriate existing code or declaration or one formulated by the institution itself.[2] It is to be understood that no such principles supersede DHEW policy or applicable law.

3. Review begins with the identification of those projects or activities which involve subjects who may be at risk. In institutions with large grant and contract programs, administrative staff may be delegated the responsibility of separating those projects which do not involve human subjects in any degree; i.e., animal and nonhuman materials studies. However, determinations as to whether any project or activity involves human subjects at risk is a professional responsibility to be discharged through review by the committee, or by subcommittees.

If review determines that the procedures to be applied are to be limited to those considered by the committee to be established, accepted, and necessary to the needs of the subject, review need go no further; and the application should be certified as approved by the committee. Such projects involve human subjects, but these subjects are not considered to be at risk.

If review determines that the procedures to be applied will place the subject at risk, review should be expanded to include the issues of the protection of the subject's rights and welfare, of the relative weight of risks and benefits, and of the provision of adequate and appropriate consent procedures.

Where required by workload considerations or by geographic separation of operating units, subcommittees or mail review may be utilized to provide preliminary review of applications.

Final review of projects involving subjects at risk should be carried out by a quorum of the committee.[3] Such review should determine, through review of reports by subcommittees, or through its own examination of applications or of protocols, or through interviews with those individuals who will have professional responsibility for the proposed project or activity, or through other acceptable procedures that the requirements of the institutional assurance and of DHEW policy have been met, specifically that:

a. The rights and welfare of the subjects are adequately protected. Institutional committees should carefully examine applications, protocols, or descriptions of work to arrive at an independent determination of possible risks. The committee must be alert to the possibility that investigators, program directors, or contractors may, quite unintentionally, introduce unnecessary or unacceptable hazards, or fail to provide adequate safeguards. This possibility is particularly true if the project crosses disciplinary lines, involves new and untried procedures, or involves established and accepted procedures which are new to the personnel applying them. Committees must also assure

[2] Some of the existing codes or statements of principles concerned with the protection of human subjects in research, investigation, and care are listed in attachment C.

[3] In the United States, the quorum reviewing investigational new drug studies must satisfy requirements of the Food and Drug Administration (21 CFR 130).

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themselves that proper precautions will be taken to deal with emergencies that may develop even in the course of seemingly routine activities.

When appropriate, provision should be made for safeguarding information that could be traced to, or identified with, subjects. The committee may require the project or activity director to take steps to insure the confidentiality and security of data, particularly if it may not always remain under his direct control.

Safeguards include, initially, the careful design of questionnaires, inventories, interview schedules, and other data gathering instruments and procedures to limit the personal information to be acquired to that absolutely essential to the project or activity. Additional safeguards include the encoding or enciphering of names, addresses, serial numbers, and of data transferred to tapes, discs, and printouts. Secure, locked spaces and cabinets may be necessary for handling and storing documents and files. Codes and ciphers should always be kept in secure places, distinctly separate from encoded and enciphered data. The shipment, delivery, and transfer of all data, printouts, and files between offices and institutions may require careful controls. Computer to computer transmission of data may be restricted or forbidden.

Provision should also be made for the destruction of all edited, obsolete or depleted data on punched cards, tapes, discs, and other records. The committee may also determine a future date for destruction of all stored primary data pertaining to a project or activity.

Particularly relevant to the decision of the committees are those rights of the subject that are defined by law. The committee should familiarize itself through consultation with legal counsel with these statutes and common law precedents which may bear on its decisions. The provisions of this policy may not be construed in any manner or sense that would abrogate, supersede, or moderate more restrictive applicable law or precedential legal decisions.

Laws may define what constitutes consent and who may give consent, prescribe or proscribe the performance of certain medical and surgical procedures, protect confidential communications, define negligence, define invasion of privacy, require disclosure of records pursuant to legal process, and limit charitable and governmental immunity (see, e.g., the University of Pittsburgh Law Manual).

b. The risks to an individual are outweighed by the potential benefits to him or by the importance of the knowledge to be gained.

The committee should carefully weigh the known or foreseeable risks to be encountered by subjects, the probable benefits that may accrue to them, and the probable benefits to humanity that may result from the subject's participation in the project or activity. If it seems probable that participation will confer substantial benefits on the subjects, the committee may be justified in permitting them to accept commensurate or lesser risks. If the potential benefits are insubstantial, or are outweighed by risks, the committee may be justified in permitting the subjects to accept these risks in the interests of humanity. The committee should consider the possibility that subjects, or those authorized to represent subjects, may be motivated to accept risks for unsuitable or inadequate reasons. In such instances the consent procedures adopted should incorporate adequate safeguards.

Compensation to volunteers should never be such as to constitute an undue inducement.

No subject can be expected to understand the issues of risks and benefits as fully as the committee. Its agreement that consent can reasonably be sought for subject participation in a project or activity is of paramount practical importance.

"The informed consent of the subject, while often a legal necessity is a goal toward which we must strive, but hardly ever achieve except in the simplest cases."

(Henry K. Beecher, M.D.)

c. The informed consent of subjects will be obtained by methods that are adequate and appropriate.

Note.—In the United States, adherence to the regulations of the Food and Drug Administration (21 CFR 130) governing consent in projects involving investigational new drugs (IND) is required by law.

Informed consent is the agreement obtained from a subject, or from his authorized representative, to the subject's participation in an activity.

The basic elements of informed consent are:

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;**
6. **An instruction that the subject is free to withdraw his consent and to discontinue participation in the project or activity at any time.**

In addition, the agreement, written or oral, entered into by the subject, should include no exculpatory language through which the subject is made to waive, or to appear to waive, any of his legal rights, or to release the institution or its agents from liability for negligence.[4]

Informed consent must be documented (see Documentation, p. 16).

Consent should be obtained, whenever practicable, from the subjects themselves. When the subject group will include individuals who are not legally or physically capable of giving informed consent, because of age, mental incapacity, or inability to communicate, the review committee should consider the validity of consent by next of kin, legal guardians, or by other qualified third parties representative of the subjects' interests. In such instances, careful consideration should be given by the committee not only to whether these third parties can be presumed to have the necessary depth of interest and concern with the subjects' rights and welfare, but also to whether these third parties will be legally authorized to expose the subjects to the risks involved.

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[4] Use of exculpatory clauses in consent documents is considered contrary to public policy. *Tunkl vs. Regents of University of California*, 60 Cal. 2d 92, 32 Cal. Rptr.33, 383 P. 2d 441 (1963), Annot., 6 A.L.R. 3d 693 (1966).

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The review committee will determine if the consent required, whether to be secured before the fact, in writing or orally, or after the fact following debriefing, or whether implicit in voluntary participation in an adequately advertised activity, is appropriate in the light of the risks to the subject, and the circumstances of the project.

The review committee will also determine if the information to be given to the subject, or to qualified third parties, in writing or orally, is a fair explanation of the project or activity, of its possible benefits, and of its attendant hazards.

Where an activity involves therapy, diagnosis, or management, and a professional/patient relationship exists, it is necessary "to recognize that each patient's mental and emotional condition is important . . . and that in discussing the element of risk, a certain amount of discretion must be employed consistent with full disclosure of fact necessary to any informed consent." [5]

Where an activity does not involve therapy, diagnosis, or management, and a professional/subject rather than a professional/patient relationship exists, "the subject is entitled to a full and frank disclosure of all the facts, probabilities, and opinions which a reasonable man might be expected to consider before giving his consent." [6]

When debriefing procedures are considered as a necessary part of the plan, the committee should ascertain that the e will be complete and prompt.

B. *Continuing Review*

This is an essential part of the review process. While procedures for continuing review of ongoing projects and activities should be based in principle on the initial review criteria, they should also be adapted to the size and administrative structure of the institution. Institutions which are small and compact and in which the committee members are in day-to-day contact with professional staff may be able to function effectively with some informality. Institutions which have placed responsibility for eview in boards of trustees, utilization committees, and similar groups that meet on frequent schedules may find it possible to have projects re-reviewed during these meetings.

In larger institutions with more complex administrative structures and specially appointed committees, these committees may adopt a variety of continuing review mechanisms They may involve systematic review of projects at fixed intervals, or at intervals set by the committee commensurate with the project's risk. Thus, a project involving an untried procedure may initially require reconsideration as each subject completes his involvement. A highly routine project may need no more than annual review. Routine diagnostic service procedures, such as biopsy and autopsy, which contribute to research and demonstration activities generally require no more than annual review. Spot checks may be used to supplement scheduled reviews.

Actual review may involve interviews with the responsible staff, or

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[5] *Salgo vs. Leland Stanford Jr. University Board of Trustees* (154 C.A. 2nd 560; 317 P. 2d 1701).

[6] *Halushka vs. University of Saskatchewan*, (1965) 53 D.L.R. (2d).

review of written reports and supporting documents and forms. In any event, such review must be completed at least annually to permit certifications of review on noncompeting continuation applications.

C. *Communication of the Committee's Action, Advice, and Counsel*

If the committee's overall recommendation is favorable, it may simultaneously prescribe restrictions or conditions under which the activity may be conducted, define substantial changes in the research plans which should be brought to its attention, and determine the nature and frequency of interim review procedures to insure continued acceptable conduct of the research.

Favorable recommendations by an institutional committee are, of course, always subject to further appropriate review and rejection by institution officials.

Unfavorable recommendations, restrictions, or conditions cannot be removed except by the committee or by the action of another appropriate review group described in the assurance filed with the Department of Health, Education, and Welfare.

Staff with supervisory responsibility for investigators and program directors whose projects or activities have been disapproved or restricted, and institutional administrative and financial officers should be informed of the committee's recommendations. Responsible professional staff should be informed of the reasons for any adverse actions taken by the institutional committee.

The committee should be prepared at all times to provide advice and counsel to staff developing new projects or activities or contemplating revision of ongoing projects or disapproved proposals.

D. *Maintenance of an Active and Effective Committee*

Institutions should establish policy determining overall committee composition, including provisions for rotation of memberships and appointment of chairmen. Channels of responsibility should be established for implementation of committee recommendations as they may affect the actions of responsible professional staff, grants and contracts officers, business officers, and other responsible staff. Provisions should be made for remedial action in the event of disregard of committee recommendations.

ASSURANCES

A. *Negotiation of Assurances*

An institution applying to the DHEW for a grant or contract involving human subjects must provide written assurance that it will abide by DHEW policy. The assurance shall embody a statement of compliance with DHEW requirements for initial and continuing committee review of the supported activities; a set of implementing guidelines, including identification of the committee, and a description of its review procedures or, in the case of special assurances concerned with single projects or activities, a report of initial findings and pro-

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posed continuing review procedures. Institutions that have not previously filed assurances should request instructions for the preparation of an assurance from the Division of Research Grants, National Institutes of Health.

Negotiation of assurances is the responsibility of the DRG, NIH. Negotiation will be initiated on receipt of a copy of a grant application, a contract proposal, or other documentation identifying the project and the offeror or sponsoring institution.

Assurances will not be accepted from institutions or institutional components which do not have control over the expenditure of DHEW grant or contract funds unless they are an active part of a cooperative project or activity.

An assurance will be accepted only after review and approval by the DRG, NIH.

B. *Types of Assurance*

Assurances may be one of two types:

1. *General assurance.*—A general assurance describes the review and implementation procedures applicable to all DHEW-supported activities within an institution, regardless of the number, location, or types of its components (see attachment A). General assurances will be required from institutions having a significant number of concurrent DHEW projects or activities involving human subjects.

2. *Special assurance.*—A special assurance will, as a rule, describe those review and implementation procedures applicable to a single project or activity (see attachment B). Special assurances may also be approved in modified forms to meet unusual requirements either of the operating agency or of the institution receiving a grant or contract. Special assurances are not to be solicited from institutions which have accepted general assurances on file.

C. *Minimum Requirements for General Assurances*

1. *Statement of compliance.*—A formal statement of compliance with DHEW policy must be executed by an appropriate institutional official.

2. *Implementing guidelines.*—The institution must include as part of its assurance implementing guidelines that specifically provide for:

a. The statement of principles that will assist the institution in the discharge of its responsibilities for protecting the rights and welfare of subjects. This may be an appropriate existing code or declaration or one formulated by the institution itself.

b. A committee or committee structure which will conduct initial and continuing reviews. Committee members shall be identified by name, occupation or position, and by other pertinent indications of experience and competence in areas pertinent to the areas of review such as earned degrees, board certifications, licensures, memberships, etc.

c. The procedures which the institution will follow in carrying out its initial and continuing review of proposals and activities to insure that:

(1) The rights and welfare of subjects are adequately protected;
(2) The risks to subjects are outweighed by potential benefits;
(3) The informed consent of subjects will be obtained by methods that are adequate and appropriate.

d. The procedures which the committee will follow to provide advice and counsel to project and program directors with regard to the committee's actions as well as the requirement for reporting to the committee any emergent problems or proposed procedural changes.

e. The procedures which the institution will follow to maintain an active and effective committee and to implement its recommendations.

D. *Minimum Requirements for Special Assurance*

An acceptable special assurance covering a single activity consists of a properly completed statement of compliance, similar to that illustrated by attachment B. This assurance shall identify the specific grant or contract involved by its number, if known; by its full title; and by the name of the project or program director, principal investigator, fellow, or other person immediately responsible for the conduct of the activity. The assurance shall be signed by a committee of not fewer than three members and executed by an appropriate institutional official. The committee shall describe in general terms those risks to the subject that it recognizes as inherent in the activity. *Consent procedures to be used are to be described.* Any consent statement to be signed, heard, or read by the subject or responsible third parties should be attached. The assurance should outline the circumstances under which the director or investigator will be required to inform the committee of proposed changes in the activity, or of emergent problems involving human subjects. The assurance should also indicate whether the director or investigator will be required to submit written reports, appear for interview, or be visited by the committee or committees to provide for continuing review. It should also indicate the intervals at which such reviews will take place.

TIMING AND CERTIFICATION OF INSTITUTIONAL REVIEW

A. *General Assurances*

1. *Timely review.*—All proposals involving human subjects submitted by institutions with accepted general assurances should, whenever possible, be given institutional review and approval prior to submission to the DHEW. The proposal or application should be appropriately marked in the spaces provided on forms, or the following statement should be typed on the lower or right hand margin of the page bearing the name of the institutional official authorized to sign or execute applications or proposals for the institution:
"HUMAN SUBJECTS—REVIEWED AND APPROVED ON ____(date)____."
(This date should be no more than 90 days prior to the submission date, and must not be more than 12 months prior to the proposed starting date.)

2. *Pending review.*—If it will be necessary to delay the review, the

proposal is to be appropriately marked in the spaces provided on forms, or the following statement is to be typed in the lower or right hand margin of the page bearing the name of the institutional official authorized to sign or execute applications or proposals for the institution:

"HUMAN SUBJECTS—REVIEW PENDING ON ____(date)____."

(This date should be at least one month earlier than the proposed starting date of the project to avoid possible conflict with the award date.)

3. *Completion of pending review.*—Review should be initiated as soon as possible after the submission of the proposal so that final action can be completed prior to the pending review date. If this final action is disapproval, or is approval contingent on substantive changes in the proposal, the operating agency is to be notified promptly by telegram; an immediate confirmatory letter; and, where appropriate, by withdrawal of the application from further consideration by the agency.

4. *Institutional review of proposals lacking definite plans or specifications for the involvement of human subjects.*—Certain types of proposals are submitted with the knowledge that human subjects are to be involved within the project period, but definite plans for this involvement cannot properly be included in the proposal. These include (1) certain training grants where trainee projects remain to be selected, and (2) research, pilot, or developmental studies in which involvement depends upon such things as the completion of instruments, or of prior animal studies, or upon the purification of compounds.

Such proposals should be reviewed and certified in the same manner as more complete proposals. The initial certification indicates institutional approval of the applications as submitted, and commits the institution to later review of the plans when completed. Such later review should be completed prior to the beginning of the budget period during which actual involvement of human subjects is to begin.

5. *Institutional review of proposals not submitted with the intent of involving human subjects.*—If a proposal, at the time it is submitted to the DHEW, does not anticipate involving or intend to involve human subjects, no certification should be submitted. In those instances, however, where funds are awarded in response to the proposal and it later becomes appropriate to use all or parts of these funds for activities which will involve human subjects, such use must be reviewed and approved in accordance with the institutional assurance prior to the use of subjects:

a. Where support is provided by project grants or contracts, review and approval of such changes must be certified to the awarding agency or contracting agency, together with a description of the proposed change in the project plan or contract workscope. Subjects should not be used prior to receipt of approval from agency staff or from the project officer concerned.

b. Where support is provided by a mandatory grant or institutional grant, in which cases the institution determines within broad guidelines the project or activities supported, including the use of human

subjects (i.e., general research support grants, clinical research center projects), review must be carried out in accordance with the institutional assurance. Certification for individual projects need not be forwarded to the awarding agency.

Whenever the committee is uncertain as to whether a change should or should not be reported, the question should be referred to the operating agency concerned.

All certifications are subject to verfication by DHEW representatives authorized to examine institutional and committee records.

B. *Special Assurances*

When a special assurance is submitted, it provides certification for the initial grant or contract period concerned. No additional documentation is required. If the terms of the grant or contract provide for additional years of support, with annual obligation or funds, the noncompeting renewal application or proposal shall be certified in the manner described in the preceding section.

COOPERATIVE ACTIVITIES

Cooperative activities are those which involve other than the grantee or prime contractor (such as a contractor under a grantee or a subcontractor under a prime contractor). In such instances the grantee or prime contractor may obtain access to all or some of the human subjects involved through the cooperating institution. Regardless of the distances involved and the nature of the cooperative arrangement, the basic DHEW policy applies and the grantee or prime contractor remains responsible for safeguarding the rights and welfare of the subjects. The manner in which this responsibility can be discharged depends on whether the grantee or contractor holds an institutional general assurance or an institutional special assurance.

A. *Institutions with General Assurances*

1. Initial and continuing institutional review may be carried out by one or a combination of procedures:

—By the grantee's or contractor's committee;
—By the committee reviews conducted at both institutions; or
—Through cooperation of appropriate individuals or committees representing the cooperating institution.

The procedures to be followed must be made a matter of record in the institutional files for the grant or contract before funds are released by the grantee or contractor for the cooperative project. There are three relationships that may govern in reference to the cooperating institution:

a. Cooperating institutions with accepted general assurances When the cooperating institution has on file with the DHEW an accepted general assurance, the grantee or contractor may request the cooperator to conduct its own independent review and to report to the grantee's or contractor's committee the cooperating committee's recommendations on those aspects of the activity that concern indi-

viduals for whom the cooperating institution has responsibility in accordance with its own assurance. The grantee or contractor may, at its discretion, concur with or further restrict the recommendations of the cooperating institution. It is the responsibility of the grantee or contractor to maintain communication with the cooperating institutional committees. The cooperating institution should promptly notify the grantee or contracting institution whenever the cooperating institution finds the conduct of the project or activity within its purview unsatisfactory.

b. Cooperating institution with no accepted general assurance When the cooperating institution does not have an accepted assurance on file with the DHEW, the awarding agency concerned may request the DRG, NIH, to negotiate an assurance.

c. Interinstitutional joint reviews.—The grantee or contracting institution may wish to develop an agreement with cooperating institutions to provide for a review committee with representatives from cooperating institutions. Representatives of cooperating institutions may be appointed as *ad hoc* members of the grantee or contracting institution's existing review committee or, if cooperation is on a frequent or continuing basis as between a medical school and a group of affiliated hospitals, appointments may be made permanent. Under some circumstances component subcommittees may be established within cooperating institutions. All such cooperative arrangements must be accepted by the Department as part of a general assurance, ar as an amendment to a general assurance, or in unusual situations as determined by the DRG, NIH, as a special assurance.

B. *Institutions with Special Assurances*

While responsibility for initial and continuing review necessarily lies with the contractor, the DHEW will also require acceptable assurances from those cooperating institutions having immediate responsibility for subjects.

If the cooperating institution has on file with the DHEW an accepted general assurance, the contractor shall request the cooperator to conduct its own independent review of those aspects of the project or activity which will involve human subjects for which it has immediate responsibility. Such a request shall be in writing and should provide for direct notification of the contractor's committee in the event that the cooperator's committee finds the conduct of the activity unsatisfactory.

If the cooperating institution does not have an accepted general assurance on file with the DHEW, the operating agency concerned must request the DRG, NIH, to negotiate an assurance.

INSTITUTIONAL ADMINISTRATION OF ASSURANCES

A. *Institutional Responsibility*

The grantee or contracting institution's administration is accountable to the Department for effectively carrying out the provisions of the institutional assurance for the protection of human subjects as ac-

cepted and recognized by the Department. Revisions in the institutional assurance, including the implementing procedures, are to be reported to the Department prior to the date such revisions become effective. Revision without prior notification may result in withdrawal of departmental recognition of the institution's assurance.

B. *Executive Functions*

Specific executive functions to be conducted by the institutional administration include institutional policy formulation, development, promulgation, and continuing indoctrination of personnel. Appropriate administrative assistance and support must be provided for the committee's functions. Implementation of the committee's recommendations through appropriate administrative action and followup is a condition of acceptance of an assurance. Committee approvals and recommendations are, of course, subject to review and to disapproval or further restriction by institutional officials. Committee disapprovals, restrictions, or conditions cannot be rescinded or removed except by action of the committee or another appropriate review group as described and accepted in the assurance filed with the Department.

C. *Assurance Implementation*

Under no circumstances shall proposed activity plans, not approved by the committee, be implemented with Department funds. The principal investigator, program or project director, or other responsible staff must be notified as promptly as possible of committee actions, including any restrictive recommendations made by the institutional committee or the administration. They must also be informed and reminded of their continuing responsibility to bring to the attention of the committee any proposed significant changes in project or activity plans or any emergent problems that will affect human subjects. Where continuing review of projects involves the channels of administrative authority in the institution, notification of committee actions should be sent through these channels. Establishment of mechanisms for consultation and appeal by investigators and subjects may be an important condition of acceptance of an assurance by the Department.

D. *Documentation*

1. *General.*—Development of appropriate documentation and reporting procedures is an essential administrative function. The files must include copies of all documents presented or required for initial and continuing review by the institutional review committee and transmittals on actions, instructions, and conditions resulting from review committee deliberations addressed to the activity director are to be made part of the official institutional files for the supported activity. Committee meeting minutes including records of discussions of substantive issues and their resolution are to be retained by the institution and be made available upon request to representatives of the DHEW.

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2. *Informed consent.*—An institution proposing to place any individual at risk is obligated to obtain and document his informed consent; the terms "at risk" and "informed consent" will apply as defined previously.

The actual procedure in obtaining informed consent and the basis for committee determinations that the procedures are adequate and appropriate are to be fully documented. The documentation will follow one of the following three forms:

a. Provision of a written consent document embodying all of the basic elements of informed consent. *This form is to be signed by the subject or his authorized representative.* A sample of the form as approved by the committee is to be retained in its records. Completed forms are to be handled in accordance with institutional practice.

b. Provision of a "short" form written consent document indicating that the basic elements of informed consent have been presented orally to the subject. Written summaries of what is to be said to the patient are to be approved by the committee. *The "short" form is to be signed by the subject or his authorized representative and an auditor-witness to the oral presentation and to the subject's or his authorized representative's signature.* A copy of the approved summary, annotated to show any additions, is to be signed by the persons obtaining the consent on behalf of the institution and by the auditor-witness. Sample copies of the consent form and of the summaries as approved by the committee are to be retained in its records. Completed forms are to be handled in accordance with institutional practice.

c. Modification of either of the above two primary procedures. *All such modifications must be approved by the committee in the minutes signed by the committee chairman.* Granting of permission to use modified procedures imposes additional responsibility upon the review committee and the institution to establish that the risk to any subject is minimum, that use of either of the primary procedures for obtaining informed consent would surely invalidate objectives of considerable immediate importance, and that any reasonable alternative means for attaining these objectives would be less advantageous to the subject.

The committee's reasons for permitting modification or elimination of any of the six basic elements of informed consent, or for altering requirements for a subject's signature, or for signature of an auditor-witness, or for substitution (i.e., debriefing), or other modification of full, complete, written prior consent, must be individually and specifically documented in the minutes and in reports of committee actions to the institutional files. Approval of any such modifications should be regularly reconsidered as a function of continuing review and as required for annual review, with documentation of reaffirmation, revision, or discontinuation as appropriate.

3. *Reporting to DHEW.*—No routine reports to DHEW are required. Significant changes in policy, procedure, or committee structure shall, however, be promptly reported to the DRG, NIH, for review and acceptance. Review of these changes or of institutional and other records of performance under the terms and conditions of DHEW

policy, may require renegotiation of the assurance or such other action as may be appropriate.

ENFORCEMENT

The DRG, NIH, will follow up reports by reviewers, evaluators, consultants, and staff of the DHEW indicating concern for the welfare of subjects involved in approved and funded grants or contracts, and of subjects potentially involved in activities approved but not funded, and in disapproved proposals. On the basis of these reports and of other sources of information, the DRG, NIH, may, in collaboration with the operating agency concerned, correspond with or visit institutions to discuss correction of any apparent deficiencies in its implementation of the procedures described in its institutional assurance.

If, in the judgment of the Secretary, an institution has failed in a material manner to comply with the terms of this policy with respect to a particular DHEW grant or contract, he may require that it be terminated in the manner provided for in applicable grant or procurement regulations. The institution shall be promptly notified of such finding and of the reason therefor.

If, in the judgment of the Secretary, an institution fails to discharge its responsibilities for the protection of the rights and welfare of the individuals in its care, whether or not DHEW funds are involved, he may question whether the institution and the individuals concerned should remain eligible to receive future DHEW funds for activities involving human subjects. The institution and individuals concerned shall be promptly notified of this finding and of the reasons therefor.

DEPARTMENTAL REVIEW OF ASSURANCES

All assurances submitted for approval are to be forwarded to the DRG, NIH, for review and acceptance on behalf of the Department. Review will be principally concerned with the adequacy of the proposed committee in the light of the probable scope of the applicant institution's activities, and with the appropriateness of the proposed initial and continuing review in the light of the probable risks to be encountered, the types of subject populations involved, and the size and complexity of the institution's administration. Institutions submitting inadequate assurances will be informed of deficiencies. The appropriate operating agency will be kept informed, on request, of the status and acceptance of an assurance.

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ATTACHMENT A

EXAMPLE OF A STATEMENT OF COMPLIANCE PART ONE OF A GENERAL INSTITUTIONAL ASSURANCE

The (name of institution) will comply with the policy for the protection of human subjects participating in activities supported directly or indirectly by grants or contracts from the Department of Health, Education, and Welfare. In fulfillment of its assurance:

This institution will establish and maintain a committee competent to review projects and activities that involve human subjects. The committee will be assigned responsibility to determine for each activity as planned and conducted that:

The rights and welfare of subjects are adequately protected.
The risks to subjects are outweighed by potential benefits.
The informed consent of subjects will be obtained by methods that are adequate and appropriate.

This institution will provide for committee reviews to be conducted with objectivity and in a manner to ensure the exercise of independent judgment of the members. Members will be excluded from reviews of projects or activities in which they have an active role or a conflict of interests.

This institution will encourage continuing constructive communication between the committee and the project directors as a means of safeguarding the rights and welfare of subjects.

This institution will provide for the facilities and professional attention required for subjects who may suffer physical, psychological, or other injury as a result of participation in an activity.

This institution will maintain appropriate and informative records of committee reviews of applications and active projects, of documentation of informed consent, and of other documentation that may pertain to the selection, participation, and protection of subjects and to reviews of circumstances that adversely affect the rights or welfare of individual subjects.

This institution will periodically reassure itself through appropriate administrative overview that the practices and procedures designed for the protection of the rights and welfare of subjects are being effectively applied and are consistent with its assurance as accepted by the Department of Health, Education, and Welfare.

Official signing for the Institution

Signature _____

Title _____

Date _____

Enclosure: Implementing Guidelines, Part Two of a General Institutional Assurance.

ATTACHMENT B

EXAMPLE OF A SPECIAL INSTITUTIONAL ASSURANCE AND CERTIFICATION OF REVIEW OF SINGLE PROJECTS INVOLVING HUMAN SUBJECTS

(0) The (name of institution) will comply with the provisions of the Department of Health, Education, and Welfare policy as outlined in the "Institutional Guide to DHEW Policy on Protection of Human Subjects." This institution has established a committee competent to review the project or activity identified below. The committee's membership, maturity, and expertise assure respect for its advice and counsel. No member of the committee has a vested professional interest in the project or activity that will conflict with the need for independent review for the purpose of safeguarding the rights and welfare of subjects.
The initial review of the proposal identified as (give proposed title, project director's or investigator's or fellow's name, and grant or contract or RFP number as applicable) indicates that:

(1) In the opinion of this committee the risks to the rights and welfare of the subjects in this project or activity are:
The committee agrees that the following safeguards against these risks are adequate:

(2) In the opinion of the committee the potential benefits of this activity to the subjects outweigh any probable risks. This opinion is justified by the following reasons:

(3) In the opinion of the committee the following informed consent procedures based upon the six elements of informed consent as noted will be adequate and appropriate. Documentation is attached:

(4) The committee agrees to arrange for a continuing exchange of information and advice between itself and the investigator or director, particularly to the criteria cited above. This exchange will be implemented by the following procedures:

(5) The signatures, names, and occupations or titles of the members of the committee are listed below. None of these signatories have a vested or professional interest in this project or activity that conflicts with the need for independent review.

Signature	Name	Occupation or Title
Signature	Name	Occupation or Title
Signature	Name	Occupation or Title
Signature	Name	Occupation or Title

(Continued page 20)

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(Add as many signature spaces as necessary. Review of projects involving investigational new drugs (IND's) requires a minimum of two persons licensed to administer drugs and one person not so licensed. Review for other purposes should utilize committees of equal or greater breadth.)

Date of Committee Approval _____

I certify that this review was carried out in accordance with the provisions of DHEW policy.

(6) Official signing for institution _____

Signature

_____

Name

_____

Title

_____

Institution

_____

Address

_____

_____

Telephone Number

_____

Date

ATTACHMENT B
INSTRUCTIONS

An acceptable special institutional assurance consists of a properly completed formal statement of compliance with Department of Health, Education, and Welfare policy (see attachment B), signed by a committee of not less than three members and by an official authorized to sign for the institution. The explanatory paragraphs which follow refer to the corresponding section of the attachment.

(0) This should identify the application for a grant, contract, or award by its identifying number, where known, or by its full title. The name should be that of the investigator, program director, fellow, or other individual immediately responsible for the conduct of the work.

(1) The committee should identify in general terms those risks that it recognizes as probable occurrences; i.e., "Aggravation of anxiety status through contact with interviewers," "Preservation of confidentiality of data," "Renal injury subsequent to multiple biopsy," "Possibility of side reactions to drugs," "Possible local hematosis and nerve injury associated with venipuncture."

(2) The committee should identify the benefits to the subject or to mankind in general that will accrue through the subject's participation in the project. This should be followed by a brief discussion, weighing the risks against the benefits.

(3) Consent procedures should be described and the minimum statement to be used should be attached. "Students responding to the attached advertisement will be interviewed." "The project outline will be submitted to the executive council of the PTA." "Individual teachers will be asked to allow an observer in the rooms chosen." "Superintendents of several State mental hospitals will be approached. The attached statement to the next of kin or guardian will be signed by the principal investigator and the superintendent." "The following special consent form will be signed by each subject and his or her spouse or next of kin before acceptance of the subject." "No prior consent will be sought. The following debriefing schedule will be followed within 30 minutes after completion of the test."

(4) This should indicate whether the investigator or director will be required to submit written reports, or to appear for interviews, or will be visited by the committee or committee representatives, and at approximately what intervals these steps will be carried out.

(5) No further explanation is necessary. (The committee must be composed of sufficient members with varying backgrounds to assure complete and adequate review of the project. The committee may be an existing one, or one especially appointed for the purpose. The institution may utilize staff, consultants, or both. The membership should possess not only broad competence to comprehend the nature of the project, but also other competencies necessary in the judgments as to acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. The com-

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mittee's maturity and experience should be such as to justify respect for its advice and counsel.)

(No individual involved in the conduct of the project shall participate in its review, except to provide information to the committee.)

(Committee members should be identified in the assurance by name, positions, earned degrees, board certifications, licensures, memberships, and other indications of experience, competence, and interest.)

The completed assurance should be attached to the application, or returned directly to the office requesting its submission.

ATTACHMENT C

Codes or statements of principles which are concerned with the protection of human subjects in research, investigation, and care have been issued by:

Organization	Code; adoption date	Reference
World Medical Association 10 Columbus Circle New York, N.Y. 10019 (code available from AMA; see address listed herein)	The Declaration of Helsinki; Recommendations Guiding Doctors in Clinical Research; 1964	J.A.M.A., 197(11):32, Sept. 12, 1966
Nuernberg Military Tribunals: U.S. v. Karl Brandt	Text from which the "Nuernberg Code" is derived.	Trials of War Criminals Before the Nuernberg Military Tribunals, vol. II, pp. 181–82; GPO 1949
American Medical Association 535 North Dearborn Street Chicago, Ill. 60610	AMA Ethical Guidelines for Clinical Investigation; Nov. 30, 1966	←
(British) Medical Research Council 20 Park Crescent London W.1, England	Responsibility in Investigations on Human Subjects; 1964	Report of the Medical Research Council for 1962–1963, (Cmnd. 2382), pp. 21–25
(Canadian) Medical Research Council Montreal Road Ottawa 7, Ontario, Canada	Medical Research Council; Extramural Programme; 1966	←
American Association on Mental Deficiency 5201 Connecticut Avenue, N.W. Washington, D. C. 20015	Statement on the Use of Human Subjects for Research; May 1969	American Journal of Mental Deficiency, 74 (1):157, July 1969
American Nurses' Association 10 Columbus Circle New York, N.Y. 10019	The Nurse in Research; ANA Guidelines on Ethical Values; January 1968	←
American Personnel and Guidance Association 1607 New Hampshire Avenue, N.W. Washington, D.C. 20009	American Personnel and Guidance Association; Code of Ethical Standards; no date specified	←
American Psychological Association, Inc. 1200 17th Street, N.W. Washington, D.C. 20036	Ethical Standards of Psychologists; Copyrighted January 1963	American Psychologist, 18 (1):56–60, January 1963
International League of Societies for the Mentally Handicapped 12 Rue Forestiere. Brussels 5, Belgium	Declaration of General and Special Rights of the Mentally Retarded; Oct. 24, 1968	←

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Organization	Code; adoption date	Reference
National Association of Social Workers 2 Park Avenue New York, N.Y. 10016	NASW Code of Ethics; Oct. 13, 1968	←
American Anthropological Association 1703 New Hampshire Avenue, NW. Washington, D.C. 20009	Principles of Professional Responsibility; May, 1971	←
American Sociological Association 1722 N Street, NW. Washington, D.C. 20036	Code of Ethics September 1, 1971	←
Catholic Hospital Association St. Louis, Missouri 63104	Ethical and Religious Directives for Catholic Health Facilities September, 1971	←
Commission on Synagogue Relations Federation of Jewish Philanthropies of New York 130 East 59th Street New York, N.Y. 10022	A Hospital Compendium 1969	←

[ITEM I.B.2]

Title 45—Public Welfare

SUBTITLE A—DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, GENERAL ADMINISTRATION

PART 46—PROTECTION OF HUMAN SUBJECTS

In the FEDERAL REGISTER of October 9, 1973 (38 FR 27882), a notice of proposed rulemaking was published in which it was proposed to amend Subtitle A of the Department's regulations to codify, with some changes, an existing Departmental policy set forth in Chapter 1-40 of the DHEW Grants Administration Manual. These regulations would provide that no activity involving any human subjects at risk supported by a DHEW grant or contract shall be undertaken unless a committee of the applicant or offering organization has reviewed and approved such activity and submitted to DHEW a certification of such review and approval. In addition any organization receiving a grant or contract must establish a mechanism to provide for continuing review of the supported activity to insure its continued acceptability. The notice provided for the filing of comments within 30 days, ending November 8, 1973.

Comments were received from more than 140 representatives of grantee and contractor organizations, from approximately 20 public groups or organizations, and from over 40 individuals. They include over 500 criticisms of individual sections of the proposed rules. These comments and the Department's conclusions are principally as follows:

A. The applicability and scope of the policy were challenged by several respondents. Suggestions included limiting the policy to physical risks only, differentiation of biomedical risks from behavioral risks, expanding the policy to protect all persons regardless of the nature of the risk or source of support, and unequivocal limitation of the policy to DHEW grants and contracts as contrasted to other organizational activities. Requests were also made for the provision of special exemptions for subject groups such as prisoners, academic colleagues, students, and laboratory personnel; or exemptions for specific procedures such as those involving manipulation of the diet within normal ranges, the taking of blood and urine samples, surgical and autopsy specimens, and the use of hair, nail clippings, and placental materials.

It was also proposed that the policy deal specifically with certain subjects such as the prisoner, the child, the fetus, the abortus, and the candidate for sterilization or psychosurgery.

The Department, having considered these frequently conflicting recommendations, concludes that the language of the regulations should be changed to emphasize their concern with the risks involved in research, development, and related activities. It concludes that the arguments advanced for specifically including or exempting certain activities and procedures from the scope of the policy frequently reflect considerations applicable only to individual projects or conditions in particular institutions and lack broad applicability. It therefore seems appropriate to reserve to the Secretary the right to designate activities which necessarily fall within the scope of these regulations or to which the regulations are inapplicable. Such designations will be made only following careful study and through publication in the FEDERAL REGISTER. These changes are incorporated in § 46.1. At the same time it should be noted that the Department is now developing policies dealing more specifically with research, development, and related activities involving the prisoner, the child, the fetus, the abortus, and institutionalized individual with mental disability. The Department intends to issue one or more notices of proposed rule making in the FEDERAL REGISTER no later than July 30, 1974, dealing with these subjects. Policies are also under consideration which will be particularly concerned with the candidate for psychosurgery, the candidate for sterilization and, separately, with the subject of social science research.

B. Criticisms of the basic policy statement centered about the requirement that organizational committee review determine "that the risks to an individual are outweighed by the potential benefits to him, or by the importance of the knowledge to be gained." Suggestions included inserting the word "significant" before "risks" and adding after the word "gained" such phrases as "provided the experimental procedure accords decent respect for the opinion of mankind" and "or by the potential benefit to society." Objections were also raised concerning the requirement that informed consent be qualified as "adequate" and to the omission of a requirement that it be "legally effective." It was also argued that the sole purpose of the reviews should be to determine that the subject is fully informed.

The Department, having considered these comments, concludes that the addition of the term "significant" would tend to weaken, not to strengthen the requirement, and that the intent of the proposed change is better served by provisions, in § 46.1 giving the Secretary authority to designate activities, including methods and procedures, to which the policy is inapplicable. The suggested changes in the risk-benefit clause appear to be more admonitory than substantive. Objections to the use of the term "adequate" appeared to be based on an assumption that the term was used in the sense of "barely sufficient" rather than "lawfully and reasonably." The Department concurs that the requirement is strengthened by the substitution of the phrase "legally effective." It does not agree that the sole purpose of the review should be to determine that the subject is fully informed. It is essential that the committee, representing a wide spectrum of those expert professional skills essential to a clear recognition of an activity's inherent risks and probable benefits, carefully weigh such risks and benefits before determining that the benefits favor a decision to allow the subject to accept these risks. It is also important that the committee determine that the subject will receive adequate protection against known risks. These conclusions and certain editorial changes are reflected in § 46.2.

C. Objections were raised to several of the definitions incorporated into the regulations: (i) since the DHEW may make grants to certain Federal agency components only on the same terms as to non-Federal institutions, it was suggested that the term "Organization" should be expanded to include Federal agencies, (ii) objections were also raised to the term "sociological harm" as meaningless, and to the use of the term "harm," rather than the common legal term "injury," (iii) the definition of "infodmed consent" was challenged on several counts. It was suggested that the definition should be couched in terms similar to those of the Nuernberg Code which provides that "the person involved should have legal capacity to give consent: should be so situated as to be able to exercise free power of choice without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion." It was also suggested (iv) that the requirement for an instruction that the subject be free to withdraw his consent be amended to read additionally "without prejudice to his future care."

Additional suggestions included: (v) add to each of the elements of informed consent the initial phrase "full and fair," (vi) eliminate the requirement for a description of "any appropriate alternative procedures" since there might not be any such procedures; (vii) add a requirement that the patient be informed of alternatives if he is unable or refuses to continue as a research subject; and (viii) that patients be informed of the consequences should the research fail.

The recommendations having been duly considered it is concluded that suggested changes (i) through (iv) should be incorporated into the regulations with some editorial changes, particularly elimination of the phrase "to his future care" from the addition suggested in (iv) above. Prejudice could extend to other matters such as reimbursement of expenses, compensation, employment status, etc. The remaining recommendations (v-viii) are considered for the most part redundant and additional changes appear unnecessary.

These conclusions are reflected in § 46.3. Definitions of certain additional terms have been included as required by changes made elsewhere in this part.

D. With regard to the submission of assurances, criticisms were voiced concerning the requirement that the organization report to DHEW any emergent problems. Respondents emphasized that the term "emergent problems" was vague and, if strictly interpreted, could lead to enormous amounts of unnecessary paperwork at great cost both to the organization and to the DHEW. Respondents were also critical of the requirement for "immediate notification" and questioned the value of such data.

These comments having been considered, it is concluded that they have some merit. The requirement has been modi-

fied, removed from its original position in the regulations, and inserted elsewhere. The terms "emergent problems" and "immediate notification" have been eliminated. These changes are reflected in §§ 46.6, 46.6(d), and 46.7(c).

Comments were also concerned with the proposed requirement that no "committee or quorum of a committee shall consist entirely of employees of the organization." Respondents stated that in most institutions it would be difficult, and in some impossible, to find, attract, and hold qualified, interested nonemployees; that the absence of such a person from a quorum could block consideration of unexpected problems, make difficult the scheduling of meetings to meet L/HEW imposed deadlines for the preparation of grants and contracts, and invest such persons with "absentee veto" power. Also, that the provision would deny reasonable compensation to outsiders currently or possibly serving on committees, and deny legal protection and the protection of organizational liability insurance to outsiders who were not in an employee status while serving on a committee subject to suit.

Most suggestions for alternate wordings of the provision would either drop the mandatory requirement for nonemployees, or suggest that the requirement be made optional, the choice to depend upon the judgment of the Secretary or the organizational committee as to whether or not such nonemployee representation was necessary. Other recommendations suggested that "nonemployee" be defined in terms of sole employment by the organization, full or part-time employment, or short-term employment. Some respondents suggested more restrictive requirements, providing that the nonemployee group be defined to include nonhealth professionals who would either represent population groups, or subject populations. Finally, objections were raised to the requirement that the committee be able to ascertain acceptability of the proposal in terms of community attitudes. It was suggested that such attitudes are vague, nebulous, and fluctuating and, since a wide range of communities may be involved, impossible of representation.

These comments having been considered, it is concluded that the requirement for nonemployee members on organizational committees is an essential protection against the development of insular or parochial committee attitudes, that it assists in maintaining community contacts, and would augment the credibility of the committee's independent role in protection of the subject. However, it is agreed that the requirement that nonemployees be included in quorums appears to be impractical, and that the requirement should not be so phrased as to prevent a committee member from being considered an employee within the scope of the organization's liability coverage or legal protection. The arguments against committee consideration of community attitudes are considered generally to be offset by equally strong reasons for taking these attitudes into consideration. It should be emphasized that the term "community" is intended to be applied in the sense of the larger community served by the organization, not necessarily the smaller community involved in a particular supported activity or project, that this is a requirement for overall committee membership, and not a requirement that must be varied proposal by proposal. The Department's conclusions are reflected by § 46.6(b) (2), (4), (5), and (6).

E. Comments on the requirements for special assurances were largely editorial. It is concluded that changes should be made so as to insure better agreement between the wording of these requirements and those for general assurances. These changes are reflected in § 46.7.

F. Comments on the obligation to secure informed consent pointed out that there appeared to be conflict between this requirement and the section on documentation of informed consent, since the latter permits some modification of written procedures. Other respondents suggested changes in language similar to that found in the Nuernberg Code and already incorporated into the definition of informed consent in § 46.3(c), or sought changes to define conditions under which substituted consent could be obtained on behalf of individuals who are incompetent, either because of age or mental incapacity, to consent for themselves. Among other matters it was suggested that such substituted consent should only be given by a court of competent jurisdiction.

These comments having been considered, it is concluded that there is no substantial conflict between this section and the documentation requirements, that the suggestion of inclusion of the Nuernberg Code language has been met elsewhere, and that problems relating to participation by minors, the mentally ill and mentally retarded, and by prisoners and others are already the subject of a draft proposed rulemaking (See 38 FR 31738 et seq.).

G. Objections were raised to the clause prohibiting the use of exculpatory language on the grounds that it makes organizational review committees subject to suit as agents of the organization and negates any protection offered by organizational liability insurance. The Department's Office of General Counsel has been able to find no legal support for this unsubstantiated assertion concerning limitations on insurance protection and has advised that the use of exculpatory language should be prohibited as a matter of public policy.

H. Comments on documentation of informed consent centered largely about the term "authorized representative." Suggestions included substitution of the term "legal representative" or use of "authorized representative," variously defined with regard to his association with any organization having custody of the subject, or proposing to seek the subject's consent, or having simultaneous responsibility for the subject's health and welfare. Additional comments focused on the concept of the "auditor-witness," emphasizing the impracticability of implementing such a concept in mass surveys and in emergency situations. Others raised doubts as to the need for written consent procedures in connection with low risk procedures. Several respondents suggested that it be required that the subject receive a copy of the completed consent document. One respondent suggested a 24-hour lapse between the time of receiving information and the time of giving consent.

The Department, having considered these comments, concludes that the substitution of "legally authorized representative," as defined in § 46.3(h), for "authorized representative" and that the provisions for modification of either of the two primary methods of informed consent allow all necessary flexibility for the development of consent procedures. The suggestions that a copy of the completed consent document be provided to the subject, and that provision be made for a 24-hour waiting period, are matters to be left to the discretion of the organization. The necessary changes have been made in § 46.10.

I. Various commentators raised questions with regard to the review and approval of assurances. An additional section describing evaluation and disposition of assurances has been inserted as § 46.10. The language of this section is consistent with current policy as stated in DHEW Grants Administration Manual Chapter 1-40.

J. A large number of organizations were concerned with the proposed requirement that organizational review and approval be completed and certified prior to the submission of proposals to DHEW. Although the majority of respondents favored retaining the present policy, an almost equal number suggested that they could complete all of their reviews within a few weeks following submission to DHEW. Emphasis was laid on the need for time for revision, resubmission, and review of proposals found unacceptable at the time of first submission.

A few public groups commended this requirement as a substantial improvement over present policy which, in their opinion, presented a local committee with an impossible task in questioning a project which had already received review and approval at a national level.

These comments having been considered, it is concluded that the right to relax this requirement, and to extend a grace period for completion and certification of review after submission of the proposal should be reserved to the Secretary. In no event will processing of a proposal by DHEW be completed until such certification has been received by DHEW. These conclusions are reflected by changes in §§ 46.11 and 46.12.

By separate notice, the Department will provide that for a period of one year from the effective date of these regulations, organizations having approved general assurances may give proposals

review and approval after submission to DHEW provided that such certification is received by DHEW no later than 30 days following the deadline for which the proposal was submitted, or, if no deadline is specified, 30 days following the submission date of the proposal. Organizations not having a significant number of concurrent DHEW-supported activities must submit a special assurance and certification of review and approval to DHEW within 30 days of the date of a letter requesting such submission.

K. With regard to the section on proposals lacking definite plans for involvement of human subjects, a majority of respondents objected to the provision calling for submission of completed plans to DHEW for its prior review and approval. Commentators pointed out the problems inherent in delay in the implementation of short-term projects, and the problems to be encountered by DHEW in providing adequate review of such projects on a demand basis. Suggestions included: (i) a requirement for institutional review without submission to DHEW; (ii) review with notification to DHEW; and (iii) review and submission of plans to DHEW, such plans to be implemented if no DHEW objections were interposed within 30 days of submission.

These comments having been considered, it is concluded that the proposed requirement for DHEW review of final stage plans for previously reviewed and approved proposals is impractical and unrealistic. Section 46.13 has been rewritten to require institutional review and approval, and for certification of such action to DHEW prior to involvement of human subjects.

L. Comments on the requirements for organizational and DHEW review of proposed plans to involve human subjects in activities initially funded with the understanding that human subjects would not be involved, were similar to those described in the preceding paragraphs. Again, respondents objected that the requirement for DHEW review would unnecessarily delay research, create unnecessary paperwork, and create substantial fiscal and administrative burdens. Suggestions were made for submission of plans to DHEW, such plans to be implemented if no DHEW objections were interposed within 30 days of submission.

These comments, having been considered, the Department sees no viable alternative to the rules as proposed. Where the DHEW is aware of the intent to involve human subjects, as in the type of proposal described in § 46.13, it can take into consideration the probable nature of the involvement and the probable risks and benefits to the subjects. If necessary it may acquire additional information prior to review, or make any such approval contingent on submission of final stage plans. These opportunities are not available to DHEW if it is not informed in advance of potential involvement of human subjects.

No changes have been made in § 46.14.

M. In order to emphasize the Secretary's authority to conduct further evaluation of proposed activities involving human subjects and to disapprove, defer, or approve such proposals, and to impose conditions on such approvals, § 46.15 has been inserted. The language of this section is consistent with current policy in DHEW Grants Administration Manual Chapter 1-40.

N. Comments on the proposed regulations governing cooperative activities were in frequent conflict. Alternative suggestions included: (i) changes making it possible for a prime contractor or grantee to assume all responsibility for the conduct of work by cooperating organizations, (ii) changes which would eliminate all responsibility by the prime contractor or grantee for work done by cooperating organizations, (iii) changes which would discourage any requirement for submission for assurance by cooperating organizations, (iv) inclusion of language limiting a prime contractor or grantee responsibility for work performed by a subcontractor, (v) inclusion of language spelling out the instruments and documents to be provided by the cooperating organization, (vi) elimination of any requirement that would require a domestic contractor or grantee to be aware of local laws and community attitudes in foreign countries.

The Department having reviewed these comments, concludes that these often conflicting suggestions fail to provide any better alternatives than the regulations as proposed. There appears to be no reasonable alternative to requiring the prime contractor to remain responsible for safeguarding the rights and welfare of subjects, either directly under the provision of his own assurance, or through the mechanisms provided by assurances submitted by cooperating organizations. The proposed regulations permit a contractor or grantee some flexibility to meet the requirements of the policy. The proposed rules are incorporated unchanged in § 46.16.

O. Requirements for the submission of investigational new drug (IND) numbers prior to issuance of an an award were criticized on several counts. One respondent felt that the regulations would make it difficult if not impossible to obtain DHEW support for studies leading to the development of a new drug. Not all compounds requiring IND's are actual drugs under development, but are employed for other purposes. Another respondent pointed out that the pertinent FDA regulations (21 CFR 130.3(a)(2)) make no reference to the IND number, but require a 30-day delay period prior to use of drugs in human subjects.

These comments having been considered, the Department agrees that references to the IND number should be replaced by reference to the FDA 30-day delay requirement. The Department does not agree that a requirement for submission of identification on IND's would cause undue delay in studies preliminary to submission of an IND exemption, since such studies are necessarily conducted in animal species. Section 46.18 has been altered accordingly.

P. With regard to retention of records, several respondents pointed out conflict between the proposed requirements for retention of records and recently published DHEW Administration of Grant regulations (45 CFR 74). Other comments reflected concern over the confidentiality of information which would be subject to DHEW inspection.

The Department, having reviewed these comments, concludes that the record retention and inspection requirements contained herein are redundant and should be deleted. A provision concerning confidentiality has been added. The appropriate changes have been made in § 46.19.

Q. Comments on the proposed sanctions for noncompliance with provisions of this part focused on two issues: (i) the absence of provisions for due process in the imposition of sanctions and, (ii) apparent intervention by DHEW in the employer-employee relationship in proposing to determine that an individual was no longer eligible to serve in the capacity of a principal investigator or in any similar capacity with respect to a DHEW grant or contract. Reference was made to clause 21 of the "General Provisions for Negotiated Cost-Reimbursement Type Contracts * * *" (HEW 315) which provides that "the Contractor agrees to assign (named personnel) * * * to the performance of work under this contract; and shall not remove or replace any of them * * *."

The Department has considered these comments and has concluded that, actions under § 46.21(a), which refers to applicable grant and procurement regulations, would be subject to due process as provided for in these regulations. Sections 46.21 (b) and (c) have been deleted, however, and replaced with a new provision which simply allows the Secretary to take into consideration past deficiencies of an institution or investigator, with regard to the protection of human subjects, in evaluating subsequent applications from that institution or involving that investigator. While it would appear from review of clause 21 of HEW 315 that it does not prevent the Department from effecting the removal of personnel from performance of work under a DHEW contract, it is agreed that the responsible organization should be a party to the notification and conference procedures necessary to the making of any such decision.

R. Several respondents suggested significant additions to the policy to provide among other matters for (i) the establishment of a National Commission to undertake a comprehensive investigation and study to develop basic ethical principles and guidelines which should govern biomedical and behavioral research, (ii) a conscience clause, prohibiting among other matters, discrimination in the employment of persons who, because of religious beliefs or moral convictions, perform or refuse to perform a research or service activity prohibited by the en-

tity on the basis of religious beliefs or moral convictions, and (iii) providing for the regulation of unapproved uses of approved drugs.

It is concluded that these suggestions would require changes not properly within the scope of these regulations and, in the case of regulation of unapproved uses of approved drugs, are the subject of regulations proposed as 37 FR 16503 on August 15, 1972.

8. Addition to the regulations of section of "Evaluation and disposition of assurances" has made unnecessary an earlier section on "Implementation and revision of assurances." Similarly, issuance of 45 CFR 74 has made unnecessary the earlier section entitled "Withholding of funds."

Effective date. This part shall become effective on July 1, 1974: *Provided, however,* That with respect to programs administered by the Office of Education and the National Institute of Education, this part shall become effective upon adoption or implementation in regulations issued by, respectively, the Commissioner of Education and the Director of the National Institute of Education, with the approval of the Secretary of Health, Education, and Welfare.

Dated: May 22, 1974.

CASPAR W. WEINBERGER,
Secretary.

Accordingly, Subtitle A of Title 45 of the Code of Federal Regulations is amended by adding a new Part 46, as follows:

Sec.
46.1 Applicability.
46.2 Policy.
46.3 Definitions.
46.4 Submission of assurances.
46.5 Types of assurances.
46.6 Minimum requirements for general assurances.
46.7 Minimum requirements for special assurances.
46.8 Evaluation and disposition of assurances.
46.9 Obligation to obtain informed consent; prohibition of exculpatory clauses.
46.10 Documentation of informed consent.
46.11 Certification, general assurances.
46.12 Certification, special assurances.
46.13 Proposals lacking definite plans for involvement of human subjects.
46.14 Proposals submitted with the intent of not involving human subjects.
46.15 Evaluation and disposition of proposals.
46.16 Cooperative activities.
46.17 Investigational new drug 30-day delay requirement.
46.18 Organization's executive responsibility.
46.19 Organization's records; confidentiality.
46.20 Reports.
46.21 Early termination of awards; evaluation of subsequent applications.
46.22 Conditions.

AUTHORITY: § U.S.C. 301.

§ 46.1 Applicability.

(a) The regulations in this part 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.

(b) The Secretary may, from time to time, determine in advance whether specific programs, methods, or procedures to which this part is applicable place subjects at risk, as defined in § 46.3 (b). Such determinations will be published as notices in the FEDERAL REGISTER and will be included in an appendix to this part.

§ 46.2 Policy.

(a) Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the organization which receives or is accountable to DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this organizational responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless a committee of the organization has reviewed and approved such activity, and the organization has submitted to DHEW a certification of such review and approval, in accordance with the requirements of this part.

(b) This review shall determine whether these subjects will be placed at risk, and, if risk is involved, whether:

(1) The 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; and

(4) the conduct of the activity will be reviewed at timely intervals.

(c) No grant or contract involving human subjects at risk shall be made to an individual unless he is affiliated with or sponsored by an organization which can and does assume responsibility for the subjects involved.

§ 46.3 Definitions.

(a) "Organization" means any public or private institution or agency (including Federal, State, and local government agencies).

(b) "Subject at risk" means any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service.

(c) "Informed consent" means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

(1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;

(2) a description of any attendant discomforts and risks reasonably to be expected;

(3) a description of any benefits reasonably to be expected;

(4) a disclosure of any appropriate alternative procedures that might be advantageous for the subject;

(5) an offer to answer any inquiries concerning the procedures; and

(6) an instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.

(d) "Secretary" means the Secretary of Health, Education, and Welfare or any other officer or employee of the Department of Health, Education, and Welfare to whom authority has been delegated.

(e) "DHEW" means the Department of Health, Education, and Welfare.

(f) "Approved assurance" means a document that fulfills the requirements of this part and is approved by the Secretary.

(g) "Certification" means the official organizational notification to DHEW in accordance with the requirements of this part that a project or activity involving human subjects at risk has been reviewed and approved by the organization in accordance with the "approved assurance" on file at DHEW.

(h) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to such subject's participation in the particular activity or procedure.

§ 46.4 Submission of assurances.

(a) Recipients or prospective recipients of DHEW support under a grant or contract involving subjects at risk shall provide written assurance acceptable to DHEW that they will comply with DHEW policy as set forth in this part. Each assurance shall embody a statement of compliance with DHEW requirements for initial and continuing committee review of the supported activities; a set of implementing guidelines, including identification of the committee and a description of its review procedures; or, in the case of special assurances concerned with single activities or projects, a report of initial findings of the committee and of its proposed continuing review procedures.

(b) Such assurance shall be executed by an individual authorized to act for the organization and to assume on behalf of the organization the obligations imposed by this part, and shall be filed in such form and manner as the Secretary may require.

§ 46.5 Types of assurances.

(a) *General assurances.* A general assurance describes the review and implementation procedures applicable to all DHEW-supported activities conducted by

an organization regardless of the number, location, or types of its components or field activities. General assurances will be required from organizations having a significant number of concurrent DHEW-supported projects or activities involving human subjects.

(b) *Special assurances.* A special assurance will, as a rule, describe those review and implementation procedures applicable to a single activity or project. A special assurance will not be solicited or accepted from an organization which has on file with DHEW an approved general assurance.

§ 46.6 Minimum requirements for general assurances.

General assurances shall be submitted in such form and manner as the Secretary may require. The organization must include, as part of its general assurance, implementing guidelines that specifically provide for:

(a) A statement of principles which will govern the organization in the discharge of its responsibilities for protecting the rights and welfare of subjects. This may include appropriate existing codes or declarations, or statements formulated by the organization itself. It is to be understood that no such principles supersede DHEW policy or applicable law.

(b) A committee or committee structure which will conduct initial and continuing reviews in accordance with the policy outlined in § 46.3. Such committee structure or committee shall meet the following requirements:

(1) The committee must be composed of not less than five persons with varying backgrounds to assure complete and adequate review of activities commonly conducted by the organization. The committee 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 committee must be able to ascertain the acceptability of proposals in terms of organizational commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The committee must therefore include persons whose concerns are in these areas.

(2) The committee members shall be identified to DHEW by name; earned degrees, if any; position or occupation; representative capacity; and by other pertinent indications of experience such as board certification, licenses, etc., sufficient to describe each member's chief anticipated contributions to committee deliberations. Any employment or other relationship between each member and the organization shall be identified, i.e., full-time employee, part-time employee, member of governing panel or board, paid consultant, unpaid consultant. Changes in committee membership shall be reported to DHEW in such form and at such times as the Secretary may require.

(3) No member of a committee shall be involved in either the initial or continuing review of an activity in which he has a conflicting interest, except to provide information requested by the committee.

(4) No committee shall consist entirely of persons who are officers, employees, or agents, of, or are otherwise associated with the organization, apart from their membership on the committee.

(5) No committee shall consist entirely of members of a single professional group.

(6) The quorum of the committee shall be defined, but may in no event be less than a majority of the total membership duly convened to carry out the committee's responsibilities under the terms of the assurance.

(c) Procedures which the organization will follow in its initial and continuing review of proposals and activities.

(d) Procedures which the committee will follow (1) to provide advice and counsel to activity directors and investigators with regard to the committee's actions, (2) to insure prompt reporting to the committee of proposed changes in an activity and of unanticipated problems involving risk to subjects or others and (3) to insure that any such problems, including adverse reactions to biologicals, drugs, radioisotope labelled drugs, or to medical devices, are promptly reported to the DHEW.

(e) Procedures which the organization will follow to maintain an active and effective committee and to implement its recommendations.

§ 46.7 Minimum requirements for special assurances.

Special assurances shall be submitted in such form and manner as the Secretary may require. An acceptable special assurance shall:

(a) Identify the specific grant or contract involved by its number, if known; by its full title; and by the name of the activity or project director, principal investigator, fellow, or other person immediately responsible for the conduct of the activity. The assurance shall be signed by the individual members of a committee satisfying the requirements of § 46.6(b) and be endorsed by an appropriate organizational official.

(b) Describe the makeup of the committee and the training, experience, and background of its members, as required by § 46.6(b)(2).

(c) Describe in general terms the risks to subjects that the committee recognizes as inherent in the activity, and justify its decision that these risks are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant the committee's decision to permit the subject to accept these risks.

(d) Describe the informed consent procedures to be used and attach documentation as required by § 46.10.

(e) Describe procedures which the committee will follow to insure prompt reporting to the committee of proposed changes in the activity and of any unanticipated problems involving risks to subjects or others and to insure that any such problems, including adverse reactions to biologicals, drugs, radioisotope labelled drugs, or to medical devices are promptly reported to DHEW.

(f) Indicate at what time intervals the committee will meet to provide for continuing review. Such review must occur no less than annually.

§ 46.8 Evaluation and disposition of assurances.

(a) All assurances submitted in accordance with §§ 46.6 and 46.7 shall be evaluated by the Secretary through such officers and employees of the DHEW and such experts or consultants engaged for this purpose as he determines to be appropriate. The Secretary's evaluation shall take into consideration, among other pertinent factors: the adequacy of the proposed committee in the light of the anticipated scope of the applicant organization's activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in the light of the probable risks, and the size and complexity of the organization.

(b) On the basis of his evaluation of an assurance pursuant to paragraph (a) of this section, the Secretary shall (1) approve, (2) enter into negotiations to develop a more satisfactory assurance, or (3) disapprove. With respect to approved assurances, the Secretary may determine the period during which any particular assurance or class of assurances shall remain effective or otherwise condition or restrict his approval. With respect to negotiations, the Secretary may, pending completion of negotiations for a general assurance, require an organization otherwise eligible for such an assurance, to submit special assurances.

§ 46.9 Obligation to obtain informed consent; prohibition of exculpatory clauses.

Any organization proposing to place any subject at risk is obligated to obtain and document legally effective informed consent. No such informed consent, oral or written, obtained under an assurance provided pursuant to this part shall include any exculpatory language through which the subject is made to waive, or to appear to waive, any of his legal rights, including any release of the organization or its agents from liability for negligence.

§ 46.10 Documentation of informed consent.

The actual procedure utilized in obtaining legally effective informed consent and the basis for committee determinations that the procedures are adequate and appropriate shall be fully documented. The documentation of consent will employ one of the following three forms:

(a) Provision of a written consent document embodying all of the basic elements of informed consent. This may be read to the subject or to his legally authorized representative, but in any event he or his legally authorized representa-

tive must be given adequate opportunity to read it. This document is to be signed by the subject or his legally authorized representative. Sample copies of the consent form as approved by the committee are to be retained in its records.

(b) Provision of a "short form" written consent document indicating that the basic elements of informed consent have been presented orally to the subject or his legally authorized representative. Written summaries of what is to be said to the patient are to be approved by the committee. The short form is to be signed by the subject or his legally authorized representative and by an auditor witness to the oral presentation and to the subject's signature. A copy of the approved summary, annotated to show any additions, is to be signed by the persons officially obtaining the consent and by the auditor witness. Sample copies of the consent form and of the summaries as approved by the committee are to be retained in its records.

(c) Modification of either of the primary procedures outlined in paragraphs (a) and (b) of this section. Granting of permission to use modified procedures imposes additional responsibility upon the review committee and the organization to establish: (1) that the risk to any subject is minimal, (2) that use of either of the primary procedures for obtaining informed consent would surely invalidate objectives of considerable immediate importance, and (3) that any reasonable alternative means for attaining these objectives would be less advantageous to the subjects. The committee's reasons for permitting the use of modified procedures must be individually and specifically documented in the minutes and in reports of committee actions to the files of the organization. All such modifications should be regularly reconsidered as a function of continuing review and as required for annual review, with documentation of reaffirmation, revision, or discontinuation, as appropriate.

§ 46.11 Certification, general assurances.

(a) *Timely review.* Unless the Secretary otherwise provides, all proposals involving human subjects submitted by organizations having approved general assurances must be given review and, when found to involve subject at risk, approval, prior to submission to DHEW. In the event the Secretary provides for the performance of organizational review of a proposal after its submission to DHEW, processing of such proposal by DHEW will under no circumstances be completed until such organizational review and approval has been certified. Unless the organization determines that human subjects are not involved, the proposal or application should be appropriately certified in the spaces provided on forms, or one of the following certifications, as appropriate, should be typed on the lower right hand margin of the page bearing the name of an official authorized to sign or execute applications or proposals for the organization.

Human Subjects Reviewed, Not at Risk. ..... (date)

Human Subjects Reviewed, At Risk. Approved..... (date)

(b) *Proposals not certified.* Proposals not properly certified, or submitted as not involving human subjects and found by the operating agency to involve human subjects, will be returned to the organization concerned.

§ 46.12 Certification, special assurances.

(a) An applicant organization not having on file with DHEW an approved general assurance must submit for each application or proposal involving human subjects a separate special assurance and certification of its review and approval.

(b) Such assurance and certification must be submitted within such time limits as the Secretary may specify. An assurance and certification prepared in accordance with this part and approved by DHEW shall be considered to have met the requirement for certification for the initial grant or contract period concerned. If the terms of the grant or contract recommend additional support periods, certification shall be provided by the organization with applications for continuation or renewal of support in the manner prescribed in § 46.11(a).

§ 46.13 Proposals lacking definite plans for involvement of human subjects.

Certain types of proposals are submitted with the knowledge that subjects are to be involved within the support period, but definite plans for this involvement would not normally be set forth in the proposal. These include such activities as (a) institutional type grants where selection of projects is the responsibility of the institution, (b) training grants where training projects remain to be selected, and (c) research, pilot, or developmental studies in which involvement depends upon such things as the completion of instruments, or of prior animal studies, or upon the purification of compounds. Such proposals shall be reviewed and certified in the same manner as more definitive proposals. The initial certification indicates organizational approval of the applications as submitted, and commits the organization to later review of the plans, when completed. Such later review and certification to the DHEW should be completed prior to the beginning of the budget period during which actual involvement of human subjects is to begin. Review and certification to the DHEW must in any event be completed prior to involvement of human subjects.

§ 46.14 Proposals submitted with the intent of not involving human subjects.

If a proposal does not anticipate involving or intend to involve human subjects, no certification should be included with the initial submission of the proposal. In those instances, however, when later it becomes appropriate to use all or part of awarded funds for one or more activities which will involve subjects, each such activity shall be reviewed and approved in accordance with the assurance of the organization prior to the involvement of subjects. In addition, no such activity shall be undertaken until the organization has submitted to DHEW: (a) a certification that the activity has been reviewed and approved in accordance with this part, and (b) a detailed description of the proposed activity (including any protocol or similar document). Also, where support is provided by project grants or contracts, subjects shall not be involved prior to certification and organizational receipt of DHEW approval and, in the case of contracts, prior to negotiation and approval of an amended contract description of work.

§ 46.15 Evaluation and disposition of proposals.

(a) Notwithstanding any prior review, approval, and certification by the organization, all grant and contract proposals involving human subjects at risk submitted to the DHEW shall be evaluated by the Secretary for compliance with this part through such officers and employees of the Department and such experts or consultants engaged for this purpose as he determines to be appropriate. This evaluation may take into account, among other pertinent factors, the apparent risks to the 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.

(b) Disposition. On the basis of his evaluation of an application pursuant to paragraph (a) of this section and subject to such approval or recommendation by or consultation with appropriate councils, committees, or other bodies as may be required by law, the Secretary shall (1) approve, (2) defer for further evaluation, or (3) disapprove support of the proposed activity in whole or in part. With respect to any approved grant or contract, the Secretary may impose conditions, including restrictions on the use of certain procedures, or certain subject groups, or requiring use of specified safeguards or informed consent procedures when in his judgment such conditions are necessary for the protection of human subjects.

§ 46.16 Cooperative activities.

Cooperative activities are those which involve organizations in addition to the grantee or prime contractor (such as a contractor under a grantee or a subcontractor under a prime contractor). If, in such instances, the grantee or prime contractor obtains access to all or some of the subjects involved through one or more cooperating organizations, the basic DHEW policy applies and the grantee or prime contractor remains responsible for safeguarding the rights and welfare of the subjects.

(a) *Organization with approved general assurance.* Initial and continuing review by the organization may be car-

ried out by one or a combination of procedures:

(1) Cooperating organization with approved general assurance. When the cooperating organization has on file with DHEW an approved general assurance, the grantee or contractor may, in addition to its own review, request the cooperating organization to conduct an independent review and to report its recommendations on those aspects of the activity that concern individuals for whom the cooperating organization has responsibility under its own assurance to the grantee's or contractor's committee. The grantee or contractor may, at its discretion, concur with or further restrict the recommendations of the cooperating organization. It is the responsibility of the grantee or contractor to maintain communication with the committees of the cooperating organization. However, the cooperating organization shall promptly notify the grantee or contracting organization whenever the cooperating organization finds the conduct of the project or activity within its purview unsatisfactory.

(2) Cooperating organization with no approved general assurance. When the cooperating organization does not have an approved general assurance on file with DHEW, the DHEW may require the submission of a general or special assurance which, if approved, will permit the grantee or contractor to follow the procedure outlined in the preceding subparagraph.

(3) Interorganizational joint review. The grantee or contracting organization may wish to develop an agreement with cooperating organizations to provide for a review committee with representatives from cooperating organizations. Representatives of cooperating organizations may be appointed as ad hoc members of the grantee or contracting organization's existing review committee or, if cooperation is on a frequent or continuing basis as between a medical school and a group of affiliated hospitals, appointments for extended periods may be made. All such cooperative arrangements must be approved by DHEW as part of a general assurance, or as an amendment to a general assurance.

(b) *Organizations with special assurances.* While responsibility for initial and continuing review necessarily lies with the grantee or contracting organization, DHEW may also require approved assurances from those cooperating organizations having immediate responsibility for subjects.

If the cooperating organization has on file with DHEW an approved general assurance, the grantee or contractor shall request the cooperating organization to conduct its own independent review of those aspects of the project or activity which will involve human subjects for which it has responsibility. Such a request shall be in writing and should provide for direct notification of the grantee's or contractor's committee in the event that the cooperating organization's committee finds the conduct of the activity to be unsatisfactory. If the cooperating organization does not have an approved general assurance on file with DHEW, it must submit to DHEW a general or special assurance which is determined by DHEW to comply with the provisions of this part.

§ 46.17 Investigational new drug 30-day delay requirement.

Where an organization is required to prepare or to submit a certification under §§ 46.11, 46.12, 46.13, or 46.14 and the proposal involves an investigational new drug within the meaning of The Food, Drug, and Cosmetic Act, the drug shall be identified in the certification together with a statement that the 30-day delay required by 21 CFR 130.3(a)(2) has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects; or that the Food and Drug Administration has waived the 30-day delay requirement; provided, however, that in those cases in which the 30-day delay interval has neither expired nor been waived; a statement shall be forwarded to DHEW upon such expiration or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received.

§ 46.18 Organization's executive responsibility.

Specific executive functions to be conducted by the organization include policy development and promulgation and continuing indoctrination of personnel. Appropriate administrative assistance and support shall be provided for the committee's functions. Implementation of the committee's recommendations through appropriate administrative action and followup is a condition of DHEW approval of an assurance. Committee approvals, favorable actions, and recommendations are subject to review and to disapproval or further restriction by the organization officials. Committee disapprovals, restrictions, or conditions cannot be rescinded or removed except by action of a committee described in the assurance approved by DHEW.

§ 46.19 Organization's records; confidentiality.

(a) Copies of all documents presented or required for initial and continuing review by the organization's review committee, such as committee minutes, records of subject's consent, transmittals on actions, instructions, and conditions resulting from committee deliberations addressed to the activity director, are to be retained by the organization, subject to the terms and conditions of grant and contract awards.

(b) Except as otherwise provided by law information in the records or possession of an organization acquired in connection with an activity covered by this part, which information refers to or can be identified with a particular subject may not be disclosed except:

(1) with the consent of the subject or his legally authorized representative or;

(2) as may be necessary for the Secretary to carry out his responsibilities under this part.

§ 46.20 Reports.

Each organization with an approved assurance shall provide the Secretary with such reports and other information as the Secretary may from time to time prescribe.

§ 46.21 Early termination of awards; evaluation of subsequent applications.

(a) If, in the judgment of the Secretary an organization has failed materially to comply with the terms of this policy with respect to a particular DHEW grant or contract, he may require that said grant or contract be terminated or suspended in the manner prescribed in applicable grant or procurement regulations.

(b) In evaluating proposals or applications for support of activities covered by this part, the Secretary may take into account, in addition to all other eligibility requirements and program criteria, such factors as: (1) whether the offeror or applicant has been subject to a termination or suspension under paragraph (a) of this section, (2) whether the offeror or applicant or the person who would direct the scientific and technical aspects of an activity has in the judgment of the Secretary failed materially to discharge his, her, or its responsibility for the protection of the rights and welfare of subjects in his, her, or its care (whether or not DHEW funds were involved), and (3) whether, where past deficiencies have existed in discharging such responsibility, adequate steps have in the judgment of the Secretary been taken to eliminate these deficiencies.

§ 46.22 Conditions.

The Secretary may with respect to any grant or contract or any class of grants or contracts impose additional conditions prior to or at the time of any award when in his judgment such conditions are necessary for the protection of human subjects.

[FR Doc.74-12269 Filed 5-29-74;8:45 am]

[Item I.B.3]

Excerpts From the Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel

Report on Charge III

To: The Assistant Secretary for Health.
From: Tuskegee Syphilis Study Ad Hoc Advisory Panel.
Topic: Final report on charge III.

(This report was prepared by the Subcommittee on Charge III (Jay Katz, M.D., chairman, Ronald H. Brown, J.D., Seward Hiltner, Ph.D. and Fred Speaker, J.D.). The subcommittee chairman wishes to thank his research assistant Stephen H. Glickman, a third year law student at Yale University, for his valuable contributions to this report. Special thanks go also to Dr. Robert C. Backus, Mrs. Bernice M. Lee and Ms. Jackie Eagle who in many ways facilitated the work of the subcommittee.)

I. INTRODUCTION

In his third charge to the Tuskegee Syphilis Study Ad Hoc Advisory Panel, Dr. Merlin K. DuVal, the HEW Assistant Secretary for Health and Scientific Affairs, has asked us to determine whether existing policies to protect the rights of patients participating in health research conducted or supported by the Department of Health, Education, and Welfare are adequate and effective and to recommend improvements in these policies, if needed.

Our response to this charge, embodied in this report, should not be viewed simply as a reaction to a single ethically objectionable research project. For the Tuskegee Syphilis Study, despite its widespread publicity was not an isolated phenomenon. We believe that the revelations from Macon County merely brought to the surface once again the unresolved problems which have long plagued medical research activities. Indeed, we hasten to add that although we refer in this report almost exclusively to physicians and to biomedical investigations, the issues we explore also arise in the context of non-medical investigations with human beings, conducted by psychologists, sociologists, educators, lawyers and others. The scope of the DHEW Policy on Protection of Human Subjects, broadened in 1971 to encompass such research, attests to the increasing significance of non-medical investigations with human beings.

Our initial determination that the protection of human research subjects is a current and widespread problem should not be surprising, especially in light of the recent Congressional hearings and bills focusing on the regulation of experimentation. In the past decade the press has publicized and debated a number of experiments which raised ethical questions: for example, the injection of cancer cells into aged patients at the Jewish Chronic Disease Hospital in Brooklyn, the deliberate infection of mentally retarded children with hepatitis at Willowbrook, the development of heart transplantation techniques, the enormous amount of drug research conducted in American prisons, the whole-body irradiation treatment of cancer patients at the University of Cincinnati, the advent and spread of "psychosurgery," and the Tuskegee Syphilis Study itself.

With so many dramatic projects coming to the attention of the general public, more must lie beneath the surface. Evidence for this too has been forthcoming. In 1966, Dr. Henry K. Beecher, the eminent Dorr Professor of Research in Anesthesia at the Harvard Medical School, charged in the prestigious New England Journal of Medicine that "many of the patients (used in experiments which Dr. Beecher investigated and reported) never had the risk satisfactorily explained to them, and . . . further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered as the direct result . . ."[1] Dr. Beecher concluded that "unethical or questionably ethical procedures are not uncommon."[2] Quite recently this charge has been corroborated by the sociologist Bernard Barber and his associates, who interviewed biomedical researchers about their own research practices.[3] Despite the expected tendency of researchers to minimize ethical problems in their own

[1] Beecher, "Ethics and Clinical Research," 274 New Eng. J. Med. 1354 (1966).
[2] *Ibid.*, p. 1355.
[3] Barber, Lally, Makarushka, and Sullivan, *Research on Human Subjects: Problems of Social Control in Medical Experimentation* (Russell Sage Foundation 1973) (hereinafter, *Barber et al.*).

work, Barber *et al.* were able to conclude that "while the large majority of our samples of biomedical researchers seems to hold and live up to high ethical standards, a significant majority may not." [4]

The problem of ethical experimentation is the product of the unresolved conflict between two strongly held values: the dignity and integrity of the individual, and the freedom of scientific inquiry. Professionals of many disciplines, and researchers especially, exercise unexamined discretion to intervene in the lives of their subjects for the sake of scientific progress. Although exposure to needless harm and neglect of the duty to obtain the subject's consent have generally been frowned upon in theory, the infliction of unnecessary harm and infringements on informed consent are frequently accepted, in practice, as the price to be paid for the advancement of knowledge. How have investigators come to claim this sweeping prerogative? If the answer to this question is that "society" has authorized professionals to choose between scientific progress and individual human dignity and welfare, should not "society" retain some control over the research enterprise? We agree with philosopher Hans Jonas that "a slower progress in the conquest of disease wou'd not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having." [5]

We have, as will be seen, made far-reaching recommendations for change. We do not propose these changes lightly. But throughout, in accordance with our mandate, our concern has not been just to define the ethical issues, but also to examine the structures and policies thus far devised to deal with those issues. In urging greater societal involvement in the research enterprise, we believe that the goal of scientific progress can be harmonized with the need to assure the protection of human subjects.

II. SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

A. Evaluation of Current DHEW Policies for the Protection of Human Research Subjects

1. No uniform Departmental policy for the protection of research subjects exists. Instead one policy governs "extramural" research—research supported by DHEW grants or contracts to institutions outside the Federal Government and conducted by private researchers—and another policy governs "intramural" research—research conducted by personnel of the Public Health Service. Furthermore, Food and Drug Administration (FDA) regulations promulgated to protect subjects in drug research, whether or not supported by DHEW or conducted by the PHS, incorporate variations of their own. The lack of uniformity in DHEW policies creates confusion, and denies some subjects the protection they deserve.

Moving to the next higher level, no uniform Federal policies exist for the protection of subjects in Government-sponsored research. Other agencies wholly separate from DHEW—most notably, the Department of Defense—support or conduct human research. DHEW policies do not govern such research. Here too, the Federal Government's failure to develop a uniform policy has been detrimental to the welfare of research subjects.

2. Under current DHEW policies for the protection of research subjects, regulation of research practices is largely left to the biomedical professions. Since the conduct of human experimentation raises important issues of social policy, greater participation in decisionmaking by representatives of other professions and of the general public is required.

3. The present reliance by DHEW on the institutional review committee as the primary mechanism for the protection of research subjects was an important advance in the continuing effort to guarantee ethical experimentation. Prior peer review of research protocols is a requirement which should be retained.

4. The existing review committee system suffers from basic defects which seriously undermine the accomplishment of the task assigned to the committees:

a. The governing standards promulgated by DHEW which are intended to guide review committee decisions in specific cases are vague and overly general.

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[4] *Barber, et al., supra,* footnote 3, at 52.

[5] Jonas, "Philosophical Reflections on Experimenting with Human Subjects," 98 *Daedalus* 219, 245 (1969).

b. No provisions are made for the dissemination or publication of review committee decisions. Their low level of visibility hampers efforts to evaluate and learn from committee attempts to resolve the complex problems of human research.

c. Although the informed consent of the research subject is one of the most important requirements of research ethics, DHEW policies for obtaining consent are poorly drafted and contain critical loopholes. As a result, one crucial task of institutional review committees—the implementation of the informed consent requirement—is commonly performed inadequately. In particular, consent is far too often obtained in form alone and not in substance.

d. DHEW policies do not give sufficient attention to the protection of such special research subjects as children, prisoners and the mentally incompetent. The use of these subjects in human experimentations presents grave dangers of abuse.

e. The obligation of institutional review committees to conduct continuing review of research projects after their initial approval is undefined and as a consequence often neglected.

f. Inefficient utilization of institutional review committees contributes to their ineffectiveness. Committees are overburdened with a variety of separate functions, and could operate best if their tasks were narrowly defined to encompass mainly the implementation of research policies adequately formulated by others.

g. Effective procedures for enforcing DHEW policies, when those policies are disregarded, have not been devised.

6. No policy for the compensation of research subjects harmed as a consequence of their participation in research has been formulated, despite the fact that no matter how careful investigators may be, unavoidable injury to a few is the price society must pay for the privilege of engaging in research which ultimately benefits the many. Remitting injured subjects to the uncertainties of the law court is not a solution.

B. Policy Recommendations

1. Congress should establish a permanent body with the authority to regulate *at least* all Federally supported research involving human subjects, whether it is conducted in intramural or extramural settings, or sponsored by DHEW or other government agencies, such as the Department of Defense. Ideally, the authority of this body should extend to all research activities, even those not Federally supported. But such a proposal may raise major jurisdictional problems. The body could be called the National Human Investigation Board. The Board should be independent of DHEW, for we do not believe that the agency which both conducts a great deal of research itself and supports much of the research that is carried on elsewhere is in a position to carry out dispassionately the functions we have in mind. The members of the Board should be appointed from diverse professional and scientific disciplines, and should include representatives from the public at large.

2. The primary responsibility of the National Human Investigation Board should be to formulate research policies, in much greater detail and with much more clarity than is presently the case. The Board must promulgate detailed procedures to govern the implementation of its polices by institutional review committees. It must also promulgate procedures for the review of research decisions and their consequences. In particular, this Board should establish procedures for the publication of important institutional committee and Board decisions. Publication of such decisions would permit their intensive study both inside and outside the medical profession and would be a first step toward the case-by-case development of policies governing human experimentation. We regard such a development, analogous to the experience of the common law, as the best hope for ultimately providing workable standards for the regulation of the human experimentation process.

3. The National Human Investigation Board should develop appeals procedures for the adjudication of disagreements between investigators and the institutional review committees.

4. The National Human Investigation Board should also develop a "no fault" clinical research insurance plan to assure compensation for subjects harmed as a result of their participation in research. Institutions which sponsor Federally supported research activities should be required to participate in such a plan.

5. With the establishment of adequate policy formulation and review mechanisms, the structure and functions of the institutional review committees should be altered to enhance the effectiveness of prior review. In place of the amorphous institutional review committee as it now exists, we propose the creation of an Institutional Human Investigation Committee (IHIC) with two distinct subcommittees. The IHIC should be the direct link between the institution and the National Human Investigation Board, and should establish local regulations consistent with national policies. The IHIC should also assume an educational role in its institutions, informing participants in the research enterprise of their rights and obligations. The implementation of research policies should be left to the two subcommittees of the IHIC:

a. A Protocol Review Group (PRG) should be responsible for the prior review of research protocols. The PRG should be composed mainly of competent biomedical professionals.

b. A Subject Advisory Group (SAG) should be responsible for aiding subjects in their decisionmaking whenever they request its services. Subject must be made aware of the existence of the SAG. The primary concern of the SAG should be with procedures for obtaining consent, and with the quality of consents obtained. The SAG should be composed of both professionals and laymen.

III. DEVELOPMENT OF CURRENT DHEW POLICIES

A. Historical Background

Experimentation with human beings is not a modern phenomenon; it dates back to the beginning of recorded history. However, until the advent of scientific medicine, "research" was largely conducted unsystematically in the context of clinical practice which benefited, harmed, or did nothing to untold patients. Indeed, harmful consequences most often accrued to countless patients who were given treatments whose value had not been established by carefully controlled clinical investigations.[6] Since the individuals involved in "research" were generally also considered potential recipients of the knowledge gained, few questions were raised about the propriety of these interventions by either the medical or legal profession. As far as the medical profession was concerned, the systematic use of human beings for research purposes, a trend which began in the late nineteenth century and has accelerated ever since, did not lead until relatively recently to a sustained exploration of the need to safeguard research subjects. A notable exception was Claude Bernard who in 1865 published his influential *An Introduction to the Study of Experimental Medicine*,[7] in which he not only demonstrated the need for experimentation on human subjects but also began to formulate rules of ethical conduct.

Similarly the law has had little to say about the rights of human subjects in the research enterprise. Indeed prior to the nineteen-sixties, no specific federal or state statutes regulated research institutions or investigators in their use of human subjects for experimental purposes. Though beginning with the English case of *Slater* v. *Baker and Stapleton*[8] in 1767 and the American case of *Carpenter* v. *Blake*[9] in 1871, courts were from time to time confronted with the claim of experimentation in malpractice actions, the resulting opinions evinced concern about "experimentation" but did not provide any meaningful legal guidelines for investigators to follow. Perhaps the fact situations in these cases, which often raised other important issues besides experimentation, precluded judges from speaking out more clearly on the legal limits to human research. Through the first third of the twentieth century, the generally accepted legal rule seemed to be that a physician experimented "at his peril" if his patients were harmed thereby.[10] Eventually, the distinction between rash human experimentation and careful, scientific and ethical experimental practice was acknowledged by the courts. In 1935, the Supreme Court of Michigan stated in a malpractice case:

"We recognize the fact that if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on;

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[6] See, e.g., Modell, "Let Each New Patient Be a Complete Experience," 174 J.A.M.A. 1717 (1960).

[7] Bernard, *An Introduction to the Study of Experimental Medicine*, H. C. Greene (Transl.) (Macmillan, 1927).

[8] 95 Eng. Rep. 860 (1767).

[9] 60 Barb. 488 (N.Y., 1871).

[10] See Curran, "Governmental Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," 98 Daedalus 542, 543 (1969).

but such experiments must be done with the knowledge and consent of the patient or those responsible for him and must not vary too radically from the accepted method of procedure." [11]

Although this dictum was a broad generalization, made in a therapeutic context, and was not directed at nontherapeutic investigations, it signalled the ascendency of a more balanced judicial attitude toward medical research involving human beings.

This posture was sorely tested by the revelations of the horrifying atrocities perpetrated under the Nazis by German physicians and scientists in the name of clinical research.[12] The disclosures at Nuremberg disturbed the medical community, and many physicians and research scientists called for worldwide acceptance of ethical standards to assure the protection of subjects in biomedical research. However, the impact of their concern was blunted by the cruelty of the concentration camp experiments which obscured the fundamental fact that similar problems of research ethics, though not of the same magnitude, had characterized the research enterprise from its beginnings. Nonetheless, the trial of the Nazi physicians led the Military Tribunal to set forth ten basic principles, the so-called Nuremberg Code,[13] which must be observed in human experimentation "in order to satisfy moral, ethical, and legal concepts." The following principles illustrate the nature of the Code:

1. The voluntary consent of the human subject is absolutely essential. . . .

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods of study, and not random and unnecessary experiments in nature.

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6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

The widely felt need to supplement and modify the provisions of the Nuremberg Code led to the proliferation of other "improved" codes of research ethics. The World Medical Association's Helsinki Declaration (1964),[14] the American Medical Association's Ethical Guidelines for Clinical Investigation (1966)[15] and the draft code of the American Psychological Association (1972)[16] are three which have received the most attention.

The promulgation of such documents helped to focus attention on the ethical problems inherent in research activities involving human subjects. However, as the number of documents increased their limitation become more evident to concerned observers. As one of us has elsewhere remarked:

"The proliferation of such codes testifies to the difficulty of promulgating a set of rules which do not immediately raise more questions than they answer. By necessity these codes have to be succinctly worded and, being devoid of commentary, their meaning is subject to a variety of interpretations. Moreover, since they generally aspire to ideal practices, they invite judicious and injudicious neglect. Consequently, as long as they remain unelaborated tablets of exhortation, codes will at best have limited usefulness in guiding the daily behavior of investigators." [17]

Furthermore, discrepancies between codes have helped to sow confusion. Discussing the Helsinki Declaration and the A.M.A. Guidelines, Professors Katz and Capron observed:

"The significant discrepancies between these two documents highlight the need for mechanisms which would permit their reconciliation. . . . Unlike the Helsinki Declaration, the AMA guidelines propose that '(m)inors or mentally incompetent subjects may be used as subjects only if (t)he nature of the

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[11] Fortner v. Koch, 272 Mich., 273, 282; 261 N.W. 762, 765 (1935).

[12] See *Trials of War Criminals Before the Nuremberg Military Tribunals, Volumes I and II, The Medical Case*, Washington, D.C.: U.S. Government Printing Office (1948). For excerpts which indicate the nature of the offenses and the resulting judgments, see Katz, *Experimentation with Human Beings*, pp. 292–306 (Russell Sage Foundation, 1972) (Hereinafter *Katz*).

[13] *Katz, supra* footnote 12, at 305.

[14] 271 N. Eng. J. Med. 473 (1964).

[15] American Medical Association, *Operations and Reports of the Judicial Council*, pp. 9–11 (Chicago, 1969).

[16] American Psychological Association, *Ethical Principles in the Conduct of Research with Human Participants* (Draft Document, 1972).

[17] Katz, "The Education of the Physician Investigator," 98 *Daedalus* 480, 482-3 (1969).