UNIVERSITY OF DELAWARE
NEWARK, DELAWARE
19711

UNIVERSITY FACULTY SENATE
303 HULLIHEN HALL
PHONE: 302-738-2829

December 30, 1974

MEMORANDUM

TO: All Faculty Members

FROM: E. Paul Catts, Vice President
University Faculty Senate

SUBJECT: Regular Senate Meeting, January 6, 1975

In accordance with Section IV, paragraph 6 of the Constitution, the regular meeting of the University Faculty Senate will be held on Monday, January 6, 1975, at 4 PM in Room 110 Memorial Hall.

AGENDA

I. Adoption of the Agenda.

II. Approval of Minutes of December 2, 1974.

III. Announcements

IV. Old Business (None)

V. New Business

A. Recommendation from the Graduate Studies Committee as amended and approved by the Committee on Undergraduate Studies concerning policy on 600-level courses for undergraduates (Attachment 1).

B. Recommended policy from the Graduate Studies Committee concerning opening all Ph.D. dissertation defenses to all graduate faculty as follows:

> "That the policy be adopted that all Ph.D. dissertation defenses be open to the graduate faculty and that an announcement of the time, place, subject, candidate's name, and the title of the dissertation be published in the University Newsletter prior to the defense."

C. Proposed regulations from the Committee on Undergraduate Admissions and Standing to implement Senate-approved policy on Satisfactory Progress Toward Degree (Attachment 2).

D. Recommendation from the Committee on Research concerning policy on Involvement of Human Subjects in Research and Research-Related Activities (Attachment 3).

NOTE: A reference copy of the Federal Regulations from the Department of Health, Education, and Welfare is in the Senate Office for anyone interested in studying the rulings on which this policy is based.

E. Summary of opinions of the Committee on Research concerning establishment of a University of Delaware Press (Attachment 4).

F. Such items as may come before the Senate. (No motion introduced at this time may be acted upon until the next meeting of the Senate.)

Attachments are in the hands of your Senators. Distribution also includes one copy for each ten faculty members of each department.

EPC/dpe

Attachments: 1 through 4

POLICY ON 600-LEVEL COURSES FOR UNDERGRADUATES

600-level courses are graduate courses, some of which are open to advanced undergraduates with the consent of the instructor. There should be a single standard of expectation and grading. In those few cases where the number of either undergraduate or graduate students does not permit adequate offerings, a graduate course at the 600 level may be combined with a separately numbered undergraduate course in the same section. The graduate component must be offered at the graduate level as indicated above. The approval of 600-level courses is subject to review by the Committee on Undergraduate Studies as to the appropriation for enrollment for undergraduate credit.

dpe

December 30, 1974

ATTACHMENT 2

PROPOSED REGULATIONS TO IMPLEMENT POLICY ON SATISFACTORY PROGRESS TOWARD DEGREE

On December 2, 1974, the Committee on Undergraduate Admissions and Standing unanimously approved the following regulations as a means of implementing the policy approved by the Faculty Senate on November 5, 1973.

1. To meet the conditions of this policy, a full-time student in any two consecutive semesters must register for and complete at least 12 credit hours in one of the semesters.

   For example, a full-time student satisfies the progress toward the degree requirement if in one semester the student completes 12 credit hours, but in the next following or last preceding semester completed less than 12 credit hours. A full-time student who completes less than 12 credit hours in one semester and also completed less than 12 credit hours in the next following or last preceding semester does not meet the conditions of progress toward the degree.

2. A full-time undergraduate student is one (a) who is classified as full-time and/or (b) one who is registered at the end of the late registration period in any semester for 12 or more credit hours. Students are admitted to the University as either full-time or part-time degree candidates. Following matriculation, this status is determined each semester based on the number of credit hours for which the student is initially registered at the end of the late registration period.

3. A course will be considered as completed and the credit hours will be applied toward the minimum required for satisfactory progress if the final grade for the course is A, B, C, D, F, or P. Courses graded with the temporary grades of I, S, or U at the end of a given semester must be completed with a final grade of A, B, C, D, F, or P in order to count toward satisfactory progress in the subsequent review at the end of the next semester in which the student has enrolled. A course will not be considered as completed and the credit hours will not be applied toward fulfillment of the minimum required for satisfactory progress if the final grade is L, LW, W, WF, or Z, or the temporary grade is N.

4. The progress toward the degree requirement applies only to the first and second semesters in each academic year. Undergraduate students are not required to enroll in or meet progress requirements in the Winter Session or the Summer Session.

5. Students who are dropped for failure to make progress may qualify for readmission by enrolling in the Winter Session, the Summer Session, or through the Division of Continuing Education. Such students must enroll for at least 6 credit hours (minimum of two courses) in each semester or session for which enrolled and must receive a final grade of A, B, C, D, F, or P in each course for which enrolled. Such students will not qualify for readmission if the final grade is L, LW, W, WF, Z, or with a temporary grade of I, S, U, or N. Temporary grades must be removed prior to approval for readmission.

6. Students enrolled in the Division of Continuing Education in order to qualify for readmission will not be permitted to register for regular daytime courses, except in those cases in which no courses offered through the Division of Continuing Education are applicable to the remaining degree requirements of the student.

7. The Committee on Undergraduate Records and Certification will evaluate each case individually at the end of each semester. The committee will evaluate mitigating circumstances as reported by the dean or other college representatives, by faculty, or by the student through direct petition to the committee. When circumstances warrant, the committee may reinstate students who fail to make progress as specified in this policy or give warning that failure to meet the policy in the next enrollment period will result in dismissal. In implementing this policy, the committee will consider illness, accident, or other circumstances beyond the control of the student, as well as the student's efforts to maintain progress through enrollment in the Winter and Summer Sessions.

The policy approved by the Faculty Senate on November 5, 1973, states as follows:

> It is expected that full-time undergraduate students will register for and complete a minimum of 12 credit hours each semester. Full-time students who fail to complete 12 credit hours in any two consecutive semesters (including F and excluding L and W) will, except in unusual circumstances, be dropped from the University of Delaware for failure to make adequate progress toward a degree.
>
> To become eligible for readmission, students dropped under these conditions must complete a minimum of 6 credit hours (two courses) in a summer session or a minimum of 6 credit hours (two courses) in a regular semester through the Division of Continuing Education. (Students will not be permitted to register in the Division of Continuing Education for regular daytime courses.) Grades of W or L will not be acceptable in meeting this requirement.

dpe

December 30, 1974

UNIVERSITY OF DELAWARE POLICY ON THE INVOLVEMENT OF HUMAN SUBJECTS IN RESEARCH AND RESEARCH-RELATED ACTIVITIES

I. UNIVERSITY RESPONSIBILITY

The protection of the individual as a research subject is an obligation recognized and assumed by this University. Therefore, any study which involves human subjects must be performed under conditions which insure the rights and welfare of the subject through adequate safeguards and the informed consent of those involved. Such consent is valid, however, only if the individual is first given a fair explanation of the procedures to be followed, their possible benefits and attendant hazards and discomforts, and the reasons for pursuing the research and its general objectives. This is particularly important when the experimentation or research is not for the direct benefit of the subject. Safeguards should be especially stringent when the subject is legally or physically unable to give consent himself, as in the case of minors.

In order to assure a uniform implementation of the foregoing principles, it is the policy of this University to require review and approval of individual projects by an appropriate committee to assure that:

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; and

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

II. INVESTIGATOR RESPONSIBILITY

Each university investigator who is planning a project which will involve the use of human subjects in research is expected to: 1) make available to the Review Committee the plans for anticipated research prior to beginning the project and in sufficient time to allow the committee to take action; 2) make clearly evident in the written research plan, or through any further information which may be needed, precisely how the rights and welfare of the research subjects are to be protected, how informed consent of human subjects is to be obtained, and whether written consent forms are to be utilized; and 3) during the course of the project make

known to the committee any changes in protocol or any emerging problems of investigation which may significantly alter the original concept.

III. DEFINITION OF HUMAN SUBJECT

A human subject is considered to be 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, training or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or increases the ordinary risks of daily life, including the recognized risks inherent in a chosen field of service. Subjects also may include persons involved in environmental or epidemiological studies; donors of services; and living donors of body fluids, organs or tissues.

IV. APPLICABILITY

This policy applies to every project which includes research procedures that go beyond the diagnostic and therapeutic needs of the subject as determined by the Review Committee. Such projects may involve the procurement of human materials or services and may be classified as research, training, development, or related activities; and may be internally supported by University funds or externally supported through a grant, contract, fellowship, or traineeship. The applicability of this policy is most obvious in medical and behavioral science research involving procedures that may induce a potentially harmful altered state or condition. Surgical procedures; the removal of organs or tissues for biopsy, transplantation or banking; the administration of drugs or radiation; the use of indwelling catheters or electrodes; the requirement of strenuous physical exertion; subjection to deceit, public embarrassment, or humilitation are all examples of procedures which require thorough scrutiny by the institutional committee. (See also Section E, Procedure.)

There is a wide range of medical, social and behavioral research in which no immediate risk to the subject is involved. However, some of these may impose varying degrees of discomfort, irritation, and harassment. In addition, there may be substantial potential injury to the subject's rights if attention is not given to maintenance of the confidentiality of information obtained from the subject and the protection of the subject from misuse of findings. In this category are projects which may involve the use of data obtained previously for purposes other than the research in question.

There is also research concerned solely with discarded human materials obtained at surgery or in the course of diagnosis or treatment. The use of these materials involves no possible element of risk to the subject. In such instances, the only requirement that need be considered is a review of the circumstances under which the materials are to be procured.

- The final determination of what constitutes human involvement is the proper concern of the University Review Committee.

V. IMPLEMENTATION

A. The Review Committee

The Review Committee will have responsibility for the final review and approval of projects involving human subjects. One member must not be a University employee but the other members will ordinarily be from the University community. Membership will be made up of:

A Sociologist
An Anthropologist
A Psychologist
A University employed Medical Doctor
A Nurse with Graduate Degree
A Medical Doctor
The Coordinator of Research
The Associate Provost for Research, Chairman
The Dean of Students.

Whenever it is deemed advisable, independent consultants may be called upon to assist the Review Committee.
A quorum of five members is required to render decisions.

B. Information Required for Committee Consideration

The proposal in its final form, together with a brief protocol describing human subject protection, shall be submitted to the committee (9 copies). In the event that the final draft of the proposal has not been completed in time to meet the deadline for committee review, rough drafts (9) may be submitted with the protocol. The final draft must conform to the original protocol and one copy must be submitted to the Coordinator of Research as soon as possible.

The following information is required in the protocol:

1. The title of the project and the investigator's name.

2. Research objectives.

3. A description of the study with particular respect to methodology and plan of action, including information on the following:
   a. The manner and the extent to which human subjects will be involved.
   b. The procedures, tools, etc. to be employed. Include examples and a description of all questionnaires. Copies of the questionnaires must be submitted to the committee for review before use.

c. What the subjects will be told about their involvement in the study.
d. How informed consent will be obtained and recorded.
e. Whether there will be any potential risks to the subject.
f. What measures will be taken to safeguard the welfare of the subject, his right of privacy and the confidentiality of information being handled.
g. Whether minors will be involved.
h. Whether personality tests or inventories will be used.
i. What inducements, if any, will be offered the subject.

4. Current statement of ethics for the discipline. (If not already on file in the Research Office.)

C. Informed Consent

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;

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; and

7. in the case of minors the consent of a legally authorized representative is required.

The University is obligated to obtain and document legally effective informed consent when any research proposes to place any subject at risk. No such informed consent, oral or written, shall include any exculpatory language. The consent will be documented in one of the three following forms:

1. A written consent document embodying all of the basic elements of informed consent which is signed by the subject after he has been given adequate opportunity to read it.

2. A short, written consent form document indicating that the basic elements of informed consent have been presented orally to the subject. The short form must be signed by the subject and by an auditor witness to the oral presentation and to the subject's signature.

3. A modification of either procedures 1 or 2 that is approved by the Human Subjects Committee. Such a modification must 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.

D. Confidentiality

The identify of a human subject shall not be revealed without the prior consent of the subject. If the data are used in connection with additional research, the consent of the subject must be obtained before the subject is identified with the additional research. The records identifying the subject with the research must be kept apart from the experimental data and must be kept under security conditions equivalent to "confidential data" regulations.

E. Procedure

Every proposal involving human subjects must be reviewed prior to the start of the project or submission of it to an outside sponsor. The proposal and explanatory protocol should first be submitted to the departmental chairman for approval. If there is a departmental review committee, the chairman will take the responsibility for transmitting the proposal to that committee. After departmental approval, the proposal and protocol is sent to the Office of the Coordinator of Research for transmittal to the University Review Committee. (Nine copies are required) In order to allow for any modifications, the proposal must be submitted to the committee at least fifteen (15) working days prior to any deadline date. The committee will review the proposal and respond within ten (10) working days.

On-going projects will be reviewed on an annual basis unless a significant change in protocol dictates more frequent reviews. The committee is responsible for initiating a review of protocols on a more frequent than annual basis when the committee determines this action is advisable.

Since the review process may involve either individual consideration of proposals by committee members or a formal committee meeting, questions or reservations concerning the proposed project may be communicated to the author of the proposal by either

the Committee Chairman or by an individual committee member. It is anticipated that any questions will be resolved through such communication prior to final approval by all members of the committee. After completion of committee review, the chairman will communicate the results of the review to the author of the proposal with copies to the Department and the Research Office.

Decision of the committee will be on the basis of a majority of those voting. A minority report is required from those dissenting from the majority opinion.

The preparation of files relating to the review of each project, including letters and memoranda pertaining to the resolution of problems, copies of consent forms, approvals and disapprovals, etc. will be the responsibility of the Committee Chairman. After a decision has been reached by the committee, the file will be sent to the Research Office where it will be retained.

Special Short Procedure

When there are no stipulations by a sponsoring agency and when the subject runs no apparent risk of bodily harm, public embarrassment or humiliation, research may be carried out after approval by the Departmental Review Committee with the concurrence of the Coordinator of Research. An informational copy of the research protocol and the departmental approval will be sent to the chairman of the University Review Committee in all such cases.

December 30, 1974

ATTACHMENT 4

SUMMARY OF OPINIONS OF THE COMMITTEE ON RESEARCH CONCERNING ESTABLISHMENT OF A UNIVERSITY OF DELAWARE PRESS

(NOTE: This summary is intended as a platform for further discussions by the University Community concerning this matter.)

Dr. John W. Shirley, Consultant to the President, presented five options to the Committee concerning the University's support of scholarly publications as follows:

1. An independent University Press in the traditional manner with staff and facilities for the production of fifteen to twenty books a year. It would cost the University of Delaware about $3,000,000 to get underway and keep such a press, in other words, about a one-year income from UNIDEL.

2. A consortium press serving an area, such as the New England Press, which serves ten colleges. Such a press is not suitable in Delaware because of its geographical location near other existing presses.

3. A fusion of scholarship with business in which a commercial press sets up a subsidiary to act as a university press.

4. A contractual press such as the arrangement we now have with the Temple Press. However, this press is a new one without a large backlog. Johns Hopkins University has a well-established press and has shown some interest in an arrangement with Delaware.

5. The practice of subsidizing or underwriting any book written by a faculty member of the University of Delaware and accepted by other presses. Good presses will now accept subsidies although they refused to do so in the past because the practice smacked of the vanity press.

After discussing these options, the Committee agreed to the following:

1. That options 3 or 4 (above) were the more desirable of those listed.

2. That the monies necessary for establishment of such a press are needed elsewhere at this time.

3. That many years would be needed to establish prestige of such a press.

4. That temporarily, increase in faculty publication quantity might be effected by subsidizing accepted manuscripts.

dpe

December 30, 1974

UNIVERSITY OF DELAWARE
NEWARK, DELAWARE
19711

COLLEGE OF ARTS & SCIENCE
DEPARTMENT OF LANGUAGES & LITERATURE
ROOM 325, SMITH HALL
PHONE: 302-738-2591-2

December 14, 1974

MEMORANDUM

TO: The University Senate

FROM: Senate Committee on Research

DOCUMENT: University of Delaware Policy on the Involvement of Human Subjects in Research and Research-Related Activities, December 13, 1974

The Senate Committee on Research wishes to submit to the University Senate this document with Federal Registers attached: Oct. 9, 1973, Nov. 16, 1973, May 30, 1974, Aug. 23, 1974, Oct. 25, 1974.

Copies of this document dated Dec. 13, 1974 differ from copies dated Dec. 6, 1974 at the following points:

1) Paragraph II. INVESTIGATOR RESPONSIBILITY instead of FACULTY RESPONSIBILITY. "Each university investigator" instead of "each faculty member" and in the next line "research" instead of "experimentation". These changes were authorized by a majority of the Review Committee, the composition of which is described on p. 3 of the document.

2) p. 3 at the end of V.A. this sentence had been omitted:
"A quorum of five members is required to render decisions." This is the minimum quorum as specified in Federal Register (attached) for May 30, 1974, p. 18918, middle column, paragraph (6).

Submitted by:

Roger J. Steiner

Roger J. Steiner
Chairman, University Senate
Committee on Research

federal register

TUESDAY, OCTOBER 9, 1973
WASHINGTON, D.C.

Volume 38 ■ Number 194

PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

■

PROTECTION OF HUMAN SUBJECTS

PROPOSED POLICY

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

[45 CFR Part 46]

PROTECTION OF HUMAN SUBJECTS

Proposed Policy

Notice is hereby given that the Secretary of Health, Education, and Welfare proposes to amend Subtitle A of the Department's regulations by adding a new Part 46 prescribing a policy on protection of human subjects applicable to activities supported by Department grants or contracts.

The proposed regulations would, with some changes, codify existing Department policy currently set forth in Chapter 1-40 of the DHEW Grants Administration Manual, as well as DHEW Publication No. (NIH) 72-102 (December 1, 1971). Among the changes made in the existing policy are the following: Section 46.2 would make it clear that it is the function of the organizational committee established under this part to determine whether subjects are at risk; § 46.4(c) would require that each assurance contain a provision under which the organization submitting the assurance would agree to notify DHEW immediately of emergent problems affecting the rights of human subjects, including adverse reactions; § 46.6(b) would set forth a number of requirements relating to the composition and functioning of the organizational committee; section 46.8 would prohibit the use of exculpatory language under which a subject would be made to waive or appear to waive any of his legal rights; §§ 46.11, 46.13, and 46.14 would require organizations receiving general, institutional-type assistance to certify that any activity involving human subjects has been reviewed and approved by the organization in accordance with this part; § 46.11 would require organizations to carry out reviews and approval of applications and proposals prior to submission to DHEW; §§ 46.20 and 46.21 would impose record keeping and reporting requirements; and § 46.22 would permit sanctions for failure to comply with the regulations.

In addition, DHEW through the National Institutes of Health, has appointed a special study group to review and recommend policies for the protection of human subjects in biomedical research. The study group is considering, among other things, the development of special procedures for the use of incompetents or prisoners in biomedical research, compensation of persons injured in clinical investigations, and a general review of the legal ethical responsibilities in the conduct of such research. It is contemplated that the recommendations of the study group will be considered for inclusion in the DHEW regulations to be promulgated in this part.

Inquiries may be addressed and data, views, and arguments relating to the proposed regulations may be presented in writing, in triplicate, to the Chief, Institutional Relations Branch, Division of Research Grants, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments received will be available for inspection at the National Institutes of Health, Room 303, Westwood Building, 5333 Westbard Avenue, Bethesda, Maryland, weekdays (Federal holidays excepted) between the hours of 9:00 a.m. and 4:30 p.m. All relevant material received on or before November 8, 1973, will be considered.

Notice is also given that it is proposed to make any amendments that are adopted effective upon publication in the FEDERAL REGISTER.

Dated September 28, 1973.

CASPAR W. WEINBERGER,
Secretary.

It is therefore proposed to amend Subtitle A of Title 45 of the Code of Federal Regulations by adding the following new Part 46:

PART 46—PROTECTION OF HUMAN SUBJECTS

Sec.

AUTHORITY.—5 U.S.C. 301.

§ 16.1 Applicability.

The regulations in this part are applicable to all Department of Health, Education, and Welfare grants and contracts supporting activities in which human subjects may be at risk.

§ 16.2 Policy.

(a) Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is the principal 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 any human subjects at risk supported by a DHEW grant or contract shall be undertaken unless the organization has reviewed and approved such activity and submitted to DHEW a certification of such review and approval, in accordance with the requirements of this part.

(b) This review shall determine whether any human subjects are at risk and, if so, 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.

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

§ 46.3 Definitions.

(a) "Organization" means any public or private institution or agency (including State and local governments).

(b) "Subject at risk" means any individual who may be exposed to the possibility of harm—physical, psychological, sociological, or other—as a consequence of participation as a subject in any research, development or demonstration activity which goes beyond the application of those established and accepted methods necessary to meet his needs.

(c) "Informed consent" includes the following basic elements:

(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 the 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 subject is free to withdraw his consent and to discontinue participation in the project or activity at any time.

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

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

§ 46.4 Submission of assurances.

(a) Recipients or prospective recipients of DHEW assistance 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 projects or activities, a report of initial findings

and 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.

(c) Each assurance shall contain a provision requiring the organization to give DHEW immediate notification under this part of emergent problems affecting the rights of human subjects, including adverse reactions to drugs, appliances, or other substances.

§ 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 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 project or activity. Special assurances will not normally be solicited or accepted from organizations which have acceptable general assurances on file with DHEW.

§ 46.6 Minimum requirements for general assurances.

The organization must include as part of its general assurance implementing guidelines that specifically provide for:

(a) The 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 § 46.2. 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 projects and activities commonly conducted by the organization. The committee's membership, maturity, experience, and expertise must be such as to justify respect for its advice and counsel. In addition to possessing the professional competence to review specific activities, the committee must be able to determine the acceptability of the proposal in terms of the organization's commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The committee must therefore 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 DHEW.

(2) The committee members shall be identified to DHEW by name, earned degrees, if any, position or occupation, representative capacity, or by other pertinent indications of experience such as board certification, licenses, etc. Thereafter, 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 or quorum of a committee shall consist entirely of employees of the organization.

(5) No committee or quorum of a committee shall be composed entirely of members of a single professional group or lay group.

(6) The quorum of the committee shall be defined, but may in no event be less than three members convened to carry out the committee's responsibilities under the assurance.

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

(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 its requirements for reporting adverse sections, emergent problems or proposed changes in a project or other activity.

(e) The 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.

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 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 satisfying the requirements of § 46.6(b) and be executed by an appropriate organizational official.

(b) Describe the makeup of the committee and the training, experience, and background of its members;

(c) Contain the committee's description in general terms of those risks to the subject that it recognizes as inherent in the activity;

(d) Describe the consent procedures to be used and attach any consent statement(s) to be signed, heard, or read by the subject or responsible third parties;

(e) 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;

(f) Indicate whether the director or investigator will be required to submit written reports, appear for interviews, or be visited by the committee or committees to provide for continuing review.

§ 46.8 Obligation to secure informed consent; prohibition of exculpatory clauses.

Any organization proposing to place any subject at risk is obligated to obtain and document informed consent. No 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.

§ 46.9 Documentation of informed consent.

The actual procedure utilized in obtaining informed consent and the basis for committee determinations that the procedures are adequate and appropriate shall be fully documented. The documentation of consent 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 document is to be signed by the subject or his authorized representative. A sample of the document as approved by the committee is 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 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 authorized representative and 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 obtaining the consent on behalf of the organization 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 that the risk to any subject is minimal, 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 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 must be approved by the committee in the minutes signed by the committee chairman. 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.

§ 46.10 [Reserved]

§ 46.11 Certification, general assurances.

(a) *Timely review.* All proposals involving human subjects submitted by organizations should be given review and approval prior to submission to 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 official authorized to sign or execute applications or proposals for the organization.

HUMAN SUBJECTS—REVIEWED AND APPROVED ON----------

The date of review and approval must be no later than the proposal submission date unless an extension of time is granted by the Secretary. In no event will review of the proposal by the DHEW operating agency concerned be completed until review by the organization has been certified.

(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 applicant institution.

(c) *Notification of DHEW where activities supported by institutional-type grants.* In those instances in which an organization receives general assistance (e.g., institutional-type grants) not requiring DHEW approval for specific expenditures, no activity involving human subjects shall be undertaken until the organization has submitted to DHEW: (1) A certification that the activity has been reviewed and approved in accordance with this part and (2) a detailed description of the proposed activity (including any protocol or similar document).

§ 46.12 Certification, special assurances.

Institutions not having accepted general assurances on file with the DHEW must submit a special assurance with each application or proposal involving human subjects. Such an assurance shall be considered to provide certification for the initial grant or contract period concerned. No additional documentation is required. If the terms of the grant or contract recommend additional years of support, but with periodic award or obligation of funds, any noncompeting renewal application or proposal shall be certified in the manner described in the preceding section.

§ 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 project period, but definite plans for this involvement cannot properly be included in the proposal. These include (a) certain training grants where trainee projects remain to be selected, and (b) 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 definitive proposals but shall provide for resubmission to the organizational committee when definite plans have been completed if said plans involve the use of human subjects. Under such circumstances, in addition to complying with all other terms of the grant or contract, no activity involving the use of human subjects shall be undertaken until the organization has submitted to DHEW: (c) a certification that the activity has been reviewed and approved in accordance with this part after completion of definite plans and (d) a detailed description of the proposed activity (including any protocol or similar document). Where support is provided by project grants or contracts, subjects shall also not be involved prior to receipt of DHEW approval and in the case of contracts prior to any necessary negotiation and approval of an amended contract description of work.

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

If a proposal, at the time it is submitted to DHEW, does not anticipate involving or intend to involve human subjects, no certification should be submitted. In those instances, however, where it later 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). Where support is provided by project grants or contracts, subjects shall also not be involved prior to receipt of DHEW approval and in the case of contracts prior to negotiation and approval of an amended contract description of work.

§ 46.15 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). In such instances the grantee or prime contractor may obtain access to all or some of the subjects involved through one or more cooperating organizations. 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.

(a) *Organization with general assurances.* Initial and continuing review by the organization may be carried out by one or a combination of procedures:

(1) Cooperating organization with accepted general assurances. When the cooperating organization has on file with DHEW an accepted general assurance, the grantee or contractor may carry out its own review or request the cooperating organization 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 individuals for whom the cooperating organization 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 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 accepted general assurance. When the cooperating organization does not have an accepted general assurance on file with DHEW, it may submit a general or special assurance to DHEW which, if approved, will permit the grantee or contractor to follow the procedure outlined in the preceding subparagraph.

(3) Interinstitutional joint reviews. 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, permanent appointments may be made. Under some circumstances component subcommittees may be established within cooperating organizations. All such cooperative arrangements must be accepted by DHEW as part of a general assurance, or as an amendment to a general assurance, or in unusual situations as a special assurance.

(b) *Organizations with special assurances.* While responsibility for initial and continuing review necessarily lies with the organization as defined in § 46.2, DHEW will also require acceptable assurances from those cooperating institutions having immediate responsibility for subjects.

(1) If the cooperating organization has on file with DHEW an accepted 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 immediate 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.

(2) If the cooperating organization does not have an accepted general assurance on file with DHEW, it must submit a general or special assurance to DHEW which is determined by DHEW to comply with the provisions of this part.

§ 46.16 Investigational new drug number.

Where an organization is required 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 investigational new drug number issued by the Food and Drug Administration, DHEW, shall be included with said certification, provided, however, that in those cases in which the issuance of an investigational new drug number is pending, said certification shall include an assurance that such number will be forwarded upon receipt. In no event, shall DHEW award funds under a grant or contract until such number has been supplied.

§ 46.17 Implementation and revision of assurances.

The grantee or contracting organization's administration is accountable to DHEW for effectively carrying out the provisions of the assurance of the organization for the protection of human subjects as accepted and recognized by DHEW. Revision in the assurance of the organization, including the implementation procedures, are to be reported to and approved by DHEW prior to the date such revisions become effective. Revision without prior notification and approval may result in withdrawal of DHEW acceptance of the organization's assurance.

§ 46.18 Organization's executive responsibility.

Specific executive functions to be conducted by the administration of 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 follow-up is a condition of acceptance of an assurance. Committee approvals and 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 the committee or another appropriate review group as described and accepted in the assurance filed with DHEW.

§ 46.19 Withholding of funds.

Under no circumstances shall an activity involving subjects at risk be implemented with DHEW funds until said activity is reviewed and approved by organizational committee and a certification of such review and approval submitted to DHEW in accordance with this part. In addition, the organization staff responsible for such activity shall not proceed therewith until they have received notification of such approval, including any restrictive requirements made by the committee or the administration. They shall 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 subjects. Where continuing review of projects involves the channels of administrative authority in the organization, 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 DHEW.

§ 46.20 Organization's records.

(a) Copies of all documents presented or required for initial and continuing review by the organization's review committee and minutes, transmittals on actions, instructions, and conditions resulting from review committee deliberations addressed to the activity director are to be made part of the official organizational files for the supported activity.

(b) Records of subjects' consent shall be retained by the organization or organizational component in accordance with its established practice, or, if no practice has been established, in project files.

(c) Acceptance of any DHEW grant or contract award shall constitute the consent of the grantee or contracting organization to inspection and audit of records required under this part by authorized representatives of the Secretary.

(d) All documents and other records required under this part must be retained by the grantee or contracting organization for a minimum of three years following termination of DHEW support of the activity.

§ 46.21 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.

§ 46.22 Early termination of awards; sanctions for noncompliance.

(a) If, in the judgment of the Secretary, an organization has failed 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) If, in the judgment of the Secretary, an organization fails to discharge its responsibilities for the protection of the rights and welfare of the subjects in its care, whether or not DHEW funds are involved, he may, upon reasonable notice to the organization of the basis for such action, determine that its eligibility to receive further DHEW grants or contracts involving human subjects shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist.

(c) If, in the judgment of the Secretary, an individual serving as principal investigator, program director, or other person having responsibility for the scientific and technical direction of a project or activity, has failed to discharge his responsibilities for the protection of the rights and welfare of human subjects in his care, the Secretary may, upon reasonable notice to the individual of the basis for such action, determine that such individual's eligibility to serve as a principal investigator or program director or in another similar capacity shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist.

§ 46.23 Conditions.

The Secretary may with respect to any grant or contract or any class of grants or contracts impose conditions, including conditions pertaining to informed consent, 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.73-21245 Filed 10-5-73;8:45 am]

federal register

FRIDAY, NOVEMBER 16, 1973
WASHINGTON, D.C.

Volume 38 ■ Number 221

PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

■

NATIONAL INSTITUTES OF HEALTH

Protection of Human Subjects

Policies and Procedures

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

PROTECTION OF HUMAN SUBJECTS

Policies and Procedures

In the FEDERAL REGISTER of October 9, 1973 (38 FR 27882 et seq.), the Secretary of Health, Education, and Welfare issued a notice of proposed rulemaking concerning the protection of human subjects and mentioned that DHEW through the National Institutes of Health, had appointed a special study group to review and recommend policies and special procedures for the protection of children, prisoners, and the institutionalized mentally infirm in research, development, and demonstration activities. The report of this study group has been completed in *draft* form and reviewed by the Director, NIH.

There may well be elements in the recommendations which will provoke debate and controversy. We recognize that public consideration and comment are vital to the development of our final recommendations to the Secretary and are inviting such comment now even though the materials are still pending final review and completion. The product of our effort after considering public comment will be transmitted to the Assistant Secretary for Health, HEW to recommend to the Secretary, HEW that it appear again in the FEDERAL REGISTER as proposed rulemaking for further public comment. Such a procedure is consistent with long established DHEW policy for permitting extensive public opportunity to affect the promulgation of DHEW regulations.

It must be clearly understood by the reader that the material that follows is *not* proposed rulemaking in the technical sense, and is not presented as Departmental, Public Health Service, or NIH policy. Rather it is a draft working document on which early public comment and participation is invited.

Please address any comments on these draft policies and procedures to the Director, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments should be received by January 4, 1974.

Additional copies of this notice are available from the Chief, Institutional Relations Branch, Division of Research Grants, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014.

Dated: November 6, 1973.

ROBERT S. STONE,
Director,
National Institutes of Health.

RESEARCH, DEVELOPMENT, AND DEMONSTRATION ACTIVITIES: LIMITATIONS OF INFORMED CONSENT

SPECIAL POLICY CONSIDERATIONS

Summary

NOVEMBER 5, 1973.

The mission of the Department of Health, Education, and Welfare includes the improvement of the health of the Nation's people through research, development, and demonstration activities which at times involve human subjects. Thus, policies and procedures are required for the protection of subjects on whose participation these activities depend.

Informed consent is the keystone of the protection of human subjects involved in research, development, and demonstration activities. Certain categories of persons have limited capacity to concent to their involvement in such activities. Therefore, as a supplement to DHEW policies, special protections are proposed for *children, prisoners,* and the *mentally infirm* who are to be involved in research, development, and demonstration activities.

Agency "Ethical Review Boards" are to be established to provide rigorous review of the ethical issues in research, development, and demonstration activities involving human subjects, in order to make judgments regarding societal acceptability in relation to scientific value. "Protection Committees" are to be established by the applicant to provide "supplementary judgment" concerning the reasonableness and validity of the consent given by, or on behalf of, subjects. The intent of this policy is that institutions which apply for DHEW funds or submit research in fulfillment of DHEW regulations, must be in compliance with these special protections, whether or not particular research, development, or demonstration activities are Federally activities.

1. *Children.* If the health of children is to be improved, research activities involving their participation is often essential. Limitation of their capacity to give informed consent, however, requires that certain protections be provided to assure that scientific importance is weighed against other social values in determining acceptable risk to children. Therefore, research, development, and demonstration activities which involve risk to children who participate must:

a. Include a mechanism for obtaining the consent of children who are 7 years of age or older;

b. Include the applicant's proposal for use of a Protection Committee which is appropriate to the nature of the activity;

c. Be reviewed and approved, in conformity with present DHEW policy, by an Organizational Review Committee; and

d. Be reviewed by the appropriate agency Primary Review Committee, the Ethical Review Board, and the appropriate secondary review group.

2. *Special categories.*—a. *The Abortus.* No research, development, or demonstration activity involving the non-viable abortus shall be conducted which:

1. Will prolong heart beat and respiration artificially solely for the purpose of research;

2. Will of itself terminate heart beat and respiration;

3. Has not been reviewed by the agency Ethical Review Board; and

4. Has not been consented to by the pregnant woman with participation of a Protection Committee.

(An abortus having the capacity to sustain heart beat and respiration is in fact a premature infant, and all regulations governing research on children apply.)

b. *The fetus in utero.* No research involving pregnant women shall be conducted unless:

1. Primary Review Groups assure that the activity is not likely to harm the fetus;

2. the agency Ethical Review Board has reviewed the activity;

3. a Protection Committee is operating in a manner approved by the agency; and

4. the consent of both prospective legal parents has been obtained, when reasonably possible.

c. *Products of in vitro fertilization.* No research involving implantation of human ova which have been fertilized *in vitro* shall be approved until the safety of the technique has been demonstrated as far as possible in sub-human primates, and the responsibilities of the donor and recipient "parents" and of research institutions and personnel have been established. Therefore, no such research may be conducted without review of the Ethical Review Board and of a Protection Committee.

3. *Prisoners.* Research, development, and demonstration activities involving human subjects often require the participation of normal volunteers. Prisoners may be especially suitable subjects for such studies, although there are problems concerning the voluntariness of the consent of normal volunteers who are confined in institutions. Certain protections are required to compensate for the diminished autonomy of prisoners in giving voluntary consent. Research, development, and demonstration activities involving prisoners must:

a. Include the applicant's proposal for use of a Protection Committee which is appropriate to the nature of the activity;

b. Be reviewed and approved by an Organizational Review Committee which may already exist in compliance with present DHEW policy or which must be appointed in a manner approved by the appropriate DHEW agency;

c. Be reviewed by the agency Primary Review Committee; and

d. Be conducted in an institution which is accredited by the Secretary of Health, Education, and Welfare.

4. *The mentally infirm.* Insofar as the institutionalized mentally infirm might lack either the competency or the autonomy (or both) to give informed consent, their participation in research requires additional protection:

a. Research, development and demonstration activities involving the mentally infirm will be limited to investigations concerning (1) diagnosis, etiology, prevention, or treatment of the disability from which they suffer, or (2) aspects of institutional life, *per se,* or (3) information which can be obtained only from such subjects.

All research, development and demonstration activities involving such persons must:

1. Include the applicant's assurance that the study can be accomplished *only*

with the participation of the mentally infirm;

2. Include the applicant's proposal for use of a Protection Committee which is appropriate to the activity; and

3. Be reviewed and approved by an Organizational Review Committee, in conformity with present DHEW policy.

TABLE OF CONTENTS

INTRODUCTION

The mission of the Department of Health, Education, and Welfare includes the improvement of the health of the Nation's people through biomedical research. This mission requires the establishment of policy and procedures for the protection of subjects on whose participation that research depends. In DHEW policy, as well as in ethical codes pertaining to research in human subjects, the keystone of protection is informed consent.

An uncoerced person of adult years and sound mind may consent to the application of standard medical procedures in the case of illness, and when fully and properly informed, may legally and ethically consent to accept the risks of participating in research activities. Parents and legal guardians have authority to consent on behalf of their child or ward to established therapeutic procedures when the child is suffering from an illness, even though the treatment might involve some risk.

There is no firm legal basis, however, for parental or guardian consent to participation in research on behalf of subjects who are incompetent, by virtue of age or mental state, to understand the information provided and to formulate the judgments on which valid consent must depend. In addition, current policies for clinical research afford such subjects inadequate protection. Nevertheless, to proscribe research on all such subjects, simply because existing protections are inadequate, would be to deny them potential benefits, and is, therefore, inequitable. Knowledge of some diseases and therapies can be obtained only from those subjects (such as children) who suffer from the disease or who will be receiving the therapy. Their participation in research is necessary to progress in those fields of medicine. When such subjects participate in research, they need more protection than is provided by present policy.

There are other individuals who might be able to comprehend the nature of the research, but who are involuntarily confined in institutions. Insofar as incarceration might diminish their freedom of choice, and thus limit the degree to which informed consent can be freely given, they too need additional protection. Current policies do not recognize the limitations on voluntariness of consent which may emanate from incarceration.

This addition to existing policy is offered as a means of providing adequate protection to subjects who, for one reason or another, have a limited ability to give truly informed and fully autonomous consent to participate in research. The aim is to set standards which are both comprehensive and equitable, in order to provide protection and, to the extent consistent with such protection, maintain an environment in which clinical research may continue to thrive.

1. *Definitions.* For purposes of this policy:

A. *Subject at risk* means any individual who might be exposed to the possibility of harm (physical, psychological, sociological, or other) as a consequence of participation as a subject in any research, development or demonstration activity (hereinafter called "activity") which goes beyond the application of established and accepted methods necessary to meet his needs.

B. *Clinical research* means an investigation involving the biological, behavioral, or psychological study of a person, his body or his surroundings. This includes but is not limited to any medical or surgical procedure, any withdrawal or removal of body tissue or fluid, any administration of a chemical substance, any deviation from normal diet or daily regimen, and any manipulation or observation of bodily processes, behavior or environment. Clinical research comprises four categories of activity:

1. Studies which conform to established and accepted medical practice with respect to diagnosis or treatment of an illness.

2. Studies which represent a deviation from accepted practice, but which are specifically aimed at improved diagnosis, prevention, or treatment of a specific illness in a patient.

3. Studies which are related to a patient's disease but from which he or she will not necessarily receive any direct benefit.

4. Investigative, non-therapeutic research in which there is no intent or expectation of treating an illness from which the patient is suffering, or in which the subject is a "normal control" who is not suffering from an illness but who volunteers to participate for the potential benefit of others.

It is important to emphasize that "non-therapeutic" is not to be understood as meaning "harmful." Understanding of normal processes is essential; it is the prerequisite, in many instances, to recognition of those deviations from normal which define disease. Important knowledge can be gained through such studies of normal processes. Although such research might not in any way benefit the subjects from whom the data are obtained, neither does it necessarily harm them.

Patients participating in studies identified in paragraph B–1, above, are not considered to be at special risk by virtue of participating in research activities, and this policy statement offers no special protection to them. When patients or subjects are involved in procedures identified in paragraphs B2, B3, and B4, they are considered to be "at risk," and the special policy and procedures set forth in this document pertain. Excluded from this definition are studies in which the risk is negligible, such as research requiring only, for example, the recording of height and weight, collecting excreta, or analysing hair, deciduous teeth, or nail clippings. Some studies which appear to involve negligible physical risk might, however, have psychological, sociological or legal implications which are significant. In that event, the subjects are in fact "at risk," and appropriate procedures described in this document shall be applied.

C. *Children* are individuals who have not attained the legal age of consent to participate in research as determined under the applicable law of the jurisdiction in which the proposed research is to be conducted.

D. *Pregnancy* encompasses the period of time from implantation until delivery. All women during the child bearing years should be considered at risk of pregnancy; hence, prudence requires definitive exclusion of pregnancy when women in this period of life are subjects for experimentation which might affect the fetus.

E. *Fetus* means the product of conception from the time of implantation to the time of delivery from the uterus.

F. *Abortus* means a fetus when it is expelled whole, whether spontaneously or as a result of medical or surgical intervention undertaken with the intention of terminating a pregnancy, prior to viability. This definition, for the purpose of this policy, excludes the placenta, fetal material which is macerated at the time of expulsion, a dead fetus, and isolated

fetal tissue or organs excised from a dead fetus.

G. *Viability of the fetus*, means the ability of the fetus, after either a spontaneous delivery or an abortion, to survive to the point of independently maintaining vital functions; such a "viable" fetus is a premature infant. Determination of viability entails a subjective and objective judgment by the physician attending labor or examining the product of conception, and must be made by a physician other than the investigator wishing to use fetal tissue in research. In general, and all other circumstances notwithstanding, a beating heart is not sufficient evidence of viability. At least one additional necessary condition is the possibility that the lungs can be inflated. Without this precondition, no currently available mechanisms to initiate or maintain respiration can sustain life; and in this case, though the heart is beating, the fetus or abortus is in fact non-viable.

H. *In vitro fertilization* is any fertilization of human ova which occurs outside the body of the female, either through admixture of donor sperm and ova or by any other means.

I. *Prisoner* is any individual involuntarily confined in a penal institution. The term in intended to encompass individuals sentenced to such an institution under a criminal or civil statute, or individuals detained by virtue of statutes which provide alternatives to criminal prosecution.

J. *Mentally infirm* includes the mentally ill, the mentally retarded, the emotionally disturbed, the psychotic, the senile, and others with impairments of a similar nature, residing as patients in an institution, regardless of whether or not the individual has been determined to be legally incompetent.

K. *Informed consent* has two elements: comprehension of adequate information and autonomy of consent. Consent is a continuing process. The person giving consent must be informed fully of the nature and purpose of the research and of the procedures to be used, including identification of those procedures which are experimental, the possible attendant short or long term risks and discomforts, the anticipated benefits to himself and/or others, any alternative methods of treatment, expected duration of the study, and of his or her freedom to ask any questions and to withdraw at any time, should the person wish to do so. There must also be written evidence of the process used for obtaining informed consent, including grounds for belief that the subject has understood the information given and has sufficient maturity and mental capacity to make such choices and formulate the requisite judgment to consent. In addition, the person must have sufficient autonomy to choose, without duress, whether or not to participate. Both the comprehension of information and the autonomy of consent are necessary elements; to the extent that either of these is in doubt, the adequacy of informed consent may be in doubt.

L. *Supplementary judgment* is the judgment made by others to assent, or to refuse to assent, to procedures for which the subject cannot give adequate consent on his or her own behalf. For the purposes of this document, supplementary judgment will refer to judgments made by local committees in addition to the subject's consent (when possible) and that of the parents or legal guardian (where applicable), as to whether or not a subject may participate in clinical research. This supplementary judgment is to be confirmed by the signature of the Chairman of the Protection Committee on the consent form. In accordance with the procedures approved by the agency for the Protection Committee, the Chairman's signature may be affixed on a standard consent form, or may need to be withheld until the Committee approves the participation of the individual subject.

II. *General policy considerations*. In general, clinical research, like medical practice, entails some risk to the subjects. When the potential subject is unable fully to comprehend the risks which might be involved, or to make the judgment essential to consent regarding the assumption of those risks, current guidelines suggest obtaining the consent of the parents or legal representative.

Whereas it is clear by law that consent of a parent or legal representative is valid for established and generally accepted therapeutic procedures performed on a child or an incompetent adult, it is far from clear that it is adequate for research procedures. In practice, parental or guardian consent generally has been accepted as adequate for therapeutic research, although the issue has not been definitively resolved in the courts. When research might expose a subject to risk without defined therapeutic benefit or other positive effect on that subject's well-being, parental or guardian consent appears to be insufficient.

In the case of prisoners, confinement imposes limitations on freedom of choice which brings into question their ability to give voluntary consent. A prisoner's ability to give consent may be restricted by overt or potential coercion, or by the loss of personal autonomy generally considered to result from incarceration itself. Therefore, additional protection must be afforded this group even though an individual's competency to understand what is involved might not be in doubt.

The institutionalized mentally infirm are doubly limited: as with children, they might not be competent to make informed judgments, and, as with prisoners, they are confined under conditions which limit their civil freedom and autonomy. Therefore, their participation in research requires special protections.

The law is not clear on these issues. Even if the law were clear, however, ethical questions would remain; specifically, whether, and under what conditions research involving these subject groups may proceed. Resolution of these ethical questions requires judgments concerning both the ethics of conducting a particular research project, and the adequacy of procedures for protecting the individual subjects who will be asked to participate. The intention of this policy is to broaden the scope of review, preclude or resolve conflicts of interest, and invoke social as well as scientific judgments to protect potential subjects who might have diminished capacity to consent.

The proposed mechanism for protecting subjects with limited ability to give informed consent culminates in a form of supplementary judgment, which is to be supportive and protective of the subject's best interests and wishes, to the extent that he or she is capable of formulating and expressing a judgment. In the case of children and the mentally infirm, it will supplement their judgment and that of their parents or guardians. In the case of competent individuals who have restricted autonomy, it will support and protect their wishes. Through this mechanism, these subjects will be protected as fully as possible by community review; however, the nature of some research procedures might be such that, in addition, court review ultimately will be required.

III. *Participation of children in research*—A. *Policy considerations*. Children have generally been considered inappropriate subjects for many research activities because of their inability to give informed consent. There are circumstances, however, which not only justify, but even require their participation. Children do differ from adults in their physiologic responses, both to drugs and to disease; if the health of children is to be improved, it is necessary to know the nature and extent of these differences, and to have a full understanding of normal patterns of growth and development, metabolism, and biochemistry in the perinatal, infant, early childhood pubertal and adolescent stages of development. Studies of normal physiology and behavior can also provide significant benefit to children suffering from disease; children are the only subjects from whom these data can be obtained. Furthermore, there are diseases which cannot be induced in laboratory animals, and occur only rarely, if at all, in human adults. In such cases, children are the only subjects in whom the disease process and possible modes of therapy can be studied.

The Kefauver-Harris Act[1] requires that drugs be tested for safety, efficacy and dosage in children and pregnant women before being approved for use to treat illness in such patients. Food and Drug Administration (FDA) approval for the use of a new drug depends upon submission of proposed labeling for a new drug, which must include "adequate directions for use" and "adequate warnings" as to unapproved uses.[2] Acceptance of a new dru

[1] Federal Food, Drug, and Cosmetic Act 1962 (FDC Act), 21 U.S.C. Sec. 301 et. seq.
[2] FDC Act Sec. 502(f), 21 U.S.C. Sec. 352(f

rests on the adequacy of the research reports submitted with the application to support the proposed labeling.[1] Thus, in order for a drug to be distributed in interstate commerce for use in children or pregnant women, sufficient testing must have taken place in children or pregnant women to substantiate claims on the label regarding safety, efficacy, and dosage for those groups. If the safe and efficacious dosage for children and pregnant women has not been determined, the label must so state. Thus, participation of children in drug research might be the only means of meeting licensing requirements for new drugs for use in children, just as studies in pregnant women might be the only means of meeting licensing requirements for new drugs for use in that class of patients.

When the risk of a proposed study is generally considered not significant, and the potential benefit is explicit, the ethical issues need not preclude the participation of children in biomedical research. However, the progression from innocuous to noxious, in terms of risk, is often subtle. Therefore, additional review procedures are necessary for research activities which expose children to risk, in order to provide sharp scrutiny, vigorous review, and stringent procedural safeguards for all subjects of such research.

Judgments concerning the ethical propriety of research depend partly upon the scientific assessment of the potential risks and benefits. Risk has several important elements: severity, probability, frequency, and the timing of possible adverse effects. While it might not always be easy to distinguish these elements, they must be evaluated in the assessment of risk, and in the determination of the acceptable limits of specific risk for an anticipated benefit. The first judgment to be made is whether it is possible to assess the risk. If studies in animals or adults do not provide sufficient information to assess these elements of risk, then the research should not be conducted on children. If the risks can be determined from studies in animal and adult human populations, application to children may be considered.

In addition to results from investigations on animals and adult subjects, there are unknowns which must be considered in the weighing of risk to children. These include: (1) differences in physiologic or psychologic response from adult patterns; (2) delayed expression of injury (for example, until puberty); (3) effects on developing organs (especially the central nervous system); (4) degree of interference with normal routine required by the study; and (5) possibility of misuse of data by institution or school personnel.

Once the severity and probability of risks in a particular study have been identified, a second judgment must be made: given potential benefits of described dimensions, what are the acceptable limits of risk to which children ethically may be subjected? Value judgments which must be weighed here transcend scientific issues and suggest that the decision requires interaction among individuals in society with diverse training and perspectives. Further, given the complexity of the issues and the opportunity for conflict among the interests of several parties (the child, the parents or guardian, the attending physician, and the research personnel), decisions regarding participation of individual subjects in research activities involving children should not rest solely with persons directly involved in the research.

In order to provide both impartial ethical review of projects and maximum protection of individual subjects, two procedures are proposed in addition to those currently required: review by an Ethical Review Board at the sponsoring DHEW agency, and participation by a Protection Committee at the institution in which the research is to be conducted. Both groups will provide community involvement in decisions and attempt to balance scientific value and societal acceptability of proposed research involving children.

B. *Ethical Review Board: Ethical review of projects.* Each DHEW agency shall appoint an Ethical Review Board to provide rigorous review of ethical issues in research involving human subjects by people whose interests are not solely those of the scientific community. Its functions will include:

1. Advising the agency on ethical issues including review of questions of policy, and development of guidelines and procedures;

2. Fostering inter-agency coherence through cognizance of the policies and procedures of other agencies;

3. Reviewing specific proposals or classes of proposals submitted to the Board by the agency. These will include proposals stipulated herein as requiring review by the Board, as well as proposals submitted on an *ad hoc* basis by agency staff. In addition, the Board may recommend that certain additional classes of research be reviewed.

The acceptability of a research project rests on questions of scientific merit as well as on questions of ethics. The agency Primary Review Committees are responsible for evaluating scientific merit and experimental design. The Ethical Review Board will be concerned with ethical issues and questions of societal acceptability in relation to scientific value. In reaching its determination of acceptability, the Board will rely upon the Primary Review Committees for judgments on scientific merit and design, existence of prerequisite animal and adult human studies, estimated risks and benefits (taking into account the competence and experience of investigators and the adequacy of their resources), and scientific importance. It will review proposals received from these Primary Review Committees.

An investigator proposing research activities which expose children to risk must document, as part of the application for support, that the information to be gained can be obtained in no other way. The investigator must also stipulate either that the risk to the subjects will be insignificant, or that although some risk exists, the potential benefit is significant and far outweighs that risk. In no case will research activities be approved which entail substantial risk, except in the case of clearly therapeutic procedures in which the benefit to the patient significantly outweighs the possible harm. The Ethical Review Board shall review all proposals approved by Primary Review Committees involving children in research activities, except when the Primary Review Committees determine that the subjects are not at risk.

In addition to reviewing ethical issues, the Board will review procedures proposed in the research application to be employed by the institution's Protection Committee (see below), and may suggest modifications of these procedures. The Board's recommendation may vary from a general concurrence with the proposal, as submitted by the investigator, to a recommendation that each parental and subject consent must be obtained with the concurrence of the full Protection Committee. Any specific recommendations for procedures to be followed by the Protection Committee will be included in the report of the Ethical Review Board which will be forwarded to the National Advisory Councils or other secondary review groups of the agency. Appropriate information will be provided by the agency to assist the Protection Committee.

Inasmuch as the articulation of decisions might clarify both the objectives and the assumptions on which they are based, records of testimony and deliberations, as well as final decisions, should be maintained pursuant to existing regulations. Such records will serve additionally as the basis for public accountability and will facilitate the review of any decision, should such action be requested.

Members of the Board, which shall number 15, shall be drawn from the general public, and shall include, for example, research scientists (including social scientists), physicians, lawyers, clergy, or ethicists, and other representatives of the public, none of whom shall be employees of the agency establishing the Board. Appointments shall be made by the agency, which will establish the terms of office and other administrative procedures of the Board. No more than 1/3 of the members of the Board may be actively engaged in research, development, or demonstration activities involving human subjects.

C. *Protection Committee: Protection of individual subjects.* The determination that it is justifiable to conduct a particular investigation in children, however, does not mean that all children are equally appropriate subjects for inclusion in that research. Numerous considerations might affect the proper choice of subjects. Therefore, the sponsoring institution shall designate a Protection Committee to oversee: (1) the process of

[1] FDC Act Sec. 505 (b), (d), 21 U S C Sec. 355 (b), (d).

selection of subjects who may be included in the project; (2) the monitoring of their continued willingness to participate in the research; and (3) the design of procedures to permit intervention on behalf of the subject, should that become necessary. This Committee should consider the reasonableness and validity of the consent of the child participants (see below) as well as that of the parents, and should assure that the issue of risk and discomfort has been fully and fairly disclosed to parents and subjects. The procedure employed by the institution to achieve these goals will vary; the latitude for such procedures will be great since it will be related in part to the issue of risk. Investigators proposing research involving children shall include a description of their planned use of the Protection Committee in their research proposal; the proposed use of this Committee will be considered an integral part of the research proposal under review by the agency. Relevant information arising in the review process, including information about safety, risk, efficacy, and protection procedures, will be provided to the Protection Committee by the agency supporting the research.

One member of the Committee shall be designated a representative for the project to whom any participant (or parent of a participant) may go to discuss questions or reservations concerning the child's continued participation in the project.

The signature on the consent form of the Chairman of the Protection Committee, when all the stipulations and conditions identified above have been met, will constitute, for DHEW, *supplementary judgment* on behalf of the child subject.

The institution's Protection Committee shall be comprised of at least 5 members so selected that the Committee will be competent to deal with the medical, legal, social, and ethical issues involved in the research, and to represent the community from which the subject population is to be drawn. The Committee should include members of both sexes. No more than two of the members may be employees of the institution sponsoring or conducting the research. The Protection Committee may operate as a subcommittee of the Organizational Review Committee. The composition of the Committee must be approved by the awarding agency.

D. *Special provisions*—1. *Consent of both parents.* Even where State law may permit one parent alone to consent to medical care, both parents have an interest in the child, and therefore, consent of both parents should be obtained before any child may participate in research activities. Since the risks of research entail the possibility of additional burdens of care and support, the consent of both parents to the assumption of those risks should be obtained,[4] except when the identity or whereabouts of either cannot be ascertained or either has been judged mentally incompetent. If the consent of either parent is not obtained, written explanation or justification should be provided to the Protection Committee. Consent of school or institutional authorities is no substitute for parental concern and consent.

2. *The child's consent.* An important addition to the requirement for parental consent is the consent of the child subject. Clearly infants have neither the comprehension nor the independence of judgment essential to consent; older children might or might not have these capabilities. Although children might not have the capacity to consent on their own to participate in research activities, they must be given the opportunity (so far as they are able) to refuse to participate. The traditional requirement of parental consent for medical procedures is intended to be protective rather than coercive. Thus, while it was held to be unlawful to proceed merely with the consent of the child, but without consent of the parent or legal guardian,[5] the reverse should also hold. Therefore, in addition to consent of both parents, consent of the child subject must also be obtained when the child has attained the common law "age of discretion" of 7 years, unless the agency Ethical Review Board specifically exempts a project from this requirement.

3. *Exclusions.* Despite all the protections afforded by these procedures, certain children are categorically excluded from participation in research involving risk. These include children with no natural or adoptive parents available to participate in consent deliberations, and children detained by court order in a residential facility, whether or not natural or adoptive parents are available.

E. *The fetus.* Respect for the dignity of human life must not be compromised whatever the age, circumstance, or expectation of life of the individual. Therefore, all appropriate procedures providing protection for children as subjects in biomedical research must be applied with equal rigor and with additional safeguards to the fetus.

The recent decision of the Supreme Court on abortion[6] does not nullify the ethical obligation to protect the developing fetus from avoidable harm. This obligation, along with the right of every woman to change her decision regarding abortion, requires that no experimental procedures entailing risk to the fetus be undertaken in anticipation of abortion. Further, since the fetus might be at risk in research involving pregnant women, all research involving pregnant women must be reviewed by the Ethical Review Board, unless the Primary Review Committee determines that the research involves no risk to the fetus. Recruitment of pregnant subjects for research reviewed by the Board must involve the institution's Protection Committee in a manner approved by the Board, to provide supplementary judgment.

The consent of both parents must be obtained for any research involving the fetus, any statutes to the contrary on consent for abortion notwithstanding. Both the mother and the father have an interest in the fetus, and legal responsibility for it, if it is born. Therefore the father's consent must be obtained for experimental procedures involving the fetus; consent of the father may be waived if his identity or whereabouts cannot be ascertained, or if he has been judged mentally incompetent.

IV. *Special categories*—A. *The abortus.* Prematurity is the major cause of infant death in this country; thus, research aimed at developing techniques to further viability is of utmost importance. Such research has already contributed significantly to improvement in the care of the pregnant woman and of her fetus. In addition, knowledge of fetal drug metabolism, enzyme activity, and the development of organs is essential to progress in preventing or offsetting certain congenital defects. After thorough research in animal models, it often eventually becomes essential to undertake studies in the non-viable human fetus.

The decision of the Supreme Court on abortion does not eliminate the ethical issues involved in research on the non-viable human fetus. No procedure should be undertaken on the non-viable fetus which clearly affront societal values. Nevertheless, certain research essential to improve both the chance of survival and the health status of premature infants. Such research must meet ethical standards as well as show a clear relation either to the expectation of saving the life of premature infants through the development of rescue techniques, or to the furthering of our knowledge of human development and thereby our capacity to offset the disabilities associated with prematurity. It is imperative, however, that the investigator first demonstrate that appropriate studies on animals have in fact been exhausted and that therefore the research in question requires that the work be done on the non-viable human fetus. Specific reasons for this necessity must be identified. A thorough review of the ethical issues in proposed research involving the non-viable fetus is of utmost importance.

It must be recognized that consent for abortion does not necessarily entail a real interest on the part of the pregnant woman in what happens to the product of conception. Some women feel strongly about what may, or may not, be done to the aborted fetus; others do not. In order to give every woman the opportunity to declare her wishes, consent of the pregnant woman for application of any research procedures to the aborted fetus must be secured at the time of admission to the hospital for the abortion.

Because research on the abortus involves ethical as well as scientific issues, all projects involving the abortus must be reviewed by the Ethical Review Board and recruitment of individual pregnant women for such research must in-

[4] 59 *Am. Jur.* 2d, Sect. 129, p. 229.

[5] *Bonner v. Moran*, 75 U.S. App. D.C. 156, 126 F. 2d 131, 139 A.L.R. 1366 (1941).

[6] *Roe v. Wade*, 410 U.S. 113 (1973).

the institution's Protection Committee in a manner approved by the Board to provide supplementary judgment. In addition to the requirement for maternal consent, both the Ethical Review Board and the Protection Committee shall, in their deliberations, consider the ethical and social issues surrounding research on the non-viable fetus. The Protection Committee must be satisfied that maternal consent is freely given and based on full disclosure, each time approved research is conducted on an abortus.

In order to insure that research considerations do not influence decisions as to timing, method, or extent of a procedure to terminate a pregnancy, no investigator engaged in the research on the abortus may take part in these decisions. These are decisions to be made by the woman and her physician.

The attending physician, not the investigator, must determine the viability of the abortus at the termination of pregnancy. If there is a reasonable possibility that the life of the fetus might be saved, experimental and established methods may be used to achieve that goal. Artificial life-support techniques may be employed only if the physician of record determines that the fetus might be viable. If the physician determines that the fetus is not viable, it is not acceptable to maintain heart beat or respiration artificially in the abortus for the purpose of research. Experimental procedures which of themselves will terminate respiration and heart beat may not be undertaken.

This policy and these protections apply with equal force to the products of spontaneous abortions.

B. *The products of in vitro fertilization.* In the interest of improving human health and development, the biology of human fertilization and the early events surrounding this phenomenon, including implantation, should be studied. To the extent that in vitro studies of human fertilization might further this aim, they are permissible at the present time within the limits outlined below.

Current technology limits the in vitro development of the human fertilized ovum to a period of several days. This is a rapidly advancing field of biomedical research, however, and the time might come when it is possible to extend in vitro development beyond the stage of early cell division and possibly even to viability.

It is contrary to the interests of society to set permanent restrictions on research which are based on the successes and limitations of current technology. Still, it is necessary to impose restraints prospectively in order to provide reasonable protections, while at the same time permitting scientific advancements which might well benefit society. A mechanism is required to weigh, at any given time, the state of the art, a specific proposal, legal issues, community standards, and the availability of guidelines to govern the research situation. This mechanism is provided by the Ethical Review Board. Ultimately, the Board will determine the acceptability of a project involving in vitro fertilization, and by recognizing the state of the art, as well as societal concerns, propose appropriate research policy.

Care must be taken not to bring human ova fertilized *in vitro* to viability—whether in the laboratory or implanted in the uterus—until the safety of the technique has been demonstrated as far as possible in sub-human primates. To this end:

1. All proposals for research involving human in vitro fertilization must be reviewed by the Ethical Review Board.

2. No research involving the implantation of human ova fertilized in the laboratory into recipient women should be supported until the appropriate scientific review boards are satisfied that there has been sufficient work in animals (including sub-human primates) to demonstrate the safety of the technique. It is recommended that this determination of safety include studies of natural born offspring of the products of in vitro fertilization.

3. No implantation of human ova fertilized in the laboratory should be attempted until guidelines are developed governing the responsibilities of the donor and recipient "parents" and of research institutions and personnel.

V. *Prisoners*—A. *Policy considerations.* Clinical research often requires the participation of normal volunteers; for example, in the early stages of drug or vaccine evaluation. Sometimes, the need for standardization certain variables, or for monitoring responses over an extended period of time, requires that the subjects of research remain in a controlled environment for the duration of the project. Prisoners may be especially suitable subjects for such studies, since, unlike most adults, they can donate their time to research at virtually no cost to themselves. However, the special status of prisoners requires that they have special protection when they participate in research.

While there is no legal or moral objection to the participation of normal volunteers in research, there are problems surrounding the participation of volunteers who are confined in an institution. Many aspects of institutional life may influence a decision to participate; the extent of that influence might amount to coercion, whether it is intended or not. Where there are no opportunities for productive activity, research projects might offer relief from boredom. Where there are no opportunities for earning money, research projects offer a source of income. Where living conditions are unsatisfactory, research projects might offer a respite in the form of good food, comfortable bedding, and medical attention. While this is not necessarily wrong, the inducement (compared to the deprivation) might cause prisoners to offer to participate in research which would expose them to risks of pain or incapacity which, under normal circumstances, they would refuse. In addition, there is always the possibility that the prisoner will expect participation in research to be viewed favorably, and to his advantage, by prison authorities (on whom his other few privileges depend) and by the parole board (on whom his eventual release depends). This is especially true when the research involves behavior modification and may be termed "therapeutic" with respect to the prisoner. In such instances, participation inevitably carries with it the hope that a successful result will increase the subject's chances for parole. Thus, the inducement involved in therapeutic research might be extremely difficult to resist; and for this reason, special protection is necessary for prisoners participating in research, whether or not the research is therapeutic.

The first principle of the Nuremburg Code requires that subjects of biomedical research must be "so situated as to be able to exercise free power of choice" concerning their participation. Whether prisoners can be considered to be "so situated" is ultimately a matter for the courts and the legislatures to resolve. In the meantime, it must be recognized that where liberty is limited, and where freedom of choice is restricted, there is a corresponding limitation of the capacity to give truly voluntary consent. Although the prisoner might be adequately informed, and competent to make judgments, the voluntariness of the person's consent remains open to question. This policy statement is designed to provide additional protections to prisoners participating in research.

The mission of the Department of Health, Education, and Welfare does not include rendering judgments on the administration of justice or the management of the correctional system. At the same time, the Department should not support activities which take unethical advantage of those who are under the jurisdiction of the courts and who, for that reason, lack some of the usual defenses to their personal integrity. Participation of prisoners in the research activities of the DHEW in the pursuit of medical knowledge might be beneficial to all concerned, but the relationship which involves a class of persons with diminished autonomy requires careful supervision.

Many prisoners are strongly motivated to participate in research, and view as unfair suggestions that they be denied this opportunity. Unless society, through its judicial and legislative bodies, decides that such participation should be halted, it is essential to develop mechanisms to protect those who may participate, or who are now participating, from the coercive aspects of incarceration which diminish their capacity for voluntary consent. Pursuant to the obligation to protect the rights of all subjects participating in research conducted under its auspices, the DHEW is proposing special guidelines for the protection of prisoners as subjects in any biomedical or behavioral research.

Two aspects of research involving prison populations require special review and procedural safeguards in addition to those provided by current DHEW policies.

First, when research is conducted under the auspices of a commercial manufacturer or an individual investigator, it is not always subject to review by an Organizational Review Committee, as is required for similar research conducted at a hospital or a university. Thus, local review has not heretofore been required for ethical considerations or for specific problems related to the population or institution which is to be directly involved. Second, because of the loss of individual dignity, the limitations of personal freedom, and the possibility of real or potential coercion which may accompany confinement in an institution, special safeguards must be provided to mitigate the inequalities of bargaining power between the prisoners and those who are in positions of authority. While it is important that prisoners have the opportunity to participate in research, it is equally important that they not feel compelled to do so.

B. *Organizational Review Committee.* All research involving prisoners must be conducted at an accredited correctional facility (see Section F, below) and be reviewed initially, and on a continuing basis, either by the Organizational Review Committee of that correctional facility or by the Organizational Review Committee of the institution sponsoring the research. The Organizational Review Committee shall have the duties and responsibilities identified in current DHEW regulations. In addition, for each project, it shall determine the adequacy of clinic or hospital facilities for the particular activity to be conducted, assess the appropriateness of the subject population for that activity, and weigh the questions of scientific importance, social need, and ethical acceptability. In addition to the foregoing, the Organizational Review Committee shall have the following duties, with respect to research involving prisoners as subjects:

1. To review and approve or modify the process proposed by the principal investigator for involvement of the Protection Committee (see below) in overseeing the selection of subjects who may be included in the research, and the process of obtaining their voluntary and informed consent.

2. To set rates of remuneration, if any, consistent with the expected duration and discomfort or risk of the proposed study, and consistent with other opportunities for employment, if any, at the facility in question.

3. To monitor the progress of the research as required by the sponsoring DHEW agency.

The recommendations of this Committee, along with a report describing any site visits, shall be included with the investigator's application to the agency. For facilities which have filed no general assurance, composition as well as recommendations of the Organizational Review Committee will be considered an integral part of the proposal in the agency review.

C. *Protection Committee.* The primary function of the Protection Committee is to provide supplementary judgment by overseeing the selection of subjects who may be included in a research project to assure that their consent is as voluntary as possible under the conditions of confinement.

Consent is a continuing process. To assure the voluntariness of consent, subjects must be able to withdraw from the research project without prejudice. Each Protection Committee shall establish such a withdrawal mechanism.

The duties of the Protection Committee, therefore, shall include:

1. Reviewing the information given the potential subjects, with special attention to: adverse effects, the importance of reporting all deviations from normal function, the continuing option of withdrawing from participation at any time, and the identification of a member of the committee who will be available, at reasonable intervals upon request, for consultation regarding the research project. All of this information shall appear on the consent form, a copy of which will be given to each participant. When oral representations are made procedures described under DHEW regulations shall be followed.

2. Overseeing the process of selection of subjects who may be included in the research, to the extent stipulated in the recommendation of the Organizational Review Committee. This may vary from overall approval of the recruitment process, to reviewing a sample of subject selections, to interviewing as a full Committee each individual subject to be included in the project.

3. Visiting the institution on a regular basis to invite questions, to monitor the progress of the research, and to assess the continued willingness of subject participation. The frequency of these visits will be determined by the nature of the research, and any recommendations of the Organizational Review Committee. Depending upon the circumstances and the number of subjects involved, these visits may be made either on a rotating basis by various members of the Committee, or by the full Committee.

4. Maintaining records of its activities including contacts initiated by subjects in the project between regular site visits. These records shall be made available to the agency upon request.

The Protection Committee shall be comprised of at least 5 members so selected that the Committee will be competent to deal with the medical, legal, social, and ethical issues involved. No more than ⅓ of the members shall be scientists engaged in biomedical research or physicians; at least 1 shall be a prisoner or a representative of an organization concerned with the prisoners' interests; no more than 1 (except prisoners or their representatives) shall have any affiliation with the prison facility or with the unit of government having jurisdiction over the facility, with the exception of persons employed by the department of education of a relevant jurisdiction in a teaching capacity. The composition and the investigator's proposed use of the Committee must be reviewed and approved by the DHEW agency.

D. *Payment to prisoners.* The amount paid for participation in research will vary according to the risks and discomforts involved, and the other employment opportunities in the facility in which the research is to be conducted. The specific amount for each project will be determined by the Organizational Review Committee, which will forward its recommendation as part of the application to the sponsoring agency. The amount paid shall provide a compensation for services, but shall not be so great as to constitute undue inducement to participate.

Any reduction of sentence as a consequence of participation in research shall be comparable to other opportunities at the facility for earning such a reduction.

Any subject who is required by the investigator or prison physician to withdraw, for medical reasons, before completion of the investigation, shall continue to be paid for a period to be determined by the Protection Committee in consultation with the investigator. This does not apply to subjects who withdraw for other reasons. Any disputes regarding certification of withdrawal for medical reasons shall be heard and resolved by the Protection Committee.

Prisoners who serve on the Protection Committee shall be paid an amount consistent with that received by the research subjects.

E. *Accreditation.* The Secretary, DHEW, shall establish standards for the accreditation of correctional facilities offering to act as sites for the performance of clinical research, or offering to act as a source of volunteer subjects for clinical research when the research is supported in whole or in part by Department funds or the research is to be performed in compliance with requirements of Federal statutes.

The review for certification shall include, but not be limited to:

1. Standard of living in the prison facility.

2. Other opportunities for employment and/or constructive activity, either within the prison, or in a work-release program.

3. Adequacy of (a) medical care for the general prison population (so that participation in research is not the only means of obtaining medical attention) and (b) the proposed methods for maintaining medical records and for protecting the confidentiality of those records.

4. The nature, structure, function, and composition of the Organizational Review Committee (whether located at the prison or at the institution sponsoring the research) which is to review clinical research in that correctional facility.

The Secretary shall also set general guidelines to assist the Organizational Review Committees in determining rates of remuneration, and shall include groups who may be considered to represent the prisoners' interests for the purpose of appointment to membership on the Protection Committee. No institution shall be accredited if research, whether or not supported by funds from DHEW, is conducted under its aus-

or by members of its staff, which is not in conformity with these guidelines. No DHEW funds will be granted for research in institutions lacking such accreditation.

F. *Special provisions.* 1. Persons detained in a correctional facility while awaiting sentence, or in a hospital facility for pre-sentence diagnostic observation, are excluded from participation in research.

2. A child may not be included as a subject in research involving risk if he is detained in an institutional setting pursuant to a court order, whether or not the parents and the child have consented to the child's participation.

VI. *The mentally infirm.*—A. *Policy considerations.* The institutionalized mentally infirm are doubly limited with respect to participation in research activities. First, as with children, they might lack the clear capacity to comprehend relevant information, and to make informed judgments concerning their participation. Second, as with prisoners, they experience a diminished sense of personal integrity as a result of confinement in an institution. Such confinement restricts their freedom of choice and imposes elements of coercion, which limit their capacity to give truly voluntary consent. In addition, the mentally infirm who are confined in institutions have more pressures to cooperate with custodial authorities than do prisoners, for their release might depend entirely upon their behavior and on the impression they make upon those having the power to make decisions concerning termination of their confinement.

Legal guardians, who have authority to consent for medical treatment, might have interests in the matter which do not necessarily coincide with those of the patient. Long-term management of patients with mental disabilities is expensive and time-consuming. Any proposal which might reduce either the expense or the supervision required in caring for such persons might be appealing, whether or not there is correlative benefit to the patient. This is certainly the case in projects offering new therapy; it might also occur, albeit in a more subtle form, where free medical or custodial services are perceived to be contingent upon the patient's participation as a subject in research.

The courts have begun to recognize that persons confined in institutions might not be able to give truly voluntary consent in such matters. It is important to recognize, as well, that persons encumbered with the economic or custodial responsibility for the mentally infirm might not be sufficiently objective to make judgments which are fully in the best interest of the institutionalized person.

The circumstances are limited under which it is justifiable to include the mentally infirm as subjects in biomedical research. These circumstances include projects in which: the proposed research concerns diagnosis, treatment, prevention, or etiology of the disability from which they suffer; the necessary information can be obtained only from those subjects; or the studies concern institutional life *per se*. With these exceptions, the general rule is that the participation of the mentally infirm as subjects in research is not acceptable.

B. *Ethical review of projects and protection of subjects.* In instances in which a research protocol requires the participation of mentally infirm subjects, the research must be overseen by a Protection Committee in the manner described in Section III–C, pertaining to children. This Protection Committee must be supervised on a continuing basis, as described in Section V–B, by the Organizational Review Committee of the institution in which the research is to be conducted or of the institution sponsoring the research.

VII. *General provisions.* These provisions apply to all research activities covered by this policy.

A. *Referrals to the Ethical Review Board.* Whenever a Primary Review Committee, secondary review group, or the agency staff perceives an apparent and significant question of ethics or an unusual element of risk—whatever the subject group involved—the research proposal in question may be forwarded to the Ethical Review Board for an opinion. In addition to offering an opinion of acceptability from an ethical viewpoint, the Board may choose to recommend the establishment of a Protection Committee, and suggest guidelines for its operation.

B. *Procedures requiring special consideration.* All other recommendations notwithstanding, DHEW may identify certain procedures which: (1) Require Protection Committee review of the selection of each individual subject; (2) are acceptable for stipulated subjects only if approved by affirmative declaratory judgment of a court of competent jurisdiction; or (3) are unacceptable.

C. *Research conducted in Foreign Countries.* All regulations governing research conducted in the United States apply to research conducted in foreign countries under DHEW auspices, and the ethical review must be of equal rigor.

There are sometimes special constraints encountered in foreign settings. Therefore, in addition to the requirement that consent procedures for research to be conducted abroad conform with the policy and regulations set forth in this document, there must be written assurance that the proposed research enjoys local acceptance, and offends no local ethical standards.

D. *Research submitted pursuant to DHEW regulatory requirements.* Research or testing which is performed pursuant to or in fulfillment of any regulation issued by any agency of the DHEW will be acceptable to the government only if conducted in compliance with these procedures and regulations.

E. *Clinical research not funded by DHEW.*

If, in the judgment of the Secretary, an organization has failed 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.

If, in the judgment of the Secretary, organization fails to discharge its responsibilities for the protection of the rights and welfare of the subjects in its care, whether or not DHEW funds are involved, he may, upon reasonable notice to the organization of the basis for such action, determine that its eligibility to receive further DHEW grants or contracts involving human subjects shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist.

If, in the judgment of the Secretary, an individual serving as principal investigator, program director, or other person having responsibility for the scientific and technical direction of a project or activity, has failed to discharge his responsibilities for the protection of the rights and welfare of human subjects in his care, the Secretary may, upon reasonable notice to the individual of the basis for such action, determine that such individual's eligibility to serve as a principal investigator or program director or in another similar capacity shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist.[1]

In reaching a determination on compliance, with respect to subjects with limited capacity for consent, the Secretary will consider the extent and the nature of the procedures by which the institution offers protection in all studies conducted in or by that institution regardless of the source of funds, with the expectation that there shall be an ethical review similar to that required of the agency Ethical Review Board (III–B). The existence of a Protection Committee, overseen by an Organizational Review Committee and acting to afford supplementary judgment, will be accepted as evidence of responsibility in this regard.

F. *Confidentiality of information and records.* Nothing in this policy shall be construed as permitting the release of confidential research protocols nor the violation of State law applicable to the confidentiality of individual medical records.

VIII. *Draft additions to proposed regulations* (See FEDERAL REGISTER, Vol. 38, No. 194, Part 2, Tues., Oct. 9, 1973, pp. 27882–27885).

To amend the proposed Part 46 of Subtitle A of Title 45 of the Code of Federal Regulations by deleting §§ 46.20 through 46.23, redesignating §§ 46.1 through 46.19 thereof as Subpart A, and adding the following new Subparts B through F:

SUBPART B—ADDITIONAL PROTECTIONS FOR CHILDREN INVOLVED AS SUBJECTS IN DHEW ACTIVITIES

Sec.
46.21 Applicability.
46.22 Purpose.
46.23 Need for legally effective consent.
46.24 Definitions.
46.25 Ethical Review Board; Composition; Duties.

[1] FEDERAL REGISTER, Vol. 38, No. 194, Part 2, Tuesday, October 9, 1973, § 46.22, p. 27885.

Sec.
46.26 Protection Committees; Composition; Duties.
46.27 Certain children excluded from participation in DHEW supported activities.
46.28 Activities to be performed outside the United States.

SUBPART C—ADDITIONAL PROTECTIONS FOR CERTAIN CLASSES OF DHEW ACTIVITIES

46.31 Applicability.
46.32 Purpose.
46.33 Definitions.
46.34 Duties of the Ethical Review Board.
46.35 Maternal consent to activities involving the abortus.
46.36 Additional conditions for activities involving the abortus.
46.37 Prohibition on certain activities involving pregnant women where the fetus may be adversely affected.
46.38 Parental consent to activities which may affect the fetus.
46.39 Activities to be performed outside the United States.

SUBPART D—ADDITIONAL PROTECTIONS FOR PRISONERS INVOLVED AS SUBJECTS IN DHEW ACTIVITIES

Sec.
46.41 Applicability.
46.42 Purpose.
46.43 Definitions.
46.44 Additional duties of Organizational Review Committee where prisoners are involved.
46.45 Protection Committees; Duties; Composition.
46.46 Prohibition on participation in activities prior to conviction.
46.47 Remuneration to subjects.
46.48 Accreditation.
46.49 Activities to be performed outside the United States.

SUBPART E—ADDITIONAL PROTECTIONS FOR THE INSTITUTIONALIZED MENTALLY INFIRM INVOLVED AS SUBJECTS IN DHEW ACTIVITIES

46.51 Applicability.
46.52 Purpose.
46.53 Definitions.
46.54 Limitations on activities involving the institutionalized mentally infirm.
46.55 Additional duties of Organizational Review Committee where the mentally infirm are involved.
46.56 Protection Committees; Duties; Composition.
46.57 Activities to be performed outside the United States.

SUBPART F—GENERAL PROVISIONS

46.61 Applicability.
46.62 Organization's records.
46.63 Reports.
46.64 Early termination of awards; sanctions for noncompliance.
46.65 Conditions.

AUTHORITY: 5 U.S.C. 301.

SUBPART B—ADDITIONAL PROTECTIONS FOR CHILDREN INVOLVED AS SUBJECT IN DHEW ACTIVITIES

Section 46.21 *Applicability.* (a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare research, development, or demonstration activities in which children may be at risk.

(b) The requirements of this subpart are in addition to those imposed under subpart A of this part.

Section 46.22 *Purpose.* It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable inasmuch as the potential subjects in activities conducted thereunder might be unable fully to comprehend the risks which might be involved and are legally incapable of consenting to their participation in such activities.

Section 46.23 *Need for legally effective consent.* Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will necessarily result in a legally effective consent under applicable State or local law to a subject's participation in any activity; nor in particular does it obviate the need for court approval of such participation where court approval is required under applicable State or local law in order to obtain a legally effective consent.

Section 46.24 *Definitions.* As used in this subpart:

(a) "'DHEW activity" means:

(1) The conduct or support (through grants, contracts, or other awards) of biomedical or behavioral research involving human subjects; or

(2) Research, development, or demonstration activities regulated by any DHEW agency.

(b) "Subject at risk" means any individual who might be exposed to the possibility of harm—physical, psychological, sociological, or other—as a consequence of participation as a subject in any DHEW activity which goes beyond the application of those established and accepted methods necessary to meet his needs.

(c) "Child" means an individual who has not attained the legal age of consent to participate in research as determined under the applicable law of the jurisdiction in which such research is to be conducted.

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

Section 46.25 *Agency Ethical Review Board; composition; duties.* (a) The head of each agency shall establish an Ethical Review Board, hereinafter referred to as the "Board," to review proposals for research, development, and demonstration activities to which this subpart is applicable, as well as to advise him or her on matters of policy concerning protection of human subjects. The Board shall be composed of research scientists (biomedical, behavioral, and/or social), physicians, lawyers, clergy, ethicists, and representatives of the public. It shall consist of 15 members appointed by the agency head from outside the Federal Government. No more than one-third of the members may be individuals engaged in research, development, or demonstration activities involving human subjects.

(b) It shall be the function of the Board to review each proposed activity to which this subpart applies, and advise the agency concerning the acceptability of such activities from the standpoint of societal need and ethical considerations, taking into account the assessment of the appropriate Primary Review Committees as to: (1) The potential benefit of the proposed activity, (2) scientific merit and experimental design, (3) whether the proposed activity entails risk of significant harm to the subject, (4) the sufficiency of animal and adult human studies demonstrating safety and clear potential benefit of the proposed procedures and providing sufficient information on which to base an assessment of the risks, and (5) whether the information to be gained may be obtained from further animal and adult human studies.

(c) The Board shall review the procedures proposed by the applicant to be followed by the Protection Committee, provided for in § 46.26 of this subpart, in carrying out its functions as set forth in § 46.26. In addition, the Board may recommend additional functions to be performed by the Protection Committee in connection with any particular activity.

(d) In decisions regarding activities covered by this subpart, the agency shall take into account the recommendations of the Board.

Section 46.26 *Protection Committees, composition; duties.* (a) No activity covered by this subpart will be approved unless it provides for the establishment by the applicant of a Protection Committee, composed of at least five members so selected that the Committee will be competent to deal with the medical, legal, social and ethical issues involved in the activity. None of the members shall have any association with the proposed activity, and at least one-half shall have no association with any organization or individual conducting or supporting the activity. No more than one-third of the members shall be individuals engaged in research, development, or demonstration activities involving human subjects. The composition of the Protection Committee shall be subject to DHEW approval.

(b) The duties of the Protection Committee, proposed by the applicant, and reviewed by the agency including the Ethical Review Board shall be to oversee: (1) The selection of subjects who may be included in the activity; (2) the monitoring of the subject's continued willingness to participate in the activity; (3) the design of procedures to permit intervention on behalf of one or more of the subjects if conditions warrant; (4) the evaluation of the reasonableness of the parents' consent and (where applicable) the subject's consent; and (5) the procedures for advising the subject and/or the parents concerning the subject's continued participation in the activity. Each subject and his or her parent or guardian will be informed of the name of a member of the Protection Committee who will be available for consultation concerning the activity.

(c) The Protection Committee shall establish rules of procedure for conducting its activities, which must be reviewed by DHEW, and shall conduct its activities at convened meetings, minutes of which shall be prepared and retained.

Section 46.27 *Certain children excluded from participation in DHEW activities.* A child may not be included as a subject in DHEW activities to which this subpart is applicable if:

(a) The child has no known living parent who is available and capable of participating in the consent process: *Provided*, That this exclusion shall be inapplicable if the child is seriously ill, and the proposed research is designed to substantially alleviate his condition; or

(b) The child has only one known living parent who is available and capable of participating in the consent process, or only one such parent, and that parent has not given consent to the child's participation in the activity; or

(c) Both the child's parents are available and capable of participating in the consent process, but both have not given such consent;

(d) The child is involuntarily confined in an institutional setting pursuant to a court order, whether or not the parents and child have consented to the child's participation in the activity; or

(e) The child has not given consent to his or her participation in the research: *Provided*, That this exclusion shall be inapplicable if the child is 6 years of age or less or if explicitly waived by the DHEW; or

(f) The Protection Committee established under § 46.26 of this subpart has not reviewed and approved the child's participation in the activity.

Section 46.28 *Activities to be performed outside the United States.* In addition to satisfying all other applicable requirements in

this subpart, an activity to which this subpart is applicable, which is to be conducted outside the United States, must include written documentation satisfactory to DHEW that the proposed activity is acceptable under the legal, social, and ethical standards of the locale in which it is to be performed.

SUBPART C—ADDITIONAL PROTECTION FOR CERTAIN CLASSES OF DHEW ACTIVITIES

Section 46.31 *Applicability.* (a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare research, development, or demonstration activities: (1) Involving pregnant women, unless there is a finding by DHEW that the activity will have no adverse effect on the fetus, or is clearly therapeutic with respect to the fetus involved, (2) involving the abortus or the non-viable fetus, or (3) involving in vitro fertilization of human ova.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) To the extent the requirements of subpart A of this part are applicable to activities also covered by this subpart, the requirements of this subpart are in addition to those imposed under subpart A.

Section 46.32 *Purpose.* It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

Section 46.33 *Definitions.* As used in this subpart:

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

(b) "DHEW activity" means:

(1) The conduct or support (through grants, contracts, or other awards) of biomedical or behavioral research involving human subjects; or

(2) Research, development, or demonstration activities regulated by any DHEW agency.

(c) "Board" means the Board established under § 46.25.

(d) "Protection Committee" means a committee referred to in § 46.26.

(e) "Pregnancy" means the period of time from implantation of a fertilized ovum until delivery.

(f) "Fetus" means the product of conception from implantation until delivery.

(g) "Abortus" means the fetus when it has been expelled whole, whether spontaneously or as a result of medical or surgical intervention to terminate a pregnancy, prior to viability. This definition, for the purpose of this policy, excludes the placenta, fetal material which is macerated at the time of expulsion, a dead fetus, and isolated fetal tissue or organs excised from a dead fetus.

(h) "Viability of a fetus" means capability given the benefit of available therapy, of independently maintaining heart beat and respiration.

(i) "In vitro fertilization" means any fertilization of human ova which occurs outside the body of a female, through admixture of human sperm and such ova.

Section 46.34 *Duties of the Ethical Review Board.* (a) It shall be the function of the Board to review each activity to which this subpart applies and advise the agency concerning the acceptability of such activities from the standpoint of societal need and ethical considerations, taking into account the assessment of the appropriate Primary Review Committees as to: (1) The potential benefit of the proposed activity, (2) scientific merit and experimental design, (3) the sufficiency of studies involving animals demonstrating the clear potential benefit of the proposed procedures and (4) whether the information to be gained may be obtained from further animal or adult human studies.

(b) The Board may recommend the establishment by the sponsoring institution of a Protection Committee to carry out such functions as the Board deems necessary.

Section 46.35 *Maternal consent to activities involving the abortus.* (a) No activity to which this subpart is applicable may involve an abortus or a non-viable fetus unless maternal consent has been obtained.

(b) No activity to which this subpart is applicable may involve an abortus or a non-viable fetus unless: (1) Individuals involved in the activity will have no part in the decision as to timing, method, or extent of the procedure used to terminate the pregnancy, or in determining viability of the fetus at the termination of the pregnancy; (2) vital functions of the abortus will not be maintained artificially for purposes of research; and (3) experimental procedures which would terminate heart beat or respiration in the abortus will not be employed.

Section 46.37 *Prohibition on certain activities involving pregnant women where the fetus may be adversely affected.* The Board shall review all research, development, and demonstration activities involving pregnant women. No activity to which this subpart is applicable may involve a pregnant woman if the Primary Review Committee finds that the fetus might be adversely affected, unless the primary purpose of the activity is to benefit that fetus. In addition, no activity to which this subpart is applicable may involve pregnant women unless all the requirements of this subpart are satisfied.

Section 46.38 *Parental consent to activities which might affect the fetus.* No activity involving a pregnant woman which might affect the fetus but which nevertheless is permissible under § 46.37 shall be conducted unless maternal consent has been obtained, as well as the consent of the father if he is available and capable of participating in the consent process.

Section 46.39 *Activities to be performed outside the United States.* In addition to satisfying all other applicable requirements in this subpart, activities to which this subpart is applicable, which are to be conducted outside the United States, must include written documentation satisfactory to DHEW that the proposed activity is acceptable under the legal, social, and ethical standards of the locale in which it is to be performed.

SUBPART D—ADDITIONAL PROTECTIONS FOR PRISONERS INVOLVED AS SUBJECTS IN DHEW ACTIVITIES

Section 46.41 *Applicability.* (a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare research, development, and demonstration activities involving prisoners as subjects.

(b) The requirements of this subpart are in addition to those imposed under subparts A and B of this part.

Section 46.42 *Purpose.* It is the purpose of this subpart to provide additional safeguards for activities to which this subpart is applicable inasmuch as the potential subjects in activities conducted thereunder, because of their incarceration, might be under constraints which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate in such activities.

Section 46.43 *Definitions.* As used in this subpart:

(a) "DHEW activity" means:

(1) the conduct or support (through grants, contracts, or other awards) of biomedical or behavioral research involving human subjects; or

(2) research, development, or demonstration activities regulated by any DHEW agency.

(b) "Prisoner" means any individual involuntarily confined in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute and also individuals detained by virtue of statutes which provide alternatives to criminal prosecution.

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

Section 46.44 *Additional duties of Organizational Review Committee where prisoners are involved.* (a) In carrying out its responsibilities under subpart A of this part for activities also covered by this subpart, the Organizational Review Committee provided for under subpart A shall also certify: (1) That there will be no undue inducements to participation by prisoners as subjects in the activity, taking into account among other factors, the sources of earnings generally available to the prisoners as compared with those offered to participants in the activity, (2) that the clinic and hospital facilities are adequate for the proposed activity, (3) that all aspects of the activity would be appropriate for performance on nonprisoners, and (4) that no prisoner will be offered any reduction in sentence or parole for participation in such activity which is not comparable to that offered for other activities at the facility not of a research, development, demonstration or similar nature.

(b) In addition, the Organizational Review Committee shall have the following duties: (1) To review, approve, or modify the procedures proposed for the Protection Committee in carrying out its functions as set forth in § 46.45; (2) To recommend any additional functions to be performed by the Protection Committee in connection with a particular activity; (3) To set rates of remuneration, if any, consistent with the anticipated duration, discomfort, and/or risk of the activity but not in excess of that paid for other employment generally available to inmates of the facility in question; and (4) To carry out such other responsibilities as may be stipulated by DHEW in the contract or grant award.

(c) Activities to which this subpart is applicable must provide for the designation of an Organizational Review Committee, where no such Committee has been established under subpart A.

Section 46.45 *Protection Committees; duties; composition.* (a) No activity covered by this subpart will be approved unless it provides for the establishment of a Protection Committee to carry out the following functions, as well as any others recommended by the Organizational Review Committee or by DHEW: (1) Reviewing the procedure for soliciting participation by prisoners in the research activity to determine that all elements of informed consent, as outlined in § 46.3, are satisfied; (2) overseeing the selection of prisoners who may participate in the activity; (3) monitoring the progress of the research and the continued willingness of subject participation; and (4) intervening on behalf of one or more subjects if conditions warrant. In addition, each subject will be informed of the name of a member of the Protection Committee who will be available to the subject for consultation concerning the activity.

(b) Each Protection Committee shall be composed of at least five members appointed by the applicant and so selected that the Committee will be competent to deal with the medical, legal, social, and ethical issues involved. At least one member of the Committee shall be either a prisoner or a representative of an organization having as a primary concern protection of the interests of prisoners.

No more than one-third of the members may be physicians or scientists engaged in biomedical or behavioral research, and no more than one member, other than a prisoners' representative, may have any affiliation with the prison facility or the legal entity having jurisdiction over the facility, except for persons employed by a Department of Education in a teaching capacity. Any prisoners serving on the Committee shall be compensated at a rate consistent with that set for prisoners participating as subjects in activities at the facility to which this subpart is applicable.

(c) The Protection Committee shall establish rules of procedure for conducting its activities which must be reviewed by DHEW, and shall conduct its activities at convened meetings, minutes of which shall be prepared and retained. The composition of the Committee shall be subject to DHEW approval.

Section 46.46 *Prohibition on participation in activities prior to conviction.* No individual confined pending arraignment, trial, or sentencing for an offense punishable as a crime may be used as a subject in any activity supported in whole or in part by a grant or contract to which this subpart is applicable.

Section 46.47 *Remuneration to subjects.* Where rates of remuneration are set pursuant to § 46.44 of this subpart, any subject who, for medical reasons, is required by a representative of the prison facility, grantee, contractor, or sponsor of the activity, to withdraw before completion of his or her participation in the activity shall continue to be compensated for a period to be set by the Protection Committee after consultation with the grantee or contractor.

Section 46.48 *Accreditation.* It is the intention of DHEW to accredit prison facilities as sites for the performance of activities to which this subpart applies. Accreditation will be based on certification of the acceptability of the facilities and compliance with the procedures required by this subpart, as determined by the Secretary. No activity covered by this subpart may involve prisoners incarcerated in a facility not accredited by Secretary of DHEW.

Section 46.49 *Activities to be performed outside the United States.* In addition to satisfying all other applicable requirements in this subpart, an activity to which this subpart is applicable, which is to be conducted outside the United States, must include written documentation satisfactory to DHEW that the proposed activity is acceptable under the legal, social, and ethical standards of the locale in which it is to be performed.

Subpart E—Additional Protections for Institutionalized Mentally Infirm Individuals Involved as Subjects in DHEW Activities

Section 46.51 *Applicability.* (a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare activities involving the institutionalized mentally infirm as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein in connection with activities permitted under § 46.54 of this subpart will necessarily result in a legally effective consent under applicable State or local law to a subject's participation in such an activity; nor in particular does it obviate the need for court approval of such participation where court approval is required under applicable State or local law in order to obtain a legally effective consent.

(c) The requirements of this subpart are in addition to those imposed under Subparts A, B, and D of this part.

Section 46.52 *Purpose.* It is the purpose of this subpart to provide additional safeguards for the mentally infirm involved in research, development, and demonstration activities, inasmuch as the potential subjects in such activities are: (1) Confined in an institutional setting; (2) might be unable fully to comprehend the type risks which may be involved; and (3) might be legally incompetent to consent to their participation in such activities.

Section 46.53 *Definitions.* As used in this subpart:

(a) "DHEW activity" means:

(1) The conduct or support (through grants, contracts, or other awards) of biomedical or behavioral research involving human subjects; or

(2) Research, development, or demonstration activities regulated by any DHEW agency.

(b) "Mentally infirm" includes the mentally ill, the mentally retarded, the emotionally disturbed, the psychotic, the senile, and others with impairments of a similar nature, regardless of whether or not the individual has been determined to be legally incompetent.

(c) "Institutionalized" means confined, whether by court order or voluntary commitment, in an institution for the care and/or treatment of the mentally infirm.

Section 46.54 *Limitations on activities involving the institutionalized mentally infirm.* No institutionalized mentally infirm individual may be included as a subject in a DHEW activity unless:

(a) The proposed activity is concerned with: (1) The diagnosis, treatment, prevention, or etiology of the impairment with which he or she is afflicted; or (2) the proposed activity is concerned with the effect of institutional life on the subject and involves no risk of harm to the subject; or (3) the information can be obtained only from such subjects.

(b) The individual's legal guardian has given consent to the individual's participation in such activity;

(c) Where the individual has sufficient mental competency to understand what is proposed and to express an opinion as to his or her participation, the individual's consent to such participation has also been secured; and

(d) The Protection Committee, provided for in § 46.56 of this subpart, has reviewed and approved subject participation in the activity (by class or by individual).

Section 46.55 *Additional duties of Organizational Review Committee where the mentally infirm are involved.* (a) In addition to its responsibilities under Subpart A of this part, the Organizational Review Committee shall, with respect to activities to which subpart applies:

(1) Certify that all aspects of the activity would be ethically appropriate for performance on healthy individuals;

(2) Conduct at least one on-site visit to the institution and prepare a report of the visit, including discussion of such matters as living conditions, availability of medical care, and quality of food, to be submitted to DHEW along with the application;

(3) Review and approve or modify the procedures proposed by the applicant to be followed by the Protection Committee, provided for in § 46.56, in overseeing the recruitment of the mentally infirm subjects who may be included in such activity;

(4) Recommend any additional functions to be performed by the Protection Committee in connection with any particular activity; and

(5) Carry out such other responsibilities as may be recommended by DHEW.

(b) Activities to which this subpart is applicable must provide for the designation of an Organizational Review Committee where no such Committee has been established under subpart A.

Section 46.56 *Protection Committees; duties; composition.* (a) No activity covered by this subpart will be approved unless it provides for the establishment of a Protection Committee to carry out the following functions, as well as any others prescribed by the Organizational Review Committee or by DHEW: (1) Overseeing the process of selection of subjects who may be included in the activity, (2) monitoring the progress of the activity with special attention to adverse effects on subjects, (3) intervening on behalf of one or more of the subjects if conditions warrant, (4) evaluating the process and reasonableness of consent of the legal guardian and (where applicable) of the subject, and (5) advising the legal guardian and/or the subject concerning the latter's continued participation in the activity if conditions warrant.

(b) The composition of each Protection Committee shall conform to the requirements set forth in § 46.26(a).

(c) The Protection Committee shall establish rules of procedure for conducting its activities, which must be reviewed by DHEW, and shall conduct its activities at convened meetings, minutes of which shall be prepared and retained.

Section 46.57 *Activities to be performed outside the United States.* In addition to satisfying all other applicable requirements in this subpart, an activity to which this subpart is applicable, which is to be conducted outside the United States, must include documentation satisfactory to DHEW that the proposed activity is acceptable under the legal, social, and ethical standards of the locale in which it is to be performed.

Subpart F—General Provisions

Section 46.61 *Applicability.* The following regulations are applicable to all activities covered by this part.

Section 46.62 *Records.* (a) Copies of all documents presented or required for initial and continuing review by any Organizational Review Committee or Protection Committee and minutes, transmittals on actions, instructions, and conditions resulting from committee deliberations are to be made part of the official files of the grantee or contractor for the supported activity.

(b) Records of subject's and representative's consent shall be retained by the grantee or contractor in accordance with its established practice, or, if no practice has been established, in project files.

(c) Acceptance of any DHEW grant or contract award shall constitute consent of the grantee or contracting organization to inspection and audit of records pertaining to the assisted activity by authorized representatives of the Secretary.

(d) All documents and other records required under this part must be retained by the grantee or contracting organization for a minimum of three years following termination of DHEW support of the activity.

Section 46.63 *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.

Section 46.64 *Early termination of awards; sanctions for noncompliance.* (a) If, in the judgment of the Secretary, an organization has failed to comply with the terms of this part with respect to a particular Federal activity, he may require that said grant or contract be terminated or suspended in the manner prescribed in applicable grant or procurement regulations.

(b) If, in the judgment of the Secretary, an organization fails to discharge its responsibilities for the protection of the rights and welfare of the subjects in its care, whether or not DHEW funds are involved, he may, upon reasonable notice to the organization of the basis for such action, determine that its eligibility to receive further DHEW grants or contracts or participate in DHEW assisted activities involving human subjects, shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist.

(c) If, in the judgment of the Secretary, an individual serving as principal investigator, program director, or other person having responsibility for the scientific and technical direction of a project or activity, has failed to discharge her or his responsibilities for the protection of the rights and welfare of human subjects in his or her care, the Secretary may, upon reasonable notice to the individual of the basis for such action, determine that such individual's eligibility to serve as a principal investigator or program director or in another similar capacity shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist.

Section 46.65 *Conditions.* The Secretary may with respect to any activity or any class of activities impose conditions, including conditions pertaining to informed consent, prior to or at the time of the approval of any activity when in the Secretary's judgment such conditions are necessary for the protection of human subjects.

[FR Doc.73-23922 Filed 11-15-73;8:45 am]

federal register

THURSDAY, MAY 30, 1974

WASHINGTON, D.C.

Volume 39 ■ Number 105

PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

■

PROTECTION OF HUMAN SUBJECTS

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 §§ 46.4, 46.6(d), and 46.7(e).

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 DHEW 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 that a wide range of communities may be involved [illegible] of representation.

The comments having been considered, it is concluded that the requirement [illegible] nonemployee [illegible] on organizational committees [illegible] the designation of [illegible] or parochial community attitudes, but it [illegible] in maintaining community [illegible] and would [illegible] the evaluation of the committee [illegible] protection of the subject. However, it is noted that the requirement that nonemployees be included in committees appears to be [illegible], 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 informal 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.

AUTHORITY: 5 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 comforts 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 § 46.2. 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, standard 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 or 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 limit 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 understaken 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 orgnization 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.

§ 16.17 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.

§ 16.18 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.

§ 16.19 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.

§ 16.20 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.

§ 16.21 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.

§ 16.22 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]

federal register

FRIDAY, AUGUST 23, 1974

WASHINGTON, D.C.

Volume 39 ■ Number 165

PART III

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

■

PROTECTION OF HUMAN SUBJECTS

Proposed Policy

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

[45 CFR Part 46]

PROTECTION OF HUMAN SUBJECTS

Proposed Policy

In the FEDERAL REGISTER of May 30, 1974 (39 FR 18914), regulations were published as Part 46 of Title 45 of the Code of Federal Regulations providing generally for the protection of human subjects involved in research, development, or related activities supported by Department grants or contracts. At that time it was indicated that notices of proposed rulemaking would be developed concerning minors, fetuses, abortuses, prisoners, and the institutionalized mentally disabled.

Coincidentally with the development of the notice of proposed rulemaking set forth below, both Houses of Congress reached agreement on the "National Research Act," and the President signed P.L. 93-348 into law. Among other things, the Act establishes an eleven-member National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research to "• • • (I) conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects, (II) develop guidelines which should be followed in such research to assure that it is conducted in accordance with such principles, and (III) make recommendations to the Secretary (I) for such administrative action as may be appropriate to apply such guidelines to biomedical and behavioral research conducted or supported under programs administered by the Secretary, and (II) concerning any other matter pertaining to the protection of human subjects of biomedical and behavioral research."

This notice of proposed rulemaking is published today to continue the public dialogue begun in November 1973 when the Director of the National Institutes of Health published draft proposals on these issues in the FEDERAL REGISTER. The comments addressed in this preamble are the result of that issuance.

The comments received as a result of this notice of proposed rulemaking will not only assist the Department to develop final regulations but will also be available to the Commission for their use during the course of their deliberations over the next two years.

In the light of the 450 responses received as a result of the November issuance, largely from grantee and contractor organizations, the Department now proposes that, in addition to the protection afforded generally to all subjects of research, development, and related activities supported by the Department by virtue of Part 46, further protective measures should be provided for those subjects of research whose capability of providing informed consent is or may be absent or limited.

This would be accomplished by amending Part 46 to delete § 46.19 through 46.22, redesignating § 46.1 through 46.18 as Subpart A, and adding new Subparts B through F. If this proposal is accepted, the regulations would be structured as follows:

Subpart A would be the basic regulation, substantially as promulgated on May 30, 1974. This provides that no activity involving any human subject at risk shall be supported by a DHEW grant or contract unless the applicant or offering organization has established an organizational review committee which has reviewed and approved such activity and submitted to DHEW a certification of such review and approval. This subpart also provides that all grant and contract proposals involving human subjects at risk are to be additionally evaluated by the Secretary for compliance with the requirements of said subpart.

Subpart B is reserved for a separate, future proposed rulemaking providing additional protection for children.

Subpart C as described in the present proposed rulemaking would call for the utilization of two special mechanisms for the protection of the pregnant woman and unborn child or fetus, where the pregnant woman participates in a research, development, or related activity. While these mechanisms are designed to allow sufficient flexibility for the pursuit of new information about the perinatal process, they are also designed to provide additional safeguards to assure that the research is acceptable from an ethical standpoint.

Subpart D as described in the present proposed rulemaking would give added responsibilities to an organizational review committee where the contemplated research would involve prisoners as subjects and also would require in such instances that a consent committee be established to supervise the selection and participation of prisoners in the research. Prisoner groups are particularly valuable in properly conducted clinical trials since they provide a stable subject population which can be followed over a period of weeks or months rather than days or hours. From the point of view of the prisoner subject, participation in research offers an opportunity to make a contribution to society and to provide an income, much as other jobs in prison do. Nevertheless, the dangers of abuse of prisoners' rights are obvious. For this reason, the proposed rulemaking calls for additional safeguards for the rights of prisoners whose capability to provide informed consent may be affected by the very fact of their incarceration.

Subpart E as described in the present proposed rulemaking offers additional protections for the rights of the mentally ill, the mentally retarded, the emotionally disturbed, and the senile who are confined to institutions, whether by voluntary or involuntary commitment. Such persons, by the very nature of their disabilities, may be severely limited in their capacity to provide informed consent to their participation in research. At the same time, the nature of their disabilities requires extensive research efforts to the study of the etiology, pathogenesis, and therapy of their conditions. The proposed rulemaking limits the research in which such subjects may be allowed to participate to that which is most likely to be of assistance to them or to persons similarly disabled.

In developing the present proposed rulemaking, the Department has taken into consideration the public's comments relevant to certain parts of the Introduction, Definition, and General Policy Sections of the draft regulations published at 39 FR 18914, November 16, 1973, as well as to the draft regulations themselves. The major comments, and the Department's present proposals, are as follows:

INTRODUCTION, GENERAL POLICY CONSIDERATIONS

A. Commentators suggested, in several different contexts, that the regulations should (i) apply to all research, regardless of the degree of risk or academic discipline concerned, and (ii) provide for the exclusion of certain types of research, particularly behavioral and social science research as distinguished from biomedical research.

The Department, having considered these comments, notes that the applicability provisions of the basic regulations (45 CFR 46.1) permit the Secretary to determine whether specific programs place subjects at risk. Such determination is to be made only after careful study and publication in the FEDERAL REGISTER, providing an opportunity for comment on the merits of each determination. With respect to research in the social sciences, the Department has already indicated its intention of issuing public rulemaking on this matter (see 39 FR 18914, paragraph A).

B. Comments also included suggestions that regulations should be proposed specifically dealing with activities involving students, laboratory employees, seriously ill or terminal patients, the non-institutionalized mentally disabled, and other special groups.

The Department considers that any abuses relating to these groups are less evident and that they are afforded the protection of the existing regulations published in 39 FR 18914.

C. Several comments suggested the provision of additional guidelines with respect to the distinction between established and accepted methods on the one hand and experimental procedures on the other.

While the Department recognizes the theoretical desirability of such guidelines, and that the practical necessity of making such a distinction is arising with increasing frequency, the feasibility of making this distinction on a generalized basis has yet to be demonstrated. At the moment a regulatory approach to this issue does not appear justified.

D. It was suggested that all meetings of organizational review committees and similar groups established pursuant to

these regulations should be open to the public.

The Department notes that since the purpose of these committees is, for the most part, to advise with respect to the conduct of individual projects and proposals by individual investigators, a blanket provision to this effect would appear to be inconsistent with the need to protect the confidentiality of the proceedings and records of institutional review and evaluation committees.

DEFINITIONS

A. Comments on the definition of "Subject at Risk" suggested changes in language that would (i) limit the concept of risk to that encountered only in addition to that normally experienced, (ii) eliminate demonstration projects as a possible source of risk, since these are nominally limited to application of established and accepted methods, (iii) specifically identify failure to maintain confidentiality as a source of risk, and (iv) provide a mechanism for identifying activities essentially free of risk.

These comments are similar to those made with respect to the same definition as incorporated in an earlier proposed rulemaking (38 FR 27882). In responding to the criticism, the Department has already (i) redefined "Subject at Risk" in 45 CFR 46.3(b) so as to exclude any activity which does not increase the ordinary risks of daily life or the recognized risks inherent in a chosen occupation or field of service, (ii) substituted in 45 CFR 46.1(a) the term "development" for "demonstration," (iii) provided in 45 CFR 46.19(b) specific prohibitions against disclosures of information which refers to or can be identified with a particular subject, and (iv) provided in 45 CFR 46.1(b) authority for determination in advance as to whether a particular Federal program or an investigational method or procedure may place subjects at risk.

B. Comments on the definition of "Clinical Research" suggested inclusion in said definition of the behavioral aspects of research and facets of medical research necessarily concerned with diagnosis and other nonetherapeutic aspects of research.

Since the term "clinical research" does not occur in the present rulemaking, the Department reserves its opinion with respect to these suggestions. However, the proposed regulations are applicable to all departmental research, development, and related activities except with respect to Subpart C, where applicability is limited to "biomedical research" (§ 46.303(b)).

C. Comments on "Informed Consent" suggested the addition of language concerning (i) full and complete disclosure, (ii) the likelihood of success or failure of the experiment, (iii) the use of placebos or other control procedures, (iv) provision of information as to the progress of the research, (v) publication of names of all persons, institutions, and review committees involved in approval of consent procedures, (vi) provision of legal counsel and technical advice, and (vii) assurance that the subject comprehends the disclosure.

The Department, having considered these comments, notes that "Informed Consent" is presently defined in 45 CFR 46.3(c) and not in the present proposed rulemaking. With respect to the specific suggestions the Department notes that: as far as (i) is concerned, the regulations already call for a "fair explanation" of the procedures and a description of risks and benefits reasonably to be expected; (ii) reflects a basic misunderstanding of the experimental process which begins, essentially, with the comparison of two or more methods, procedures, or modalities on the *a priori* hypothesis that there will be no difference; (iii) is implicit in the existing regulations and is better emphasized in interpretive materials; (iv) would not be an element of informed consent unless interim findings affected the risk of benefit involved; and (v) touches on the subject of a possible future proposed rulemaking and the Department reserves its options for the present. The suggestion in (vi) is met in part by the proposals in the present proposed rulemaking to employ consent committees to advise potential subjects. The last suggestion (vii) goes beyond requirements for informed consent as they have generally been articulated by the courts.

D. Comments also included suggestions for the inclusion of additional definitions of (i) Institutions, (ii) Legal Guardian, (iii) Organizational Review Committee, (iv) Institutionalized Mentally Infirm, and (v) Children (with regard to age of consent), Parents, and Father.

The Department, having reviewed these comments, notes that (i) "Organization" is defined for the purpose of these regulations to include "institutions" at 45 CFR 46.3(a); (ii) "Legally authorized representative" is defined for the purpose of these regualtions to include legal guardian at 45 CFR 46.3(h); (iii) the definition of "organizational review committee" is implicit in 45 CFR 46.6; (iv) "Institutionalized mentally disabled" has been defined in the present proposed rulemaking at 46.503(d) to meet the suggestion; and (v) definition of "Children," "Parents," and "Father" will be reconsidered prior to the issuance of a future rulemaking covering research on children.

E. Several commentators criticized provisions of the draft policy that would have required that activities to be conducted outside the United States satisfy all requirements of the Departments regulations including those based on ethical concepts peculiar to the Judeo-Christian moral heritage or to English common law. It was noted that this would create substantial problems for United States investigators working overseas since these concepts are often inconsistent if not in conflict with normal, ethical, and legal concepts in certain foreign countries. For the same reasons, it was argued that these provisions would create problems for United States citizens assigned, detailed, seconded, or acting as consultants to international organizations or to foreign governmental or private institutions.

Having considered these objections, the Department proposes to retain the basic concept that activities supported by departmental funds should, in general, be subject to a uniform ethical policy wherever they are conducted, but to permit the Secretary to modify consent procedures if it can be demonstrated to his satisfaction that such procedures, as modified, are acceptable under the legal, social, and ethical standards of the locale in which the activities are to be performed.

FETUSES, ABORTUSES, AND PREGNANT WOMEN

Since comments on the draft provisions in 38 CFR 31738 providing additional protections for fetuses, abortuses, *in vitro* fertilization, and pregnant women were integrated with those on children, it is difficult to identify the communications specifically concerned with these subjects. However, it is estimated that the majority of the more than 400 letters received on research with children, born and unborn, touched on one or more aspects of research with fetuses, abortuses, and pregnant women.

A. A large number of respondents disagreed entirely with the idea of permitting research with the fetus, with the abortus (whether living or dead), or with the pregnant woman if the research might conceivably endanger the fetus.

The Department, having carefully considered these comments and similar proposals reflected in general correspondence and in articles in the public media, notes that their adoption would seriously hamper the development of needed improvements in the health care of the pregnant woman, the fetus, and the newborn. The opposition to research involvement of the fetus and abortus appears to be based in part on the assumption that the needed information can be obtained through research with animal species or with adults. Unfortunately, these assumptions are not valid. While much useful research can be conducted in animals, differences in species are nevertheless so great that any research finding in nonhuman species must ultimately be repeated in man before its general application in human medicine. In addition, the fetus and the newborn are not small adults. They suffer from some diseases not encountered in the adult. They may react differently to the diseases commonly affecting both adult and young, and they may have a different response to the same treatment, both with regard to its effectiveness and to its safety. The Department therefore proposes that (i) the ethical probity of any application or proposal for the support of any activity covered by subpart C be reviewed by an Ethical Advisory Board as described in § 46.304, and (ii) the conduct of any such activity supported by the Department be subject to oversight and monitoring by a consent committee as described in § 46.305.

B. Opinion was divided as to the need for an Ethical Advisory Board. Many respondents called it a welcome addition in the review process. Others felt that it would duplicate the function of the local organizational review committee and that its existence would encourage the organizational review committee to be less critical and would impose an additional roadblock that would delay or prohibit important research while needlessly consuming time, energy, and money, and posing potential danger to a patient waiting for treatment. Complaints were voiced that such decisions should be made locally, not in Washington, and that the investigator should be able to present his case in person. Numerous comments suggested that the Board's function should be limited to advising on policy, guidelines, or procedures, and not be concerned with the review of individual projects. This would avoid duplicating the function of the organizational review committee. Others suggested that the Ethical Advisory Board should serve as an appeal body from the organizational review committee.

There were also numerous comments to the effect that it is unwise and impossible to totally separate ethical and scientific review. Approval based only on ethics would be unethical if the science were bad. Both should be reviewed jointly.

The Department, having reviewed these comments, concludes that Ethical Advisory Board remains, in concept, a useful addition to the review process. It does not duplicate the functions of the local organizational review committee, since the latter is primarily concerned with matters of organizational regulations, local standards of professional practice, applicable law within its jurisdiction, and local community attitudes. The Ethical Advisory Board will be primarily concerned with similar issues at the national level. Applications and proposals should be capable of passing scrutiny at both levels. It is therefore proposed that the Ethical Advisory Board be retained as part of the additional protection mechanism.

Specific comments regarding the establishment of an Ethical Advisory Board touched principally on (i) the possibility that appointment of members at an agency level might lead to "loaded" Boards, while appointment at a higher level, i.e., by a joint Congressional committee or by independent outside bodies, might produce a more objective group, and (ii) disagreement as to the proper balance between scientist and nonscientist members, with a majority of the commentators suggesting that more than one-third of the members should have the scientific expertise necessary to identify risks and their possible consequences. It was specifically suggested that different sizes, compositions, and administrative locations of the Board be tried before selecting a final mechanism. In addition, it was suggested (iii) that a fifteen member Board was too large, (iv) that all members be human geneticists, (v) that at least one member be a psychologist, if behavioral issues were to be considered, (vi) that there be an absolute ban on departmental agency employees, (vii) that all proceedings be confidential, (viii) that all meetings be open to the public, and (ix) that an appeal mechanism be established.

The Department, having considered these views, proposes that while an Ethical Advisory Board to deal with biomedical research involving fetuses, abortuses, pregnant women, and *in vitro* fertilization might logically be established at the National Institutes of Health, (i) the power of appointment should be reserved to the Secretary, (ii) while the membership should include research scientists, physicians, lawyers, clergy or ethicists, and representatives of the general public, the balance between callings should rest with the Secretary as should also (iii) the number of members, so that the membership (iv, v) can be adjusted to the needs of the Board as the workload and the issues before it dictate. The specific suggestion (see vi) that departmental agency employees be excluded is adopted and expanded to include all full-time employees of the Federal Government. The decisions with regard to suggestions (vii) and (viii) will be governed by the provisions of the Federal Advisory Committee Act which generally require that meetings of similar advisory groups be open to the public for the purposes of policy discussion, but closed and confidential for the purpose of review of specific applications and proposals. Since the Board will be advisory to funding agencies, the final action will be that of existing awarding authorities, and appeal mechanisms (ix) will be provided only to the extent available under other existing departmental regulations and policies. These proposals are incorporated into § 46.304.

C. A number of respondents recommended that the policy governing *in vitro* fertilization be strengthened, on the one hand, or liberalized, on the other. The Department has considered these recommendations, and has provisionally chosen not to stipulate at this time protections for the product of *in vitro* fertilization which is not implanted, but rather to leave that series of issues to the Ethical Advisory Board established under § 46.304(a). The Board will be required to weigh, with respect to specific research proposals, the state of the art, legal issues, community standards, and the availability of guidelines to govern each research situation.

Because biomedical research is not yet near the point of being able to maintain for a substantial period the nonimplanted product of *in vitro* fertilization, no clear and present danger arises from not stipulating in these regulations the protections for it. Given the state of the research, we believe that such stipulation would be premature.

It is the Department's intent that the definition of the term "fetus" (§ 46.303 (d)) be construed to encompass both the product of *in vitro* conception and the product of *in vitro* fertilization which is subsequently implanted in the donor of the ovum. Whatever the nature of the conception process, it is intended that upon implantation the protections of subpart C apply to all fetuses. It is only with respect to the protections available to the non-implanted product of *in vitro* fertilization that the regulations are silent.

With respect to the fertilization of human ova *in vitro*, it is expected that the Board will consider the extent to which current technology permits the continued development of such ova, as well as the legal and ethical issues surrounding the initiation and disposition of the products of such research.

With respect to implantation of fertilized human ova, it is expected that the Board will consider such factors as the safety of the technique (with respect to offspring) as demonstrated in animal studies, and clarification of the legal responsibilities of the donor and recipient parent(s) as well as the research personnel.

Since the Department does reserve the option of later specifying such protections by regulation, we invite comment on the question of appropriate regulations in the future.

D. The draft proposals included a suggestion for the establishment of a protection committee which elicited numerous comments that the use of the term "protection committee" implies that the Department recognizes a clear, present need for protection against the investigator, the uncertain relation of this committee to the organizational review committee, and the uniform need for and desirability for such protection.

Having reviewed these comments, the Department proposes an extensive revision in this innovative concept. Initially, it acknowledges that the term "protection committee" is pejorative and proposes the term "consent committee" as more appropriate and consistent with the primary purpose of such bodies. Further, it proposes to eliminate specific requirements for the size and composition of such committees. Instead, applicants and offerors are to propose the establishment of such a committee, specifying its size, composition, and rules of procedure. In addition, where the applicant or offeror believes that the activity involves only negligible risks, it may ask the Secretary to waive or modify the requirement for a consent committee. All proposals for the establishment, modification, or waiver of a consent committee shall be subject to review and approval at the local level by the organizational review committee and at the departmental level by the Ethical Advisory Board. The Ethical Advisory Board may prescribe additional duties for the consent committee. These changes are incorporated in § 46.305. In view of this drastic change in concept of the committee, detailed discussion of the many excellent and often thought-provoking comments concerned with details of the original draft seems inappropriate.

E. Many critical comments were addressed to the definitions used in this subpart, specifically:

1. "Pregnancy." It was suggested that pregnancy should be defined (i) conceptually to begin at the time of fertilization of the ovum, and (ii) operationally by actual test unless the woman has been surgically rendered incapable of pregnancy.

While the Department has no argument with the conceptual definition as proposed above, it sees no way of basing regulations on the concept. Rather, in order to provide an administerable policy, the definition must be based on existing medical technology which permits confirmation of pregnancy. This approach is reflected by § 46.303(c).

2. "Viability of the Fetus". Many recommendations were received concerning the definition of viability of the fetus after premature delivery or abortion. Some respondents urged that presence of fetal heartbeat be definitive (whether or not there is respiration) while others urged that identifiable cortical activity be specified as an alternative sign of viability. The Department has concluded that the issue of viability is a function of technological advance, and therefore must be decided with reference to the medical realities of the present time. We reserve the option of redefining the parameters as conditions warrant.

Only upon the basis of a definition which is both precise and consistent with current medical capability can a regulation realistically be interpreted and enforced. Current technology is such that a fetus, given the benefit of available medical therapy, cannot survive unless the lungs can be inflated so that respiration can take place. Without this capability, even if the heart is beating, the fetus is nonviable. In the future, if technology has advanced to the point of sustaining a fetus with non-inflatable lungs, the definition can and should be modified.

The Department has therefore chosen to specify, in the definition of viability of the fetus (§ 46.303(e)), that heart beat and respiration are, jointly, to be the indicator of viability.

3. "Abortus." Various comments noted that this definition is more restrictive than the usual medical definition of the abortus as a "nonviable fetus," and suggested substitution of the broader definition.

The Department proposes to retain the original definition for the purposes of these regulations. There is general agreement that there are distinct ethical problems involved in decisions concerning research use of the intact fetus, or use of organs or tissues obtained from a fetus that has died *in utero* or from an abortus at autopsy. The definition recurs with minor editorial changes in § 46.303(f).

F. Several comments were critical of the draft regulation's provisions limiting activities involving pregnant women to those not adversely affecting the fetus, except where the primary purpose of the activity was to benefit the fetus. It was suggested that the regulations (i) should contain language permitting exceptions for research necessary to meet the health needs of the mother, and (ii) should grant the right to participate in research aimed at improvement of methods of abortion, birth control, and genetic intervention.

The Department concurs with the first suggestion, (i), and proposes that the regulations permit research whose primary interest is to benefit the particular fetus or to respond to the health needs of the pregnant woman. It does not fully accept the second suggestion, (ii), and proposes that the regulations permit fetal research concerned with diagnosis and prevention of perinatal disease, and to offset the effects of genetic abnormality or congenital injury, but only when such research is done as part of a procedure properly performed to terminate a pregnancy. These changes are incorporated into § 46.306(a). The Department has tentatively concluded that consideration of risk vs. benefit with respect to fetal research does not seem to be appropriate.

G. Draft regulation provisions required maternal consent and the consent of the father if he were available and capable of participating in the consent process. This provision was strongly criticized on the grounds that it could permit the father of the fetus to deny needed health care to the woman or to the fetus even though he had no marital obligations, and that it might result in undue delay in the delivery of health care. It was also pointed out that the regulation did not touch on the question of the validity of consent by a pregnant minor.

The Department agrees. It is now proposed that paternal consent be sought only if the activity is not responding to the health needs of the pregnant woman and the father is reasonably available. These changes are reflected by § 46.306(b).

H. The Department has provisionally chosen, in § 46.306(a), to permit research to be undertaken from which there will be risk of harm to the fetus if such research is conducted as part of the abortion procedure. This decision, upon which we invite comment, has been made in the expectation that such research may produce new technology which will enable countless premature infants to live who now cannot.

It is not intended that this provision be construed to permit fetal research in anticipation of abortion prior to the commencement of the termination procedure itself.

While it is true that the class of fetuses for whom abortion is contemplated will be placed at greater research risk than all fetuses in general, such risk can arise only after implementation of the double safeguard of parental consent to the contemplated abortion, and second parental consent to the research procedure itself.

I. Comments regarding activities involving the abortus were concerned with the issue of maintaining vital functions and signs. It was argued that maintaining vital functions at the level of the organ, tissue, or cell is essential to studies and involves no prolongation of the dying of the abortus. At the same time, it was argued that termination of the heart beat should not be prohibited since temporary cardiac arrest has proved essential in the development of surgical techniques necessary to correct congenital heart defects.

Neither of these objections appear valid and no significant changes in § 46.307 are proposed. However, in order to emphasize again the distinction between research with the whole fetus or abortus, functioning as an organism with detectable vital signs, and with the dead fetus or abortus, the Department has added § 46.308, concerning activities involving a dead fetus or abortus, and § 46.309, concerning the abortus as an organ or tissue donor. Also § 46.307(d) has been expanded to permit the artificial maintenance of vital functions of an abortus where the purpose is to develop new methods for enabling the abortus to survive to the point of viability.

The Department feels that there is evident distinction between "termination" and "arrest" of the clinical signs as applied to the fetus or premature infant, but that no such distinction is valid or applicable where the abortus is concerned.

Prisoners

Forty-seven responses spoke to the provisions regarding additional protection for prisoners involved as subjects. Of these, two were from individuals identifying themselves as prisoners, seven were from State correctional institutions or State agencies, and four were from representatives of the pharmaceutical industry.

A. In comments directed at the overall nature of the draft regulations providing additional protection for prisoners, approximately equal numbers of respondents (i) denied that any significant additions were necessary, and (ii) proposed either the exclusion of prisoners from any research or experimentation not intended for the personal benefit of a prisoner, or highly restrictive regulations to accomplish the same purpose.

The Department, having reviewed these comments, has not been persuaded that any change should be made in the initial proposal.

B. A number of comments were concerned with the relationship between the existing organizational review committees and the proposed Protection Committee. It was pointed out by several that, as proposed, the two committees would not only have overlapping functions and authority but could operate independently of each other with conflicting directives and objectives that would not practicably provide additional protection of prisoners used as subjects.

The Department, recognizing the importance of preserving the authority of the organizational review committee as the primary institutional focus for the implementation of the Department of Health, Education, and Welfare regulations, proposes to assign to the organizational review committee the additional duties specified under § 46.404(a).

A committee auxiliary to the organizational review committee, now designated the consent committee, will have the character and responsibilities specified in § 46.406. In keeping with this modified position it should be noted that when the organizational review committee determines that an activity would involve no risk or negligible risk to any prisoner while serving as a subject, the organization may request the Secretary to consider a modification or waiver of the requirement for a consent committee.

C. Comments on the proposed prohibition of research involvement of persons awaiting arraignment, trial, or sentencing expressed doubts that these individuals should be denied the benefits of innovative procedures, particularly those concerned with sociological research.

The Department agrees that the uniform exclusion of any such person from research should not be mandatory and proposes to permit his participation in an activity as a subject when the risk is negligible and the intent of the activity is therapeutic for him or relates to the nature of his confinement. This modification is incorporated into § 46.406.

D. The draft requirement for DHEW accreditation of prison facilities as sites for the performance of research, development, and related activities involving prisoner subjects was severely criticized, principally because of the jurisdictional problems inherent in any attempt to impose a Federal regulatory requirement on an autonomous State facility.

The Department concludes that this draft proposal was ill-advised. However, in order to attain the objective on an activity basis, certain specific prerequisites for the protection of prisoner subjects within facilities have been added to § 46.404(a) to properly relate conditions in a facility to the issue of undue inducements to participation by prisoners as subjects in an activity.

MENTALLY DISABLED

Over 40 of the responses spoke directly to the section of the draft concerned with the "mentally infirm." Many of these objected initially to the use of the word "infirm" as reflecting an antiquated notion of mental illness.

The Department agrees, and proposes to substitute "disabled" for "infirm," though noting that there is no clearly preferable collective term for the groups described.

A. Comments on the purpose of this section expressed satisfaction with the intent to provide additional protection for this group but dissatisfaction with the actual language employed. Specifically, they noted that not institutionalization but rather the limitation of personal rights and freedom imposed by institutionalization is the determining issue. Similarly, it is not only the potential subject's difficulty in comprehending risks that is at issue, but his ability to comprehend generally.

The Department concurs. Proposed changes in language are incorporated in § 46.52.

B. Many of the respondents objected to one or more of the definitions peculiar to this subpart. The criticisms and the Department's proposed changes are as follows:

1. "Mentally infirm." In addition to requesting substitution of another term for "infirm," respondents raised conflicting objections to the definition's coverage. Some felt that it was overly inclusive; others felt it was too narrow. Some felt that epileptics should be specifically included, as well as those who are temporarily or permanently mentally incapacitated as a result of a physical condition such as stroke, brain damage, trauma, etc.

The Department, having carefully reviewed these comments, proposes no basic change in the definition. It concurs with many reviewers in the opinion that the definition is broad enough to include any category of subjects proposed for specific addition. Minor editorial changes have been made in § 46.503(b).

2. "Institutionalized." Commentators noted that (i) the regulations should cover all mentally disabled persons regardless of institutionalization, (ii) not all involuntary commitments are by order of a court, (iii) the draft refers to "residence" and "confinement" in similar contexts, though the terms do not carry the same connotation, and (iv) the definition does not specify halfway houses, lodges, day/night hospitals, nursing homes, and psychiatric wards of hospitals as places where subjects might be institutionalized.

The Department notes that (i) the non-institutionalized mentally disabled are covered by the existing regulations published as 39 FR 18914 and need not be included under these additional protections. Such individuals are not necessarily subject to all limitations on their freedom and rights as described in § 46.502 of this proposed rulemaking. Consideration will be given, however, to dealing with the noninstitutionalized legally incompetent who are mentally disabled in a subsequent notice of proposed rulemaking. With regard to (ii), the implication that court orders are the sole basis for involuntary confinement is incorrect and should be removed. Editorial changes have been made in § 46.503 to emphasize that concern therein is with those "* * * confined * * * in a residential institution * * *" (see iii) and, in order to designate the type of institutions concerned (see iv), it is proposed to separately define "Institutionalized mentally disabled individuals" in § 46.503 to include examples of such institutions. These changes are incorporated in § 46.503(c) and § 46.503(d).

C. While most respondents endorsed the intent of the draft limitations on activities involving the institutionalized mentally disabled, there were several specific criticisms of the terms used. Several persons suggested that any limitation of research to that related to a particular subject's "impairment" be worded so as to include any illness from which the person suffers so that, for example, an institutionalized mentally disabled person with cancer could not be denied the benefits of research in cancer therapy.

Further, this limitation could exclude the use of such subjects as controls in research which might benefit those suffering from a mental disability other than the specific one from which a particular subject suffers. Still further, mentally disabled people should be involved as subjects in research on infirmities other than their own because of lack of knowledge of the causes of mental and emotional disorders.

Many respondents felt that there was inadequate recognition of the need for research with the mentally disabled on basic psychological processes (e.g., learning, perception, and cognitive functions) which are fundamental to the study of the treatment, etiology, pathogenesis, prevention, and treatment of such disabilities.

The Department agrees that the language of the draft limiting research to the disease entities affecting individual subjects is probably not in the interests of the institutionalized mentally disabled as a class. The Department does not agree that it would be appropriate to permit this class of subjects to be involved in research unrelated to the causes, nature, or circumstances of their institutionalization. While there are possible disadvantages to the institutionalized mentally disabled inherent in this restriction, the possible risks of using the mentally disabled in such research outweigh its advantages. The proposed changes are incorporated in § 46.504(a). Editorial changes are reflected in § 46.504(b) and § 46.504(c).

D. Criticisms of the draft's suggestion of the establishment or a protection committee in connection with each activity conducted in an institution for the mentally retarded were similar to those aimed at the protection committee to be established in connection with research on the pregnant woman and on the fetus. The Department proposes to change the title of the committee to "consent committee" and to change the regulations governing size, composition, and operating rules to conform to those previously described for § 46.305. Such changes are incorporated in § 46.506.

E. With respect to § 46.603(b), the Department reserves the right to amend this section if legislation now being developed by the Executive Branch on the safe guarding of individually linked data used for statistical and research purposes is enacted.

Written comments concerning the proposed regulation are invited from interested persons. Inquiries may be addressed and data, views, and arguments relating to the proposed regulations may be presented in writing, in triplicate, to the Chief, Institutional Relations Branch, Division of Research Grants, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments received will be available for inspection at the National Institutes of

Health, Room 303, Westwood Building, 5333 Westbard Avenue, Bethesda, Maryland, weekdays (Federal holidays excepted) between the hours of 9:00 a.m. and 4:30 p.m. All relevant material received on or before November 21, 1974 will be considered.

Notice is also given that it is proposed to make any amendments that are adopted effective upon publication in the FEDERAL REGISTER.

Dated: August 15, 1974.

CASPAR W. WEINBERGER,
Secretary.

It is therefore proposed to amend Part 46 of Subtitle A of Title 45 of the Code of Federal Regulations by:

1. Revising §§ 46.19 through 46.22 and renumbering them as §§ 46.603 through 46.606, reading as set forth in Subpart F below.

2. Designating §§ 46.1 through 46.18 as Subpart A, renumbering these §§ 46.101 through 46.118, and modifying all references thereto accordingly.

3. Reserving Subpart B.

4. Adding the following new Subparts C through F.

Subpart C—Additional Protections Pertaining to Biomedical Research, Development, and Related Activities Involving Fetuses, Abortuses, Pregnant Women, and In Vitro Fertilization

Sec.
46.301 Applicability.
46.302 Purpose.
46.303 Definitions.
46.304 Ethical Advisory Board.
46.305 Establishment of a consent committee.
46.306 Activities involving fetuses *in utero* or pregnant women.
46.307 Activities involving abortuses.
46.308 Activities involving a dead fetus or abortus.
46.309 Activities involving the abortus as an organ or tissue donor.
46.310 Activities to be performed outside the United States.

Subpart D—Additional Protections Pertaining to Activities Involving Prisoners as Subjects

46.401 Applicability.
46.402 Purpose.
46.403 Definitions.
46.404 Additional duties of the organizational review committee where prisoners are involved.
46.405 Establishment of a consent committee.
46.406 Special restrictions.
46.407 Activities to be performed outside the United States.

Subpart E—Additional Protections Pertaining to Activities Involving the Institutionalized Mentally Disabled as Subjects

46.501 Applicability.
46.502 Purpose.
46.503 Definitions.
46.504 Activities involving the institutionalized mentally disabled.
46.505 Additional duties of the organizational review committee where the institutionalized mentally disabled are involved.
46.506 Establishment of a consent committee.
46.507 Activities to be performed outside the United States.

Subpart F—General Provisions

46.601 Applicability.
Sec.
46.602 Multiple consent committee requirements.
46.603 Organization's record; confidentiality.
46.604 Reports.
46.605 Early termination of awards; evaluation of subsequent applications.
46.606 Conditions.
46.607 Activities conducted by Department employees.

AUTHORITY: 5 U.S.C. 301.

Subpart C—Additional Protections Pertaining to Biomedical Research, Development, and Related Activities Involving Fetuses, Abortuses, Pregnant Women, and In Vitro Fertilization

§ 46.301 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare grants and contracts supporting biomedical research, development, and related activities involving: (1) the fetus *in utero*, (2) the abortus, as that term is defined in § 46.303, (3) pregnant women, and (4) *in vitro* fertilization. In addition, these regulations are applicable to all such activities involving women who could become pregnant, except where the applicant or offeror shows to the satisfaction of the Secretary that adequate steps will be taken in the conduct of the activity to avoid involvement of women who are pregnant.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.302 Purpose.

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

§ 46.303 Definitions.

As used in this subpart:

(a) "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.

(b) "Biomedical research, development, and related activities" means research, development, or related activities involving biological study (including but not limited to medical or surgical procedures, withdrawal or removal of body tissue or fluid, administration of chemical substances or input of energy, deviation from normal diet or hygiene, and manipulation or observation of bodily processes).

(c) "Pregnancy" encompasses the period of time from confirmation of implantation until delivery.

(d) "Fetus" means the product of conception from the time of implantation to the time of delivery.

(e) "Viability of the fetus" means the ability of the fetus, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. If the fetus has this ability, it is v[illegible] and therefore a premature infant.

(f) "Abortus" means a fetus when it is expelled whole, prior to viability, whether spontaneously or as a result of medical or surgical intervention. The term does not apply to the placenta: fetal material which is macerated at the time of expulsion; or cells, tissue, or organs excised from a dead fetus.

(g) "*In vitro* fertilization" means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor sperm and ova or by any other means.

§ 46.304 Ethical Advisory Board.

(a) All applications or proposals for the support of activities covered by this subpart shall be reviewed by an Ethical Advisory Board, established by the Secretary within the National Institutes of Health, which shall advise the funding agency concerning the acceptability of such activities from an ethical standpoint.

(b) Members of the Board shall be so selected that the Board will be competent to deal with medical, legal, social, and ethical issues and shall include, for example, research scientists, physicians, lawyers, and clergy and/or ethicists, as well as representatives of the general public. No Board member may be a regular, full-time employee of the Federal Government.

§ 46.305 Establishment of a cons[illegible] committee.

(a) Except as provided in paragraph (c) of this section, no activity covered by this subpart may be supported unless the applicant or offeror has provided an assurance acceptable to the Secretary that it will establish a consent committee (as provided for in the application or offer and approved by the Secretary) for each such activity, to oversee the actual process by which individual consents required by this subpart are secured, to monitor the progress of the activity and intervene as necessary, and to carry out such other duties as the Secretary (with the advice of the Ethical Advisory Board) may prescribe. The duties of the consent committee may include:

(1) Participation in the actual selection process and securing of consents to assure that all elements of a legally effective informed consent, as outlined in § 46.3, are satisfied. Depending on what may be prescribed in the application or offer approved by the Secretary, this might require approval by the committee of individual participation in the activity or it might simply call for verification (e.g., through sampling) that procedures prescribed in the approved application or offer are being followed.

(2) Monitoring the progress of the activity. Depending on what may be prescribed in the application or offer approved by the Secretary, this might

include: visits to the activity site, identification of one or more committee members who would be available for consultation with those involved in the consent procedure (i.e., participants) at the participant's request, continuing evaluation to determine if any unanticipated risks have arisen and that any such risks are communicated to the participants, periodic contact with the participants to ascertain whether they remain willing to continue in the activity, providing for the withdrawal of any participants who wish to do so, and authority to terminate participation of one or more participants with or without their consent where conditions warrant.

(b) The size and composition of the consent committee must be approved by the Secretary, taking into account such factors as: (1) the scope and nature of the activity; (2) the particular subject groups involved; (3) whether the membership has been so selected as to be competent to deal with the medical, legal, social, and ethical issues involved in the activity; (4) whether the committee includes sufficient members who are unaffiliated with the applicant or offeror apart from membership on the committee; and (5) whether the committee includes sufficient members who are not engaged in research, development, or related activities involving human subjects. The committee shall establish rules of procedure for carrying out its functions and shall conduct its business at convened meetings, with one of the members designated as chairperson.

(c) Where a particular activity, involving fetuses *in utero* or pregnant women, presents negligible risk to the fetus, an applicant or offeror may request the Secretary to modify or waive the requirement in paragraph (a) of this section. If the Secretary finds that the risk is indeed negligible and other adequate controls are provided, he may (with the advice of the Ethical Advisory Board) grant the request in while or in part.

(d) The requirements of this section and § 46.304 do not obviate the need for review and approval of the application or offer by the organizational review committee, to the extent required under Subpart A of this part.

§ 46.306 Activities involving fetuses in utero or pregnant women.

(a) No activity to which this subpart is applicable, involving fetuses *in utero* or pregnant women, may be undertaken unless: (1) the purpose of the activity is to benefit the particular fetus or to respond to the health needs of the mother, or (2) the activity conducted as part of (but not prior to the commencement of) a procedure to terminate the pregnancy and is for the purpose of evaluating or improving methods of prenatal diagnosis, methods of prevention of premature birth, or methods of intervention to offset the effects of genetic abnormality or congenital injury.

(b) Activities covered by this subpart which are permissible under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their consent, except that the father's consent need not be secured if: (1) the purpose of the activity is to respond to the health needs of the mother or (2) his identity or whereabouts cannot reasonably be ascertained.

(c) Activities covered by this subpart which are permissible under paragraph (a) (2) of this section may not be undertaken unless individuals engaged in the research will have no part in: (1) any decisions as to the timing, method, or procedures used to terminate the pregnancy, and (2) determining the viability of the fetus at the termination of the pregnancy.

§ 46.307 Activities involving abortuses.

No activity to which this subpart is applicable, involving an abortus, may be undertaken unless:

(a) Appropriate studies on animals have been completed;

(b) The mother and father are legally competent and have given their consent, except that the father's consent need not be secured if his identity or whereabouts cannot reasonably be ascertained;

(c) Individuals engaged in the research will have no part in: (1) any decisions as to the timing, method, or procedures used to terminate the pregnancy, and (2) determining the viability of the fetus at the termination of the pregnancy;

(d) Vital functions of an abortus will not be artificially maintained except where the purpose of the activity is to develop new methods for enabling the abortus to survive to the point of viability; and

(e) Experimental procedures which would terminate the heart beat or respiration of the abortus will not be employed.

§ 46.308 Activities involving a dead fetus or abortus.

Activities involving a dead fetus or abortus shall be conducted in accordance with any applicable State or local laws governing autopsy.

§ 46.309 Activities involving the abortus as an organ or tissue donor.

Activities involving the abortus as an organ or tissue donor shall be conducted in accordance with any applicable State or local laws governing transplantation or anatomical gifts.

§ 46.310 Activities to be performed outside the United States.

Activities to which this subpart is applicable, to be conducted outside the United States are subject to the requirements of this subpart, except that the consent procedures specified herein may be modified if it is shown to the satisfaction of the Secretary that such procedures, as modified, are acceptable under the laws and regulations of the country in which the activities are to be performed and that they comply with the requirements of Subpart A of this part.

Subpart D— Additional Protections Pertaining to Activities Involving Prisoner Subjects

§ 46.401 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare grants and contracts supporting research, development, and related activities involving prisoners as subjects.

(b) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.402 Purpose.

It is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable, inasmuch as, because of their incarceration they may be under constraints which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate in such activities.

§ 46.403 Definitions.

As used in this subpart:

(a) "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.

(b) "Prisoner" means any individual involuntarily confined in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute and also individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution.

§ 46.404 Additional duties of the organizational review committee when prisoners are involved.

(a) In addition to the responsibilities prescribed for such committees under Subpart A of this part, the applicant's or offeror's organizational review committee shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that there will be no undue inducements to participation by prisoners as subjects in the activity, taking into account such factors as whether the earnings, living conditions, medical care, quality of food, and amenities offered to participants in the activity would be better than those generally available to the prisoners;

(2) Determine that (i) all aspects of the activity would be appropriate for performance on nonprisoners, or (ii) the activity involves negligible risk to the subjects and is for the purpose of studying the effects of incarceration on such subjects;

(3) Determine that the application or proposal contains adequate procedures for selection of subjects, securing consents, monitoring continued subject participation, and assuring withdrawal with-

out prejudice, in accordance with § 46.405 of this subpart;

(4) Determine that rates of remuneration are consistent with the anticipated duration of the activity, but not in excess of that paid for other employment generally available to inmates of the facility in question, and that withdrawal from the project for medical reasons will not result in loss of anticipated remuneration; and

(5) Carry out such other responsibilities as may be assigned by the Secretary.

(b) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an organizational review committee, subject to approval by the Secretary, where no such committee has been established under Subpart A of this part.

(c) No award may be issued until the applicant or offeror has certified to the Secretary that the organizational review committee has made the determinations required under paragraph (a) of this section.

§ 46.405 Establishment of a consent committee.

(a) Except as provided in paragraph (c) of this section, no activity covered by this subpart may be supported unless the applicant or offeror has provided an assurance acceptable to the Secretary that it will establish a consent committee (as provided for in the application or offer and approved by the organizational review committee and the Secretary) for each such activity, to oversee the actual process by which individual subjects are selected and their consents secured, to monitor the progress of the activity (including visits to the activity site on a regular basis) and the continued willingness of the subjects to participate, to intervene on behalf of one or more subjects if conditions warrant, and to carry out such other duties as the Secretary may prescribe. The duties of the consent committee may include:

(1) Participation in the actual process by which individual subjects are selected and their consents secured to assure that all elements of a legally effective informed consent, as outlined in section 46.3 of this part, are satisfied. Depending on what may be prescribed in the application or offer approved by the Secretary, this might require approval by the committee of each individual's participation as a subject in the activity or it might simply call for verification (e.g., through sampling) that procedures prescribed in the approved application or offer are being followed.

(2) Monitoring the progress of the activity and the continued willingness of subjects to participate. Depending on what may be prescribed in the application or offer approved by the Secretary, this might include: visits to the activity site, identification of one or more committee members who would be available for consultation with subjects at the subjects' request, continuing evaluation to determine if any unanticipated risks have arisen and that any such risks are communicated to the subjects, periodic contact with the subjects to ascertain whether they remain willing to continue in the study, providing for the withdrawal of any subjects who wish to do so, and authority to terminate participation of one or more subjects with or without their consent where conditions warrant.

(b) The size and composition of the consent committee must be approved by the Secretary, taking into account such factors as: (1) the scope and nature of the activity; (2) the particular subject groups involved; (3) whether the membership has been so selected as to be competent to deal with the medical, legal, social, and ethical issues involved in the activity; (4) whether the committee includes a prisoner or a representative of an organization having as a primary concern protection of prisoners' interests; (5) whether the committee includes sufficient members who are unaffiliated with the applicant or offeror apart from membership on the committee; and (6) whether the committee includes sufficient members who are not engaged in research, development, or related activities involving human subjects. The committee shall establish rules of procedure for carrying out its functions and shall conduct its business at convened meetings, with one of its members designated as chairperson.

(c) Where a particular activity involves negligible risk to the subjects, an applicant or offeror may request the Secretary to modify or waive the requirement in paragraph (a) of this section. If the Secretary finds that the risk is indeed negligible and other adequate controls are provided, he may grant the request in whole or in part.

§ 46.406 Special restrictions.

Persons detained in a correctional facility pending arraignment, trial, or sentencing or in a hospital facility for pre-arraignment, pre-trial, or pre-sentence diagnostic observation are excluded from participation in activities covered by this subpart, unless (a) the organizational review committee finds that the particular activity involves only negligible risk to the subjects and (b) the activity is therapeutic in intent or relates to the nature of their confinement.

§ 46.407 Activities to be performed outside the United States.

Activities to which this subpart is applicable, to be conducted outside the United States, are subject to the requirements of this subpart, except that the consent procedures specified herein may be modified if it is shown to the satisfaction of the Secretary that such procedures, as modified, are acceptable under the laws and regulations of the country in which the activities are to be performed and that they comply with the requirements of Subpart A of this part.

Subpart E—Additional Protections Pertaining to Activities Involving the Institutionalized Mentally Disabled as Subjects

§ 46.501 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare grants and contracts supporting research, development, and related activities involving the institutionalized mentally disabled as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will necessarily result in a legally effective consent under applicable State or local law to a subject's participation in such an activity; nor in particular does it obviate the need for court approval of such participation where court approval is required under applicable State or local law in order to obtain a legally effective consent.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.502 Purpose.

It is the purpose of this subpart to provide additional safeguards for the protection of the institutionalized mentally disabled involved in activities to which this subpart is applicable, inasmuch as: (a) they are confined in an institutional setting where their freedom and rights are potentially subject to limitation; (b) they may be unable to comprehend sufficient information to give an informed consent, as that term is defined in § 46.103; and (c) they may be legally incompetent to consent to their participation in such activities.

§ 46.503 Definitions.

As used in this subpart:

(a) "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.

(b) "Mentally disabled" includes those institutionalized individuals who are mentally ill, mentally retarded, emotionally disturbed, or senile, regardless of their legal status or basis of institutionalization.

(c) "Institutionalized" means confined, whether by voluntary admission or involuntary commitment, in a residential institution for the care or treatment of the mentally disabled.

(d) "Institutionalized mentally disabled individuals" includes but is not limited to patients in public or private mental hospitals, psychiatric patients in general hospitals, inpatients of community mental health centers, and mentally disabled individuals who reside in halfway houses or nursing homes.

§ 46.504 Activities involving the institutionalized mentally disabled.

Institutionalized mentally disabled individuals may not be included in an activity covered by this subpart unless:

(a) The proposed activity is related to the etiology, pathogenesis, prevention, diagnosis, or treatment of mental disability or the management, training, or rehabilitation of the mentally disabled and seeks information which cannot be obtained from subjects who are not institutionalized mentally disabled;

(b) The individual's legally effective informed consent to participation in the

activity or, where the individual is legally incompetent, the informed consent of a representative with legal authority so to consent on behalf of the individual has been obtained; and

(c) The individual's assent to such participation has also been secured, when in the judgment of the consent committee he or she has sufficient mental capacity to understand what is proposed and to express an opinion as to his or her participation.

§ 46.505 Additional duties of the organizational review committee where the institutionalized mentally disabled are involved.

(a) In addition to the responsibilities prescribed for such committees under Subpart A of this part, the applicant's or offeror's organizational review committee shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that all aspects of the activity meet the requirements of § 46.50 (a) of this subpart;

(2) Determine that there will be no undue inducements to participation by individuals as subjects in the activity, taking into account such factors as whether the earnings, living conditions, medical care, quality of food, and amenities offered to participants in the activity would be better than those generally available to the mentally disabled at the institutions;

(3) Determine that the application or proposal contains adequate procedures for selection of subjects, securing consents, protecting confidentiality, and monitoring continued subject participation, in accordance with § 46.506 of this subpart; and

(4) Carry out such other responsibilities as may be assigned by the Secretary.

(b) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an organizational review committee, subject to approval by the Secretary, where no such committee has been established under Subpart A of this part.

(c) No award may be issued until the applicant or offeror has certified to the Secretary that the organizational review committee has made the determinations required under paragraph (a) of this section.

§ 46.506 Establishment of a consent committee.

(a) Except as provided in paragraph (c) of this section, no activity covered by this subpart may be supported unless the applicant or offeror has provided a separate assurance acceptable to the Secretary that it will establish a consent committee (as provided for in the application or offer and approved by the organizational review committee and the secretary) for each such activity, to oversee the actual process by which individual subjects are selected and consents required by this subpart are secured, to monitor the progress of the activity (including visits to the activity site on a regular basis) and the continued willingness of the subjects to participate, to intervene on behalf of one or more subjects if conditions warrant, and to carry out such other duties as the Secretary may prescribe. The duties of the consent committee may include:

(1) Participation in the actual process by which individual subjects are selected and their consents secured to assure that all elements of a legally effective informed consent, as outlined in § 46.3, are satisfied. Depending on what may be prescribed in the application or offer approved by the Secretary, this might require approval by the committee of each individual's participation as a subject in the activity or it might simply call for verification (e.g., through sampling) that procedures prescribed in the approved application or offer are being followed.

(2) Monitoring the progress of the activity and the continued willingness of subjects to participate. Depending on what may be prescribed in the application or offer approved by the Secretary, this might include: visits to the activity site, identification of one or more committee members who would be available for consultation with subjects at the subjects' request, continuing evaluation to determine if any unanticipated risks have arisen and that any such risks are communicated to the subjects, periodic contact with the subjects to ascertain whether they remain willing to continue in the study, providing for the withdrawal of any subjects who wish to do so, and authority to terminate participation of one or more subjects with or without their consent where conditions warrant.

(b) The size and composition of the consent committee must be approved by the Secretary, taking into account such factors as: (1) the scope and nature of the activity; (2) the particular subject groups involved; (3) whether the membership has been so selected as to be competent to deal with the medical, legal, social, and ethical issues involved in the activity; (4) whether the committee includes sufficient members who are unaffiliated with the applicant or offeror apart from membership on the committee; and (5) whether the committee includes sufficient members who are not engaged in research, development, or related activities involving human subjects. The committee shall establish rules of procedure for carrying out its functions and shall conduct its business at convened meetings, with one of its members designated as chairperson.

(c) Where a particular activity involves negligible risk to the subjects, an applicant or offeror may request the Secretary to modify or waive the requirement in paragraph (a) of this section. If the Secretary finds that the risk is indeed negligible and other adequate controls are provided, he may grant the request in whole or in part.

§ 46.507 Activities to be performed outside the United States.

Activities to which this subpart is applicable, to be conducted outside the United States, are subject to the requirements of this subpart, except that the consent procedures specified herein may be modified if it is shown to the satisfaction of the Secretary that such procedures, as modified, are acceptable under the laws and regulations of the country in which the activities are to be performed and that they comply with the requirements of Subpart A of this part.

Subpart F—General Provisions

§ 46.601 Applicability.

Sections 46.602 through 46.606 are applicable to all grant or contract supported activities covered by this part.

§ 46.602 Multiple consent committee requirements.

Where an application or proposal would involve human subjects covered by more than one consent committee requirement imposed under this part, upon approval by the Secretary, these multiple requirements may be satisfied through use of a single consent committee appropriately constituted to take account of the nature of the subject group.

§ 46.603 Organization's records; confidentiality.

(a) Copies of all documents presented or required for initial and continuing review by the organization's review committee or consent committee, such as committee minutes, records or subjects' 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 in the exercise of oversight for the protection of such subject or class of subjects.

§ 46.604 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.

§ 46.605 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 Department of Health, Education, and Welfare 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 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.

§ 46.606 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.

§ 46.607 Activities conducted by Department employees.

The regulations of this part (except for this subpart) are applicable as well to all research, development, and related activities conducted by employees of the Department of Health, Education and Welfare, except that: (a) subpart C is applicable only to biomedical research, development, and related activities and (b) each agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint.

[FR Doc.74-19300 Filed 8-20-74;8:45 am]

RECEIVED

1974

GRADUATE COLLEGE

ADDRESSEE

This is a PROPOSED rulemaking, NOT a regulation in final form. Your comments, views, and arguments may well affect the ultimate form of these rules.

To expedite the handling of your comments on this complex notice, 39 F.R.: 30648 ; it would be appreciated if comments on the individual Subparts (C, Fetuses, Abortuses, Pregnant Women; D, Prisoners; and E, Institutionalized Mentally Disabled) could be submitted on separate pages. This will facilitate prompt access to your remarks, and speed review and development of final policy. Where appropriate comments should identify the appropriate Sections (e.g. § 46.306) of the rules.

Comments should be addressed as required at the end of the preamble page. It should be noted that the preamble is simply an historical introduction to the proposed rules and is not in itself an appropriate subject for comment.

ROGER STEINER

LANGUAGE & LITERATURE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

[45 CFR Part 46]

PROTECTION OF HUMAN SUBJECTS

Correction of Preamble to Proposed Policy

In the August 23, 1974 issue of the FEDERAL REGISTER (39 FR 30648), the Department of Health, Education, and Welfare published a notice of proposed rulemaking governing research, development, and related activities, supported by the Department, involving the fetus, abortus, pregnant women, in vitro fertilization, prisoners, and the institutionalized mentally disabled.

After publication the following errors were noted in the preamble to the proposed rulemaking:

(1) The initial three paragraphs of Section C on page 30650 fail to indicate that, because of the Department's concern about the ethical issues surrounding in vitro fertilization (whether or not implantation is contemplated), the proposed rulemaking would require that all activities involving in vitro fertilization be reviewed by the Ethical Advisory Board prior to funding. In order to make clear this concern these paragraphs have been revised to read as follows:

• • • • •

C. A number of respondents recommended that the policy governing in vitro fertilization be strengthened, on the one hand, or liberalized, on the other. The Department has considered these recommendations, and concluded that while it is necessary to impose certain restraints, it is contrary to the interests of society to set permanent restrictions on research which are based on the successes and limitations of current technology. Therefore, the Department would expect the Ethical Advisory Board, which must review all applications involving in vitro fertilization (whether or not implantation is contemplated) to weigh, with respect to specific proposals, the state of the art, legal issues, community standards, and the availability of guidelines to govern each research situation. In sum, if there is a possibility that the conceptus might be sustained in vitro beyond the earliest stages of development, the Ethical Advisory Board is to consider this possibility, and determine what guidelines should govern decisions affecting that fetus, if the research is to be permitted. If, on the other hand, implantation is attempted and achieved, then regulations governing the fetus in utero shall apply.

• • • • •

(2) Several sentences were inadvertently omitted from the first and second paragraphs of the discussion of "Viability of the Fetus" in the first column on page 30651. These sentences are now inserted and as revised, the paragraphs read as follows:

2. "Viability of the Fetus." Some respondents suggested specific criteria such as birth weight, crown-rump length, or gestational age, similar to those used in England, such criteria to be reviewed and reissued periodically by the Department. It was emphasized that the use of such objective criteria might simplify problems involved in determining what types of research might be permissible. Some respondents urged that presence of fetal heartbeat be definitive (whether or not there is respiration) while others urged that identifiable cortical activity be specified as an alternative sign of viability. Others objected strenuously to any distinction as to the nature of fetal life, holding that the physician's obligation should be the same to any fetus regardless of weight, size, or age of gestation.

The Department, having reviewed these comments, concludes that the distinction between a viable and a nonviable fetus is both valid and meaningful. At the same time, the Department does not believe that the use of weight, size, gestational age and/or cortical activity is a valid substitute for the judgment of a physician, particularly in view of the wide variation in the facilities and arts available to him both in this country and abroad. The Department further concludes that the issue of viability is a function of technological advance (see § 46.303(e) of the regulations), and therefore must be decided with reference to the medical realities of the present time, while reserving the right to redefine the parameters as conditions warrant."

• • • • •

(3) Section H on page 30651 incorrectly implies that, under the proposed rulemaking, fetuses for which abortion is contemplated may be placed at greater risk than fetuses in general. In fact, however, as is stated already in section F on page 30651, the proposed rulemaking bans the undertaking of research, development, or related activities involving the fetus prior to the commencement of the abortion procedure, at which point the question of risk to the fetus is no longer an issue. Such activities which are permitted under the regulations would be reviewed by the Ethical Advisory Board prior to funding. Section H should therefore be deleted and section I on the same page relettered section H.

Dated: October 21, 1974.

CASPAR W. WEINBERGER,
Secretary.

[FR Doc.74-24994 Filed 10-24-74;8:45 am]