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
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 categorized 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; subject to deceit, public embarrassment, or humiliation are all examples of procedures which require thorough scrutiny by the institutional committee. (See also Section I, 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.


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
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
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


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.I. 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:

[Signature]

Roger J. Steinert
Chairman, University Senate Committee on Research
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. The purpose of this policy is to provide a basis for protecting the rights and welfare of human subjects participating in 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. 78, dated December 1, 1970 (1). The changes made in the current policy are the following: Sec. 46.2 would make it clear that the condition of an organizational committee established in the organization for review is an effective part of the decision-making process. Sec. 46.2(a) would require that each assurance provide a provision under which the organization submitting the assurance would agree to notify DHEW immediately of any incidents that would be considered to be as serious as those requiring specific reporting under the Code of Federal Regulations. Sec. 46.2(b) would prohibit the use of an exculpatory clause in any assurance. Sec. 46.2(c) would require organizations receiving receipt of the assurance to certify that any activity involving human subjects has been reviewed and approved by the organization in accordance with this policy. Sec. 46.2(d) would require organizations to certify that they carry out reviews of and approval of applications and proposals prior to submission. Sec. 46.2(e) would require organizations to keep records of their review activities. Sec. 46.2(f) would require organizations to assign a single point of contact for review activities.

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 incompetent persons in biomedical research, the protection of persons injured in medical investigations, and the general review of the 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 duplicate, 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 5:30 p.m. All relevant materials 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.


CASPER W. WINSTEINER, 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. 46.1 Applicability.
46.2 Policy.
46.3 Definitions.
46.4 Submission of assurances.
46.5 Type of assurances.
46.6 Minimum requirements for general assurances.
46.7 Minimum requirements for special assurances.
46.8 Obligation to secure informed consent; prohibition of exculpatory clauses.
46.9 Documentation of informed consent.
46.10 Reserved.
46.11 Certification, general assurances.
46.12 Certification, special assurances.
46.13 Proposals lacking definite plans for the involvement of human subjects.
46.14 Proposed material not submitted with the intent of involving human subjects.
46.15 Cooperative activities.
46.16 Investigational new drug number.
46.17 Implementation and revision of assurances.
46.18 Organization's executive responsibility.
46.19 Withholding of funds.
46.20 Organization's records.
46.21 Report.
46.22 Early termination of awards; sanctions for noncompliance.
46.23 Conditions.

AUTHORITY: 5 U.S.C. 301.

§ 46.1 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.

§ 46.2 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. To ensure that the requirements of these regulations are carried out, the principal investigator and the principal department of the organization are responsible for the protection of the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW. The investigator shall be responsible for the protection of the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW. The investigator shall be responsible for the protection of the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW.

(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. It shall be determined that the risks to the individual are outweighed by the potential benefits to himself or her 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" 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 project or program 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 procedure to be followed, and their purposes, including identification of any procedures which are experimental.

(2) An assurance that the attendant discomforts and risks are 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 subject, an offer to provide for his withdrawal of the consent, an offer to continue participation in the project or activity at his own risk.

(6) "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.

(7) "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 human 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 review of the supported activities, a set of implementing guidelines, including identification of the committees and a description of its review procedures; or, in the case of special assurances concerning specific single projects or activities, a report of initial findings.

FEDERAL REGISTER, VOL. 38, NO. 194—TUESDAY, OCTOBER 9, 1973
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 type of its components or field activities. General assurances will be required from organizations with 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 policies, 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. (2) The committee's membership, maturity, experience, and expertise must be such as to justify its advice and counsel. In addition to possessing the professional competence to review the 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.

§ 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, by inducement or by 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 determination that the procedures are adequate and appropriate shall be fully documented. The documentation of consent will follow one of the following forms:

(a) Provision of a written consent document embodying all of the basic elements of informed consent. This document must 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 to 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 person presenting 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 objections of considerable immediate importance and that any reasonable alternative means for obtaining 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

FEDERAL REGISTER, VOL. 28, NO 194—TUESDAY, OCTOBER 9, 1973
required for annual review, with documents 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 DHW.

The proposal will be reviewed by the Secretary. In no event be reviewed by the DHEW operating agency concerned and completed before review by the organization has been completed.

(b) Proposals not certified. Proposals not properly certified, or submitted as not involving human subjects and found by the operating agency to involve such 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 the general assistance (e.g., institutional-type grants) not requiring DHEW approval for specific expenditures, any activity involving human subjects must be undertaken until the organization has submitted to DHW:

(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 submitted to provide certification for the initial grant or contract period concerned. No additional documentation is required. If the terms of the grant or contract require additional years of support, but with periodic award or obligation of funds, any noncompeting renewal application or proposal involving human subjects shall be reviewed in the manner described in the preceding section.

§ 46.13 Proposal lacking a definite plan for involvement of human subjects.

Certain types of proposals are submitted with the knowledge that subjects are to be involved within the project period. Such projects cannot properly be included in an application. These include (a) contracts for 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 prior animal studies, or upon the purification or destruction of human subjects. Such proposals should be reviewed and certified in the same manner as more definitive proposals, but may be certified for resubmission to the organizational committee who shall have completed their review. If such plans involve the use of human subjects. Under such circumstances, in addition to complying with all other terms of the contract, no activity involving the use of human subjects 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 after completion of definite plans and (b) a detailed description of the proposed activity (including any protocol or similar document). Where support is provided by DHEW, does not anticipate involvement of subjects with 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 DHEW, does not anticipate involvement of subjects with human subjects, no certification should be submitted in the manner described in the preceding section.

§ 46.15 Cooperative activities.

Cooperative activities are those which involve organizations in addition to the general contractor task or subcontractor (such as an under the grantee or a sub-subcontractor under a prime contractor). In such instances the general 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 review policy applies and the general 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 the following:

(1) Cooperative organization with accepted general assurances. When the cooperative organization has on file with DHEW an accepted general assurance, the grantee or contractor may carry out a 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 organization recommends his or the recommendation that concern individuals for whom the cooperation organization has responsibility in accordance with its own assurance.

(b) Proposals submitted with the intent of not involving human subjects.

If a proposal, at the time it is submitted to DHEW, does not anticipate involvement of subjects with human subjects, no certification should be submitted. In those instances, however, where it later becomes appropriate to involve 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 DHEW, does not anticipate involvement of subjects with human subjects, no certification should be submitted in the manner described in the preceding section.
PROPOSED RULES

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 regulations.

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 shall be 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 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, the Secretary 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.
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 ill in research, development, and demonstration activities. The report of the study group that had 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 we are still in the process of 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 in the Federal Register as proposed rulemaking for further public comment. Such a procedure is consistent with the long established DHEW policy for permitting extensive public opportunity to affect the promulgation of DHEW regulations.

It must be clearly understood by the reader of this notice that follows is not a new 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 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.


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

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

SPECIAL POLICY CONSIDERATIONS

Summary


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. The 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 consent to involvement in such activities. Therefore, as a supplement to DHEW policies, special protections are proposed for children, prisoners, and the mentally ill 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 in use 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 provisions whether or not particular research, development, or demonstration activities are Federally active.

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

FEDERAL REGISTER VOL. 18, NO 221—FRIDAY, NOVEMBER 16, 1973.
NOTICES

Table of Contents

Introduction
I. Definitions
II. General policy considerations.
III. Children
A. Policy considerations
B. Agency Ethical Review Board
C. Protection Committee
D. Special provisions
IV. Special categories
A. The abortus
B. The products of in vitro fertilization
V. Prisoners
A. Policy considerations
B. Organizational Review Committee
C. Protection Committee
D. Payment to prisoners
E. Accreditation
F. Records
VI. The mentally ill
A. Policy considerations
B. Ethical review of projects and protection of subjects
VII. General provisions
A. Referral to Ethical Review
B. Procedures requiring special consideration
C. Research conducted in foreign countries
D. Research submitted pursuant to DHESW regulatory requirements
E. Clinical research not funded by DHESW
F. Confidentiality of information and records
VIII. Draft regulations

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 DHESW policy, as well as in ethical codes pertaining to research in human subjects, the key tone 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 illnesses, and when fully and properly informed, may legally and freely give consent to accept the risks of participating in research activities. Parents and legal guardians shall 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 protection. Nevertheless, to prescribe research on all such subjects, simply because existing protections are inadequate, would be too deny them potential benefits, and is therefore, inequitable. Knowledge of some diseases and therapies can be obtained only from such subjects, whether children or adults, who will 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 thereby impair 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 those 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:

Subject at risk means any individual who might be exposed to the possibility of harm, physical, psychological, sociological, or otherwise, as a consequence of participation as a subject in any research, development or demonstration activity thereafter called "activity" which involves the application of established and accepted methods necessary to meet his needs.

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:

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 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 contact 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 paragraphs 1, 2, and 3, 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 receive special policy and procedures set forth in this document. 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 to be 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. Conceptus should be considered at risk 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 necrated at the time of expulsion, a dead fetus, and isolated
NOTICES

L. Supplementary judgment is the judgment made by others to the person giving consent to the procedure, for which the subject cannot give adequate consent. The person giving consent to the procedure must be made to believe that the subject is not competent to make such a judgment. The purpose of supplementary judgment is to protect the rights of the subject, which may be violated by the procedure, and to protect the subject from the consequences of the procedure.

II. General policy considerations. In general, clinical research, like medical practice, entails some risk to the subject. The potential subject is unable fully to comprehend the risks which might be involved in the research procedure, 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 of the subject. Where it is clear by law that consent of a parent or legal representative is valid for established and generally accepted therapeutic procedures, the same consent for research is valid. In practice, parental or guardian consent generally has been accepted as a prerequisite for all therapeutic research although the issue has not been definitively resolved in the courts. When research might expose a subject to risk, without the consent of the subject, the research should not be conducted.

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. However, there are circumstances, however, which not only justify, but even require their participation. Children do differ from adults in their psychological responses, both to drugs and to procedures. The well-being of children is improved, in this sense, by the laws of development, and in this respect, no one is more significant to children suffering from disease. Children are the only subjects whom this data can be obtained. Furthermore, these data 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 requires that drugs be tested for safety, efficacy, and dosage in children and pregnant women before being approved for use in treatment illness in such patients. Food and Drug Administration (FDA) approves for the use of a new drug depend upon submission of proposed labeling for a new drug which must include adequate directions for use "adequate warnings" as to unproved uses. Acceptance of a new drug

---

2 FDCA Act Sec. 505 (f), 21 U.S.C. Sec. 355 (f)
rests on the adequacy of the research reports submitted with the application to support the proposed labeling. Thus, in order to approve a drug to be distributed in interstate commerce with children or pregnant women, sufficient testing must have taken place in children or pregnant women to substantiate claims on the labeling for safety, efficacy, and dosage for those groups. If the safe and efficacious dosage for children and pregnant women has not been determined, the label will state so. 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 sharper scrutiny of the medical, safety, and stringent procedural safeguards for all subjects of such research.

Judgments concerning the ethical risks of research depend partly upon the scientific judgment of the expected 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 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 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 would need to be made directly involving those 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 DH&H agency, and participation by a Protection Committee at the institution in which the research is to take place. 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 DH&H agency shall appoint an Ethical Review Board to provide review of ethical issues in research involving human subjects by people whose interests are not solely those of the scientific community. Its function 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 review 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 required 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 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 appropriate 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 impact. However, review proposals received from these Primary Review Committees.

An investigator proposing research activities which expose children to risk must document part of the application for support, that the information to be gained can be obtained in no other way. The investigators also stipulate 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 the Board approve any projects which entail substantial risk. The Protection 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 all parental and subject consent must be obtained by the study, to full Protection Committee involvement in the research. Numerous recommendations for procedures to be followed by the Protection Committee will be included in the report of the Ethical Review Board which is 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 10, shall be drawn from the general medical, and other professional knowledge (for example, research scientists (including social scientists), physicians, lawyers, clergy, or ethicists, and other representatives of the public, none of whom shall be employed by the Board or affiliated with the Board. Appointments shall be made by the agency, which will establish the terms of office and other administrative procedures for 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.

Protection Committee: Protection of individual subject. 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. Considerations might affect the proper choice of subjects. Therefore, the sponsoring institution shall designate a Protection Committee to oversee: (1) the process of
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 the consent 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 about the review process, including information about safety, risk, efficacy, and protection procedures, will be provided to the Protection Committee by the agency sponsoring 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 DIEW, supplementary judgment on behalf of the child subject.

The institution's Protection Committee shall be comprised of at least 5 members to select 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 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 sponsoring agency.

D. Special provisions. Consent of both parents. Even where State law may permit only one parent 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, 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 not substituting for parental concern and consent.

2 The child's consent. An important addition to the requirement for parental consent is the requirement for the child subject's consent. Clearly infants have neither the comprehension nor the independence of judgment to consent; older children might or might not have the necessary 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 requirement of parental consent for medical procedures is intended to be protective rather than coercive. Thus, while it was held not to be unlawful to proceed with the consent of the child, but without consent of the parent or legal guardian, the reverse should hold. Therefore, in addition to consent of both parents, consent of the child 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, foster or otherwise.

4. The fetus. Respect for the dignity of human life must not be compromised whatever the age, circumstances, 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 vigor and with additional safeguards for the fetus. The recent decision of the Supreme Court on abortion does not nullify the ethical obligation to protect the developing fetus from avoidable harm. This may mean that 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 Committee, unless the Protection Committee determines that the research involves no risk to the fetus. Recruitment of pregnant subjects for research reviewed by the Board shall involve the institution's Protection Committee in the institution's 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. Consent for abortion notwithstanding. Both the mother and the father have an interest in the life and legal rights 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 whereabouts are unknown or he is deemed 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 that further viability is of utmost importance. Such research has already contributed significantly to improved care in the care of the premature. Knowledge of fetal drug metabolism, enzyme activity, and the development of organs is essential to progress in preventing or offsetting certain conditions prevailing 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 only underscores the ethical issues involved in research on the non-viable human fetus. No procedures should be undertaken on the non-viable fetus which clearly cause suffering or death, certain research essential to improve both the chance of survival and the health status of premature infants. Such research might meet ethical standards as well as the standards of appropriateness of knowledge of human development necessary in this area, given the increased capacity to offset the disabilities associated with prematurity.

It is imperative, however, that the inquirer first demonstrate that appropriate benefits on animals have in fact been exhausted and that therefore the research is necessary in the first place. A thorough review of 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 an interest on the part of the pregnant woman in what happens to the product of conception. Some women feel strongly that abortion may not be, or may be obtained for the aborted fetus; others do not. In order to give every woman the opportunity to declare her wishes, consent of the pregnant woman for participation of any research involving 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 such scientific projects involving the abortus must be reviewed by the Ethical Review Board and recruitment of individual pregnant women for such research must in
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 ensure 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 those 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 must be employed 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 non-viable, it is not possible 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 human fertilized ova 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 for the protection of those who are conceived. These restraints must be of such nature and scope as to be consistent with the development of sound and beneficial medical procedures. Under the same time permitting scientific advancement which might well benefit society. A mechanism is required to weigh, at any given time, the value of the art, a specific investigation, alternative approaches, local community norms and standards, and the availability of guidelines to govern the research situation. This mechanism is provided by the Ethical Review Board. Broadly, this Board will determine the acceptability of a project involving in vitro fertilization, and by recognizing the state of the art, and as well as societal concerns, propose appropriate research policy.

Care must be taken not to bring human ovum 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. Research involving the implantation of human ova fertilized in the laboratory into recipient women should be supported until the appropriate scientific review board is satisfied that there has been sufficient study of such subjects (including sub-human primates) to demonstrate the safety of the technique. It is recommended that this determination of safety be made after 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 ethical guidelines are developed governing the donor and recipient "parents" and of research institutions and personnel.

V. Prisoners—A. Policy considerations.

Prisoners in research often require 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 more extended periods 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 prison subjects 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 associated with prisoners who are confined in an institution. Many aspects of institutional life may influence a decision to participate; the content of the request for participation, 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 goals for which to earn money, research projects offer a source of income. Where living conditions are unsatisfactory, research projects might offer a chance for accommodation. 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, upon whom his other 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 unethical as to respect to the prisoner. In such instances, participation inevitably carries with it the hope that a successful result will improve the subject 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 Nuremberg Code requires that subjects of biomedical support activities, which are defined 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 Board 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 informed consent. Although the subject might be adequately informed, and competent to make judgments, the voluntariness of the person's consent remains in 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 judgment on the administration of justice or the management of the correctional system. At the same time, the Department should not be expected to provide the additional protections to prisoners participating in research.

Most 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 participation. These rights and protections are today being considered as they apply to research conducted under its auspices, the DHHS is proposing special guidelines for the protection of prisoners confidential 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 DHHS policies.

FEDERAL REGISTER, VOL 38, NO. 221—FRIDAY, NOVEMBER 16, 1973
NOTICES

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 heretofore been required for ethical considerations or for specific problems reported 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 to ensure 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 DH&EW 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 the 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 or the organization of the Protection Committee (see below) in order to see that the selection of subjects who may be included in the research is not influenced by the existence of specific research projects.

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 so required by the sponsoring DH&EW 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 not established assurance, composition as well as recommendations of the Organizational Review Committee shall be considered an essential 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 an orderly mechanism for withdrawal.
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. This is a model. 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 consideration.

The institutionalization of mentally infirm is 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 certain institutional procedures. Such confinement restricts their freedom of choice and imposes elements of coercion, which limit their capacity to give truly voluntary consent. 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 both below and on the impressions 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, but there is no sure 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 en-cumbered 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 these 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.

2. A Ethic 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 of the ethical review of projects and protection of subjects shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reason for it no longer exist.

If, in the judgment of the Secretary, an individual serving as principal investigator, program director or an individual 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 separate 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 reason for it no longer exist.

In reaching a determination on compliance, with respect to subjects with limited capacity for consent, the Secretary will consider the competence 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, or an institutional review committee and to adequate, 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 or 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, 1972, 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 46.25 redesignating §§ 46.21 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

Secs. 46.21 Applicability.
46.22 Informed consent.
46.23 Need for legally effective consent.
46.24 Definitions.
46.25 Ethical Review Board; Composition; Duties.
NOTICES

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
46.41 Applicability.
46.42 Purpose.
46.43 Definitions.
46.44 Duties of Organizational Review Committee where prisoners are involved.
46.45 Protection Committees; Duties; Composition.
46.46 Prohibition on participation in activities involving prisoners.
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 INFERM 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 G—ADDITIONAL PROTECTIONS FOR CHILDREN INVOLVED AS SUBJECT IN DHEW ACTIVITIES
Section 46.21 Applicability. (a) The regulations in this part 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 research activities to which this subpart applies. These safeguards are imposed in such a manner as to minimize the potential risks to children in activities conducted thereunder.

(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; and duties. The Board shall be composed of members who shall be selected by the DHEW. The members shall be selected as to their qualifications for such services in the public interest. The Board shall be composed of at least five members who shall be selected by the DHEW. The members shall be selected as to their qualifications for such services in the public interest.

NOTICE

FEDERAL REGISTER, VOL. 38, NO. 221—FRIDAY, NOVEMBER 16, 1973
NOTICES

FEDERAL REGISTER, VOL. 38, NO. 221—FRIDAY, NOVEMBER 16, 1973

this subpart, an activity to which this subpart is applicable, is that which is to be conducted outside the United States. Information to be written documentation satisfactory to DHEDW 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 4831 Applicability. (a) The regulations of DHEDW are applicable to all Department of Health, Education, and Welfare research, development, or demonstration activities involving pregnant women, unless there is written documentation satisfactory to DHEDW that the proposed activity is applicable, or that no activity to which this subpart is applicable may involve: (1) an abortus or a non-viable fetus unless maternal consent has been obtained; (2) activity will have no adverse effect on the fetus, or is clearly therapeutic with respect to the fetus involved; (3) involving the abortus or the non-viable fetus, or (3) involving in vitro fertilization of human eggs.

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 by subpart A.

Section 4832 Purpose. It is the purpose of this subpart to provide additional safeguards in research, demonstration, or activities involving pregnant women so that they are applicable to assure that they conform to appropriate ethical standards and relate to important public health objectives.

Section 4833 Definitions. As used in this subpart:

(a) "DHEDW" 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;

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

(c) "Board" means the Board established under §425.4.

(d) "Protection Committee" means a committee referred to in §425.2.

(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 from the uterus, or as a result of normal or surgical intervention to terminate a pregnancy, prior to viability. (See §4831 for definition of this term.) This regulation does not apply to activities that, under this policy, excludes the abortion.

(h) "Viability of a fetus" means capability of the fetus to survive outside the body of a female, through administration of human semen and such events.

Section 4834 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 ethical and social acceptability of activities from the standpoint of societal need and ethical considerations, taking into account the substantive needs of the affected population. (b) The Protection Committee of a medical or behavioral research involving human subjects, or

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

(b) "Prisoners" 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, or individuals detained by virtue of statutes which provide alternatives to criminal prosecution. The term includes all Department of Health, Education, and Welfare, and the Federal Bureau of Prisons.

Section 4841 Additional duties of Organizational Review Committee. (a) Wherever prisoners are involved, (1) in carrying out the responsibilities under subpart A of this part for activity 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; 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 suitable for performance on nonprisoners; and (4) that no prisoner will be offered any reduction in sentence or other correction only for his participation in such activity which is not comparable to that offered for other activities at the facility not related to the development, demonstration or similar nature.

(b) In addition, the Organizational Review Committee shall have the following duties: (1) To review and approve or modify the procedures proposed for the Protection Committee carrying out its functions as set forth in §485. (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, 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 DHEDW in the contract or grant.

(c) Activities to which this subpart is applicable must provide for the designation of an Organizational Review Committee, where necessary. (d) A Committee has been established under subpart A. (e) Protection Committees: duties, composition. (a) No activity covered by this subpart will be approved by DHEDW unless it provides for the establishment of a Protection Committee to carry out the following functions as recommended by the Organizational Review Committee: (1) By DHEDW: (1) Reviewing the procedures for selecting participation by prisoners in the research activity to determine that all terms of informed consent, as outlined in §485, are satisfied; (2) monitoring the progress of the research and the continued willingness of subject, as well as the anticipated needs of the subject, to make a truly voluntary and uncoerced decision whether or not to participate in such activities.

Section 4835 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, are to be conducted outside the United States, if: (1) 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 Protection for Prisons Involved as Subjects in DHEW Activities

Section 4841 Applicability. (a) The regulations of DHEDW are applicable to all Department of Health, Education, and Welfare, research, demonstration, and development activities involving prisoners as subjects.

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

Section 4842 Purpose. It is the purpose of this subpart to provide additional safeguards for activities to which this subpart is applicable to protect the prisoners from the risk of victimization, as much as possible, in activities conducted thereunder, because of their incarceration, might be under conditions not comparable to the liberty to make a truly voluntary and uncoerced decision whether or not to participate in such activities.

Section 4843 Definitions. As used in this subpart:

(a) "FWA 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) "Prisoners" 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, or individuals detained by virtue of statutes which provide alternatives to criminal prosecution. The term includes all Department of Health, Education, and Welfare, and the Federal Bureau of Prisons.
NOTICES

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 physician, may be a government official with the prison facility or the legal entity having jurisdiction over the facility, except for persons employed by the department in a teaching capacity. Any prisoners serving on the Committee shall be compensated at a rate consistent with the rate paid for prisoners participating in activities at the facility to which this subpart is applicable.

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

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 subject is not in a ward of a mental hospital. Confining a mentally infirm individual to an institutional setting (2) might be unable to comprehend the type risks which may be involved in such activities, and (3) may 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 of support (through grants,兴致, 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, either by court order or voluntary commitment, in an institution for the care and/or treatment of mentally infirm individuals.

Section 46.54 Limitations on activities involving the institutionalized mentally infirm individual may be included as a subject in a DHEW activity unless:
(a) The individual’s consent to the activity is concerned with: (1) The diagnosis, treatment, prevention, or etiology of the impairment which while seated in an institution, must be obtained only from those subject; or (2) the proposed activity is concerned with the effect of institutional life on the subject and involves no risk to the individual’s consent to such participation has been, or can be secured; and
(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 whether or not the proposed activity is to be participated in by the individual, the individual’s consent to such participation has been, or can be secured; and
(d) The Protection Committee, provided for in §46.58 of this subpart, has reviewed and approved subject participation in the activity (by class or by individual).

Section 46.55 Additional provisions for institutions where mentally infirm individuals are involved as subjects in DHEW activities.

5.211.Friday, November 16, 1973

FEDERAL REGISTER VOL. 38, NO. 221

Section 46.55 Protection Committees; duties; composition. (a) No activity covered shall be conducted unless it provides for the establishment of a Protection Committee to carry out the following duties: (1) Overseeing the process of selecting the mentally infirm individual who may be included in the activity, (2) monitoring the progress of the activity with special attention to adverse effects on subjects, (3) advising the mental guardian and/or the subject concerning the latter’s continued participation in the activity if conditions warrant, (b) The composition of such Protection Committee shall conform to the requirements set forth in §46.36(a).

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

Section 46.57 Activities to be performed outside the United States. In addition to the 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, cultural, and ethical standards of the locale in which it is to be performed.

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 grantees or contractors for that 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 a grant or contract award shall constitute consent of the grantee or contracting organization to inspection and audits of records pertaining to the conduct of the activity.
NOTICES

(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 DHHS funds are involved, he may, upon reasonable notice to the organization of the basis for such action, determine that its eligibility to receive further DHHS grants or contracts or participate in DHHS 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 therefore 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 therefore 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 73-32922 Filed 11-15-73; 8:45 am]

FEDERAL REGISTER, VOL. 38, NO. 221—FRIDAY, NOVEMBER 16, 1973
RULES AND REGULATIONS

In the Federal Register of October 8, 1973 (38 FR 27892), 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 of those of the Department, the internal policies of the policy set forth in Chapter 1-40 of the DH&H Grants Administration Manual. These regulations would provide that no activity involving any human subject as a risk supported by DH&H that a contract shall be undertaken unless a committee of the applicant or offering organization has reviewed and approved such activity and submitted to DH&H a certificate 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 activity to maintain its continued acceptability. The notice provided for the filing of comments within 30 days, ending November 8, 1973.

Comments were received from more than 146 representatives of grantee institutions and organizations, from approximately 72 public groups or organizations, and from over 30 individuals. They include over 600 criticisms of individual sections of the proposed rule. The comments and the Department's conclusions are as follows:

A. The applicability and scope of the policy were challenged by several respondents. Suggestions included the following: 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, and the source of support, and unequivocal limitation of the policy to DH&H grants and contracts as contrasted to other organizational activities. Comments were also made for the provision of exceptions for subject groups such as prisoners, academic colleagues, students, and laboratory personnel, or exceptions for specific procedures such as those that include the injection of the diet within normal ranges, the taking of blood and urine samples, surgical and autopsy specimens, and the use of hair, nasal oropharyngeal, and placental materials.

B. It was also proposed that the policy only be applicable to specific subjects such as the prisoner, the child, the fetus, the abortus, the animal, and the candidate for sterilization or psychosurgery.

The Department, having considered these frequently conflicting recommendations, concludes that the language of the comments should be emphasized in their concern with the risks involved in research, development, and related activities. It concludes that the comments advanced for specificity in including or exempting certain activities are not derivable 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 solicits comments to revise the policy to include any activity which necessarily falls 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 not proposing to designate the specific 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 experiments.

B. Criticisms of the basic policy statement centered around the requirement that organizational committee review determinations be as effective as or more effective than the individual signer or that the individual signer or the committee be as effective as the individual signer. It was also suggested that the regulation require a new review of the requirements for informed consent to 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 review should be to determine that the subject is fully informed.

The Department, having considered these comments, concludes that the term “significant” would tend to weaken not to strengthen the requirement, and that the intent of the proposed change is better served by providing an opportunity for the responsible authority to designate activities, including methods and procedures, to which the policy is inapplicable. The proposed changes in the risk-benefit clause appear to be more amenable 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 “barred sufficient” rather than “lawfully, reasonably.” The Department concurs that the requirement is strengthened by the substitution of the phrase “legally effective.” It does not propose to reserve the right to the committee to determine that the subject is fully informed. It is essential that the committee representing a wide spectrum of whose expert professional skills coexist, in no other activity the regulation of an activity’s inherent risks, and who can provide the proper judgment, weigh such risks and benefits before determining that the benefits accepted these risks. It is also important that the committee determine that the subject will receive adequate protection against known risks. These conclusions lead to certain editorial changes which are reflected in § 46.2.

C. Objectives were raised to several of the definitions incorporated into the regulations: (i) since the DH&H may make grants to any agency, and (ii) in some instances, (iii) objections were also raised, (iv) to the term “sociological harm” as meaningless, and to the use of the term “harm,” rather than the common legal term “injury.” (v) The definition of “informed consent” was challenged or several of the definitions incorporated into the regulations: (i) since the DH&H may make grants to any agency, and (ii) in some instances, (iii) objections were also raised, (iv) to the term “sociological harm” as meaningless, and to the use of the term “harm,” rather than the common legal term “injury.” (v) The definition of “informed consent” was challenged or several of the definitions incorporated into the regulations: (i) since the DH&H may make grants to any agency, and (ii) in some instances, (iii) objections were also raised, (iv) to the term “sociological harm” as meaningless, and to the use of the term “harm,” rather than the common legal term “injury.” (v) The definition of “informed consent” was challenged or several of the definitions incorporated into the regulations: (i) since the DH&H may make grants to any agency, and (ii) in some instances, (iii) objections were also raised, (iv) to the term “sociological harm” as meaningless, and to the use of the term “harm,” rather than the common legal term “injury.” (v) The definition of “informed consent” was challenged or several of the definitions incorporated into the regulations: (i) since the DH&H may make grants to any agency, and (ii) in some instances, (iii) objections were also raised, (iv) to the term “sociological harm” as meaningless, and to the use of the term “harm,” rather than the common legal term “injury.” (v) The definition of “informed consent” was challenged or,
RULES AND REGULATIONS

ED removed from its original position in the regulations, and inserted elsewhere. The terms "eminent problems" and "immediate notification" have been eliminated. These changes are reflected in 49 part 9, 49 parts 16, and 49 parts 75.

Comments were also concerned with the proposed requirement that any committee or quorum of a committee shall consist of at least five members. The authorization to conduct business at a quorum in the absence of such a person from a quorum could not be considered as a substitute for the determination of the issue. The comments of the Department's conclusions are reflected in 49 parts 6(b) (2), (4), (15), and (16).

E. Comments on the requirement for special assurance 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 § 49.67.

F. Comments on the requirement to secure written consent point out that the requirement appeared to be in conflict with the procedures and the section on documentation of written procedures, since the latter permits some modification of written procedures. Other respondents suggested changes in language similar to that found in § 49.62. The comments on § 49.62 were also incorporated into § 49.67.

These comments have been considered in § 49.67 to mean that there is no substantial conflict between this section and the other section on documentation of written procedures. The comments on § 49.62 were also incorporated into § 49.67.

1. Various commentators raised questions with regard to the review and approval of documents. An additional section describing reporting and disposition of documents has been added in § 49.10. The language of this section is consistent with current policy as stated in DHEW Guide on Management Manual Chapter 1-40.

J. A large number of organizations were concerned with the proposed requirement that organizational documents and approval be corrected and certified prior to the submission of documents to DHEW. Although the majority of respondents favored retaining the present policy, several organizations suggested that they would complete all of their reviews within a few days and submit the documents to DHEW. The comments on § 49.67 are not applicable to the time of first submission. A few public bodies commented this requirement as a substantial improvement over the present policy which, in their opinion, provided a great deal of working space, 49.34-49.35, and approval at a national level.

These comments have been considered in § 49.67 and it is concluded that the right to relax this requirement, and to extend a grace period for completion and certification of documents after submission of the proposal, should be extended to the Secretary. In no event will the Secretary accept for review documents after submission of the proposal. The comments on § 49.67 are not applicable to the time of first submission. A few public bodies commented this requirement as a substantial improvement over the present policy which, in their opinion, provided a great deal of working space, 49.34-49.35, and approval at a national level.

These comments have been considered in § 49.67 and it is concluded that the right to relax this requirement, and to extend a grace period for completion and certification of documents after submission of the proposal, should be extended to the Secretary. In no event will the Secretary accept for review documents after submission of the proposal. The comments on § 49.67 are not applicable to the time of first submission. A few public bodies commented this requirement as a substantial improvement over the present policy which, in their opinion, provided a great deal of working space, 49.34-49.35, and approval at a national level.
M. In order to emphasize the Secretary's authority to conduct further evaluation of proposed activities involving human subjects, the regulations provide for a process to approve, disapprove, or take action on 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 DHHS Conduct Administration Manual Chapter I-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 reduce all responsibility of the prime contractor under the provision for work done by cooperating organizations, (iii) changes which would not require submission for approval in the cooperating organization, (iv) elimination of any requirement that would restrict the prime 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 or through the mechanisms provided by the cooperating organizations. The proposed regulations permit a contractor or grantee some flexibility in terms of 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, necessary for the performance of investigational new drugs under development, were criticized on several counts. One respondent felt that the regulations would make it difficult if not impossible to obtain DHHS support for studies leading to the development of a new drug. Not all compounds requiring INDs are actual drugs under development, but are employed for other purposes. Another respondent pointed out that the pertinent FDA regulations (21 CFR 131.3(a) (2)) make no reference to the IND number, but require a 30-day delay prior to use of drugs in human subjects.

The comments having been considered, the Department agrees that references to the IND number should be replaced by reference to the 30-day delay requirement. The Department does not agree that there is a need for submission of identification on INDs which 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.

For the record to facilitate accurate definition, several respondents pointed out the difficulty of the several requirements for retention of records and recently published DHHS Administration of Grant regulations (45 CFR 74). Other comments reflected concern over the confidentiality of information which would be subject to DHHS 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 the rules 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 DHHS in the employee-employer 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 DHHS 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, sections under § 46.21(a), which refers to applicable grant and procurement regulations, would be subject to due process as provided for in those 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 investigator. While it would appear from review of clause 21 of HEW 315 that it does not prevent the Department from taking into consideration past deficiencies of an investigator, 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.

P. 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 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
The Secretary may, from time to time, determine in advance whether specific programs, methods, or procedures to which this part is applicable are subject to the limitations as defined in § 463. Such determinations will be published as notices in the Federal Register and will be included in an appendix to this part.

§ 462. Policy.

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

(b) This review shall determine whether the 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.

§ 463. Definitions.

(a) "Organization" means any public or private institution or agency (including Federal, State, and local government agencies) of the United States or any such organization in which the subject of an approved grant or contract is located.

(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 risks of death or serious injury inherent in a chosen occupation or field of service.

(3) 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, duress, over other form of constraint or coercion. The basic elements of inform consent 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; and

(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) "DHHS" 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 DHHS in accordance with the requirements of this part that a particular activity involving human subjects at risk involved in an approved and approved by the organization in accordance with the "approved assurance" on file at DHHS.

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

§ 464. Submission of assurances.

(a) Recipients or prospective recipients of DHHS support under a grant or contract involving subjects at risk shall provide written assurance acceptable to DHHS that they will comply with DHHS policies as set forth in this part. Each assurance shall be in a statement of compliance with DHHS requirements for initial and continuing committee review of the supported activities; a set of implementation guidelines, including identification of the continuing activities and a description of its review procedures; or, in the case of special assurances concerning 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 or 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.

§ 465. Types of assurances.

(a) General assurances. A general assurance describes the review and implementation procedures applicable to all DHHS-supported activities conducted by...
an organization regardless of the number, location, or type of its components or field activities. General assurances shall be required from organizations having a significant number of concurrent DHEW-supported projects or activities involving human subjects.

(b) Special assurance. A special assurance will be 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 failed to file DHEW an approved general assurance.

§ 16.6 Minimum requirements for general assurances.

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

(a) A statement of principles which will govern the organization and shall constitute all of its responsibilities for protecting the rights of its subjects. This may include appropriate existing codes or declarations, or statements formulated to provide protection similar to that afforded in any analogous law. 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 § 16.2. 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 an adequate and adequate review of activities commonly conducted by the organization. The committee must be sufficiently qualified through the maturity, experience, and expertise of its membership and diversity of its membership to assure 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 assure the acceptability of proposals in terms of organizational commitments and regulations, applicable law, standards of professional conduct and practice, and required for the committee.

(2) The committee must include persons who are in these areas.

(c) The committee shall be identical to DHEW by name; earned degree, if any, position or occupation; required protective capacity, and by other pertinent indications of experience such as board certification, licenses, etc., sufficient to describe each member's chief area of responsibility for each committee determination. Any employment or other relationship between the committee member and the organization shall be identified. The committee shall follow its rules of conduct and regulations. Changes in committee membership shall be reported to DHEW in such form and at such times as the Secretary may require.

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

(e) A committee shall consist entirely of persons who are officers, employees, or agents, of, or are otherwise associated with the organization, except from their membership on the committee.

(f) No committee shall consist entirely of persons of the same professional group.

(g) The quorum of the committee shall be defined but may not be less than a majority of the total membership duly convened to carry out the committee's responsibilities under the terms of the assurance.

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

(i) 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 assure prompt reporting to the committee of proposed changes in an action or anticipated problems involving risk to subjects or others and (3) to review and approve assurance.

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

§ 16.7 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, personnel immediately responsible for the conduct of the activity. The assurance shall be signed by the individual members of a committee satisfying the requirements of § 16.9. An organization consented to an appropriate organizational official.

(b) Describe the makeup of the committee and the training, experience, and background of its members, as required by § 16.9.

(c) Describe in general terms the risks to subjects that the committee recognizes as inherent in the activity, and justify its decision on risks, as if shall be weighed 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 § 16.10.

(e) Describe procedures which the committee will follow in its initial and continuing review of the committee of proposed changes in the activity and of any anticipated problems, involving risks to subjects or others and to assure that any such problems, including adverse reactions to biologicals, drugs, radiolabeled drugs, or to medical devices are promptly reported to DHEW.

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

§ 16.8 Evaluation and disposition of assurances.

(a) All assurances submitted in accordance with §§ 16.5 and 16.6 shall be evaluated by the Secretary through such officers and employees of the DHEW and such experts or consultants engaged for such 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 means of its completion or coordination.

(b) On the basis of its 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 conclusion of negotiations with an organization otherwise eligible for such an assurance, to submit special assurances.

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

Any organization proposing to place any subject at risk will be obligated to obtain consent. No such informed consent, oral or written, obtained under any 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.

§ 16.10 Documentation of informed consent.

The actual procedure utilized in obtaining legally effective informed consent and the conditions 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 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 the committee 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 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 retained 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 no risk of harm upon the review committee and the individual is not to be put to more inconvenience or risk than if an unmodified procedure were to be used. The modification of either of the primary procedures for obtaining informed consent is not intended to invalidate objectives of considerable immediate importance, and (3) that any reasonable alternative means for obtaining the consent would be less advantageous to the subject. The committee is permitted to modify both procedures for obtaining informed consent, but modifications should be regularly reconsiders as a function of continuing reviews and as required for annual review, with documentation of reaffirmation, revision, or discontinuation, as appropriate.

§ 46.11 Certification, general assurance.

(a) Timely review. Unless the Secretary otherwise provides, all proposals involving human subjects submitted by organizations having approved general assurances must be given reviewed, and when found to involve subject at risk, approved, prior to submission to DHEW. In the event the Secretary provides for the performance of an 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, if any, has been completed. 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 in a form of the following certification:

If a proposal does not anticipate involving or intend to involve human subjects, no certification is to 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 activity shall be undertaken until the organization has submitted to DHEW: (a) a certification that the activity has been reviewed and approved in accordance with this part, and (b) a detailed description of the proposed activity (including any protocol or similar document). Also, where support is provided by project grants or contracts, subjects shall not be involved prior to certification and organizational receipt of DHEW approval and, in the case of contracts, prior to negotiation and approval of an amended contract description of work.

§ 46.13 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 certificate of 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, each prepared in accordance with this part, must be submitted 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 or 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).

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

Cooperative activities are those which involve organizations in addition to the cranite or prime contractor (such as a consultant under a grantee or a subcontractor under a prime contractor). If, in such instances, a contractor 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 is responsible for safeguarding the rights and welfare of the subjects.

§ 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 representatives of the Department and such experts or consultants engaged for this purpose as he determines to be appropriate. All proposals shall be examined by 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 paragraphs (a) of this section and subject to such approval or recommendation by or consultation with appropriate councils, committees, 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 consultant under a grantee or a subcontractor under a prime contractor). If, in such instances, a contractor 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 is responsible for safeguarding the rights and welfare of the subjects.
RULES AND REGULATIONS

ried out by one or a combination of procedures:

1. Cooperating organization with approved general assurance. When the cooperating organization has on file with DHEW an approved general assurance, the grantee or contractor may, in addition to its own review, request the cooperating organization to conduct an independent review and 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 committee of the cooperating organization. However, the cooperating organization shall promptly notify the grantee or contractor 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, it shall include its review and make such findings as it deems appropriate, and forward them to DHEW, but shall not be required to submit the submission of a general or special assurance which, if approved, will permit the grantee or contractor to follow the procedures 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 committee or contracting organization’s existing review committee or, if the cooperating committee is on a frequent or continuing basis as between a medical school and a group of affiliated hospitals or universities, periodic meetings 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 that organizations with special assurances. While responsibility for initial and continuing review necessarily lies with the grantee or contracting organization, DHEW may also require approval of the arrangements through cooperation with the agencies 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 § 16.11, 16.12, 16.13, or 16.14 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 been waived 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 expired before the waiver is effective 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 follow up is a condition of DHEW approval of an assurance. Committee appointments, actions, and recommendations are subject to review and 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 subject, shall be retained by the organization, subject to the terms and conditions of grant and contract awards.

(b) Except as otherwise provided by law 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 material 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 offer or applicant has been subject to a termination or suspension under paragraph (a) of this section,

(2) whether the offerer 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 or her responsibilities in 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 been taken to eliminate these deficiencies.

§ 16.22 Conditions.

The Secretary may with respect to any grant or contract or any phase of a grant or contract 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.

[FED REG 34 12580 Filed 5-29-74 Eff 6-4-74]
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 20, 1974 (39 FR 18141), 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, 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 independent Commission for the Protection of Human Subjects in Biomedical and Behavioral Research to (i) conduct a comprehensive investigation and report on ethical principles of research involving human subjects, (ii) develop guidelines which should be followed in the conduct of research to ensure that research is conducted in accordance with such principles, and (iii) make recommendations to the Secretary (A) 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 (B) 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 December 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 discussion.

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 in the November issuance, largely from grantees and contractor organizations, the Department now proposes that, in addition to the protection afforded generally to all subjects of research, development, or 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.

PROPOSED RULES

This would be accomplished by amending Part 46 to delete §§ 46.22, 46.22, redesignates § 46.1 through 46.16 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 conducted or supported by a 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 Subpart B.

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 her 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 significant and needed research, 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 such institutions that a consent committee be established to supervise the solicitation and participation of prisoners in the research. Prisoner groups are particularly concerned with the ethical implications of 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, the power to refuse enrollment 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 by 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 is limited 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 elderly 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 Introductions, Definitions, and General Policy Sections of the draft regulations published at 39 FR 18141, November 15, 1974, 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 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, distinguished from biomedical research.

The Department, having considered these comments, notes that the applicability 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 18141, paragraph A).

B. Comments also included suggestions that regulations should be proposed specifically dealing with research involving students, laboratory employees, seriously ill or terminal patients, the noninstitutionalized 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 18141.

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. The Department has not included 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 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." The suggested changes in language that would (i) link 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 applications 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 set forth in an earlier proposed rulemaking (38 FR 77272). Responding to the criticism, the Department had already (i) redefined "Subject at Risk" in 45 CFR 46.1(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 project" (iii) 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 poses unusual risk to subjects at risk.

B. Comments on the definition of "Clinical Research." The suggested changes in the definition of "Clinical Research" were not included in the proposed regulation, but are essentially concerned with diagnosis and other nontherapeutic 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." The suggestion of the addition of language concerning the need for complete disclosure, (i) the likelihood of success or failure of the experiment, (ii) the use of placebo or other control procedures, (iv) provision of information as to the progress of the investigation, (v) publication of names of all persons involved, 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 currently defined in 45 CFR 46.3(c) and would continue to be a proposed rulemaking. With respect to the specific suggestions the Department notes that: (i) as (i) is concerned, the regulations already provide 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 information affected the risk of benefit involved; and (v) pertains to the subject of a possible future proposal to change the Department and the Department reserves its options for the present. The suggestion in (v) is met by the provisions in the present proposed rulemaking to employ consent committees to advise potential subjects. The last suggestion (vii) goes beyond the requirements for informed consent as they are generally been articulated by the courts.

D. Comments also included suggestions for the inclusion of additional definitions of (a) Institutions, (b) Local Guardian, (c) Institutional Review Committee, (d) Institutionalized Mentally Infirm, and (e) 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 regulations to include legal guardian at 45 CFR 46.3(b); (iii) the definition of "organizational review committee" is implicit in 45 CFR 46.6; (iv) "Institutionalized Mentally Infirm" is specifically defined in the present proposed rulemaking at 46.503(d) to the same suggestion, and (v) definition of Children, Parents, and "Father" will be considered prior to the issuance of a future rulemaking covering research on children.

Several commentators criticized provisions of the draft policy that would have required activities to be conducted outside the United States to satisfy all requirements of the Department regulations including those based on ethical concepts similar to the Judeo-Christian moral heritage or to something more in the connotation of the ethical concept of the Judeo-Christian moral heritage or to something more in the connotation of which the research community is not comfortable. They urged the Department to delete the substantial problems for United States investigators working overseas since these concepts are often inconsistent if not in conflict with existing ethical, legal, and ethical concepts in certain foreign countries. For the same reasons, it was urged that these provisions would create problems for United States citizens assigned, detailed, seconded, acting as committeens to international organizations or to foreign governmental or private institutions.

Having considered these objections, the Division proposes to retain the concept that activities supported by partamental funds should, in general, be subject to uniform ethical policy wherever the activity may be. To the extent that activities, as modified, are funded, 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 information affected the risk of benefit involved; and (v) pertains to the subject of a possible future proposal to change the Department and the Department reserves its options for the present. The suggestion in (v) is met by the provisions in the present proposed rulemaking to employ consent committees to advise potential subjects. The last suggestion (vii) goes beyond the requirements for informed consent as they are generally been articulated by the courts.

A. A large number of respondents disagreed entirely with the idea of permitting research with the fetus, with the abortus (while living or dead), or with the pregnant woman. It is 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 certainly hamper the development of needed improvements in the health care of the pregnant woman, the abortus, and the newborn. The opposition to research involving the fetus and abortus appears to be based in part on the assumption that the research conception can be obtained through research on animal species or with children. Unfortunately, these assumptions are not valid. While much research can be conducted on 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 disease not encountered in the adult. They may react differently to the diseases affecting both adult and young, and there may be different response to the same treatment, both with regard to its effectiveness and to its safety. The Department therefore proposes to the ethical propriety of any application or proposal for the support of any activity covered by this 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, contending that it would enable the function of the local organizational review committee and that its existence would encourage the organizational review committee to be less circumspect. Others contended that an additional institutional 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 allow technical functions of the Board to be performed by 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 ethical concerns could be unethical if the science were bad. Both should be reviewed jointly.

The Department, having reviewed these comments, concludes that Ethical Advisory Boards are indispensable. 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 by the Board, and the Board is thus expected to consider 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, agreement as to the proper balance between scientist and non-scientist in the Board is essential. The comments from Congress and the public were based on the assumption that the Ethical Advisory Board will be selected by the Board on the basis of the personal qualifications of the members and of the Board itself. The Board’s role is to advise on policy, guidelines, or procedures. 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 allow technical functions of the Board to be performed by the organizational review committee. The Board’s role is to advise on policy, guidelines, or procedures.

Specific comments regarding the establishment of an Ethical Advisory Board focused on (i) the possibility that appointment of members at an agency level might be better handled by a Board selected by the Board on the basis of the personal qualifications of the members and of the Board itself, (ii) the need for an independent outside body to review the establishment of additional protection mechanisms, (iii) the need for a Board selected by the Board on the basis of the personal qualifications of the members and of the Board itself, (iv) the need for a Board selected by the Board on the basis of the personal qualifications of the members and of the Board itself, (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 the Board be instructed to work with the Board on the basis of the personal qualifications of the members and of the Board itself, (viii) that all meetings be open to the public, and (ix) that an appeal mechanism be established.

The Department, having considered these views, believes that while an Ethical Advisory Board to deal with biomedical research involving fetuses, abortuses, pregnant women, and in vitro fertilization will 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 (vi) that all employees be excluded is adopted and expanded to include full-time employees of the Federal Government. The decisions with regard to suggestions (vii) and (viii) will be governed by the spirit of the Federal Advisory Committee Act which generally require that meetings of similar advisory groups be open to the public for the purpose of policy discussion, but it is clear that meetings 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 agencies. The Board’s role is to advise on policy, guidelines, or procedures.

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 adopted the recommendation, 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 decision to the Board. 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, the ethical standards, and the availability of guidelines to govern each research situation.

Because biomedical research is not yet at the point of being able to maintain for a substantial period the non-implanted product of in vitro fertilization, no clear and present danger arises from not stipulating in these regulations the protection of the woman and 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 “etus” § 46.303 (d) be construed to encompass both the living concept of fertilization as the product of in vitro fertilization which is subsequently implanted in the donor of the ovum. Whatever the nature of the concept conception, it is intended that upon implantation, the product of conceptions by in vitro fertilization and the Department’s intent that the definition of the term “etus” § 46.303 (d) be construed to encompass both the living concept of fertilization as the product of in vitro fertilization which is subsequently implanted in the donor of the ovum.
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 administrable policy, the definition must be based on existing medical technology which permits therapeutic abortion. 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 definitive rather than any other sign of viability. The Department has concluded that the issue of viability is a function of technological advance, and therefore must be defined with reference to the medical realities of the present time. We reserve the option of defining the parameters as conditions warrant.

Only upon the basis of a definition which is both precise and consistent with current medical capability can regulations realistically be interpreted and enforced. Current technology is such that a fetus, given the benefit of available medical care, 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 advances to the point of sustaining a fetus with non-inflatable lungs, the definition can and should be modified.

The Department has therefore chosen to define viability of the fetus as § 46.301(e) requires that beat and respiration are, jointly, to be the indicator of viability.

3. "Abortion." Various comments misled the Department to believe that the definition of abortion as "not viable 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 removal of the intact fetus, or use of oxygen or drugs obtained from a fetus that has died in utero or from an abortion at autopsy. The definition reverts with minor editorial changes in § 46.301(f).

Several comments were critical of the draft regulation's provisions limiting activities involving pregnant women to those not adversely affecting the fetus. In the present proposal, the primary purpose of the activity was to benefit the fetus, it was suggested that the regulations 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 intent 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 § 46.303(a). The Department tentatively concluded that consideration of risk to benefit with respect to fetal research does not seem to be appropriate.

G. Draft regulation provisions required 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 risks to the fetus. The present draft regulations of such research is conduct 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 risk of harm in general, such risk can arise only after implementation of the decision to obtain a second parental consent to the contemplated abortion, and second parental consent to the research procedure itself.

I. Comments regarding activities involved the abortions were concerned with the issue of maintaining vital functions and signs. It was urged that maintaining vital functions at the level of the organism 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 no such distinct techniques necessary to correct congenital defects.

Neither of these objections appear valid and no significant changes in § 46.306(c) 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, and that the present 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 involved as subjects of these regulations, 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 specified group. The Department is in the process of the 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 proposed regulations.

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 practically provide additional protection of prisoners used as subjects.

The Department, recognizing the implications of these comments, refers to the authority of the organizational review committee as the primary institutional focus for the implementation of the Department of Health, Education, and Welfare regulations. It is proposed to the organizational review committee the additional duties specified under § 46.304(a).
PROPOSED RULES

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 committee and the review committee determine that an activity would involve no risk or negligible risk to any prisoner while serving as a facility, the organization may make a modification or waiver of the requirement for a consent committee.

C. Comments on the proposed prohibition of research involving 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 mandated 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 related to the nature of his confinement. The modification is incorporated into §46.406.

D. The draft requirement for DHEW accreditation of prison facilities as sites for the performance of research and 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 notion 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 agreed, and proposes to substitute "disabled" for "infirm," though noting that there is no clearly preferable collective term for the groups described.

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, they noted only the potential of the branch'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 Department and the department's proposed changes are as follows:

1. "Mentally infirm." In addition to requesting substitution of another term for "infirm," respondents objected to the definition's coverage. Some felt that it was overly inclusive; others felt that it was too narrow. Some felt that epileptics should be specifically excluded 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 should be broad enough to include any category of subjects proposed for specific addition. Minor editorial changes have been made in §46.503(b).

2. "Institutionalized mentally disabled." Commentators noted that the regulations should cover all mentally disabled persons regardless of institutionalization. In §46.503(b) of this proposed rulemaking, the requirement that only involuntary commitments are by order of a court (i.e., the draft refers to "residential and "confinement") in similar contexts, though the terms do not carry the same connotation, and (iv) the definition does not specify halfway houses, nursing homes, and psychiatric wards of hospitals, or places subjects might be institutionalized.

The Department notes that (i) the non-institutionalized mentally disabled are covered by the existing regulations published as 38 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.

While concerns are given, however, to dealing with the "institutionalized legally incompetent," who are mentally disabled in a subsequent notice of proposed rulemaking. With regard to (ii), the justification for court orders are the sole basis for involuntary confinement is correct and should be removed. Editorial changes have been made in §46.503 to emphasize that concern there is in those (e.g., (c), (e), confined) * * * in a residential institution * * * (see §46.503(c) and, in order to designate the type of institutions concerned (e.g., it), is proposed to separately define "institutionalized mentally disabled individuals." In §46.503 to include examples of such in §46.503(c) and in §46.503(d). These changes are incorporated in §46.503(e) and (f).

C. While most respondents endorsed the intent of the proposed 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 that related to a particular subject's "impairment" be worded so as to include any illness from which the person suffered 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 research 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. Further, mentally disabled people should be involved in research on infirmities other than their own because of a 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 institutionally 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 their disabilities, 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 responds to 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 §46.303. 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 same general subject matter should take root. The Department does not wish to delay publication of the final regulations as long as possible, but this is not the place to make decisions that may later be changed.

Written comments concerning the proposed regulations and proposals from interested parties by address and data, views, and arguments relating to the proposed regulations may be presented in writing, in triplicate, to the Chief, Institutional Relations 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.
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 P below.

2. Designating §§ 46.1 through 46.18 as Subpart A, renumbering these as §§ 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

§ 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 § 46.5, (3) pregnant women; and (4) in addition, these regulations are applicable to all such activities involving women who could become pregnant, except where the application or offer 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 in 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, 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 impregnation 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.

Subpart D—Provisions Related 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.

It is proposed to make any amendments that are adopted effective upon publication in the Federal Register.


Casper W. Weinberger, Secretary.
include: visits to the activity site, identification of one or more committee members who are available for consultation with those involved in the consent procedure (i.e., participants) at the participant's request, continuing permission to determine if any unanticipated risks have arisen and that such risks are communicated to the participants, periodic contact with the participants to ascertain whether they still wish 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 or without the consent of the parents for reasons of the activity's safety.

(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 subject group 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 not affiliated with the applicant or offeror 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.

(c) Where a particular activity, involving a fetus or pregnant women, presents a reasonable 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 whole or in part.

(d) The requirements of this section and § 46.304 do not oblige the need for review and approval of the application or offer by the organizational review committee, to the extent required under § 46.205 of this part.

§ 46.306 Activities involving fetal or pregnancy sperm.

(a) No activity to which this subpart is applicable. Involving activities in vivo or pregnant women, may be undertaken unless: (1) the purpose of the activity is to be used in the particular fetus or to respond to the health needs of the mother, or (2) the activity conducted as part of the activity conducted as part of (a) to the health needs of the mother, or (b) the 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) the identity of the mother is unknown or the whereabouts of the mother cannot reasonably be ascertained.

(b) Activities covered by this subpart which are permissible under paragraph (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 autopsies.

§ 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 are 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.

§ 46.401 Purpose.

This is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable. It is intended to ensure that prisoners may be under constraints which could affect their ability to make a voluntary and informed decision whether or not to participate in such activities.

§ 46.402 Definitions.

As used in this subpart:

(a) "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 authority has been delegated;
(b) "Prisoner" means any individual involuntarily confined in a penal institution.

§ 46.404 Additional duties of the organizational review committee.

In addition to the responsibilities prescribed for such committees and Subpart A of this part, the applicant's or offeror's organizational review committee, with respect to activities covered by this subpart, shall 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 the earnings, living conditions, medical care, quality of food, amenities offered to participants in the activity which would be better than those generally available to the prisoners;
(2) Determine that all aspects of the activity would be appropriate for performance on prisoners, 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-
PROPOSED RULES

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 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 aspects involved in the activity; (4) whether the committee includes a prisoner or a representative of an organization having a primary concern for 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 is composed of sufficient members who are not engaged in research, development, or related activities involving human subjects. The committee shall establish rules of procedure for carrying on its activities 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 that adequate controls are provided, he may grant the request in whole or in part.

§ 16.106 Special restrictions.

Persons detained in a correctional facility pending arraignment, trial, or sentencing in or a hospital facility for pre-arrangement, pre-trial, or pre-sentence investigation, or other persons may request the Secretary to modify or waive the requirement in paragraph (a) of this section.

§ 16.107 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 by Subjects

§ 16.501 Applicability.

(c) 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 provisions set forth herein will necessarily result in a legally effective consent under applicable State or local law to a subject's participation in such activity; nor in particular does it obviate the need for court approval of such participation where such 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.

§ 16.502 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, as much as: (a) they are confined in an institutional setting where their freedom and rights are potentially subject to limitation with the procedures and information to give an informed consent, as that term is defined in § 16.103; and (c) they may be legally incompetent to consent to their participation in such activities.

§ 16.503 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 resident institution for the care or treatment of the mentally disabled.
(d) "Institutionally mentally disabled individuals" includes but is not limited to patients in public or private mental hospitals, patients in general hospitals, patients in residential living facilities, individuals in community mental health centers, and mentally disabled individuals who reside in halfway houses or nursing homes.

§ 16.504 Activities involving the institutionalized mentally disabled.

Institutionally 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 that cannot be obtained from subjects who are not institutionalized mentally disabled;
(b) The individual's legally effective and informed consent to participation in the
PROPOSED RULES

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.

(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.

(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, which has made the determinations required under paragraph (a) of this section.

(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 (e) of this section, no activity covered by this subpart may be supported unless the applicant or offeror has established 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 in this subpart are to be performed and the subject is the requirements of Subpart A of this part.

Subpart F—General Provisions

§ 46.601 Applicability.

Sections 46.602 through 46.608 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 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, and continuing review by the organizational review committee or consent committee, such as committee minutes, records or subjects' consent, transmittals on actions, information 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 require from time to time.

§ 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.
PROPOSED RULES

(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.

(For Doc. 74-19300 Filed 8-20-74, 8:45 am)

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 30849), 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 30850 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 the 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 conception 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: