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PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE



PROTECTION OF HUMAN SUBJECTS

PROPOSED POLICY

**DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE**

**Office of the Secretary
[45 CFR Part 46]**

**PROTECTION OF HUMAN SUBJECTS
Proposed Policy**

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

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

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

Inquiries may be addressed and data, views, and arguments relating to the proposed regulation may be presented in writing, in triplicate, to the Chief, Institutional Relations Branch, Division of Research Grants, National Institutes of

Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments received will be available for inspection at the National Institutes of Health, Room 303, Westwood Building, 5333 Westbard Avenue, Bethesda, Maryland, weekdays (Federal holidays excepted) between the hours of 9:00 a.m. and 4:30 p.m. All relevant material received on or before November 8, 1973, will be considered.

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

Dated September 28, 1973.

CASPAR W. WEINBERGER,
Secretary.

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

**PART 46—PROTECTION OF HUMAN
SUBJECTS**

- Sec. 46.1 Applicability.
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- 46.21 Reports.
- 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. In order to provide for the adequate discharge of this organizational responsibility, it is the policy of DHEW that no activity involving any human subjects at risk supported by a DHEW grant or contract shall be undertaken unless the organization has reviewed and approved such activity and submitted to DHEW a certification of such review and ap-

proval, in accordance with the requirements of this part.

(b) This review shall determine whether any human subjects are at risk and, if so, that the rights and welfare of the subjects involved are adequately protected, that the risks to an individual are outweighed by the potential benefits to him or by the importance of the knowledge to be gained, and that informed consent is to be obtained by methods that are adequate and appropriate.

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

§ 46.3 Definitions.

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

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

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

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

(2) A description of the attendant discomforts and risks reasonably to be expected;

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

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

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

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

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

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

§ 46.4 Submission of assurances.

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

and proposed continuing review procedures.

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

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

§ 46.5 Types of assurances.

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

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

§ 46.6 Minimum requirements for general assurances.

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

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

(b) A committee or committee structure which will conduct initial and continuing reviews in accordance with the policy outlined in § 46.2. Such committee structure or committee shall meet the following requirements:

(1) The committee must be composed of not less than five persons with varying backgrounds to assure complete and adequate review of projects and activities commonly conducted by the organization. The committee's membership, maturity, experience, and expertise must be such as to justify respect for its advice and counsel. In addition to possessing the professional competence to review specific activities, the committee must be able to determine the acceptability of the proposal in terms of the organization's commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The committee must therefore include persons whose primary concerns lie in these areas rather than in the conduct of research,

development, and service programs of the types supported by DHEW.

(2) The committee members shall be identified to DHEW by name, earned degrees, if any, position or occupation, representative capacity, or by other pertinent indications of experience such as board certification, licenses, etc. Thereafter, changes in committee membership shall be reported to DHEW in such form and at such times as the Secretary may require.

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

(4) No committee or quorum of a committee shall consist entirely of employees of the organization.

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

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

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

(d) The procedures which the committee will follow to provide advice and counsel to project and program directors with regard to the committee's actions, as well as its requirements for reporting adverse sections, emergent problems or proposed changes in a project or other activity.

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

§ 46.7 Minimum requirements for special assurances.

An acceptable special assurance shall:

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

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

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

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

(e) Outline the circumstances under which the director or investigator will be required to inform the committee of proposed changes in the activity, or of emergent problems involving human subjects:

(f) Indicate whether the director or investigator will be required to submit

written reports, appear for interviews, or be visited by the committee or committees to provide for continuing review.

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

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

§ 46.9 Documentation of informed consent.

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

(a) Provision of a written consent document embodying all of the basic elements of informed consent. This document is to be signed by the subject or his authorized representative. A sample of the document as approved by the committee is to be retained in its records.

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

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

required for annual review, with documentation of reaffirmation, revision, or discontinuation as appropriate.

§ 46.10 [Reserved]

§ 46.11 Certification, general assurances.

(a) *Timely review.* All proposals involving human subjects submitted by organizations should be given review and approval prior to submission to DHEW. The proposal or application should be appropriately marked in the spaces provided on forms, or the following statement should be typed on the lower or right hand margin of the page bearing the name of the official authorized to sign or execute applications or proposals for the organization.

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

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

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

§ 46.12 Certification, special assurances.

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

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

Certain types of proposals are submitted with the knowledge that subjects are to be involved within the project period, but definite plans for this involvement cannot properly be included in the proposal. These include (a) certain training grants where trainee projects remain to be selected, and (b) research,

pilot, or developmental studies in which involvement depends upon such things as the completion of instruments, or of prior animal studies, or upon the purification of compounds. Such proposals should be reviewed and certified in the same manner as more definitive proposals but shall provide for resubmission to the organizational committee when definite plans have been completed if said plans involve the use of human subjects. Under such circumstances, in addition to complying with all other terms of the grant or contract, no activity involving the use of human subjects shall be undertaken until the organization has submitted to DHEW: (c) a certification that the activity has been reviewed and approved in accordance with this part after completion of definite plans and (d) a detailed description of the proposed activity (including any protocol or similar document). Where support is provided by project grants or contracts, subjects shall also not be involved prior to receipt of DHEW approval and in the case of contracts prior to any necessary negotiation and approval of an amended contract description of work.

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

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

§ 46.15 Cooperative activities.

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

(a) *Organization with general assurances.* Initial and continuing review by

the organization may be carried out by one or a combination of procedures:

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

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

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

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

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

committee in the event that the cooperating organization's committee finds the conduct of the activity to be unsatisfactory.

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

§ 46.16 Investigational new drug number.

Where an organization is required to submit a certification under §§ 46.11, 46.12, 46.13, or 46.14, and the proposal involves an investigational new drug within the meaning of The Food, Drug and Cosmetic Act, the investigational new drug number issued by the Food and Drug Administration, DHEW, shall be included with said certification, provided, however, that in those cases in which the issuance of an investigational new drug number is pending, said certification shall include an assurance that such number will be forwarded upon receipt. In no event, shall DHEW award funds under a grant or contract until such number has been supplied.

§ 46.17 Implementation and revision of assurances.

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

§ 46.18 Organization's executive responsibility.

Specific executive functions to be conducted by the administration of the organization include policy development and promulgation and continuing indoctrination of personnel. Appropriate administrative assistance and support shall be provided for the committee's functions. Implementation of the committee's recommendations through appropriate administrative action and follow-up is a condition of acceptance of an assurance. Committee approvals and favorable actions and recommendations are subject to review and to disapproval or further restriction by the organization officials.

Committee disapprovals, restrictions, or conditions cannot be rescinded or removed except by action of the committee or another appropriate review group as described and accepted in the assurance filed with DHEW.

§ 46.19 Withholding of funds.

Under no circumstances shall an activity involving subjects at risk be implemented with DHEW funds until said activity is reviewed and approved by organizational committee and a certification of such review and approval submitted to DHEW in accordance with this part. In addition, the organization staff responsible for such activity shall not proceed therewith until they have received notification of such approval, including any restrictive requirements made by the committee or the administration. They shall also be informed and reminded of their continuing responsibility to bring to the attention of the committee any proposed significant changes in project or activity plans or any emergent problems that will affect subjects. Where continuing review of projects involves the channels of administrative authority in the organization, notification of committee actions should be sent through these channels. Establishment of mechanisms for consultation and appeal by investigators and subjects may be an important condition of acceptance of an assurance by DHEW.

§ 46.20 Organization's records.

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

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

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

(d) All documents and other records required under this part must be retained by the grantee or contracting organization for a minimum of three years fol-

lowing termination of DHEW support of the activity.

§ 46.21 Reports.

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

§ 46.22 Early termination of awards; sanctions for noncompliance.

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

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

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

§ 46.23 Conditions.

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

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