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Office of the Secretary

■

PROTECTION OF HUMAN SUBJECTS

Title 45—Public Welfare

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

PART 46—PROTECTION OF HUMAN SUBJECTS

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

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

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

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

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

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

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

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

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

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

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

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

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

fied, removed from its original position in the regulations, and inserted elsewhere. The terms "emergent problems" and "immediate notification" have been eliminated. These changes are reflected in §§ 46.4, 46.6(d), and 46.7(e).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

No changes have been made in § 46.14.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Dated: May 22, 1974.

CASPAR W. WEINBERGER,
Secretary.

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

Sec.

AUTHORITY: 5 U.S.C. 301.

§ 46.1 Applicability.

(a) The regulations in this part are applicable to all Department of Health, Education, and Welfare grants and contracts supporting research, development, and related activities in which human subjects are involved.

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

§ 46.2 Policy.

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

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

(1) The risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks:

(2) the rights and welfare of any such subjects will be adequately protected:

(3) legally effective informed consent will be obtained by adequate and appropriate methods in accordance with the provisions of this part; and

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

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

§ 46.3 Definitions.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

§ 46.4 Submission of assurances.

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

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

§ 46.5 Types of assurances.

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

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

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

§ 46.6 Minimum requirements for general assurances.

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

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

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

(1) The committee must be composed of not less than five persons with varying backgrounds to assure complete and adequate review of activities commonly conducted by the organization. The committee must be sufficiently qualified through the maturity, experience, and expertise of its members and diversity of its membership to insure respect for its advice and counsel for safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the committee must be able to ascertain the acceptability of proposals in terms of organizational commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The committee must therefore include persons whose concerns are in these areas.

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

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

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

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

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

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

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

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

§ 46.7 Minimum requirements for special assurances.

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

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

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

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

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

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

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

§ 46.8 Evaluation and disposition of assurances.

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

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

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

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

§ 46.10 Documentation of informed consent.

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

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

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

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

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

§ 46.11 Certification, general assurances.

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

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

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

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

§ 46.12 Certification, special assurances.

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

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

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

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

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

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

§ 46.15 Evaluation and disposition of proposals.

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

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

§ 46.16 Cooperative activities.

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

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

ried out by one or a combination of procedures:

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

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

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

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

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

§ 46.17 Investigational new drug 30-day delay requirement.

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

§ 46.18 Organization's executive responsibility.

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

§ 46.19 Organization's records; confidentiality.

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

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

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

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

§ 46.20 Reports.

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

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

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

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

§ 46.22 Conditions.

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

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