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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

■

NATIONAL INSTITUTES OF HEALTH

Protection of Human Subjects

Policies and Procedures

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

**National Institutes of Health
PROTECTION OF HUMAN SUBJECTS
Policies and Procedures**

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

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

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

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

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

Dated: November 6, 1973.

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

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

SPECIAL POLICY CONSIDERATIONS

Summary

NOVEMBER 5, 1973.

The mission of the Department of Health, Education, and Welfare includes

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

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

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

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

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

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

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

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

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

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

2. Will of itself terminate heart beat and respiration;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

with the participation of the mentally infirm;

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

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

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INTRODUCTION

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

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

There is no firm legal basis, however, for parental or guardian consent to participation in research on behalf of subjects who are incompetent, by virtue of age or mental state, to understand the

information provided and to formulate the judgments on which valid consent must depend. In addition, current policies for clinical research afford such subjects inadequate protection. Nevertheless, to proscribe research on all such subjects, simply because existing protections are inadequate, would be to deny them potential benefits, and is, therefore, inequitable. Knowledge of some diseases and therapies can be obtained only from those subjects (such as children) who suffer from the disease or who will be receiving the therapy. Their participation in research is necessary to progress in those fields of medicine. When such subjects participate in research, they need more protection than is provided by present policy.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

fetal tissue or organs excised from a dead fetus.

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

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

I. *Prisoner* is any individual involuntarily confined in a penal institution. The term 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.

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

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

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

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

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

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

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

The law is not clear on these issues. Even if the law were clear, however, ethical questions would remain; specifically, whether, and under what conditions research involving these subject groups may proceed. Resolution of these ethical questions requires judgments concerning

both the ethics of conducting a particular research project, and the adequacy of procedures for protecting the individual subjects who will be asked to participate. The intention of this policy is to broaden the scope of review, preclude or resolve conflicts of interest, and invoke social as well as scientific judgments to protect potential subjects who might have diminished capacity to consent.

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

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

The Kefauver-Harris Act¹ requires that drugs be tested for safety, efficacy and dosage in children and pregnant women before being approved for use to treat illness in such patients. Food and Drug Administration (FDA) approval for the use of a new drug depends upon submission of proposed labeling for a new drug, which must include "adequate directions for use" and "adequate warnings" as to unapproved uses.² Acceptance of a new drug

¹ Federal Food, Drug, and Cosmetic Act, 1962 (FDC Act), 21 U.S.C. Sec. 301 et. seq.

² FDC Act Sec. 502(f), 21 U.S.C. Sec. 352(f).

rests on the adequacy of the research reports submitted with the application to support the proposed labeling.³ Thus, in order for a drug to be distributed in interstate commerce for use in children or pregnant women, sufficient testing must have taken place in children or pregnant women to substantiate claims on the label regarding safety, efficacy, and dosage for those groups. If the safe and efficacious dosage for children and pregnant women has not been determined, the label must so state. Thus, participation of children in drug research might be the only means of meeting licensing requirements for new drugs for use in children, just as studies in pregnant women might be the only means of meeting licensing requirements for new drugs for use in that class of patients.

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

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

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

Once the severity and probability of risks in a particular study have been identified, a second judgment must be made; given potential benefits of described dimensions, what are the acceptable limits of risk to which children

ethically may be subjected? Value judgments which must be weighed here transcend scientific issues and suggest that the decision requires interaction among individuals in society with diverse training and perspectives. Further, given the complexity of the issues and the opportunity for conflict among the interests of several parties (the child, the parents or guardian, the attending physician, and the research personnel), decisions regarding participation of individual subjects in research activities involving children should not rest solely with persons directly involved in the research.

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

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

1. Advising the agency on ethical issues including review of questions of policy, and development of guidelines and procedures;
2. Fostering inter-agency coherence through cognizance of the policies and procedures of other agencies;
3. Reviewing specific proposals or classes of proposals submitted to the Board by the agency. These will include proposals stipulated herein as requiring review by the Board, as well as proposals submitted on an *ad hoc* basis by agency staff. In addition, the Board may recommend that certain additional classes of research be reviewed.

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

An investigator proposing research activities which expose children to risk must document, as part of the application for support, that the information to

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

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

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

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

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

³FDC Act Sec. 505 (b), (d), 21 U.S.C. Sec. 355 (b), (d).

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

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

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

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

D. Special provisions—1. Consent of both parents. Even where State law may permit one parent alone to consent to medical care, both parents have an interest in the child, and therefore, consent of both parents should be obtained before any child may participate in research activities. Since the risks of research entail the possibility of additional burdens of care and support, the consent of both parents to the assumption of those risks should be obtained,⁵ except when the identity or whereabouts of either cannot be ascertained or either has been judged mentally incompetent. If the

consent of either parent is not obtained, written explanation or justification should be provided to the Protection Committee. Consent of school or institutional authorities is no substitute for parental concern and consent.

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

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

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

The recent decision of the Supreme Court on abortion⁶ does not nullify the ethical obligation to protect the developing fetus from avoidable harm. This obligation, along with the right of every woman to change her decision regarding abortion, requires that no experimental procedures entailing risk to the fetus be undertaken in anticipation of abortion. Further, since the fetus might be at risk in research involving pregnant women, all research involving pregnant women must be reviewed by the Ethical Review Board, unless the Primary Review Committee determines that the research involves no risk to the fetus. Recruitment of pregnant subjects for research reviewed by the Board must involve the institution's Protection Committee in a manner approved by the Board, to provide supplementary judgment.

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

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

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

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

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

⁵ *Bonner v. Moran*, 75 U.S. App. D.C. 156, 126 F. 2d 121, 139 A.L.R. 1366 (1941).

⁶ *Roe v. Wade*, 410 U.S. 113 (1973).

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

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 abortion.

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

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

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

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

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

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

project involving in vitro fertilization, and by recognizing the state of the art, as well as societal concerns, propose appropriate research policy.

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

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

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

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

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

While there is no legal or moral objection to the participation of normal volunteers in research, there are problems surrounding the participation of volunteers who are confined in an institution. Many aspects of institutional life may influence a decision to participate; the extent of that influence might amount to coercion, whether it is intended or not. Where there are no opportunities for productive activity, research projects might offer relief from boredom. Where there are no opportunities for earning money, research projects offer a source of income. Where living conditions are unsatisfactory, research projects might offer a respite in the form of good food, comfortable bedding, and medical attention. While this is not necessarily wrong, the inducement (compared to the deprivation) might cause prisoners to offer to participate in research which would expose them to risks of pain or incapacity which, under normal circumstances, they would refuse. In addition, there is always the possibility that the prisoner will expect participation in research to be

viewed favorably, and to his advantage, by prison authorities (on whom his other few privileges depend) and by the parole board (on whom his eventual release depends). This is especially true when the research involves behavior modification and may be termed "therapeutic" with respect to the prisoner. In such instances, participation inevitably carries with it the hope that a successful result will increase the subject's chances for parole. Thus, the inducement involved in therapeutic research might be extremely difficult to resist: and for this reason, special protection is necessary for prisoners participating in research, whether or not the research is therapeutic.

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

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

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

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

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

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

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

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

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

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

C. Protection Committee. The primary function of the Protection Committee is to provide supplementary judgment by

overseeing the selection of subjects who may be included in a research project to assure that their consent is as voluntary as possible under the conditions of confinement.

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

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

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

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

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

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

The Protection Committee shall be comprised of at least 5 members so selected that the Committee will be competent to deal with the medical, legal, social, and ethical issues involved. No more than $\frac{1}{3}$ of the members shall be scientists engaged in biomedical research or physicians; at least 1 shall be a prisoner or a representative of an organization concerned with the prisoners' interests; no more than 1 (except prisoners or their representatives) shall have any affiliation with the prison facility or with the unit of government having jurisdiction over the facility, with the exception of persons employed by the department of education of a relevant jurisdiction in a teaching capacity. The composition and the investigator's proposed use of the Committee must be reviewed and approved by the DHEW agency.

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

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

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

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

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

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

1. Standard of living in the prison facility.

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

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

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

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

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

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

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

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

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

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

The circumstances are limited under which it is justifiable to include the mentally infirm as subjects in biomedical research. These circumstances include projects in which: the proposed research concerns diagnosis, treatment, prevention, or etiology of the disability from which they suffer; the necessary infor-

mation can be obtained only from those subjects; or the studies concern institutional life *per se*. With these exceptions, the general rule is that the participation of the mentally infirm as subjects in research is not acceptable.

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

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

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

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

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

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

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

E. *Clinical research not funded by DHEW.*

If, in the judgment of the Secretary, an organization has failed to comply with the terms of this policy with respect to a par-

ticular DHEW grant or contract, he may require that said grant or contract be terminated or suspended in the manner prescribed in applicable grant or procurement regulations.

If, in the judgment of the Secretary, 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.

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.⁷

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

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

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

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

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

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

⁷ FEDERAL REGISTER, Vol. 38, No. 194, Part 2, Tuesday, October 9, 1973, § 46.22, p. 27885.

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

SUBPART C—ADDITIONAL PROTECTIONS FOR CERTAIN CLASSES OF DHEW ACTIVITIES

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

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

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

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

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

SUBPART F—GENERAL PROVISIONS

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

AUTHORITY: 5 U.S.C. 301.

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

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

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

Section 46.22 *Purpose.* It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable inasmuch as the potential subjects in activities conducted there-

under might be unable fully to comprehend the risks which might be involved and are legally incapable of consenting to their participation in such activities.

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

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

(a) "DHEW activity" means:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUBPART C—ADDITIONAL PROTECTION FOR CERTAIN CLASSES OF DHEW ACTIVITIES

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

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

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

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

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

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

(b) "DHEW activity" means:

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

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

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

(d) "Protection Committee" means a committee referred to in § 46.30.

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

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

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

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

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

Section 46.34 *Duties of the Ethical Review Board*. (a) It shall be the function of the Board to review each activity to which this subpart applies and advise the agency concerning the acceptability of such activities from the standpoint of societal need and ethical considerations, taking into account the assessment of the appropriate Primary Review Committees as to: (1) The potential benefit of the proposed activity, (2) scientific merit and experimental design, (3) the sufficiency of studies involving animals dem-

onstrating the clear potential benefit of the proposed procedures and (4) whether the information to be gained may be obtained from further animal or adult human studies.

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

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

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

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

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

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

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

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

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

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

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

(a) "DHEW activity" means:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Section 46.52 *Purpose.* It is the purpose of this subpart to provide additional safe-

guards for the mentally infirm involved in research, development, and demonstration activities, inasmuch as the potential subjects in such activities are: (1) Confined in an institutional setting; (2) might be unable fully to comprehend the type risks which may be involved; and (3) might be legally incompetent to consent to their participation in such activities.

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

(a) "DHEW activity" means:

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

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

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

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

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

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

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

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

(d) The Protection Committee, provided for in § 46.50 of this subpart, has reviewed and approved subject participation in the activity (by class or by individual).

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

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

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

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

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

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

(b) Activities to which this subpart is applicable must provide for the designation of

an Organizational Review Committee where no such Committee has been established under subpart A.

Section 46.50 *Protection Committees; duties; composition.* (a) No activity covered by this subpart will be approved unless it provides for the establishment of a Protection Committee to carry out the following functions, as well as any others prescribed by the Organizational Review Committee or by DHEW: (1) Overseeing the process of selection of subjects who may be included in the activity, (2) monitoring the progress of the activity with special attention to adverse effects on subjects, (3) intervening on behalf of one or more of the subjects if conditions warrant, (4) evaluating the process and reasonableness of consent of the legal guardian and (where applicable) of the subject, and (6) advising the legal guardian and/or the subject concerning the latter's continued participation in the activity if conditions warrant.

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

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

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

SUBPART F—GENERAL PROVISIONS

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

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

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

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

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

Section 46.63 *Reports.* Each organization with an approved assurance shall provide the Secretary with such reports and other information as the Secretary may from time to time prescribe.

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

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

(c) If, in the judgment of the Secretary, an individual serving as principal investigator, program director, or other person having responsibility for the scientific and technical direction of a project or activity, has failed to discharge her or his responsibilities for the protection of the rights and welfare of human subjects in his or her care, the Secretary may, upon reasonable notice to the individual of the basis for such action, determine that such individual's eligibility to serve as a principal investigator or program director or in another similar capacity shall be terminated. Such disqualification shall

continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist.

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

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