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Office of the Secretary

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PROTECTION OF HUMAN SUBJECTS

Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled

[4110-08-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

[45 CFR Part 46]

PROTECTION OF HUMAN SUBJECTS

Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled

AGENCY: Department of Health, Education, and Welfare.

ACTION: Proposed rule.

SUMMARY: The Department Of Health, Education and Welfare (HEW) is proposing regulations to implement the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research pertaining to research involving those institutionalized as mentally disabled. Key provisions require that such research be carried out only if the methods are appropriate, the investigators competent, and the facilities adequate. Risks must be minimized, and the research performed in connection with medically indicated diagnosis and treatment wherever possible. Adequate provision must be made to obtain the subject's fully informed consent, or the consent of legal representatives if the subjects are incapable of consenting on their own behalf. Where the subject lacks full capacity to consent, provision is made for the subject's assent.

DATES: Written comments on the proposed rules are invited, and should be received on or before January 16, 1979, if they are to be given full consideration.

ADDRESSES: Send comments to: Office for Protection from Research Risks, National Institutes of Health, 9000 Rockville Pike, Bethesda, Md. 20014. Additional copies of this notice may be obtained from the same address. All comments received will be available for inspection at Room 303, Westwood Building, 5333 Westbard Avenue, Bethesda, Md., weekdays (Federal holidays excepted) between the hours of 9 a.m. and 4:30 p.m.

FOR FURTHER INFORMATION CONTACT:

Joseph R. Marches, Ph. D., Office for Protection from Research Risks, National Institutes of Health, 9000 Rockville Pike, Bethesda, Md. 20014, 301-496-7005.

SUPPLEMENTARY INFORMATION: Basic regulations governing the Protection of human subjects involved in research, development, and related activities supported by HEW through grants and contracts were published in the FEDERAL REGISTER on May 30, 1974 (30 FR 18914).

In the preamble to these regulations, HEW indicated that it would propose further rules to provide additional protection for research subjects with diminished capacity to provide informed consent, including institutionalized individuals with mental disability.

The National Research Act (Pub. L. 93-348) was signed into law on July 12, 1974, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Commission). One of the charges to the Commission was to study the nature of the research being conducted which involved what the Act referred to as the "institutionalized mentally infirm," including the mentally ill, the mentally retarded, the emotionally disturbed, and the senile, who are confined to institutions either voluntarily or involuntarily. Such persons, by the very nature of their disabilities may not be competent to provide informed consent to participation in research. At the same time, the nature of their disabilities requires extensive research efforts to study the etiology, pathogenesis, prevention, therapy, and management of their conditions. The Commission was required to recommend to the Secretary of Health, Education, and Welfare, policies defining the circumstances under which research involving the institutionalized mentally infirm might be appropriate and to make recommendations to Congress regarding the protection of subjects (including the institutionalized mentally infirm) involved in research not subject to regulation by HEW.

In discharging its duties under this mandate, the Commission studied the nature and extent of research in mental health, mental illnesses, and mental retardation, the purposes for which the research is conducted, and the issues surrounding the participation in research of the institutionalized mentally infirm. Representatives from professional societies, Federal agencies, and public interest groups, as well as private citizens presented their views to the Commission at public hearings. To assure that viewpoints of minorities would be expressed, the National Minority Conference on Human Experimentation made recommendations to the Commission on research involving the institutionalized mentally infirm. The Commission also reviewed papers and reports prepared under contract, including papers on informed consent and a survey of actual practices in research involving institutionalized subjects. Finally, the Commission conducted extensive deliberations in public and developed recommendations on the participation in research of "those institutionalized as mentally infirm."

ACTIONS ON RECOMMENDATIONS OF THE COMMISSION

Pursuant to section 205 of the National Research Act (Pub. L. 93-348), the recommendations of the Commission on research involving those institutionalized as mentally infirm were published in the FEDERAL REGISTER (43 FR 11328) on March 17, 1978. Comments were received from approximately 100 organizations, institutions, legal and medical practitioners, and private citizens. After reviewing the recommendations and the comments, the Secretary has prepared the notice of proposed rulemaking set forth below, which in essence accepts the recommendations. However, the proposed rules depart from the recommendations of the Commission in a few respects.

DEPARTMENT'S RESPONSE TO RECOMMENDATIONS

DEFINITIONS

The term "institutionalized mentally infirm" as used in section 202(a)(2) of the National Research Act, is defined to include "individuals who are mentally ill, mentally retarded, emotionally disturbed, psychotic, senile, or who have other impairments of a similar nature and who reside as patients in an institution." Thus, the term "mentally infirm" was intended to encompass a broad array of people who, because of cognitive or emotional handicaps, reside in institutions and are subject to institutional constraints. The Commission's recommendations are applicable to research involving individuals so impaired when they are residents of these institutions. However, as noted by the Commission and by the Department, the term "mentally infirm" is inadequate. First, it is not in current clinical use. Second, there is considerable debate about whether symptoms that may result in institutionalization are properly characterized as diseases or illnesses in the conventional sense, or whether they represent problems in social adaptation. Current theories of personal adjustment recognize an interaction between biological and environmental factors resulting in behavior that society regards as illness or disability. An alternative to psychiatric diagnosis, which assumes a medical or disease model, is the view that disturbing behavior is more appropriately described in terms of conditions that evoke, reinforce and perpetuate that behavior.

Third, it is increasingly recognized that labeling, by the use of such terms as "mentally infirm," may stereotype conceptions of people and their problems. Fourth, many individuals who

commented on HEW'S November 16, 1973, proposed policy (39 FR 18914) objected to the use of the term "mentally infirm" because it reflected an antiquated notion of mental illness and its scope was unclear, e g., some felt it included those incapacitated as a result of physical conditions.

HEW substituted the term "mentally disabled" in the proposed rulemaking of August 23, 1974 (39 FR 30648), and reaffirms this change here. The term is separately defined in § 46.503(c) of the proposed regulations.

The National Research Act does not separately define "institutionalized." The Commission has noted that institutionalization may result from misdiagnosis or error and that confinement to a mental institution does not necessarily establish the fact of mental disability. The Department feels that the protection of these regulations should extend to all individuals residing either voluntarily or involuntarily in residential institutions for the care and treatment of the mentally disabled, including those who are mentally ill, mentally retarded, emotionally disturbed, psychotic or senile, regardless of their legal status or reason for their being institutionalized. Such individuals include but are not limited to mentally disabled patients in public or private mental hospitals, psychiatric patients in general hospitals, inpatients of community mental health centers, and mentally disabled individuals who reside in halfway houses or nursing homes. These regulations would not include noninstitutionalized patients or out-patients who would be covered by general regulations, nor would they include patients who are not mentally disabled but who, for reasons of convenience, are temporarily housed in institutions for the care and treatment of the mentally ill. The term "individuals institutionalized as mentally disabled" is so defined in § 46.503(d).

The definition of "minimal risk" is drawn, with only minor editorial changes, from the Commission's definition. In the preparation of these proposed regulations, considerable attention focused on whether this definition adequately captures the thrust of the additional explanatory comments provided by the Commission. There was concern whether the definition of minimal risk as included here should be interpreted to mean that a minimal risk situation obtains only when the research procedures include risks for institutionalized mentally disabled subjects which are identical to those encountered by normal subjects in routine medical or psychological examinations, or whether research procedures involving risks similar to those encountered by normal subjects should be the standard. For example, should a procedure which is routinely included in examination of mentally disabled persons be regarded as involving minimal risk because it is similar to the risk encountered by normal persons, or as involving more than minimal risk simply because it is not identical to any procedure ordinarily experienced by a normal person.

The Commission proposes that risks normally encountered in the daily lives of normal persons, or in the routine medical or psychological examination of normal persons, serve as a standard against which the Institutional Review Board (Board) should judge risks for institutionalized mentally disabled subjects. The Commission notes that, for such subjects, "routine examination procedures present no more than minimal risk if the likely impact of such procedures on them is similar to what would be experienced by normal persons undergoing the procedures" (emphasis added). The Board is also charged with determining "the degree of risk that would be presented to normal Persons and then consider whether such risk is heightened by the illness or institutionalization of the prospective subjects or class of subjects." Thus, the Department believes that risks normally encountered in the daily lives or routine examination of normal persons serve as a standard against which risks for mentally disabled subjects can be judged.

Consideration was given to inserting the words "comparable to that" between "discomfort" and "normally" in the definition as presented in these proposed regulations. This would serve to emphasize the comparative, judgmental nature of the assessment of risk. However, there was concern that such a phrase, if inserted, could be interpreted to permit disabled subjects to be exposed to greater risks than intended by the Commission. Hence, the definition in § 46.503(h) of the proposed regulations adheres to the original wording of the Commission. Comments from the public are especially invited on this definition.

The Department has also added definitions of "children," "parent," "legally authorized representative," and "assent," borrowed largely from its previous proposed rulemaking with respect to research with children (43 FR 31786 at p. 31793).

A definition of "consent auditor" is included as well as a definition of "advocate." The former describes an individual whose primary role is to assure that the consent/assent process functions properly; the latter contemplates someone who would in effect serve as another representative of the subject, in addition to the legally authorized representative. One or both of these definitions will be included in the final regulations on the institutionalized mentally disabled, depending on what if any functions are assigned to consent auditors and advocates in other sections of the regulations. The rulemaking on research involving children and these regulations will be conformed before either is issued in final form.

Recommendation (1) regarding the review of research by Boards is implemented by § 46.504 substantially as proposed by the Commission. Several of the Commission's comments on the recommendation were included in the regulations for purposes of clarification.

Special Considerations Regarding Individuals Who Object To Treatment

In its recommendations (2), (3), and (4), discussed below, the Commission provides special protections for subjects who are incapable of giving fully informed consent. The Department recognizes, however, that it is often difficult to demarcate between subjects who are capable and those who are not. Also, the decision as to capability normally cannot be made until the time when each subject is involved in the research. Leaving the institution and the research investigators the discretion to decide whether individual subjects are capable of giving consent could lead to uneven protections for human subjects. In recognition of this, the Commission has provided the institutional review boards with authority to appoint consent auditors to observe the consent process and determine in fact whether proper decisions are being made regarding capacity to consent (or assent). In recommendation (4), appointment of a consent auditor is mandatory.

One alternative, which was considered by the Department for the purpose of limiting the researchers' discretion, was to require added protections whenever the subject had been declared "legally incompetent" by a court of appropriate jurisdiction. This approach is not being pursued because in fact only a small proportion of the institutionalized mentally disabled, who may be less than fully capable of giving consent, have had their status adjudicated by a court.

Recommendations (2) and (3) contain two parallel clauses, (2)(b)(iii) and (3)(D)(iv), stating generally that when a subject objects to participation in an intervention which: Involves only minimal risk (recommendation 2), or holds out the prospect of direct benefit for the subject and is available only in the context of the research (recommendation 3), the research may be conducted or supported only if the subject's participation is specifically authorized by a court of competent ju-

risdiction. Although the Commission did not specifically indicate, we interpret these provisions as applying only when the subject lacks the capacity to give informed consent.

The Commission does not provide any clarifying comment on this clause. In a dissenting opinion (43 FR 11328 at page 11358), Commissioner King suggests that: "Perhaps the Commission required court authorization to insure as fair and objective an assessment of the quality of the objection as possible. I certainly share the Commission's concern about insuring a fair and objective assessment of the quality of the prospective subject's objection. Most forms of mental illness and mental retardation are viewed as possibly impairing a patient's ability to make sound personal decisions. We should be concerned therefore about a subject's ability to refuse as well as to assent to participation in research activities." Commissioner King proceeded to dissent on the ground that a court is not necessarily in the best position to make the necessary decision as to the quality of the objection, and in the belief that the decision should be left to the Board, which could, if it wished, seek assistance from a court.

The courts themselves are divided on this issue. In a Federal case, *Wyatt* v. *Stickney* (344 F.Supp. 373 [M.D. Ala. 1972]; 344 F.Supp. 387 [M.D. Ala. 1973]) (see also *Wyatt* v. *Aderholt,* 503 F.2d. 1305 [5th Cir. 1974]), the court held (appendix A,29) only that "Residents shall have a right not to be subjected to experimental research without the express and informed consent of the resident (or) of his guardian or next of kin * * * Such proposed research shall first have been reviewed and approved by the institution's Human Rights Committee." Court approval as such was not required. though consultation with legal counsel was recommended.

More recently, the Massachusetts Supreme Judicial Court in *Belchertown State School* v. *Saikewicz* (370 N.E.2d 417) has held that questions concerning the continuation of life extending therapy in incompetent patients must go before a probate court for approval. While the case involves life extending therapy, not merely benefits, the decision tends to support the commission majority's view that the courts must play a central role in the consent process when a mentally disabled patient is unable to consent to a proposed treatment regimen.

There are arguments that neither next of kin, other legally authorized guardians, nor courts should be able to override the objection of a mentally disabled subject except in extreme cases. The Commission notes in its report the view of one of its consultants that "The burden in law for incompetence should be very high. No evidence other than a showing that the patient is comatose should ordinarily be accepted as proof of incompetence * * * To accept proxy consent is to authorize invasions of persons and personality without regard to the wishes of the research subject * * *." To date, no court has adopted such a view.

For purposes of the proposed regulations, the Department has followed the Commission's recommendations concerning authorization by a court of competent jurisdiction. At the same time, it is acknowledged that there are views in sharp conflict with this position. The Department therefore encourages further public comment on this issue.

Recommendation (2), on research that does not present more than minimal risk, is implemented by § 46.505 largely as suggested and with the Commission's recommended requirement of court approval to protect the objecting subject who lacks the capacity to give informed consent. If such a subject objects, the research must include an intervention that holds the prospect of direct benefit to the subject, or a monitoring procedure required for the well-being of the subject.

As an added protection for subjects who are incapable of giving informed consent, the Department is giving consideration to requiring that a consent auditor monitor all research covered by these regulations, including research involving no more than minimal risk. Whenever the consent auditor finds a particular subject lacks the capability to consent, the subject may not be involved in the research without the consent of an advocate (in addition to the consent of the legally authorized representative and, in the case of an objecting subject, a court). public comment is requested on this added protection.

Recommendation (3) concerns research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. Section 46.506 implements this recommendation with modifications. The term "legally authorized representative" is substituted for the term "guardian" since the latter is normally associated with persons having responsibility for minors, while these regulations apply both to adults and minors institutionalized as mentally disabled. Again, the requirement for court approval protects the objecting subject who lacks the capacity to consent. When such a subject objects, the research can proceed only if the Board finds that the intervention or monitoring procedure is available only in the context of the research.

Again, public comment is requested on a proposal to require the consent of an advocate whenever the consent auditor determines that the subject is incapable of giving informed consent.

Recommendation (4), pertaining to research involving greater than minimal risk but likely to yield generalizable knowledge about the subjects' disorder, is implemented by § 46.507. The regulation substantially follows the Commission's recommendation except with respect to subjects who are incapable of giving informed consent.

With regard to subjects who are capable of assenting (though not consenting), the Department is considering whether to follow the Commission's approach of permitting such subjects to participate if they assent and their legally authorized representative consent, or alternatively, to require in addition the consent of (1) the Secretary, based upon the advice of an expert panel, or (2) an advocate.

With regard to subjects incapable of assenting, the Department is considering whether to: (1) Bar their involvement in such research (on the assumption that needed research could be done using other subjects), (2) adopt the Commission's recommendation, which would permit their participation if they do not object and the legally authorized representative and a court of competent jurisdiction give their approval, (3) require, in addition to the approval of the legally authorized representative and the court, approval by the Secretary, or (4) require, in addition to that of the representative and the court, approval by an advocate.

Public comment is requested on the above alternatives.

The regulations proposed in § 46.508 for implementation of recommendation (5) depart slightly from paragraph B of that recommendation. Instead of referring to a national ethical advisory board as the body to review research that cannot be approved under recommendations (2), (3), and (4), § 46.508 would allow the Secretary to consult with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law). Depending on the circumstances, the panel could be a national ethical advisory board or an ad hoc panel of experts. This gives the Secretary flexibility to secure the best advice available in a particular situation.

The Department is considering whether greater specificity should be required regarding the nature of the consent process under situations covered by recommendation (5). Public comment regarding this issue is requested.

DEPARTMENT'S RESPONSE TO PUBLIC COMMENTS

In response to publication in the FEDERAL REGISTER of the Commission's recommendations on research involving those institutionalized as mentally infirm, approximately 100 comments were received from individuals, citizen groups, legal and medical practitioners, researchers, and representatives of societies, university departments, and institutions. Although the respondents objected to some points in the recommendations, they were mainly complimentary of the Commission's recommendations. Several indicated complete acceptance of the recommendations as drafted.

Described below are the public responses received on the recommendations. In general, the comments directly addressed issues and implications of the recommendations but occasionally extended into the supplementary discussion material presented by the Commission relating to each of its recommendations.

1. *Comment on the definition of "institutionalized mentally infirm".* Public response to the March 17, 1978, recommendations contained objections to this term similar to those received in response to the proposed rulemaking of August 23, 1974. The major concern was that the term reflected an antiquated concept of mental illness with an ill-defined boundary as to the kinds of disabilities and condtions that would be included.

Response. The Department agrees. As noted under "Department's response to recommendations," the term "mentally disabled" has been substituted for "mentally infirm" in § 46.503 and is utilized throughout the proposed regulations.

2. *Comment on recommdation (1).* While there was general acceptance of this recommendation as drafted, a number of those commenting questioned the reality of delegating to Boards the task of discerning (A) that "the research methods are appropriate" to the research, and (B) the "competence of the investigator." The comments also expressed a desire for clarification of the "good reason" criterion included in paragraph (D) for involving participants and the meaning of "equitable" selection presented in paragraph (G).

Response. The Department does not feel that the recommendations of the Commission that Boards consider the appropriateness of the proposed methodology and the competence of the investigator are unrealistic. Boards are required under existing regulation (45 CFR 46.106) to have the professional competence and other qualifications necessary to the review of the specific activities likely to be presented to them. Under such circumstances, a properly constituted Board should have no difficulty in making such decisions. These recommendations are implemented substantially as written in § 46.504(a) (1) and (2).

The Department agrees that the "good reason" criterion deserves further explanation. Accordingly, the Department has added in § 46.504(a)(4) a brief description of the factors to be considered in determining the appropriateness of conducting research on those institutionalized as mentally disabled.

Similarly, the Department has provided additional explanation as to what is meant by "equitable" selection and incorporated this in § 46.504(a)(7).

3. *Comment on recommendation (2)(B)(ii).* Reservation was expressed as to the adequacy of accepting "assent" or "no objection" as criteria for allowing the participation of patients who are incapable of consenting. Some public respondents felt that the opportunity to object might be vitiated by the institutional setting or the subject's lack of decisionmaking experience.

Response. The standard for "assent" requires that the subject be told what procedures will be performed in the research and on this basis choose, or not choose, to participate. The subject would be expected to be able to communicate this choice unambiguously and be aware that subjects may withdraw from participation. Assent is not intended to be a substitute for the informed consent of legally authorized representatives, but as an additional applicable standard for affirmative agreement to participate in research. Assent is to be obtained whenever a subject is not capable of giving informed consent and other conditions are satisfied. Mere failure to object is not to be construed as assent.

The "absence of an objection" criterion is appropriate only where the subject is incapable of assenting and where the research is relevant to the subject's condition and presents no more than minimal risks. These points were included in the Commission's discussion pertaining to this recommendation and serve to clarify the Department's intent.

4. *Comment on recommendations (2)(B)(iii), (3)(D)(iv), and (3)(E)(ii).* Recommendations (2) and (3) contain provisions for Court authorized participation of objecting subjects if the research holds the prospect of direct benefit to the subject or includes a monitoring procedure required for the well-being of the subject. As we have already said, we interpret these provisions as applying only when the subject is incapable of giving informed consent.

Public comment reflected varying degrees of objection to the suggested role of the court in overriding the right to refuse participation in research even when judged to be beneficial.

Reponse. The Department acknowledges the difficulty of resolving the conflicting right of a patient to refuse treatment for whatever reason, and of the right, even the duty, of the State to provide treatment when it is in the apparent best interest of the patient. This matter is discussed above under "Department's response to recommendations" and additional public comment is encouraged.

5. *Comment on recommendation (3)(D)(ii).* Several comments in connection with recommendation (3) were in reference to the concept of the guardian. Some proposed that the guardian's role be limited to concurrence with or withdrawal of the subject's consent to participation in research. Other respondents favored a change in the word "guardian" to the term "legally authorized representative" as used in subpart A of 45 CFR Part 46. It was suggested that the "legally authorized representative" concept would be more amenable to family input and patient-family decision making than the "guardian" notion.

Response. In light of these comments, the Department has substituted the term "legally authorized representative" in the wording of §§ 46.505(b)(2), 46.506(a)(4)(B), 46.507 (a)(4)(C), and 46.508(b)(2)(C) of the proposed regulations. The term "guardian" has been retained only in connection with minors.

6. *Comment on recommendation (4).* Public reaction to this recommendation was mixed as to whether persons institutionalized as mentally disabled should be involved in research with more than minimal risk and holding no prospect of direct benefit for individual subjects. At least one person supported the dissenting position of Commissioner Cooke to the effect that research involving more than minimal risk not be performed unless it can clearly be shown that the anticipated knowledge might reasonably benefit the individual subjects in the future.

Response. This recommendation is implemented by § 46.507, which requires that all of the safeguards of § 46.504 must be met. This includes the requirement in § 46.504(a)(4) that there be good reasons for using institutionalized individuals as subjects. Section 46.507(a)(3) further requires that the Board must find the research to be of vital importance for the understanding or amelioration of the type of disorder or condition affecting the subject, if the Board is to allow research under this recommendation.

If the subject is a child, § 46.507 (a)(5) requires satisfaction of §§ 46.407

and 46.409 of subpart D relating to research involving children.

Sections 46.507 (b) and (c) also state that no subject may be allowed in the research over his or her objection and that the IRB shall appoint a consent auditor to ensure the adequacy of the consent process.

7. *Comment on recommendation (5).* A number of those commenting view this Recommendation as a questionable means for extending the latitude of conditions under which research may involve institutionalized persons. They fear that the risk of abuse or exploitation would be high for the category of research encompassed by this recommendation. It was further felt that a need for specifically involving institutionalized individuals should be documented before any research could be permitted under this Recommendation. The opinion was also expressed that the need for involving a national ethical advisory board in decisionmaking was not self-evident, and that the required review (paragraph B) might be more satisfactorily handled at the Board or program level, thus negating the need for a national board.

Response. The Department acknowledges the Commission's view that only research of major significance and the presence of a serious health problem would justify the approval of research under recommendation (5). The problem addressed must be a grave one with a reasonable expectation of producing important and needed scientific information, and must be implemented by an equitable method for inviting participation among institutionalized subjects. Approval of any research under this recommendation is contingent upon the Board's determination as to the critical nature of the health problem involved. The Secretary will give the public an opportunity to review and comment on any proposed action. Hence, it gives the Secretary discretion to approve important research when conditions warrant, while providing adequate safeguards against abuse.

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

Dated: November 1, 1978.

JULIUS B. RICHMOND,
Assistant Secretary for Health.

Approved: November 6, 1978.

JOSEPH A. CALIFANO, Jr.,
Secretary.

It is therefore proposed to amend Part 46 of 45 CFR, Subtitle A, by:

§46.301 (Subpart C) [Redesignated as §46.601(SubpartF)]

1. Redesignating subpart c and § 46.301 as subpart F and § 46.601 respectively.

2. Adding the following new subpart E.

Subpart E—Additional Protections Pertaining to Biomedical and Behavioral Research Involving as Subjects Individuals Institutionalized as Mentally Disabled

Sec.
46.501 Applicability.
46.502 Purpose.
46.503 Definitions.
46.504 Additional duties of the Institutional Review Boards where individuals institutionalized as mentally disabled are involved.
46.505 Research not involving greater than minimal risk.
46.506 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
46.507 Research involving greater than minimal risk and no direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.
46.508 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of individuals institutionalized as mentally disabled.

AUTHORITY: 5 U.S.C. 301.

Subpart E—Additional Protections Pertaining to Biomedical and Behavioral Research Involving as Subjects Individuals Institutionalized as Mentally Disabled.

§ 46.501 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health, Education, and Welfare involving as subjects individuals institutionalized as mentally disabled.

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

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

§ 46.502 Purpose.

Individuals institutionalized as mentally disabled are confined in institutional settings in which their freedom and rights are potentially subject to limitation. In addition, because of their impairment they may be unable to comprehend sufficient information to give a truly informed consent. Also, in some cases they may be legally incompetent to consent to their own participation in research.

At the same time, so little is known about the factors that cause mental disability that efforts to prevent and treat such disabilities are in the primitive stages. There is widespread uncertainty regarding the nature of the disabilities, the proper identification of persons who are disabled, the appropriate treatment of such persons, and the best approaches to their daily care. The need for research is clearly manifest. It is the purpose of this subpart to permit the conduct of responsible investigations while providing additional safeguards for those institutionalized as mentally disabled.

§ 46.503 Definitions.

As used in this subpart:

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

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

(C) "Mentally disabled" individuals includes those who are mentally ill, mentally retarded, emotionally disturbed, psychotic or senile, regardless of their legal status or the reason for their being institutionalized.

(d) "Individuals institutionalized as mentally disabled" means individuals residing, whether by voluntary admission or involuntary confinement, in institutions for the care and treatment of the mentally disabled. Such individuals include but are not limited to patients in public or private mental hospitals, psychiatric patients in general hospitals, inpatients of community mental health centers, and mentally disabled individuals who reside in halfway houses or nursing homes.

(e) "Children" are persons who have not attained the legal age of consent to general medical care as determined under the applicable law of the jurisdiction in which the research will be conducted.

(f) "Parent" means a child's natural or adoptive parent.

(g) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to such subject's participation, in the particular activity or procedure. An official serving in an institutional capacity may not be considered a legally authorized representative for purposes of this subpart.

(h) "Minimal risk" is the probability and magnitude of physical or psychological harm or discomfort that is normally encountered in the daily lives, or in the routine medical or psychological examination, of normal individuals.

(i) "Assent" means a prospective subject's affirmative agreement to par-

ticipate in research. Mere failure to object shall not, absent affirmative agreement, be construed as assent. Assent can only be given following an explanation, based on the types of information specified in § 46.103(c), appropriate to the level of understanding of the subject, in accordance with procedures established by the Institutional Review Board.

(j) "Consent auditor" means a person appointed by the Institutional Review Board to ensure the adequacy of the consent process, particularly when there is a substantia1 question about the ability of a subject to consent or assent or when there is a significant degree of risk involved. Consent auditors are responsible only to the Board and should not be involved with the research, nor should they be employed by or otherwise associated with the institution conducting or sponsoring the research, or with the institution in which the subject resides. They should be persons familiar with the physical, psychological, and social needs of the class of prospective subjects as well as with their legal status.

(k) "Advocate" means an individual appointed by the Institutional Review Board to act in the best interests of the subject. The advocate will, although he or she is not appointed by a court, be construed to carry the fiduciary responsibilities of a guardian ad litem toward the person whose interests the advocate represents. No individual may serve as an advocate if the individual has any financial interest in, or other association with, the institution conducting or sponsoring the research, nor with the institution in which this research in conducted; nor, where the subject is the ward of a State or other agency, institution, or entity, may the advocate have any financial interest in, or other association with, that State, agency, institution, or entity. An advocate must be familiar with the physical, psychological, and social needs and the legal status of the class of individuals institutionalized as mentally disabled in the institution in which the research is conducted. [This definition will be retained in the final regulations if duties are assigned to "advocates."l

§ 46.504 Additional duties of the institutional review boards where individuals institutionalized as mentally disabled are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) The research methods are appropriate to the objectives of the research.

(2) The competence of the investigator(s) and the quality of the research facility are sufficient for the conduct of the research;

(3) Appropriate studies in nonhuman systems have been conducted prior to the involvement of human subjects:

(4) There are good reasons to involve institutionalized individuals as subjects of the research. In reviewing proposals to involve institutionalized persons in research, the Board should evaluate the appropriateness of involving alternative, noninstitutionalized populations in the study instead of, or along with, the institutionalized individuals. Sometimes, the participation of alternative populations will not be possible or relevant, as when the research is designed to study problems or functions that have no parallel in free-living persons, (e.g., studies of the effects of institutionalization or studies related to persons, such as the profoundly retarded or severely handicapped, who are almost always found in residential facilities.)

(5) Risk of harm or discomfort is minimized by using the safest procedures consistent with sound research design and by using procedures performed for the diagnosis or treatment of the particular subject whenever possible;

(6) Adequate provisions are made to protect the privacy of the subjects and to maintain confidentiality of data. For example, data may be disclosed to authorized personnel and used for authorized purposes only: data should be collected only if they are relevant and necessary for the purposes of the research and analysis: data should be maintained only as long as they are necessary to the research or to benefit the subjects; and all data should be maintained in accordance with fair information practices;

(7) Selection of subjects among those institutionalized as mentally disabled will be equitable. Subjects in an institution should be selected so that the burdens of research do not fall disproportionately on those who are least able to consent or assent, nor should one group of patients be offered opportunities to participate in research from which they may derive benefit to the unfair exclusion of other equally suitable groups of patients.

(8) Adequate provisions are made to assure that no prospective subject will be approached to participate in the research unless the health care professional who is responsible for the health care of the subject has determined that the invitation to participate in the research and the participation itself will not interfere with the health care of the subject;

(9) The Board shall appoint a consent auditor to ensure the adequacy of the consent procedures when, in the opinion of the Board, such a person is considered necessary, e.g., when there is a substantial question about the ability of a subject to consent or to assent or when there is a significant degree of risk involved; and

[In the event the Department decides that there should be consent auditors for all projects, the above paragraph will be appropriately modified.]

(10) The conditions of all applicable subsequent sections of this subpart are met.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secretary, in such manner as the Secretary may require, that the duties of the Board under this subpart have been fulfilled.

§ 46.505 Research not involving greater than minimal risk.

Biomedical or behavioral research that does not involve greater than minimal risk to subjects who are institutionalized as mentally disabled may be conducted or supported by DHEW provided the Institutional Review Board has determined that:

(a) The conditions of § 46.504 are met: and

(b) Adequate provisions are made to assure that no subject will participate in the research unless:

(l) The subject gives informed consent to participation:

(2) If the subject lacks the capacity to give informed consent, the research is relevant to the subject's condition, the subject assents or does not object to participation, and the subject's legally authorized representative consents to the subject's participation; or

(3) If a subject, who lacks the capacity to give informed consent, objects to participation: (i) The research includes an intervention that holds out the prospect of direct benefit to the subject, or includes a monitoring procedure required for the well-being of the subject, (ii) the subject's legally authorized representative consents to the subject's participation, and (iii) the subject's participation is authorized by a court of competent jurisdiction.

[Consideration is being given to mandating that, in addition to the above requirements: (1) A "consent auditor" be appointed by the Institutional Review Board to ensure the adequacy of the consent Process and determine whether each subject consents, or is incapable of consent but assents, or objects to participation, and (2) whenever the consent auditor determines that a subject is incapable of consenting, the subject may not par-

ticipate without the authorization of an "advocate."]

§ 46.506 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

(a) Biomedical or behavioral research in which more than minimal risk to subjects who are institutionalized as mentally disabled is presented by an intervention that holds out the prospect of direct benefit for the individual subjects, or by a monitoring procedure likely to contribute to the well-being of the subjects, may be conducted or supported provided the Institutional Review Board has determined that:

(1) The conditions of section 46.504 are met;

(2) The risk is justified by the prospect of benefit to the subjects;

(3) The relation of the risk to anticipated benefit to subjects is at least as favorable as that presented by available alternative approaches;

(4) Adequate provisions are made to assure that no adult will participate in the research unless;

(i) The subject gives informed consent to participation;

(ii) If the subject lacks the capacity to give informed consent, the subject assents to participation. and the subject's legally authorized representative consents to the subject's participation; or

(iii) If a subject who lacks the capacity to give consent, does not give assent, or objects to participation: (A) The intervention or monitoring procedure is only available in the context of the research, (B) the subject's legally authorized representative consents to the subject's participation, and (C) the subject's participation is authorized by a court of competent jurisdiction.

[Consideration is being given to mandating that, in addition to the above requirements: (1) A "consent auditor" be appointed by the Institutional Review Board to ensure the adequacy of the consent process and determine whether each subject consents, or is incapable of consent but assents, or objects to participation, and (2) whenever the consent auditor determines that a subject is incapable of consenting, the subject may not participate without the authorization of an "advocate."]

(5) Adequate provisions are made to assure that no child will participate in the research unless:

(i) The subject assents (if capable) and the subject's parent(s) or guardian(s) give permission, as provided in section 46.409 of this part; or

(ii) If the subject objects to participation, the intervention or monitoring procedure is available only in the context of the research, the subject's Parent(s) or guardian(s) give permission, and the subject's participation is authorized by a court of competent jurisdiction.

(b) Where appropriate, the Institutional Review Board shall appoint a consent auditor to ensure the adequacy of the consent process and determine whether each subject consents, or is incapable of consent but assents, or objects to participation. [This paragraph will be deleted if a consent auditor is required in all cases.]

§ 46.507 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

(a) Biomedical or behavioral research in which more than minimal risk to subjects who are institutionalized as mentally disabled is presented by an intervention that does not hold out the prospect of direct benefit for the individual subjects, or by a monitoring procedure that is not likely to contribute to the well-being of the subjects, may be conducted or supported provided an Institutional Review Board has determined that:

(1) The conditions of section 46.504 are met;

(2) The risk represents a minor increase over minimal risk;

(3) The anticipated knowledge (i) is of vital importance for the understanding or amelioration of the type of disorder or condition of the subjects, or (ii) may reasonably be expected to benefit the subjects in the future;

(4) Adequate provisions are made to assure that no adult will participate in the research unless the following conditions are met:

(i) The subject gives informed consent to participation:

(ii) If the subject lacks the capacity to give informed consent, the subject assents to participation, and the subject's legally authorized representative consents to the subject's participation; or

(iii) If the subject lacks the capacity to assent but does not object, the subject's legally authorized representative and a court of competent jurisdiction consent to the subject's participation.

[The Department is considering the following additions to the above provisions:

In § 46.507(a)(4)(B), with respect to subjects capable of consenting: (i) Adding the requirement that inclusion of each subject be approved by the Secretary based upon the advice of a panel of experts, or (ii) requiring the approval of an "advocate."

In § 46.507(a)(4)(C), with respect to subjects incapable of assenting: (i) Prohibiting use of such subjects on the theory that there is no research which can be performed only with these subjects, (ii) requiring approval by the Secretary based upon the advice of a panel of experts, or (iii) requiring the approval of an "advocate."]

(5) If the subject is a child, the requirements of §§ 46.407 and 409 of subpart D (relating to research involving children) are satisfied.

(b) No subject may be involved in the research over his or her objection.

(c) The Institutional Review Board shall appoint a consent auditor to ensure the adequacy of the consent process and determine whether each subject consents, or is incapable of consenting but assents, or is incapable of assenting but does not object, or objects to participation. [This paragraph will be deleted if a consent auditor is required for all research covered by this subpart.]

§ 46.508 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of individuals institutionalized as mentally disabled.

Biomedical or behavioral research that the Insitutional Review Board does not believe meets the requirements of §§ 46.505, 46.506, or 46.507 may nevertheless be conducted or supported by DHEW provided:

(a) The Instituional Review Board has determined the following:

(1) The conditions of § 46.504 are met; and

(2) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of individuals institutionalized as mentally disabled; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either (1) that the research in fact satisfies the conditions of §§ 46.505, 46.506, or § 46.507, as applicable, or (2) the following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of individuals institutionalized as mentally disabled;

(ii) The conduct of the research will be in accord with basic ethical principles of beneficence, justice, and respect for persons, that should underlie the conduct of research involving human subjects; and

(iii) Adequate provisions are made for obtaining consent of those subjects capable of giving fully informed consent, the assent of other subjects and the consent of their legally authorized representatives, and, where appropriate, the authorization of a court of competent jurisdiction [and if §§ 46.505, 46.506, 46.507 require an advocate, the authorization of that advocate].

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