DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

45 CFR Part 46

Additional Protections for Children Involved as Subjects In Research

AGENCY: Department of Health and Human Services.

ACTION: Final rule.

SUMMARY: The Department of Health and Human Services (Department or HHS) is prescribing additional requirements for protection of children involved as subjects in research. These regulations adopt, with some changes, the recommendations of the National Commission for the protection of Human Subjects of Biomedical and Behavioral Research (National Commission) as were presented in the notice of proposed rulemaking (NPRM) 43 FR 31786 which preceded this final rule.

Specifically, these regulations impose certain added responsibilities on Institutional Review Boards (IRBs) depending on the degree of risk involved in the research and the extent that the research is likely to be a benefit to the subject or relate to a subject's illness. The regulations also set forth requirements for obtaining permission by parents and guarding and, except under certain circumstances, assent by the children themselves. When the child is a ward of the state, the appointment of an advocate is required under some circumstances. The regulations exempt from coverage most social, economic, and educational research in which the only involvement of children as subjects will be in one or more of the following categories: (a) Research conducted in established or commonly accepted educational settings, involving normal educational practices; (b) Research involving the observation of public behavior; (c) Research involving the use of educational tests; (d) Research involving the collection or study of existing data, documents, records or specimens.

EFFECTIVE DATE: These regulations are applicable to all research reviewed after June 6, 1983 by institutional review boards established under an HHS approved Assurance of Compliance.

ADDRESS: Please send comments or requests for additional information to: Denis J. Doyle, Assistant Regulations Officer, Office for Protection from Research Risks, National Institutes of Health, 5333 Westbard Avenue, Room 3A13, Bethesda, Maryland 20205. Telephone (301) 496–7163.

FOR FURTHER INFORMATION CONTACT: Denis J. Doyle (301) 496–7163.

SUPPLEMENTARY INFORMATION: Basic regulations governing the protection of human subjects involved in research funded by HHS (formerly HEW) were first published in the **Federal Register** on May 30, 1974 (30 FR 18914).

In the preamble to those regulations, HHS indicated that it would propose further rules to provide additional protections for research subjects, including children, who may have diminished capacity to provide informed consent.

The National Research Act (Pub. L. 93–348) was signed into law on July 12, 1974, creating the National Commission One of the charges to the National Commission was to study the nature of research involving children, the purposes of such research the steps necessary to protect children as subjects, and the requirements for the informed consent of children, their parents or guardians. The National Commission was required to recommend to the Secretary, HHS, policies defining any circumstances under which research with and for children might be appropriate, and to make recommendations to Congress regarding the protection of subjects (including children) involved in research not subject to regulation by HHS.

In discharging its duties under this mandate, the National Commission studied the nature and extent of research involving children, the purposes for which the research is conducted, and other issues surrounding the participation of children in research. Representatives from professional societies, federal agencies, and public interest groups, as well as parents and other members of the public, presented their views to the National Commission at a public hearing. The National Minority Conference on Human Experimentation, convened by the National Commission to solicit minority views, made recommendations to the National Commission on research involving children.

The National Commission also reviewed papers and reports prepared under contract, on topics including informed consent and actual practices in research involving children. Finally, the National Commission conducted extensive public deliberations and developed recommendations on the participation of children in research.

Pursuant to Section 205 of the National Research Act (Pub. L. 93–348), the report and recommendations of the National Commission on research involving children were published in the **Federal Register** (43 FR 2084) on January 13, 1978.

After review of the National Commission's report and recommendations, as well as the public comments received, the Secretary published a notice of proposed rulemaking on research involving children in the **Federal Register** (43 FR 31786) on July 21, 1978. In addition to solicitation of comments on the proposed rules, public comments were also sought on the following points: (1) How could the Department provide more useful guidance to IRBs in evaluating whether only a minor increment over minimum risk is involved and (2) further comments, preferably supported by studies, concerning the issues of requiring assent from children, whether an age for requiring assent should be stated, and, if not, whether there should be guidance in the preamble regarding a suggested appropriate age for assent.

OMB Clearance: Reporting and recordkeeping requirements in Subpart A of 45 CFR Part 46 also cover research affected by this subpart. OMB approval for reporting and recordkeeping requirements contained in 45 CFR Part 46, as amended January 26, 1981, was requested and received.

Impact Analysis

Economic Impact on Small Entities—The Secretary certifies that this final rule will not have a significant economic impact on a substantial number if small entities within the meaning of the Regulatory Flexibility Act, Pub. L.96–354. Since the establishment of an institutional review board and the filing of an Assurance of Compliance is already required by 45 CFR Part 46, Subpart A, this subpart will not necessarily impose requirement which are additional to the basic conditions required of entities for receiving HHS funds to conduct or sponsor human subject research.

Classification of Rule Under E.O. 12291—The Secretary has determined that this rule is not a "major rule" under Executive Order 12291 and thus a regulatory impact analysis is not required. The Secretary's determination is based on the finding that the proposed rule would not:

(1) Have an annual effect on the economy of $100 million or more;

(2) Impose a major increase in costs or prices for consumers, individual industries, Federal, State or local government agencies, or geographic regions; or

(3) Result in significant adverse effects on competition, employment

investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

Response to Public Comment

A total of 127 public comments was received from individuals and organizations in response to the publication in the **Federal Register** of Proposed Regulations on Research Involving Children (43 FR 31786, July 21, 1978). After reviewing the comments and taking into consideration the recently amended Basic HHS Policy for the Protection of Human Research Subjects (Title 45 Part 46 Code of Federal Regulations), the Department has prepared the final rule on research involving children as human subjects. A number of provisions of the proposed rule have been deleted since they are discussed and incorporated into the amended 45 CFR 46 Subpart A published in the **Federal Register** on January 26, 1981 (46 FR 8366). The summaries of the public comment and the Department's responses and final decisions are organized below by the section and paragraph designation of the proposed rule.

Section 46.401 To what do these regulations apply?

Public Comment: Several commentators stated that specific exemptions should be included in this subpart.

HHS Response: The Department agrees that exemptions (1), (2), (5) and (6), as listed in Subpart A at § 46.101(b) should be applicable to Subpart D as well, and has reworded the final rule to reflect this.

Exemption (3), research involving survey or interview procedures, as listed in § 46.101(b) of Subpart A is not made applicable to this subpart. The Department assumes that adults have the capability to determine whether or not to participate in survey or interview research. However, the Department believes that children being surveyed or interviewed by an investigator may not be capable of recognizing that their responses to questions on sensitive issues could be potentially damaging to themselves or others. Therefore, it is appropriate that the IRB at least review such research to determine whether the rights and welfare of children participating as subjects are adequately protected and when the requirements of permission or assent can be waived, Such waivers shall be in accordance with the requirements of §§ 46.116 and 46.117 of Subpart A.

Exemption (4), research involving the observation of public behavior, as listed in § 46.101(b) of Subpart A, is applicable to Subpart D where the investigator(s) does not participate in the activities being observed. The Department believes that children involved in observation research where the investigator(s) is also participating in the activities being observed, may not have the capability to determine whether or not to participate and therefore IRB review of such research is appropriate. This modification is reflected in the final rule at § 46.101(b).

Reference is also made in this final rule to the exceptions, additions, and provisions listed in paragraphs (c) through (f) of § 46.101 of Subpart A.

In addition, two other provisions concerning applicability of other subparts of 45 CFR Part 46 or other laws or regulations that are included under § 46.101(a) are repeated in § 46.401(a).

Section 46.402 Purpose.

Public comment: There was a single comment suggesting that this section be amended to include an explicit statement regarding the value of research involving children as stated in the recommendations of the National Commission.

HHS Response: This section was hortatory in nature and served no substantive purpose.

This section is deleted in the final rule and all subsequent sections are re-numbered.

Section 46.403 Definitions.

Public Comment: There were a total of 28 comments on the definitions. "Secretary," "DHEW" (now HHS), "Parent" and "Guardian" were not the subject of comment. There were three comments on "Research" and seven on "Minimal risk." Responses to these ten comments were considered in the preamble of Subpart A, previously published (46 FR 8366).

Three commentators criticized the Department's definition of "Children" for including those "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." They pointed out that in many jurisdictions certain classes of minors are considered to be emancipated and are legally authorized to consent to certain kinds of treatment or services.

There were eight comments on the definition of "Advocate," five of which objected to the provision that such an individual should not have "any financial interest in, or other association with, the institution conducting or sponsoring the research. A reason given was that it would be difficult, if not impossible, to get qualified volunteers to serve as advocates. Other commentators questioned the legal authority of an IRB to appoint an advocate and whether an advocate might be placed in legal jeopardy if an injury or suit resulted.

Five comments on "Assent" and "Permission" as definitions were received which did not call for a major change in these definitions. Additional comments on "Assent" and "Permission" in general are summarized in the discussion of § 46.409 below.

HHS Response: The definitions of "Parent" and "Guardian" are unchanged. The terms "Research" and "Minimal risk" are removed from this subpart since they appear in subpart A (§ 46.102 (e) and (g)). The Department agrees that reference to "consent to general medical care" in the definition of children is not appropriate and has, therefore, reworded the final regulation to read "consent to treatments or procedures involved in the research." The Department does not believe that a definition of "Advocate" is needed since it has been decided to delete any requirements for an advocate other than under Section 46.409 (a) and (b) of the final rule where the duties of the advocate serve as a working definition. it is the Department's position that the role of the advocate not be compromised by association with the research, the investigator(s), or the guardian organization. Modification of the final rule, at § 46.409 reflects this position, and is consistent with the recommendations of the National Commission.

In the definitions of "Assent" and "Permission" all references to informed consent requirements have been deleted since they are discussed in § 46.409 below.

This section is redesignated as § 46.402 in the final rule.

Section 46.404 IRB duties.

Public Comment: A total of 38 commentators addressed one or more of the duties assigned to IRBs by this support in addition to those assigned in, Subpart A. The majority of the comments referred to § 46.404(a)(1) "The research methods are appropriate to the aims of the research" or to § 46.404(a)(8), "adequate provisions are made for monitoring solicitation of assent and permission * * * ."

Six commentators questioned the phrase "The competence of investigator(s) and the quality of the

research facility are sufficient for the conduct of the research."

Comments on §§ 46.404(a)(1) and 46.404(a)(2) were related and very similar to those objections received in connection with a similar provision in the Proposed Regulations Amending Basic HEW Policy for Protection of Human Research Subjects (44 FR 47688, August 14, 1979), which states that "The research methods are appropriate to the objective of the research and the field of study."

Commentators pointed out, in response to the National Commission's recommendation (7)(B) (43 FR 31789), that the Department evidently intended to have the phrase "when appropriate" precede the provision at § 46.404(a)(8) and, therefore, monitoring would be the IRB decision. Had the phrase "when appropriate" been included in the proposed regulation, most of the comments probably would not have been expressed, since objections concerned the requirement for monitoring solicitation of assent and permission for all projects.

HHS Response: On August 14, 1979, when the Department published Proposed Regulations Amending Basic HEW (now HHS) Policy for Protection of Human Research Subjects (44 FR 47688). the public comment period for soliciting responses to the proposed regulations for research involving children was also extended. In its preparation of final regulations concerning the basic policy (Subpart A of Part 46), the Department examined all comments relating to IRB duties. Therefore, the HHS believes that the comments concerning this section have been adequately addressed in the preamble and regulatory sections of the final regulations amending Subpart A, published on January 26, 1981 (46 FR 8366). Accordingly, provivions (1) through (9) of § 46.404(a) as well as § 46.404(b) and (c) have been deleted. Section 46.404(a) has been modified and redesignated as § 46.403 in the final rule.

Although subject selection was not a point of significant public comment, the Department believes, as did the National Commission, that research involving risk should be conducted first on animals and adult humans in order to ascertain the degree of risk. When this is not relevant or possible, research should be first conducted on older children if feasible before progressing to younger children.

Section 46.405 Research not involving greater than minimal risk.

Public Comment: Only two commentators addressed this section, with one stating that to require explicit permission in all minimal risk, social and educational research would greatly and unnecessarily inhibit valuable research, especially in school settings. The other commentator felt that the phrase, "except where such provisions are waived by an IRB or its equivalent," should be added after the reference to § 46.409.

HHS Response: The Department has already taken account of the comment concerning research in schools since 45 CFR 46.101(b) exempts certain types of social and educational research which are also exempted from coverage under this subpart. In response to the second comment, § 48.408 (formerly § 46.409) does provide for IRB waiver of the requirements for permission and assent under certain circumstances. Section 46.405(a), which referred to conditions of § 46.404, has been deleted.

This section, redesignated as § 46.404, reflects the above discussion in the final rule.

Section 46.406 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Public Comment: Of the five commentators who directed their remarks to this section, one felt that if this were interpreted to mean that each subject should benefit, no placebo controlled drug study could be done. The other four comments pertained to § 46.406(b). One person felt that the provisions should incorporate language from the National Commission's report describing when a risk is acceptable. Another commentator questioned how the IRB could make the required judgment in the case of an Investigational New Drug (IND) study. A third person suggested that "is believed" be inserted before "at least as favorable." Another commentator suggested deleting the section since it lacks logic in view of the fact that a research program does not allow the estimates required by this section.

HHS Response: It is the Department's position that research activities involving placebos may be conducted in accord with Subpart D, depending upon the individual activity. An IRB may find that a particular activity is approvable under sections redesignated in the final rule as §§ 46.404, 46.405, and 46.406, or, In some cases, a combination of these sections.

The Department feels that in order to provide adequate safeguards for the protection of children as research subjects, the language of § 46.406 as proposed is not only essential but is in keeping with the recommendations of the National Commission. Therefore, except for deleting § 46.406(c), the section is retained and redesignated as § 46.405 in the final rule.

Section 46.407 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Public Comment: There were a total of 12 commentators that referred to this section or to a related question posed is the proposed regulations on how the Department could provide more useful guidance to IRBs in dating when a "minor increment over minimal risk is involved."

Several commentators felt that no attempt should be made either to define the concept of "minor increment" or to provide guidance to IRBs on evaluating whether a minor increment over minimal risk is involved. These commentators believed that because of varying situations and circumstances, IRBs would have to make judgments on a case by case basis. Other commentators cited the present difficulty of dealing with the concept of minimal risk and objected to any additional category of risk if not specifically defined. A few commentators stated that attempts by IRBs and investigators to determine minor increment over minimal risk could be too frustrating and impractical.

Several commentators questioned whether IRBs would have the expertise to evaluate adequately whether the research is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of same.

HHS Response: The Department believes that it is an appropriate responsibility of the IRBs to determine when the research would involve a minor increase over minimal risk. The Department also believes that the IRBs either are qualified or will enlist the aid of consultants who are qualified to judge whether the generalizable knowledge yielded will be of vital importance for the understanding or amelioration of the subject's disorder or condition.

Except for the deletion of § 46.407(d) this section is retained and redesignated as § 46.406 in the final rule.

Section 46.408 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Public Comment: There were a total of 11 comments, the majority of which spoke to § 46.488(b). Some commentators felt that properly

constituted IRBs serve the best interest of children and should review and approve all types of research proposals. Others preferred a standing Ethics Advisory Board and pointed out that employment of expert panels could lead to a kind of situational ethics. Four commentators, however, endorsed the change to a panel of experts instead of a National Ethics Advisory Board.

One respondent questioned the apparent escalation of the level of risk to which the Department is willing to expose research subjects. The commentator pointed out that minimal risk was once being suggested as an outer limit, but now research in children is authorized by the proposed regulations which cannot even meet the relaxed and "mystifying" standard of "minor increases over minimal risk." The same commentator suggested deleting this section in its entirety.

HHS Response: The National Commission made a recommendation that provided for exceptional situations in which the problem addressed would be a grave one, the expected benefit would be of major significance, the hypothesis regarding the expected benefit would be scientifically sound, and an equitable method, would be used for selecting subjects. HHS intends that this section apply when the IRB has difficulty in applying §§ 46.405, 46.406 and 46.407 (now designated as §§ 46.404, 46.405 and 46.406 in the final rule) but considers the research of sufficient importance to warrant national review and determination by the Secretary, HHS, prior to its being conducted.

The Department believes not only that the section should be retained, but that a panel of experts, which could be an ethics advisory board or some other qualified body, offers a flexible mechanism for reaching decisions on these difficult questions. HHS further feels that consultation with the panel, in addition to IRB and peer review, with final determination being made by the Secretary, will asssure appropriate protection of children as research subjects.

Reference to § 46.404 was deleted from § 46.408(a)(1) as in the previous three sections. Section 46.408 is redesignated as § 46.407 in the final rule.

Section 46.409 Requirements for permission by parents or guardians and for assent by children.

Public Comments: Thirty-nine commentators specifically addressed this section. There were an additional 48 comments directed to the Department's request for public response to options presented in the preamble to the proposed rule (43 FR 31786, July 21, 1978) which related to whether an ego for assent should be stated and, if so, what age.

Fourteen commentators addressed the subject of soliciting assent of children. A few of these commentators felt that a child should be informed and voluntary participation assured, but that there should be no formal regulatory requirement for assent. Others stated that IRBs should not be given exact guidelines, because information provided to and assent obtained from the child should depend on a variety of factors, such as the type of research, the child's level of competence, and the potential risk and discomfort involved, Almost one half of the commentators suggested that the investigator, using appropriate criteria, should decide when to obtain assent from children on a case by case basis. A few commentators pointed out that there were no guidelines for determining what could be done in situations where subjects object to participation in the research. Some commentators were concerned that if an IRB had to make a judgment regarding the assent of each individual child in a project involving 20 children, the review task would be impossible.

In response to the first option presented by the Department concerning the age of assent, five commentators preferred requiring assent from children who are 12 years of age or older. Of these commentators, one believed that age seven or older would be more appropriate when the research involved drug testing. A number of commentators were of the opinion that children between the ages of seven and 12 be informed of the research although assent would not be required until age 12.

Five commentators preferred option (2) agreeing that it was reasonable to expect children of age seven and older to understand and actively participate in the decision-making concerning their involvement in the research.

Eleven commentators felt that option (3) was most appropriate. Under this option, the IRBs would decide when to require assent, but the preamble to the regulations would provide guidance to the IRBs concerning an appropriate age. Of these conimentators, six favored guidance recommending age 12, three favored age seven and two did not express an opinion concerning age.

Sixteen commentators favored option (4), preferring that assent be left to the discretion of the IRB and that no guidance be provided either in the regulations or in the preamble. Many of these commentators felt that option (4) presented the most flexible approach to the determination of capability, since chronological age alone is an insufficient criterion. They also believed that the best protection for children would be the thoughtful consideration of what information would be given to subjects by a competent group of scientists and lay persons, together with the informed permission of parents.

There were seven comments on option (5), other alternatives, which dealt mostly with different suggested ages for assent varying from age three to 16.

There were five comments directed to the subject of advocate which was proposed under § 46.409(b). Three commentators endorsed this section requiring that the IRB determine when to employ an advocate. One commentator stated that it would be a mistake to establish a distinct and separate class of children for whom third party permission was required. Another commentator suggested that material should be provided concerning issues relevant to the role of an advocate who would have the delicate and challenging task of decision-making. A fifth commentator opposed an advocacy plan, stating that to require the IRBs to locate and monitor advocates would greatly increase the burden of the IRBs.

Seven commentators addressed provision § 46.409(c). One commentator felt that the concept of one parent being "not reasonably available" might need further clarification or definition. Another commentator believed that no research ought to be undertaken on children unless both parents, or a single parent if the child is under the care of only one parent, consent in accordance with the requirements of informed consent. Others suggested that a section should be provided allowing the IRB to establish criteria for activities not requiring parental permission such as levels of research that do not involve risk beyond that which is expected in day to day activities. A few commentators stated that parental permission should be waived for social and educational research.

Twelve commentators responded to § 46.409(d), five of whom agreed in principle that the section as drafted was appropriate and adequate. Other comments varied as follows: additional safeguards should be listed and the IRB should not be the body to grant permission; the IRBs should not be encouraged to treat categories of children, neglected, abused or whatever, as candidates for uniform waivers and such groups of children should not be research subjects unless the research offers them direct therapeutic gains; and, a phase should be added to the parenthetical example in § 46.409(d) such as "children in educational settings

where no greater than minimal risk is involved."

There were no comments on § 46.409 (e) and (f).

HHS Response: The Department appreciates the public's response to its request for comments on the important issue of assent and after careful consideration of all the comments agrees that determination of an appropriate age for assent should be made by the IRB and that § 46.409(a) should be adopted with minor modification. The phrase "the child is so incapacitated" is changed to "the capability of some or all of the children is so limited." In addition, the last sentence referring to a subject advocate is deleted.

As discussed above under definitions. the Department does not believe that emphasis should be given to advocates, and, therefore, the appointment of an advocate should not be a provision of this section. Even in the absence of the child's assent, if the procedure holds out a prospect of direct benefit available only in the context of the research. permission of the child's parent(s) or guardian should be sufficent. Therefore all references to the use of an advocate are delated from this section in the final rule.

The Department believes that the wording of the final regulations at § 46.408(b) (formerly § 46.409(c)) is such that the IRB will require the permission of both parents in all instances if they feel that it is appropriate and that the IRB should be given the responsibility for determining when a parent is not "reasonably available." A sentence has been inserted in this provision pointing out that in soliciting permission, the requirements for informed consent set forth in § 46.116 of Subpart A shall apply. With regard to assent, the criteria set forth in § 46.116 may be used by IRBs as a guide to determine what types of information should be provided to children when soliciting their assent.

The Department agrees with the public comment suggesting that assent and parental permission or documentation of such permission may not be appropriate in some cases. Accordingly, references to § 46.116 and § 46.117 of Subpart A are added to clarify that the IRB may approve waivers under certain circumstances.

The Department considers § 46.408(c) (formerly § 46.409(d)), to be adequate as drafted since it provides flexibility for the IRB to provide an appropriate mechanism for protecting certain subject populations.

Section 46.409 (e) and (f) have been reworded and the entire section has been redesignated as § 16.408 in the final rule.

Section 46.410 Wards.

Public Comments: A total of eight commentators addressed this section. Some suggested that the common legal element of § 46.410 be removed by changing the title from "Wards" to a more neutral title such as "children removed from parental custody and care." Several commentators interpreted the specified conditions as being too restrictive if "related to their status as wards" meant that research on such an individual's condition could not be undertaken. Another was of the opinion that the circumstances under which wards of the state might be involved need to be defined more narrowly to allow research only when it presents a reasonable opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of wards as a class and only when the information cannot be obtained from other segments of the population. One questioned the role of the advocate and felt that, due to the "coercive nature of their situation and lack of parental concern," involvement of wards in nontherapeutic research should be forbidden.

HHS Response: The Department would like to point out that this section is intended to apply strictly to "wards" and not also to children who, because of various physical or mental disabilities, may be under the custody and care of some other person or facility and whose parents are still legally responsible for them. The Department emphasizes that the provisions of this section are to be applied only if wards are to be included in research approved under §§ 46.406 or 46.407 of this part, as redesignated. Therefore, this section would not affect research presenting direct benefit to the individual subjects. The Department believes that these provisions would protect such children from being involved in research not intended to be of direct benefit and from being taken advantage of because of their status. The Department has deleted § 46.410(c) because § 46.410(b) adequately covers the role of an appointed advocate.

This section is redesignated as § 46.409 in the final rule.

List of Subjects in 45 CFR Part 46

Civil rights, Government contracts, Grant programs—health, Prisoners, Research, Safety, Women, Children, Human research subjects, Research.

Dated: September 23, 1982.

Edward N. Brandt, Jr.,

Assistant Secretary for Health.

Dated: February 3, 1983.

Richard S. Schweiker,

Secretary.

PART 46—[AMENDED]

Accordingly, Part 46 of 45 CFR is amended by adding a new Subpart D to read as follows:

Subpart D—Additional Protections for Children Involved as subjects in Research

Subpart D—Additional Protections for Children Involved as Subjects In Research

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of § 46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions (1), (2), (5) and (6) as listed in Subpart A at § 46.101(b) are applicable to this subpart. Exemption (4), research involving the observation

of public behavior. listed at § 46.101(b), is applicable to this subpart where the investigator(s) does not participate in the activities being observed. Exemption (3), research involving survey or interview procedures, listed at § 46.101(b) does not apply to research covered by this subpart.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of § 46.101 of Subpart A are applicable to this subpart.

§ 46.402 Definitions

The definitions in § 46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) "Parent" means a child's biological or adoptive parent.

(e) "Guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§ 46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§ 46.404 Research not Involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in § 46.408.

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

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

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

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians. as set forth in § 46.408.

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

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

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

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.407 Research not otherwise approvable which presents an ppportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §§ 46.404, 46.405, or 46.406 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: 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 §§ 46.404, 46.405, or 46.406, 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 children;

(ii) The research will be conducted in accordance with sound ethical principles;

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.

§ 46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of tho children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with § 46.116 of Subpart A.

(b) In addition to the determinations required under, other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by § 46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under § 46.404 or § 46.405. Where research is covered by §§ 46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has

legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in § 46.116 of subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by § 46.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented

§ 46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under § 46.406 or § 46.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parantis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

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