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PART V

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

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PROTECTION OF HUMAN SUBJECTS

Research Involving Children

[4110–08]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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[45 CFR Part 46]

PROTECTION OF HUMAN SUBJECTS

Proposed Regulations on Research Involving Children

AGENCY: Department of Health, Education, and Welfare.

ACTION: Proposed rule.

SUMMARY: The Department of Health, Education, and Welfare (DHEW) is proposing regulations to implement the recommendations on research involving children of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Key provisions require that such research can be carried out only if the research methods are appropriate, the investigators competent, the facilities adequate, and the research procedures designed to contribute vitally to generalizable knowledge. Risks must be minimized, and the research performed in connection with necessary diagnosis and treatment wherever possible. Adequate provisions must be made to obtain the assent of the child and the consent or permission of the parents or guardians whenever these are necessary.

DATES: You may send written comments on the proposed rules, but they should be received on or before September 19, 1978 if they are to be given full consideration.

ADDRESSES: Send comments whenever possible, supported by studies and documentations to: Office for Protection from Research Risks, National Institutes of Health, 9000 Rockville Pike, Bethesda, Md. 20014. Additional copies of this report may be obtained from the same address. All comments received will be available for inspection at Room 303, Westwood Building, 533 Westbard Avenue, Bethesda, Md., weekdays (Federal holidays excepted) between the hours of 9 a.m. and 4:30 p.m.

FOR FURTHER INFORMATION CONTACT:

Dr. Katherine Duncan, 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 DHEW through grants and contracts were published in the FEDERAL REGISTER on May 30, 1974 (30 FR 18914).

In the preamble to these regulations, DHEW indicated that it would propose further rules to provide additional protection for research subjects with diminished capacity to provide informed consent, including children.

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 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 Commission was required to recommend to the Secretary of Health, Education, and Welfare 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 DHEW.

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

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

Action 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 children were published in the FEDERAL REGISTER (43 FR 2084) on January 13, 1978. Comments were received from 132 individuals, institutions, organizations and groups. 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. The proposed rules depart from the recommendations of the Commission in few respects.

RESPONSE TO RECOMMENDATIONS

Recommendation (1), which found research involving children important for all children and that it should be conducted and supported, is adopted implicitly since the proposed regulations would govern such research.

Recommendation (2), regarding review of research by Institutional Review Boards (Boards), is implemented by section 46.404 substantially as written, except that the requirement that the Boards determine that "the research is scientifically sound and significant" is reworded to conform to the Commission's more recent recom mendation on research with those institutionalized as mentally infirm (43 FR 11328) which provides instead that the Boards determine that "the research methods are appropriate to the objectives of the research."

Recommendations (3), (4), and (5), on minimal risk research, on research that involves more than minimal risk but is potentially beneficial, and on non-beneficial research that involves only a minor increment in minimal risk, are implemented substantially as written by sections 46.405, 46.406, and 46.407, respectively. With respect to recommendation (5), the Department is particularly interested in public comment on how it can provide more useful guidance to Boards in evaluating whether only a minor increment oyer minimal risk is involved.

The regulations that implement *Recommendation (6)* depart slightly from the terms of that recommendation. Instead of requiring review and approval by a national ethical advisory board for all research that cannot be reviewed and approved under Recommendations (3), (4), or (5), as recommended by the Commission, the Secretary will consult with an ad hoc panel including experts in appropriate specialities in research, ethics, law and other relevant disciplines and interests. A single national ethical advisory body would, in the Department's view, prove cumbersome, inflexible and unadaptable to the variety of different research problems likely to be encountered within the scope of the Department's activities. This change is reflected in Section 46.408(b).

Recommendation (7) concerns the solicitation of parent's or guardian's permission and of children's assent. The Department has adopted the substance of this recommendation but with some modifications. In the recommendation, the Commission leaves it to the Board as to whether, with respect to any particular project, the children are capable of assenting. However, in their comments on the

recommendation the Commission makes it clear that they believe assent should be required if the children are 7 years of age or older. Reaction to this comment was mixed. Some respondents endorsed the comment; others felt the age was set too low (with suggestions from 12 to 14 proposed as alternatives); still others recommended that the matter be left entirely to the Board for determination in the context of each particular case.

The Department seeks further comment, preferably supported by studies and data, on this issue. Among the options being considered are the following:

(1) Requiring assent from all children who are 12 years of age or older, if the research is not expected to be of direct benefit to the health or well being of the particular child.

(2) Same as (1), but setting the age at 7.

(3) In the regulation itself, leaving it to the discretion of the Board, but in the preamble to the regulation and in implementing policy statements recommending that assent normally be secured if the children are above a certain age (ex., 12 or 7). Depending on the type of research and the types of candidates involved as subjects, the Board may wish to take a flexible approach in selecting ages at which assent may be required.

(4) Leaving is to the discretion of the Board, with no guidance either in the preamble or in implementing policy statements.

(5) Other alternatives.

The proposed regulation set forth below, leaves the matter to the Board's discretion, but this should not be construed as indicating that any decision has been made as to which of the above options will be adopted in the final regulation.

On essentially the same grounds, the Department has omitted from the proposed regulations the Commission's recommendation that a child's objection to participation in research should be binding unless the research intervention or procedure holds out a prospect of direct benefit to the child. This provision of the Commission's recommendation would apply without respect to age. The Department feels that the solicitation of assent, at ages when, in the opinion of the Board, children are capable of such assent, is a more appropriate, consistent and positive approach.

Where the Board determines that the assent of the child is not needed, it must also decide whether or not a subject advocate should be appointed to represent the child's interests.

Technically, *recommendation (7)* requires the consent of both parents. In its discussion of this recommendation, the Commission says that the consent of one parent should be sufficient for research covered under *recommendations (3) and (4).* The Department agrees, and this is reflected in section 46.409(c) of the proposed regulations. Also, the Commission's discussion suggests the disclosure requirements for permission and assent should be the same as the disclosure requirements for consent. The Department incorporates this point in the proposed regulations through definition of assent and permission in section 46.403(e) and (f).

Recommendations (8), concerning waiver of permission, *and (9),* concerning wards of the State, have been implemented substantially as written in sections 46.409 and 46.410 respectively, but with some added protections for wards of the State and wards similarly situated.

The Department is particularly interested in receiving comment on the question of whether an alternative review mechanism should be substituted for the requirement for parental permission in situations where parents may not act in the best interests of the child—such as situations involving abused or neglected children. As currently drafted, section 46.409(d) would permit the Board to waive the parental permission requirement provided the Board devises "an appropriate mechanism" to protect the children involved. Specifically, the Department seeks comment on whether this provision is adequate; whether stronger review mechanisms should be specified; and what circumstances justify the waiver of the requirement of parental permission and the substitution of an alternative requirement.

Recommendation (10), concerning children institutionalized as mentally infirm or confined in correctional facilities, is implemented in essence in section 46.401. Complete implementation must await issuance of Department regulations concerning research with prisoners and the mentally infirm.

RESPONSE TO PUBLIC COMMENTS

In response to publication in the FEDERAL REGISTER of the Commission's recommendations on research involving children, 132 letters were received from individuals and on behalf of societies, department heads, directors of clinical research centers, institutional review boards, etc. While objecting to some points, they were generally complimentary to the Commission's efforts. In fact, some simply indicated their approval of the 10 recommendations.

Described below are the comments received on the recommendations in the order of the recommendations to which they were addressed. Many of the public comments referred to material in the Commission's own "comment" on its recommendations rather than to the recommendations themselves. For the purpose of this document in order to distinguish between public comments and the Commission's "comment" in the FEDERAL REGISTER, reference will be made to the Commission's discussion rather than "comment."

1. *Comment on Definitions of "Minimal Risk".* The only definition subject to comment was that of "minimal risk." Comments included (1) questioning if this was to be a new category of risk, intermediate between "not at risk" and "at risk;" (2) noting that the concept of "minimal risk" was a semantic improvement over the concept of "no risk," but if strictly—interpreted would cover no more than what is normally done in the course of routine pediatric care; (3) stating the definition was too vague since each IRB would set its own standard; and (4) noting the definition does not adequately provide for the vast risk differences between biomedical and psychological or educational research.

Response. The Department notes that the term "minimal risk" is found in subpart B of the current regulations on protection of human subjects, the concept of "minimal risk" includes "no risk," and any attempt at more rigid definition would necessarily collapse in the face of the varied types of risks to which children may be exposed in medical, psychological and social research. The definition is retained in section 46.403(i) as it was stated by the Commission.

2. *Comment on Definitions of "Minor Increase of Minimal Risk".* Several commenters suggested that this phrase should be defined. *Response.* The Commission's discussion reflects the obvious judgmental nature of this phrase. What constitutes a "minor" increment is necessarily a function of the nature of the "minimal" risk, of the nature and probable frequency of that risk, and of other variables. The Commission, in discussing the issue, proposes not a definition but a practical approach to a determination. It involves "a common-sense estimation of the risk; an estimation based upon investigators' experience with similar interventions or procedures; any statistical information that is available regarding such interventions or procedures; and the situation of the proposed subjects." Under the circumstances, the Department feels that definition of this term would be artificial and of limited usefulness.

3. *Comment on Definition and Scope of "Assent" and "Permission".* There appeared to be differing interpretations of what would be involved in soliciting a child's assent or parent's or guardian's permission. Several

commenters concluded that it meant signing a form, therefore questioning if both the assent and permission statements were to contain all six basic elements of informed consent as in 45 CFR 46.103.

Response. The Department agrees that these terms need clarification. Proposed definitions have been provided in section 46.403(e) and (f). Note that the explanation necessary to assent is to be "appropriate to the level of understanding of the child as determined by the Institutional Review Board" and that no age limits are specified. See also the discussion in "response to recommendations" and proposed section 46.409.

4. *Comment on Recommendation (2)(A).* This provision of the recommendations would have required IRB's to determine that research was "Scientifically sound and significant." A large number of commenters argued that IRB's, because of the requirement for diversity of membership, are not qualified to make this determination. Since they are called upon to review projects from a wide variety of disciplines, they do not necessarily have the depth necessary to consider the scientific merit of particular proposals. Their charge is to determine adequacy of measures to be employed for protection of human subjects. Only peer review groups can provide the quality of review needed to determine if research is scientifically sound and significant. The use of consultants could amplify the IRB's range and depth of expertise but would be time consuming and costly to institutions with a large number of projects. Further, it should not be within the purview of the IRB to disapprove a protocol which involves no risk solely on the basis of its perception of scientific design. As summarized by one commenter, implementation of the recommendation appears to alter the function of the IRB from review concerned with the rights and welfare of subjects, the risks and benefits to subjects and the quality of informed consent, to a combination of ethical review and scientific peer review.

Response. The Department concurs. In addition, the Commission, in a more recent series of recommendations on research with those institutionalized as mentally infirm (43 FR 11328, March 17, 1978), has recommended the IRB determine only that "The research methods are appropriate to the objectives of the research." A corresponding change has been made in section 46.404(a)(1) of the proposed regulations.

5. *Comment on Recommendation (2)(B).* This provides that "where appropriate" research be conducted first on animals and adult humans. Two commenters questioned whether, depsite the use of "where appropriate," there was a need for clarification, citing instances when meaningful research can only be done on children and infants.

Response. Since there were only a few comments on this phrase, the Department believes it sufficiently clear that prior research on animals and adults is not always possible or meaningful, and that "where appropriate" is adequate to imply this. The language of the recommendation is retained in section 46.404(a)(3).

6. *Comment on Recommendation (2)(E).* There appeared to be some uncertainty as to what was meant by selection of subjects "in an equitable manner." While granting that equitable selection is, scientifically and socially desirable, it appeared to some commenters to be a goal beyond the capability of an IRB. Though there are obvious exceptions, it seemed unreasonable to suggest that sampling equity can or should be attained in many investigations. Others commented that the statement could be interpreted as mandating that all research samples by fully representative of the general population of interest, and as forbidding research on children from a specific class, economic group, unique patient population, etc.

Response. The Department agrees that the broad language of this recommendation is not clear. It is clarified by the Commission's discussion emphasizing avoidance of overutiliation of any one group of children for scientifically irrelevant reasons. The Commission's clarification has been incorporated in the corresponding part of the regulations at section 46.404(6).

7. *Comment on Recommendation (5).* Three commenters supported the dissenting opinions of Commissioners Cooke and Turtle, or at least suggested that the lack of unanimity bespoke a need to reevaluate the issue.

Response. The Department notes and agrees with the Chairman of the Commission in his discussion of the dissenting statements. Dr. Ryan believes the dissents are based on a misunderstanding of recommendation (5). He points out that the limited circumstances, under which research not intended to directly benefit the children may be approved, clearly indicate that the research must be related to the disorder or condition affecting those subjects who are involved. Such research cannot, by its very nature, be conducted on normal subjects. These limited circumstances are commensurability of experience, likelihood of yielding generalizable knowledge about the subject's disorder, and importance of that knowledge for understanding or treating such disorder.

8. *Comment on Recommendation (6).* Comments were limited to the provision for review by a national ethical advisory board of projects not acceptable under recommendations (3), (4) or (5) (proposed section 46.405, 46.406, 46.407 respectively). Commenters noted (1) the proposed national review mechanism was cumbersome, time consuming, unworkable, and impractical, (2) that properly constituted IRB's serve the best interest of children and should be allowed to review and approve all types of research proposals without resorting to a complex and time consuming review process and (3) the possibility that if such a mechanism were provided some IRB's might be more hesitant to make certain decisions, such as those which might be unfavorable and hence unpopular locally. Further, since such a board, whether established by law or regulation, would be outside the judicial system, the legal validity and standing of a national ethical advisory board case adjudication could be seriously questioned.

Response. The comments appeared to assume that the involvement of a national ethical advisory board would be necessary in a high percentage of cases, and thus would become a major hurdle in the review and approval process. The statement of Commissioners Height, King, Louisell, Ryan and Seldin (43 FR 2084 at 2109–2110) emphasizes that the Commission was groping with "The most difficult ethical issues" in attempting to deal with research presenting more than minimal risk, but no immediate prospect of benefit to individual children. The decision with respect to most of such research, that presenting a "minor increment in a minimal risk," is covered by recommendation (5). Recommendation (6) is expected to deal only with "exceptional situations" and to be invoked only for "research that cannot be approved by an IRB." Commissioners Brady, Jonsen, Lebacqz, Louisell, Ryan and Stellar, in discussing recommendation (6) (2112), similarly conclude that these provisions need be invoked only in "exceptional situations."

The Department agrees that even if it were required to deal only with "exceptional situations," a single national ethical advisory board could prove cumbersome, unworkable and impractical. A standing body would necessarily be deficient in expertise with respect to any particular project or proposal. Consequently, §46.408(b) has been written to provide for decision by the Secretary following consultation with a panel of experts, potentially a more flexible and precise mechanism which will still permit decision on, and support for, a project at the national level.

The Department notes that it is permitted by law (5 U.S.C. 301) to issue such regulations as are necessary to

the "performance of its business." Such regulations cannot be construed as indicating that compliance with any procedures issued under that provision will render inapplicable any pertinent State or local laws as noted in §46.401(b).

9. *Comment on Recommendation (7)(A).* In general, comments regarding solicitation of children's assent and parents' permission, raised such points as whether (1) it was intended that the assent and permission statements were both to contain all six basic elements of informed consent, as in 45 CFR 46.103(c); (2) the requirement for children's assent would be prohibitive to performance of much needed research in the behavioral treatment of children; (3) unless the research could be explained in language that the child can understand, assent would be meaningless; (4) assent should be made discretionary, but when not obtained the investigator should be required to provide, in writing, to the IRB's the specific reason; (5) there is no way of telling a child the nature of the research without the reason for it, and, in cases of children with terminal illness, many parents refuse permission to have the child told; (6) a distinction should be made between children and adolescents and minors of 13 years of age or older who should consent to research, not simply assent; (7) too much emphasis was placed on the need for parental permission, for instance in cases where older children might be asked to participate in research in an educational setting. School authorities' consent should be sufficient unless the research involves more than minimal risk.

Response. The varying criticisms are dealt with in several sections of the proposed rules. On points (1), (2), (3), a definition of assent in § 46.403(e) clarifies the Department's intent that the "type of information" required by § 46.103(c) should be provided "appropriate to the level of understanding of the child." Given these conditions, and the provisions in § 46.409(a) that the IRB shall determine when assent shall be obtained and what constitutes an adequate assent, these procedures should be no more prohibitive of research with children than is consent to research with adults. Concerning comment (4), the basic principle of DHEW policy is that discretion in matters of research with human subjects lies with the collective judgment of the IRB, not with the principal investigator. Departure from this principle in the case of children would be most inappropriate. With respect to comment (5), where the research holds forth the prospect for direct benefit of the child and is covered under § 46.406, the IRB may also find, as provided in § 46.409, that the requirements for assent of the child may be set aside if the child is incapacitated or the benefits sought are available only in the context of the research. With respect to comment (6), the limits of the age of consent are defined by State laws which cannot be rendered inapplicable by these regulations as noted in § 46.401(b). Current State consent laws are noted by the Commission in its report (43 FR 2084 at 2101) in a tabulation dated June 1977. These laws are subject to change and cannot be usefully incorporated into regulation. On comment (7), the issue of the need for consent by parent and child has been addressed by the Federal Courts in *Merriken* v. *Cressman,* 364, F. Supp. 913 (USDC E.D. Pa., 1973). The case is discussed in the Commission's report (43 FR 2084 at 2100) noting that "* * * this case supports the necessity * * * of parental consent for participation of children in research."

10. *Comment on Commission's discussion of recommendation (7)(A).* Over one-half of the comments in connection with recommendation (7) were in reference to the Commission's stated belief that children 7 years of age or older are capable of assent. Three commenters agreed to the suggested age of 7, one even stated that it should be mandatory. It was also reported that the age of 7 has been recommended for obtaining consent in pediatric drug testing, admitting, however, that this age limit is controversial in the research community as being unrealistic, too restrictive, and possibly detrimental to the child's best interest. The great majority definitely opposed the age of 7, a few suggesting the age of 12, 13, or 14. The rest mentioned in general that age alone cannot be used as a criterion, since children mature emotionally and develop intellectually at different rates. Psychiatrists referred to the scientific work of Piaget and others which has clearly demonstrated that at this age children have not developed the cognitive skills required to make such assent meaningful. Opinion was expressed that children as young as 7 years of age are not capable of abstract thought and are, therefore, not able to assess the benefit to society of their participation in research.

Response. The Department seeks additional comment and data on this issue. For purposes of discussion, several options are outlined earlier in this preamble (see "Response to Recommendations" at recommendation (7)).

11. *Comment on recommendation (7)(B).* In regard to the IRB monitoring the solicitation of assent and permission, there were only two comments. One stated that although this part of the recommendations is made ambiguous by the phrase "when appropriate" prefacing the statement, the form in which an IRB discharges its responsibility should not be specified in the guidelines and, moreover, such a requirement could reinforce some individuals' views that all scientists are not trustworthy and hence require monitoring. The other commenters stated that the IRB should not be put into the role of "policeman" by being required to monitor the "solicitation of assent and permission," adding that the time and effort required would be prohibitive.

Also included in this Recommendation was a statement that a child's objection should be binding unless the research was potentially beneficial and the benefits available only in a research context. There were three comments stating that the full implication of a binding objection could be detrimental to the best interests of individual children, and there is a risk of interfering with the parent-child relationship if the child is given the right to act independently of (and in opposition to) his/her parents.

Response. "When appropriate" is felt to be a sufficient indication to the IRB that monitoring assent and permission is to be their decision and that it is not mandatory. The concerns on the "objection being binding" are resolved by giving the IRB responsibility for deciding when assent would be required as provided for in section 46.409.

12. *Comment on Commission's discussion of recommendation (7)(B).* The discussion mentioned that the IRB should assure that children participating under recommendation (5), proposed section 46.407, should be those with good relationships with their parents or guardians. The few comments received pointed out the difficulty and effort that would be involved in making such determinations, since advance clinical psychological investigations would not generally be available. The IRB is too far removed from the research project to make the evaluation.

Response. The Department agrees with the comments, but in order to provide some protection for children whose parents may have conflicting interests, the Board has been instructed to consider whether a subject advocate should be appointed to represent the child's interests in those cases in which the child's assent is not required.

13. *Comment on recommendation (8).* This provides for IRB waiver of parental permission in certain instances provided an appropriate mechanism for protecting the children subjects is substituted. One commenter suggested "appropriate mechanism" should be defined. Options for acceptable mechanisms for various categories of research should be developed.

Another commented that no direct mention is made in the recommendation—as it is in recommendation (9)—that an advocate be appointed.

Response. It would not be possible or practical to develop appropriate mechanisms for various categories of research, nor would the appointment of an advocate be appropriate in all instances. The mechanism is to be a decision of the IRB. The language of the recommendation is incorporated into the proposed regulations at § 46.409.

14. *Comment on Commission's discussion of recommendation (8).* The Commission mentions "Mature minors" as one group for which parental permission might be waived. One commenter mentioned that it was not made clear that "mature minors" may consent to minimal risk research without parental permission. Another stated that routine questionnaires administered to 17-year-old students would present difficulties of fact and law, i.e., determining whether the student is a mature minor. Another felt that "mature minors" are the very children who would be intimidated and most at risk in terms of certain biomedical research procedures. Another group the Commission gives as an example includes "neglected or abused children." One commenter noted that if the child participates in research without the parents' knowledge, this could interfere with the basic trust building that is necessary in reconstructing a family. Another commenter, in reference to an appropriate mechanism for protecting these subjects, suggested that another alternative might be to appoint a social worker, pediatric nurse, physician, or psychologist to act as surrogate parent when the research is designed, for example, to study neglected or battered children. Alternatively, there were several comments on the inadequacy of professionals involved with the treatment of such children who may find themselves unable to properly represent the best interests of children. Finally, questions were raised about the authority to appoint such a surrogate parent. In general, the appropriateness and legality of such an appointment was questioned.

Response. The Department acknowledges that these comments are generally pertinent and underscore the variable and uncertain nature of the solutions available to deal with the issue of parental consent where this is "not a reasonable requirement." Both the comments of the public and the Commission's discussion of its own recommendation stress the need for the exercise of judgment. Responsibility for making such judgment is assigned to the IRB in proposed § 46.409.

15. *Comment on recommendation (9).* Comments regarding research with children who are wards of the State varied. At one extreme, commenters expressed opinions that children who are wards of the State should not be used in research and such children have been "overexposed," research often having been done to meet the needs of the researcher rather than that of the children. At the other extreme, there is no provision for a child, particularly if old enough to make an informed assent to volunteer for participation in a research project, or older children should be offered the option to participate regardless of their custodial status. One commenter mentioned that State statutes should be compiled with regard to who could appoint an advocate. Another urged that prior court approval be required, based upon information provided in a juvenile court hearing, in all instances of research with court wards. One commenter was concerned with whether wards of the State would be allowed to receive research drugs if they had a potentially fatal disease, like cancer.

Response. The recommendation is that these children should not be included in research: (1) Involving more than minimal risk and no direct benefit (§ 46.406(b)), and (2) research that cannot be approved by an IRB (§ 46.407) unless (a) it related to their status as wards, or (b) was conducted in a setting in which the majority of children involved as subjects are not wards. If the research is approved, an advocate is to be appointed.

The Department accepts the Commission's recommendation and believes that these provisions would protect such children from being involved in nonbeneficial research or from being taken advantage of because of their status. On the other hand, the Department does not agree to suggestions from the public that there should be included a provision for such children to volunteer freely for a research project exclusive of other protective provisions. The Department finds no reason to exclude wards of the State from the benefit of research drugs (see § 46.406(a)).

16. *Comment on recommendation (10).* Comments on research with children in prisons or institutions for the mentally infirm were few. One commenter agreeing that until specifics are published or citations made to portions of other guidelines intended under this recommendation one could not actually comment. Another noted that it was not indicated how adult prison standards could be directly applied to juvenile facilities. Another commenter was concerned about severely handicapped children with disinterested parents being subjected to high-risk research. In the case of vulnerable subjects, the definition of high-risk research would need to be broadened to any research deemed to be beyond low risk. Such research should be reviewed and monitored by a group outside the institution and an advocate appointed to intervene at every step of the research.

Response. The Department agrees that until final rules relating to research with prisoners and those institutionalized as mentally infirm have been published, this recommendation cannot be fully implemented. In the meanwhile, the problem is covered by § 46.401(c).

MISCELLANEOUS

17. *Comment.* Two communications dealt entirely with the possible impact of the recommendations on vaccine development and evaluation. The commenters noted that, using the definition and the example given, it would appear that clinical evaluations of pediatric vaccines which are comparable to previously licensed vaccines would be considered as involving minimal risk. However, the commenters, on reading under Deliberations and Conclusions, noted that following a discussion of the kinds of studies that could be justified under recommendation (5) (no benefit), the examples described included "* * * the threat of an epidemic that could be offset by developing a safe and effective vaccine which would justify research involving risk greater than otherwise acceptable * * *" [emphasis supplied]. They further noted that the decision to conduct such research would have to be made at the national level (recommendation (6)) with an opportunity for public participation, since testing in the face of a threatened epidemic would be considered research of more than minimal risk and of no direct benefit. The commenters noted that no consideration seemed to have been given to the necessity of protecting the child from an active epidemic virus.

Where an epidemic is only threatened, the study would require consideration under recommendation (6), a procedure which would clearly result in significant loss of time necessary to initiate a vaccination program. Where the epidemic is active, consideration under recommendation (6) could result in excess mortality. The commenters argue that the risks to the individual child would appear to be the unanticipated risks associated with the use of new products, or the defined, but very low probability risks associated with many currently used vaccines. The commenters urge that clarification be sought as to what kinds of risk (minimal, minor increments in minimal, or other) and what potential benefits are assumed to

accrue to children in phase I, II, and III vaccine trials.

Response. Again, neither, the Commission's discussions of its recommendations nor its "Deliberations and Conclusions" constitute part of the formal recommendations. The intent of the recommendations is clearly to leave much room for judgment to individual IRB's and, in matters that are beyond the reach of IRB's, to an expert panel as provided for in section 46.408(b).

18. *Comment.* The question of compensation of children injured in research is not addressed. In present practice, there is no compensation, direct or indirect, beyond payment for the usual expenses of research treatment of the patient's disease.

Response. The question of the compensation of injured research subjects, including children, was not included in the Commission's mandate. However, it has been addressed by a secretarial task force. The report of the task force (HEW publication No. OS–77–003) was forwarded to the Secretary in January 1977. A notice of proposed rulemaking on this subject is currently under consideration by the Secretary.

19. *Comment.* One commenter suggested that IRB's should not be required for research conducted in noninstitutional settings. Pediatric drug doses may be tested following rigidly controlled phase I and II studies by providing the drug to physicians for use in phase III studies. Patients would not be hospitalized and might be located in a rural setting. The protocol for the study would no doubt have been previously established and approved by a peer review group or an IRB.

Response. These regulations (45 CFR 46) apply only to research conducted by the Department or to research supported by its grants and contracts. Clinical drug trials are controlled by comparable regulations issued by the Food and Drug Administration at 21 CFR 312 and other parts of title 21. Application of these FDA regulations is limited to institutionalized subjects. Where Department grants or contracts support clinical drug trials, support is normally limited to phase I and II studies.

20. *Comment.* Two commenters were concerned with the impact the recommendations might have on research into the sexuality of children. One stated that because sexuality is stigmatized so greatly in our society it has always been difficult to get sexual research approved. This difficulty might well be magnified unless a special provision to the contrary is built into the regulations. The other commenter urged that a special commission be set up, composed of leading psychiatrists, child specialists, and sexologists to consider the whole question of behavioral observation and research regarding children's knowledge and attitudes in the field of sexuality and to develop standards and appropriate safeguards.

Response. While the Department believes that, in general, public concern over sensitive issues can, in the long run, be reduced by continued public discussion. The general issue of the scope of these regulations is explored in some depth later in this preamble (see "Should Some Research Be Exempted From These Regulations?")

21. *Comment.* One commenter suggested that testimony during the public hearings, which questioned the practice of random assignment in clinical trials, should be ignored as long as there is assurance by the investigator to the IRB that each arm of the proposed study is appropriate in terms of safety, efficacy, and ethics.

Response. While not addressing itself specifically to the issue of clinical trials, the Commission has not prohibited any accepted clinical research procedures. The Commission's recommendations, as well as other provisions of the Department's regulations, and common law further provide that the subject or his legally authorized representative be informed as to the alternative procedures involved in a randomized clinical trial.

22. *Comment.* Several commenters mentioned that the Commission did not have a member actively engaged in biomedical research in children. One commenter added that the members were not experts in the care of human beings of preadolescent age, in particular those dying of cancer. Another suggested the need for representatives of behavioral research.

Response. Review of the membership of the Commission will show at least one member is a pediatrician who has done research in the field of mental retardation and in electrolyte physiology. A second is a physiological psychologist whose background is in motivation and learning, and a third is a clinical and experimental psychologist who has worked in behavior and behavioral psychology. Since the Commission was limited by the provisions of the National Research Act to include not more than five members "who are or have been engaged in biomedical research involved human subjects," it necessarily relied for additional expert scientific advice upon consultants, contract studies, staff and public hearings, as reflected in its report.

23. *Comment.* One commenter called attention to the chilling effect a multiplicity of government regulations might well have on scientific research. Such regulations might, in the aggregate, provide an obstacle to helping the people they are designed to protect.

Response. The Department is sensitive to the problem of over regulation and is soliciting comment on this issue later in this preamble (see "Should Some Research Be Exempted From These Regulations?").

24. *Comment.* (a) Frequent references were made by persons in the fields of behavioral, sociological, and educational research to the origins of the present regulations (45 CFR 46) in the Public Health Service, their adherence to a "medical model," and its difficult application to other fields. The general theme was that it was essential to distinguish between biomedical research where there is often more than minimal risk and most sociological and educational research where, by and large, there is minimal or less risk. Commenters suggested that there should either be separate regulations for behavioral, sociological, and educational research or differences in applicability of the regulations. It was emphasized that the risk factor in medicine is essentially different from the risk factor in nonmedical research, that research should not be reviewed as being primarily conducted at medical schools, with regulations primarily related to medical research and presented in medical terms.

(b) Commenters also argued that too much emphasis is placed on the need for consent. This is particularly true in cases where older children may be asked to participate in research in an educational setting. School authorities' consent should be sufficient unless more than minimal risk is involved. In regard to educational and sociological programs, it is inappropriate to categorize questionnaires, observational techniques and psychological tests as presenting minimal risk. Such a broad definition of minimal risk, the requirement for parental consent or permission and children's assent, and for IRB review might adversely impact educational and social service programs. The importance of benefit to the individual should be balanced more in the direction of the consideration of benefit to society as well. The use of consent procedures also rests upon an extensive body of legal determination in medical research which places consent in a very different light from that in education. If informed consent of parents and children is required, many research studies will never be conducted. School administrators are not willing to have students participate in studies requiring their time and effort to obtain informed consent. In the past, research has been conducted without obtaining parental consent. In cases where IRBs indicate there is absolutely no risk principals, administrators and teach-

ers should make the determination. School programs need evaluation. There must be some room for the school's head judgment depending upon the type of research as to no need to involve parents.

(c) Specific objections were made to the direct transferral of biomedical procedures and terminology to social and educational research, e.g., use of the term "subjects," the distinction made between research and treatment, the definition of "risk," and the use of consent procedures. "Subjects" in medical context means individual human beings. Behavioral research may be directed toward individuals or groups or classes within a population. Educational research may be directed towards individuals (e.g., students, parents, teachers, administrators), classes, schools, school districts, etc. The definition of risk does not attempt to define the nature of "minimal risk" in educational research, an area still requiring intensive study.

SHOULD SOME RESEARCH BE EXEMPTED FROM THESE REGULATIONS?

The issue of the scope of the Department's policies on protection of human subjects has been raised in the context of the children's regulations, because of the specific impact these regulations would have on educational research. However, the applicability clause in the proposed children's regulations is simply patterned after the clause which currently appears in the basic Department regulations on protection of human subjects in 45 CFR part 46. Hence, to the extent the children's applicability clause is too broad, the same would probably be true with respect to the clause in the basic regulations.

Those who object to the current, applicability clause in part 46 point out that it requires establishment of Boards by all organizations which apply to the Department for any support for research involving human subjects. In social and educational research, it is said that the research rarely presents any significant risk to the subjects. In these fields, many of the applicants are small organizations for which it is a substantial administrative and financial burden to establish Boards to satisfy part 46. Often the research is of a type that has undergone substantial review within the Govemment before it can be undertaken (e.g., certain types of survey research which must be reviewed by the Office of Management and Budget under the Federal Reports Act).

Another concern which has been raised about the scope of the regulations pertains to large scale, innovative, service delivery programs. Technically, it might be argued that a State or local subdivision may be engaged in research when it introduces an innovative modification into a service delivery program. Once the decision is made through normal governmental processes to adopt the innovation, it is said that Boards should not have the option to veto this decision, and individuals should not have the discretion to opt out of those aspects of the program that are disadvantageous to them.

In view of these objections, the Department will consider whether, as part of the overall revision of part 46 (which will take place once all the Commission's recommendations are received), the applicability clause of the basic regulations and all other regulations in part 46 should be narrowed.

Among the types of activities which may be considered for exemption from part 46 are the following:

1. Survey research, particularly where the survey form must be cleared by the Office of Management and Budget.

2. Observational research, where the researchers simply observe subjects engaged in their normal day-to-day activities.

3. Achievement and aptitude testing.

4. Research involving solely the review of already existing records.

5. Participation in instructional and other programs carried out in the normal educational setting, where the program is generally similar to other programs in the school curriculum and has been approved by a local school board or parent advisory group.

6. Research designed to study on a large scale the effects of proposed social or economic change.

7. Research designed to study on a large scale methods or systems for the delivery of or payment for social or health services.

The Department welcomes comment as to the appropriateness of narrowing the scope of part 46, through exempting some or all of the above categories of research from the regulations. The Department would also be interested in suggestions as to other categories which should be considered for exemption. Wherever possible, information and data should be submitted in support of comments.

To the extent some categories of research are exempted from part 46, the Department is also considering whether other protections should be developed to cover these categories and, if so, what these should be. Commenters who propose narrowing part 46 may wish to address these issues as well.

In connection with this reconsideration of the scope of part 46, each Principal Operating Component of the Department will be developing the capacity to review protections for human subjects, as part of their decisionmaking processes.

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

Dated: July 11, 1978.

JULIUS B. RICHMOND,
Assistant Secretary for Health.

Approved: July 12, 1978.

JOSEPH A. CALIFANO, Jr.,
Secretary.

It is therefore proposed to amend part 46 of 45 CFR, subtitle A, by:

1. Redesignating subpart C and §46.301 as subpart F and §46.601, respectively.

2. Adding the following new subpart D.

Subpart D—Additional Protections for Children Involved as Subjects in Biomedical and Behavioral Research

Sec.

AUTHORITY: 5 U.S.C. 301.

Subpart D—Additional Protections for Children Involved as Subjects in Biomedical and Behavioral Research

§ 46.401 Applicability.

(a) These regulations apply to all biomedical and behavioral research conducted or supported by the Department of Health, Education, and Welfare involving children as subjects.

(b) Compliance with these procedures will in no way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

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

§ 46.402 Purpose.

Children are normally legally incapable of consenting to their own

participation in biomedical or behavioral research and may also be unable to comprehend fully the consequences and risks which might be involved in such participation. This subpart provides additional safeguards for the protection of children involved in biomedical and behavioral research.

§ 46.403 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) "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.

(d) "Research" means a formal investigation designed to develop or contribute to generalizable knowledge in such fields as human biology and medicine and in the behavioral sciences including psychology, educational psychology, and sociology.

(e) "Advocate" means an individual appointed by the Board, or through procedures approved by the Board, to act in the best interests of the child. 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 children 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, 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."

(f) "Assent" means a child's affirmative agreement, to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as consent. Assent can only be given following an explanation, based on the types of information specified in § 46.103(c) of this part, appropriate to the level of understanding of the child, in accordance with procedures established by the Institutional Review Board.

(g) "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research. Permission can only be given following an explanation including the information specified in § 46.103(c) of this part.

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

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

(j) "Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy children.

§ 46.404 Additional duties of an Institutional Review Board where children are involved.

(a) In addition to all other responsibilities under this part, each Institutional Review Board (Board) shall review research covered by this subpart. It may approve the research only if it finds that:

(1) The research methods are appropriate to the aim 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) Where appropriate, studies have been conducted first on animals and adult humans, and then on older children before involving very young children;

(4) Risks are minimized by using the safest procedures consistent with sound research design and by using procedures performed for the examination, diagnosis, or treatment of the particular subject whenever appropriate and feasible;

(5) Adequate provisions are made to protect the privacy of children and their parents, and to maintain the 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 children; and all data should be maintained in accordance with fair information practices;

(6) The criteria for subject selection are appropriate for the research aims and will permit the selection of subjects in an equitable manner, avoiding overuse of any one group of children based solely upon administrative convenience or availability of a population;

(7) Where appropriate, adequate provisions are made for involving a parent, guardian, or advocate in the conduct or monitoring of the research, for example, in situations in which the Board finds the subjects to be incapable of assenting and the research involves more than minimal risk or more than minimal discomfort to these subjects:

(8) Adequate provisions are made for monitoring solicitation of assent and permission, as, for example, through participation by Board members or by advocate in the actual solicitation process, either for all subjects or for a sampling of subjects; and

(9) 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 sponsoring the Board 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.

§ 46.405 Research not involving greater than minimal risk.

DHEW may conduct or support, research that does not involve greater than minimal risk to children if the Board finds that:

(a) The conditions of § 46.404 are met; and

(b) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in § 46.409.

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

DHEW may conduct or support research in which the Board 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, if the Board 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;

(c) The conditions of Section 46.404 are met; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.409.

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

DHEW may conduct or support research in which the Board 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, if the Board 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:

(d) The conditions of § 46.404 are met; and

(e) Adequate provisions are made for assent of the children and permission of their parents or guardians, as set forth in section 46.409.

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

DHEW may conduct or support research that the Board does not believe meets the requirements of §§ 46.405, 46.406, or 46.407 if:

(a) The Board finds that: (1) The conditions of § 46.404 are met; and (2) the research presents a reasonable opportunity to futher 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 (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 §§ 46.405, 46.406, or 46.407, 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 the basic 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 section 46.409.

§46.409 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 Board shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the Board the children are capable of doing so. In determining whether children are capable of assenting, the Board shall take into account the ages and maturity of the children involved. This judgment may be made for all children under a particular research protocol, or on a more individualized basis, as the Board deems appropriate. If the Board determines the child is so incapacitated that he or she 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 child and is available only in the context of the research, the assent of the child need not be obtained. If the Board determines that a child is so incapacitated, and the child is not under the guardianship of a parent, then permission of both the guardian and a subject advocate must be obtained.

(b) Where the Board determines under paragraph (a) that the child's assent need not be obtained, it shall also determine whether a advocate should be appointed for the child, taking into account such factors as, for example, whether there are likely to be financial or other pressures on the parents or guardian which could affect their ability to consider solely the interests of the child in deciding whether to consent to the child's participation in the research. The role of the advocate would be to advise the Board, parents, and investigators of any concerns the advocate may have about the child's participation in the research.

(c) In addition to the determinations required under other applicable sections of this subpart, the Board shall determine that adequate provisions are made for soliciting the permission of each child's parent(s) or guardian. Where parental permission is to be obtained, the Board may find that the permission of one parent is sufficient for research to be conducted under § 46.405 or 46.406, but in doing so the Board must consider such factors as the nature of the research and the age, maturity, status, and condition of the subjects. Where research is covered by §§ 46.407 and 46.408 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unkown, incompetent, or not reasonably available, or the child belongs to a single-parent family (i.e., when only one parent has legal responsibility for the care and custody of the child).

(d) If the Board 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 (e.g., neglected or abused children); it may waive the consent requirements in subpart A of this part and paragraph (c) 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 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.

(e) The Institutional Review Board shall determine that permission by parents or guardians will be documented in accordance with the requirements of § 46.110 of this part.

(f) When the Institutional Review Board determines that assent is required, it shall also determine how assent must be documented.

§ 46.410 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in research approved under § 46.407 or 46.408 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, or similar group 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 Board shall require appointment of an advocate for each child, in addition to any other individual acting as guardian or in loco parentis for the child. The advocate will act in the best interests of the child, and will have the same opportunities to intercede normally provided parents. One individual may serve as advocate for more than one child. No individual may serve as an advocate if the individual has any financial interest in, or other association with, either the guardian organization or any institution responsible for the research.

(c) If a child who is a ward objects to participation in the research, but the child's assent is not required under § 46.409, the child may be included as a subject only with the approval of both the child's guardian and the advocate for the child.

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