Protections for Children in Research

A Report to Congress in Accord with Section 1003 of P.L. 106-310, *Children's Health Act of 2000*

May 2001

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EXECUTIVE SUMMARY

The *Children's Health Act of 2000* (P.L.106-310) requires the Secretary of Health and Human Services to conduct a review of the Department of Health and Human Services (DHHS) regulations under 45 CFR Part 46, Subpart D - *Additional Protections for Children Involved as Subjects in Research (*subsequently referred to as "Subpart D"). This evaluation should consider if any modifications to the regulations are necessary to ensure the adequate and appropriate protections of children participating in research. In conducting the review of Subpart D, the Secretary was directed to consult with specified experts and respond to several specific questions related to the provisions of Subpart D and research involving children. The Office for Human Research Protections (OHRP), within the Office of the Secretary, was assigned primary responsibility for conducting the review of Subpart D and producing the report for Congress.

Children have long been recognized as a special and vulnerable population, and are accorded special protections in many areas, including research. In 1983, based upon recommendations from the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission), DHHS promulgated the specific regulations under Subpart D to provide additional safeguards to protect the rights and welfare of children involved as subjects in research.

The regulations under Subpart D require that an Institutional Review Board (IRB) reviewing research involving children as subjects consider the risks of harm or discomfort inherent in the proposed research and the anticipated benefits to the child subjects or society in general. Based upon this assessment of risks and anticipated benefits to the child subjects or others, the IRB must classify research into one of four categories. For each category, the IRB must ensure that specific criteria stipulated by subpart D have been satisfied in order to approve the research.

For nearly two decades, Subpart D has provided the regulatory framework for biomedical and behavioral research conducted or supported by DHHS. The recent adoption of Subpart D by the Food and Drug Administration (FDA) formally extends this regulatory framework to include those studies regulated by FDA, most commonly being clinical trials of drugs, medical devices and biologics.

In preparing this report, OHRP solicited input from approximately 50 experts in the field, including pediatric pharmacologists, pediatricians, pediatric professional societies, bioethics experts, clinical investigators, institutional review boards, industry experts, appropriate Federal agencies, advocacy groups, and parents of children who have participated in research studies. The staff of the Office for Human Research Protections took into consideration comments provided by expert consultants, as well as the considerable experience acquired during its compliance oversight investigations of research involving children. Based upon its review, OHRP offers the following findings:

(1) Major Findings:

(a) The current DHHS regulations under Subpart D of 45 CFR Part 46 are sound, effective, and well-crafted, and when implemented properly by IRBs and investigators, provide adequate and appropriate protections for children of all ages and maturity levels participating in research conducted or supported by DHHS. Furthermore, these regulations are robust and flexible, and as such, are useful and appropriate for regulating all types of research involving children as subjects, including biomedical and behavioral research. Historically, problems and concerns related to research involving children generally have resulted from a failure to implement the existing regulations appropriately and consistently, not from fundamental deficiencies of the regulations.

(b) There are a number of complex issues inherent in both the conduct of research involving children and the interpretation of the provisions of the regulations under Subpart D of 45 CFR Part 46 that have contributed to the inconsistent implementation of the regulations. As a result, there is a clear need for DHHS to provide detailed guidance relevant to these complex issues to all parties engaged in the conduct and oversight of research involving children, including IRB members, investigators, institutional officials, and sponsors of research. Such guidance should enhance the level of consistency with which the regulations are applied and help ensure that the additional protections intended under the regulations are achieved for all children involved as subjects in research supported or conducted by DHHS.

(c) Specific terms and concepts within the regulations under Subpart D of 45 CFR Part 46 for which further guidance is most needed from DHHS include: (i) the meaning of "the prospect of direct benefit for the individual subject" [see 45 CFR 46.405]; (ii) the parameters for defining "a minor increase over minimal risk" [see 45 CFR 46.406(a)]; (iii) the meaning of "reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations" [see 45 CFR 46.406(b)]; (iv) the meaning of "disorder" and "condition" [see 45 CFR 46.406(c)]; (v) the parameters for defining "generalizable knowledge . . . which is of vital importance for understanding or amelioration of the subjects' disorder or condition" [see 45 CFR 46.406(c)]; and (vi) the appropriate procedures for recruiting children into research and providing them and/or their parents with some type of payment (financial or otherwise).

(d) The DHHS National Human Research Protections Advisory Committee (NHRPAC) provides an appropriate forum for broad public discussions of the

complex issues related to the conduct of research involving children and the provisions of the regulations under Subpart D of 45 CFR Part 46. NHRPAC advice resulting from these discussions should play an important role in DHHS' formulation of the guidance needed regarding the interpretation and implementation of Subpart D.

(2) Additional Findings:

(a) Under DHHS regulations at Subpart A of 45 CFR Part 46, *minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Many have strongly recommended that when interpreting the definition of *minimal risk* for research involving children as subjects conducted or supported by DHHS, IRBs should apply an absolute standard under which "daily life" is interpreted to mean the daily life of healthy children in the general population, and that standard should be applied to all research conducted or supported by DHHS that proposes involvement of children as subjects, regardless of the expected health and socioeconomic status of the children. This interpretation may be particularly appropriate given that children are a vulnerable population and unable to provide legally effective voluntary consent. However, consensus on this interpretation has not been established.

Based upon the diverse comments received regarding the interpretation of *minimal risk*, and the critical importance of this interpretation to the overall effectiveness of applying the regulation, it would be premature to adopt an absolute standard without further discussion that fully engages all of the relevant parties, including both Federal and private organizations, and the public, before definitive guidance on this point is issued.

(b) The current definitions of *assent* and *parental permission* are appropriate and well-understood and should remain unchanged. Furthermore, the procedures and requirements under Subpart D of 45 CFR Part 46 for obtaining, documenting, and waiving the assent of children involved as subjects in research and the permission of their parents are adequate and do not require modification.

(c) There is no need for the Secretary to establish DSMBs or similar mechanisms to review adverse events associated with research involving children conducted

or supported by DHHS. The DHHS regulations at Subpart A of 45 CFR Part 46 require that in order to approve any research an IRB must ensure, among other things, that (i) risks to subjects are minimized; and (ii) when appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects. When appropriate to ensure that risks to subjects are minimized for a given research protocol under review, an IRB has the authority to require establishment of a DSMB to monitor the research. For serious or life threatening conditions, an IRB may consider recommending a DSMB for planned interim monitoring and stopping rules to permit early termination of a study. For many types of research involving children as subjects, establishing a DSMB would not be necessary to ensure adequate protection of the subjects. A determination about whether a particular research study warrants oversight by a DSMB should be made by the responsible IRB, with input from the investigators and study sponsor. For certain types of research, a funding agency or research institution or sponsor may require creation of a DSMB. Beyond that, the determination of the need for a DSMB should be made by the responsible IRB.

(d) The current DHHS regulations under Subparts A and D of 45 CFR Part 46 have provisions that adequately address the issue regarding payment (financial or otherwise) that may be provided to children involved in research as subjects or their parents. In particular, under the regulations an IRB must ensure that parental permission is always sought under circumstances that minimize the possibility of coercion or undue influence. As such, in order to approve research, the IRB must ensure that the amount, type and schedule of any payment does not increase the possibility of coercion or undue influence for parents whose permission is being sought for their children to participate in research. The regulations should not be modified to prohibit such payments. Instead, additional guidance needs to be developed by DHHS regarding this issue.

RECOMMENDATIONS

DHHS recommends that the regulations under Subpart D of 45 CFR Part 46 not be modified at this time.

DHHS should provide detailed guidance relevant to the complex issues inherent in both the conduct of research involving children and the interpretation of the provisions of the regulations under Subpart D of 45 CFR Part 46 to all parties engaged in the conduct and oversight of research involving children. Guidance regarding the interpretation and implementation of Subpart D should be developed with input from the DHHS NHRPAC. Such guidance should include:

(1) Clarification for interpretation of terms and concepts of Subpart D of 45 CFR Part 46 such as "minimal risk," "the prospect of direct benefit for the individual subject," "a minor increase over minimal risk," "disorder," "condition," and the appropriate procedures for recruiting children into research.

(2) Instructions to IRBs regarding the interpretation and application of the definition of *minimal risk* for research involving children as subjects conducted or supported by DHHS.

(3) Direction regarding payment (financial or otherwise) that may be provided to children involved in research as subjects or their parents, under circumstances that minimize the possibility of coercion or undue influence.

PURPOSE

On October 17, 2000, the *Children's Health Act of 2000* (P.L.106-310) was enacted, amending the Public Health Service Act. The Act contains provisions to address a number of issues related to children's health, including vaccine injury, organ transplantation, pregnant mothers and infants, newborn and infant hearing screening, and pediatric research. Section 1003 directs the Secretary of Health and Human Services (DHHS) to conduct a review of the regulations under 45 CFR Part 46, Subpart D - *Additional DHHS Protections for Children Involved as Subjects in Research,* within 6 months of the Act's enactment. That evaluation should consider if any modifications are necessary to ensure the adequate and appropriate protection of children participating in research and its findings reported to Congress by April 17, 2001.

In conducting the review of Subpart D, the Secretary was directed to consider the following:

(1) the appropriateness of the regulations for children of differing ages and maturity levels, including legal status;

(2) the definition of "minimal risk" for a healthy child or for a child with an illness;

(3) the definitions of "assent" and "permission" for child clinical research participants and their parents or guardians and of "adequate provisions" for soliciting assent or permission in research as such definitions relate to the process of obtaining the agreement of children participating in research and the parents or guardians of such children;

(4) the definitions of "direct benefit to the individual subjects" and "generalizable knowledge about the subject's disorder or condition";

(5) whether payment (financial or otherwise) may be provided to a child or his or her parent or guardian for the participation of the child in research, and if so, the amount and type given;

(6) the expectations of child research participants and their parent or guardian for the direct benefits of the child's research involvement;

(7) safeguards for research involving children conducted in emergency situations with a waiver of informed assent;

(8) parent and child notification in instances in which the regulations have not been complied with;

(9) compliance with the regulations in effect on the date of the enactment of this Act, the monitoring of such compliance, and enforcement actions for violations of such regulations; and

(10) the appropriateness of current practices for recruiting children for participation in research.

Section 1003 also directed the DHHS Secretary, in conducting the review, to consult broadly with experts in the field including pediatric pharmacologists, pediatricians, pediatric professional societies, bioethics experts, clinical investigators, institutional review boards, industry experts, appropriate Federal agencies, and children who have participated in research studies and the parents, guardians, or families of such children.

In addition, the Secretary, in carrying out the evaluation, was directed to consider and report to Congress by April 17, 2001, concerning the following:

(1) whether the Secretary should establish data and safety monitoring boards or other mechanisms to review adverse events associated with research involving children; and

(2) whether the institutional review board oversight of clinical trials involving children is adequate to protect children.

The Office for Human Research Protections (OHRP), within the Office of the Secretary, was assigned primary responsibility for conducting the review of Subpart D and producing the report for Congress.

BACKGROUND

Regulations in Subpart D of 45 CFR 46 were adopted by DHHS on March 8, 1983 [then named the Department of Health, Education and Welfare (DHEW)] and amended on June 18, 1991. The regulations in Subpart D are not part of the Federal Policy for the Protection of Human Subjects (referred to as "Common Rule")[1] and, therefore, are not universally shared by all other signatory departments and agencies that have adopted the Common Rule.

Subpart D regulations are based on recommendations developed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) in response to a legislative mandate from Congress. The National Commission was established in 1974,

[1]Subpart A of 45 CFR Part 46 is the DHHS publication of the Common Rule. This basic policy for the protection of human research subjects has been adopted by sixteen other Federal departments and agencies, and published in regulations of those departments and agencies.

under P.L. 93-348, to develop ethical guidelines for the conduct of research involving human subjects and make recommendations for applications of such guidelines to research conducted or supported by the DHHS (then DHEW).[2] Children were one of several classes of subjects that the National Commission was directed to give particular attention to, in addition to prisoners and the institutionalized mentally infirm. P.L. 93-348 required the Commission to submit periodic reports to the President, Congress and the Secretary of DHHS (then DHEW).

The National Commission recognized that involving children in research raises serious ethical concerns due largely to their reduced autonomy and children's incompetency to give informed consent. Nevertheless, the group believed that simply restricting children's participation in research was not appropriate because conduct of research involving children is necessary for development of new treatment or preventive methods, and also to protect children from un-validated practices which may be harmful.

The National Commission's stated objective, therefore, was to answer two questions: (1) under what conditions is the participation of children in research ethically acceptable; and (2) under what conditions may such participation be authorized by the subjects and their parents? The recommendations of the Commission, released in September 1977, represent their answers to these two questions.[3]

In general, subpart D provides additional safeguards to protect the rights and welfare of children involved as subjects in research. *Children* are defined under subpart D as persons who have not attained the legal age for consent to treatment or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. The regulations require that an IRB reviewing research involving children as subjects consider the risks of harm or discomfort inherent in the proposed research and the anticipated benefits to the child subjects or society in general. Based upon this assessment of risks and anticipated benefits to the child subjects or others, the IRB must classify research into one of four categories. For each category, the IRB must ensure that specific criteria stipulated by subpart D have been satisfied in order to approve the research. The four categories of research involving children that may be approved by an IRB are as follows:

(1) Research not involving greater than minimal risk. See 45 CFR 46.404.

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[2]P.L. 93-348 also directed the National Commission to make recommendations to Congress related to the protection of human subjects in research not subject to regulations by the then-DHEW.

[3]The National Commission transmitted its report with recommendations to the President, Congress, and Secretary Joseph Califano, Jr. on September 6, 1977.

(2) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. Research in this category is approvable provided: (a) the risk is justified by the anticipated benefit to the subjects; and (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. See 45 CFR 46.405.

(3) 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. Research in this category is approvable provided: (a) the risk represents a minor increase over minimal risk; (b)the research 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; and (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. See 45 CFR 46.406.

(4) Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research in this category may be conducted or supported by DHHS provided: (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 review with a panel of experts and following an opportunity for public review and comment, determines either that (i) the research in fact satisfies the conditions of section 46.404, 46.405, or 46.406; or (ii) 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 will be conducted in accordance with sound ethical principles. See 45 CFR 46.407.

Subpart D requires that for all research involving children as subjects the IRB must ensure that there are adequate provisions for soliciting the assent of the children, when appropriate. *Assent* is defined as a child's affirmative agreement to participate in research. The regulations state that mere failure to object should not, absent affirmative agreement, be construed as assent. In determining whether children are capable of providing assent, the IRB is directed to take into account the ages, maturity, and psychological state of the children involved. 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 interventions or procedures involved in the research hold 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 the children is not required.

Subpart D also provides that for research involving children as subjects, an IRB shall determine that

adequate provision are made for soliciting the permission of each child's parents or guardian. The IRB may find that the permission of one parent is sufficient for research involving no more than minimal risk or involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. For other categories of research permissible under Subpart D, permission generally must be obtained from both parents, 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. Furthermore, in certain limited circumstances, Subpart D provides that an IRB may waive the requirement for obtaining parental permission.

For nearly two decades, Subpart D has provided the regulatory framework for biomedical and behavioral research conducted or supported by DHHS. The recent adoption of Subpart D by the Food and Drug Administration (FDA) formally extends this regulatory framework to include those studies regulated by FDA, most commonly being clinical trials of drugs, medical devices and biologics.

APPROACH

To respond to Section 1003 of the *Children's Health Act*, OHRP prepared and distributed approximately 50 letters to consult broadly with experts in the field, including pediatric pharmacologists, pediatricians, pediatric professional societies, bioethics experts, clinical investigators, institutional review boards, industry experts, appropriate Federal agencies, advocacy groups, and parents of children who have participated in research studies. Each letter listed the specific areas of interest stated in Section 1003 and was accompanied by enclosures that included: (i) the text of Subpart D; (ii) the text of Section 1003 of the *Children's Health Act*; and (iii) OHRP's draft guidance on policy and procedures dealing with Section 46.407 of Subpart D. OHRP received approximately 30 responses. Not all responses addressed every issue.

Each response was carefully reviewed by OHRP and comments germane to each of the twelve categories of inquiry of Section 1003 were abstracted and distributed to OHRP staff to analyze. A summary of consultant responses was developed, and is provided in the following section. This section also includes comments based on OHRP's recent experiences, particularly its compliance oversight evaluations of research involving children. Such evaluations often have involved interactions with parents of children who participated in research.

OHRP considered the consultant responses and its experiences in developing findings. The findings reflect majority opinions of the consultants and are concordant with positions that DHHS has held for some time.

COMMENTARY ON REQUESTED AREAS OF REVIEW UNDER SECTION 1003 OF THE *CHILDREN'S HEALTH ACT OF 2000*, SUBSECTION (b)

Consultants were asked for their input on the following issues regarding DHHS regulations under Subpart D of 45 CFR Part 46. Their responses and, where relevant, experiences of OHRP are summarized below.

(1) The appropriateness of the regulations for children of differing ages and maturity levels, including legal status.

The majority of respondents stated that the current regulations are appropriate and did not recommend a change in the regulations. Many respondents emphasized that the IRBs should retain flexibility and the ability to judge, depending on the protocol, the appropriate age for a child to provide assent, and should take into consideration differing maturity levels, needs and abilities of the children involved. This decision should incorporate the ability of the child to understand what will be done and why, as well as some consideration of the risks and benefits. Many respondents also stated that additional guidelines for the interpretation and application of Subpart D would be helpful. One respondent suggested that OHRP consider involving other Federal agencies in the development of such guidance.

One respondent stated that the current regulations should be modified to take into account the maturity of the subject or to provide for waiver of parental permission for minimal risk research.

One respondent noted that the regulations cover children from birth through the upper age limit that appropriately, and of necessity, varies in accordance with state law. This respondent noted that in most jurisdictions individuals who are self-supporting, living apart from parents and who themselves may be parents are considered to be emancipated minors and can provide consent to participate in research for themselves, and their children. Several respondents asked for clarification on this matter, and one respondent suggested that adolescents should be allowed to consent to research without parental involvement in areas in which they may legally consent to treatment, or when parental involvement might be detrimental to the interests of the adolescent. Under these circumstances one respondent recommended the inclusion of safeguards, such as a child advocate.

One respondent stated that existing regulatory protections were wholly inadequate, and that Federal protections need to be expanded to ensure children are protected from exploitation and harm.

One respondent urged OHRP to contact developmental specialists on the issues related to cognitive understanding, assent and informed consent, and that IRBs should be encouraged to develop model informed consent and assent processes for children at different ages and their parents.

Several respondents noted the common policy of obtaining assent from children aged 7 and older, unless the research holds the prospect of direct benefit for the subject.

Several respondents stated that children should not be involved in research until adequate studies had been done in animals, adults, and even older children.

(2) ***The definition of "minimal risk" for a healthy child or for a child with an illness.***

Minimal risk is defined at 45 CFR 46.102 (i) as the level of risk where "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." Several respondents agreed that "daily life" should be interpreted to mean daily life of healthy children in the general population, and that minimal risk would include activities that parents ought to allow their children to experience in every day lives and should reflect the moral boundary of parental discretion. One respondent stated that the regulations should be amended to specifically define "minimal risk" in terms of the everyday experience of normal healthy children. Several respondents stated that minimal risk should be the same for healthy, as well as sick children, yet unique for each population dependent on age, and that this definition should remain unchanged.

Several respondents explicitly stated that the definition should be absolute and not modified by a child's experience or treatment requirements. Another respondent stated that a distinction should be made between non-invasive and medical procedures in the proposed research, and noted the importance of examining the probability and degree of severity of risks. Another respondent stated that a more precise definition of minimal risk is required, one that takes into account socioeconomic variables. One respondent was concerned that liberalization of the definition could increase risks to children. One respondent noted that the risk of a procedure can be modified depending on the experience of the institution and personnel performing the procedure. One respondent felt that consideration of risk should include prevailing community standards. One respondent noted that IRBs should be allowed flexibility and judgement to assess the definitions.

Several respondents stated that a "minor increase over minimal risk" should be a relative standard, indexed to the daily life of child involved in the research. Several respondents stated that the definition of minimal risk for a healthy child is different from a child with an illness. Another respondent stated that the local IRB should define what it considers "a minor increase

over minimal risk."

One respondent was concerned that some of the language describing *minimal risk* might discourage studies that involve the administration of placebos.

One respondent stated that all research involving children which entails a minor increase over minimal risk without the potential for direct benefit should be disallowed as a matter of principle.

Additional guidance clarifying some of these issues was requested.

(3) ***The definitions of "assent" and "permission" for child clinical research participants and their parents or guardians and of "adequate provisions" for soliciting assent or permission in research as such definitions relate to the process of obtaining the agreement of children participating in research and the parents or guardians of sick children.***

It was the opinion of most respondents that the definitions of *assent* and *permission* should remain unchanged. One respondent noted that according to the principle of autonomy presented in the Belmont Report, parents provide "permission" rather than "consent," because no individual may give consent for another. Several respondents noted that the information provided to children should be age-appropriate and understandable. Several respondents also noted that dissent should be honored and children should be allowed to withdraw at any time, unless the research holds out a prospect of direct benefit and is available only in the context of research. Several respondents stated that assent should be in writing whenever possible.

Several respondents noted that the assent process requires cognitive ability and the ability to engage in abstract thinking; therefore, the ability to provide assent is not only dependent on chronologic age but developmental achievements and the familiarity with the task or procedure. Several respondents suggested that emancipated minors provide their own consent. Several respondents agreed that a child's assent may be waived if the IRB, parents, and investigators believe that the child will derive benefit from therapeutic research or the condition is life-threatening and no alternative or standard treatment is available. Under these circumstances, a child advocate could determine what is in the best interests of the child participant.

Several respondents were concerned that the requirement in Section 46.408 that both parents give permission for research covered by Sections 46.406 and 46.407 may be unreasonable and not in the best interests of children, particularly for those who live in single parent homes. One of these respondents noted that the IRB may use the language of Section 46.408 to make a determination that the other parent is "not reasonably available."

Several respondents noted that IRBs should be allowed flexibility and judgement to assess the definitions and the methods for obtaining assent. One respondent stated that "adequate provisions" be defined as a signed assent/consent form unless the child is not capable of signing, and another requested examples of "adequate provisions." Another respondent stated that "adequate provisions" include educational efforts tailored to the target population.

One respondent recommended the use of assent auditors to assure that the child understands what the assent means and that he/she can withdraw at any time. Another respondent suggested considering approval by a panel of older children and parents of greater than minimal risk research involving children too young to assent.

One respondent noted that FDA regulations require that informed consent be obtained from research subjects and that this requirement cannot be waived under FDA regulations simply because a subject is a child. They suggested clarification that permission is informed consent obtained from a parent or guardian on behalf of a child. They also noted that the regulations only allow informed consent by someone authorized by law to consent on the behalf of the subject to their participation in the procedures involved *in the research*, but Subpart D allows permission by a guardian, defined as someone authorized by law to consent on behalf of the child to *general medical care*. They were concerned about this apparent discrepancy.

Several respondents commented on institutionalized children and wards. One respondent stated that such children should rarely be considered for inclusion in research studies because institutionalization may deprive them of some of the safeguards necessary for ethical conduct of research. One respondent stated that protections for wards could be increased if the regulations had a definition for "advocate" which focused on the role of such an individual in protecting the child. Another respondent stated that children who are wards should not participate in research unless it benefits them personally.

Several respondents asked for clarification of custody issues and whether or not step-parents may give permission for children to participate in research.

Further clarification and guidance on these issues was requested.

(4) ***The definitions of "direct benefit to the individual subjects" and "generalizable knowledge about the subject's disorder or condition."***

Several respondents noted that the current language was adequate but that further clarification in the form of guidelines would be helpful. For instance, one respondent noted that it is not clear whether benefit to the individual needs to be immediate or in the future. Another respondent was unclear about the concept of "prospect" and queried how probable an outcome would need to be in order to qualify as holding out the prospect of direct benefit.

Several respondents requested clarification of the word "condition" and the concept of direct benefit as regards placebo controlled trials. One respondent stated that the analysis of direct benefit should be done prior to randomization in such a trial, and others stated that placebo controlled trials hold out the prospect of direct benefit. One respondent stated that direct benefit should be interpreted broadly to take into account the importance of learning about a disease and the understanding by the child that he/she has contributed to the study of a childhood disease.

One respondent stated that the concept of "generalizable knowledge about the subject's disorder or condition" implies that the knowledge gained be scientifically important and applicable generically to children with the same disorder or condition in order to cause amelioration of their status. One respondent expressed concern that the terms "disorder" and "condition" not be used as synonyms. One respondent noted that the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research considered the term "condition" to describe healthy children at various developmental stages. Several respondents considered a child with a predisposition to a disorder to have a condition, or that a condition could apply to a demographic or other description of a class of subjects for whom the research is likely to yield generalizable knowledge. One respondent specifically criticized this opinion, stating that it was an effort to broaden the criteria under which healthy children may be subjected to research "not otherwise approvable" under existing regulations. Another respondent stated that the concept of generalizable knowledge should include the understanding that this knowledge may directly benefit the individual child in the future.

One respondent stated that the definition of direct benefit should be improvement of physical and/or psychological health of the child, and that the definition of generalizable knowledge should be information gained about a single individual in an investigation that can be applied to others with the same disorder.

One respondent suggested that studies which have a placebo arm should include a scientific and ethical justification for the inclusion of the placebo arm. One respondent stated that the use of placebo or control groups are acceptable only if their use does not place children at increased risk. Another respondent questioned whether pediatric research should have control groups composed of healthy children. Another respondent stated that placebo controlled trials were acceptable when it is not known if a new therapy is beneficial and there is no existing standard efficacious treatment, and if there is a standard treatment they may be ethical depending on the seriousness of the disorder, the risks of the standard treatment, and the natural history of the disease.

(5) ***Whether payment (financial or otherwise) may be provided to a child or his or her parent or guardian for the participation of the child in research, and if so, the amount and type given.***

The majority of respondents who commented on this issue indicated that payment to the child and parent should not exert "undue influence" or be coercive. However, appropriate reimbursement for parental expenditures such as travel, meals, parking, babysitting or time off from work should be provided. Other respondents stated that no financial incentives other than travel expenses be allowed.

Likewise, the majority of respondents who commented on this issue stated that if payment to children were to be provided it should not be cash but rather a gift certificate or a savings bond. Several respondents stated that it should be given as a surprise, age-appropriate gift for participation at the end of the study, while others indicated that if declared in the consent form, the compensation should be prorated and not require completion of the research protocol. One respondent stated that information regarding payment for participation is inappropriate in recruitment materials for children. Several respondents stated that the payment for children should be identical to that of adults, while one respondent stated that payment is never acceptable on ethical grounds. Several respondents were concerned that some parents may exploit their children for monetary gain.

Several respondents stated that besides monetary compensation there could be other compensatory goods such as waiver of medical costs associated with the research, follow-up health care or educational assistance to the person or the community, as long as they do not constitute undue influence to participate.

One respondent asked for more guidance in this area, while several others suggested more research was necessary before issuing guidance or regulations.

Several respondents were concerned about payments to doctors for referring patients to clinical trials, and one thought such payments should be banned.

(6) ***The expectations of child research participants and their parent or guardian for direct benefits of the child's research involvement.***

In order to avoid the "therapeutic misconception" many respondents emphasized that it is imperative that the realistic possibility of direct benefit, or the possibility of no direct benefit, be made clear. One respondent stated that, while altruism exists, most parents and their children participate in clinical trials with the expectation and hope for direct benefit, and many respondents stated this expectation can be unrealistically high. One respondent stated that there should be full disclosure of the probability and magnitude of potential risks, alternatives, previous adverse events and outcomes of research performed in animals, adults and other child research participants. Another respondent stated that the investigators should obtain permission and/or assent in an atmosphere of neutrality and should stress the fact that the experimental intervention may not be more effective than alternative treatments. One respondent expressed concern regarding some parents' tendency to enroll their children in clinical trials because they

have no health insurance or other source of medical care. One respondent stated that expectations of children in research are no different from those of adult research participants.

One respondent stated that this was an area in dire need of rigorous research.

(7) ***Safeguards for research involving children conducted in emergency situations with a waiver of informed assent.***

Many of the respondents stated that the general provisions for waiver of a child's assent in emergency situations were adequate. Several respondents noted that if the research holds out the prospect of direct benefit, the IRB could waive the requirement for a child's assent but require parental permission. One respondent stated that parental permission might be waived if the condition is life-threatening or permanently disabling, the only known therapy is investigational or nonvalidated, permission cannot be obtained within the therapeutic window, and there is not accepted therapy that is clearly superior to the experimental therapy. Another respondent was not comfortable with waiver of parental permission. One respondent stated that the waiver of a child's assent should only be permissible if the emergency was life-threatening to the child and there was no available standard treatment. One respondent recommended that an independent ombudsman who is not an employee of the institution be assigned to represent the interests of the children in the absence of parental permission.

Further guidance was requested. For example, one respondent requested guidance on what is meant by "not reasonably available." Another respondent stated that it should be clarified that FDA regulations at 21 CFR 50, which address emergency research situations, applies to children as well as adults.

(8) ***Parent and child notification in instances in which the regulations have not been complied with.***

Nearly all respondents who chose to comment on this issue indicated that notification of parents and, when appropriate, children should occur in most instances where material noncompliance with the DHHS regulations for the protection of human subjects occurs. Most respondents considered such notification to be appropriate when the noncompliance may adversely affect the rights and welfare of the children participating in the research. Furthermore, most respondents stated that the IRB should be responsible for making determinations about when such notification would be appropriate. Two respondents felt that children involved in research and their parents should be notified of all instances of noncompliance with the regulations. The majority of respondents stated that new regulations were not needed regarding notification procedures.

In a small number of compliance oversight evaluations, OHRP has required that an institution notify parents and, in some cases, child subjects of serious noncompliance with the DHHS regulations. In such cases, OHRP directed the responsible IRB to develop the form and content of the notification procedure.

(9) ***Compliance with the regulations in effect on the date of the enactment of this Act, the monitoring of such compliance, and enforcement actions for violations of such regulations.***

Most respondents were unable or unwilling to provide an assessment of the degree of compliance with the regulations in effect on the date of enactment of the *Children's Health Act of 2000*. One respondent stated that most, if not all, research involving children that is currently being conducted complies with the requirements of the regulations. Another respondent indicated that there is no evidence of widespread problems with recruiting practices for research involving children. In contrast, one respondent stated that there is widespread noncompliance with the requirements of the regulations under Subpart D, and another urged that penalties, including civil monetary penalties and debarment measures, should be mandated for identified serious noncompliance.

Several respondents stated that the IRB should be responsible for monitoring investigator compliance with the IRB-approved protocol and informed consent process and additional regulations regarding compliance monitoring were not needed at this time. Several respondents also noted that the system of human subject protection relies on other organizations such as FDA, OHRP and DHHS funding components to monitor compliance with the regulations.

In several compliance oversight evaluations over the past few years, OHRP has identified instances of substantive noncompliance with the requirements of Subpart D (as well as Subpart A) for research involving children as subjects. In OHRP's experience, such noncompliance has resulted from inadequate training and education of IRB members and investigators about the provisions of the regulations, and not fundamental deficiencies of the regulations themselves.

(10) ***The appropriateness of current practices for recruiting children for participation in research.***

Many respondents noted that it is important to distribute the benefits and the risks of this research equally among the nation's children. Several respondents noted that there is little data available on the recruitment practices for children for participation in research. Some respondents expressed concern that on a national level there is advertising that emphasizes payment for participation specifically directed to children, payment to referring physicians, and other circumstances that could be viewed as creating undue influence or coercive environments. Several respondents stated that recruitment practices were inappropriate and downright exploitative, creating a moral hazard for everyone involved, and suggested the development of strict Federal rules to govern patient recruitment. However, many respondents stated that the local IRBs should be and, largely, are utilizing the existing regulations and ensuring that recruitment practices for children are appropriate. One respondent stated that guidance on methods to reduce undue influence and adherence to sound, fundamental ethical principles are of paramount importance. One respondent stated that the same standards as those in place for adult studies should be utilized.

COMMENTARY ON REQUESTED AREAS OF REVIEW UNDER SECTION 1003 OF THE *CHILDREN'S HEALTH ACT OF 2000*, SUBSECTION (d) - CONSIDERATION OF ADDITIONAL PROVISIONS

(1) ***Whether the Secretary should establish data and safety monitoring boards or other mechanisms to review adverse events associated with research involving children*.**

The majority of respondents who commented on this issue indicated that separate requirements regarding data and safety monitoring boards (DSMBs) do not need to be established for research involving children. Many respondents noted that DSMBs may provide additional safety measures for certain studies such as those with expected high risks, where there are many unknowns, or for multi-center trials. One respondent stated that, if established, they should monitor not only adverse events but also study design, recruitment, and efficacy of the therapeutic agents or devices. However, several respondents expressed the view that all medical research involving children should have DSMBs, either locally or nationally, with pediatric expertise. Several respondents commented on the important relationship between DSMBs and IRBs, and one respondent stated that DSMBs should be structured to assist IRBs in evaluations of adverse events and not to usurp this activity by the local IRBs. Another respondent stated there is a need for a database of adverse events and for long-term monitoring data for children's outcomes.

Several respondents asked for clarification of the respective roles of the IRBs, DSMBs, National Institutes of Health (NIH), FDA and DHHS with regard to adverse event reporting and evaluation, or for a comprehensive, Federal-wide set of regulations addressing adverse event reporting.

(2) ***Whether the institutional review board oversight of clinical trials involving children is adequate to protect children*.**

Many respondents stated that the current IRB system provides adequate protection for children in research. Several respondents noted that the most effective approach to protecting children in research is to have appropriately constituted, well-informed local IRBs. Several respondents stated that IRBs responsible for the protection of children in research should include pediatric experts, medical professionals knowledgeable about the disease, bioethicists, consumer advocates, unaffiliated community members, and ombudsmen who are not employees of the institution. However, several respondents expressed concern that the current system is inadequate to protect subjects, particularly children, and several respondents stated this could be addressed with more intensive education and a system of local monitoring. Several respondents stated that centralized IRBs might make sense, particularly for multi-center trials. Several respondents stated that IRBs should be separate from the institutions that employ them. One respondent noted their institution's requirement of review and approval of research involving children by a "Pediatric Research Committee" prior to IRB approval. One respondent stated that minutes of all IRB meetings should be made available to the public.

Several respondents stated that additional guidance or "Points to Consider" or "Best Practice" standards for IRB review of research involving children would be beneficial to further improve the effectiveness of IRBs in their interpretation and implementation of Subpart D of 45 CFR 46. Several respondents noted that the IRB system of oversight of research involving children is overburdened, and requires adequate funding and independent checks and balances to be adequately implemented. Several respondents stressed the importance of communication and interaction among IRBs, investigators, sponsors, the FDA and other regulatory agencies. Several respondents also noted the need for the development of measurements of IRB effectiveness and accreditation of human research protection programs.

COMMENTARY ON ADDITIONAL ISSUES

Several respondents commented on the provisions under 45 CFR 46.407 for research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. One respondent stated that guidance on the process of DHHS expert panel review for such research would allow IRBs to be more comfortable in recommending proposals for national review that could not otherwise be approved by the IRB. Another respondent noted that the requirement that the research be conducted in accordance with sound ethical principles is not explicated, and the regulations should express the appropriate principles for this research. One respondent commented that the requirement for public review and comments on the pending decision could raise issues related to non-disclosure of trade-secret and confidential commercial information. One respondent stated that the approval process involves a huge amount of effort and is complex and time-consuming, and could increase the barriers to children's participation in research.

One respondent suggested extending the Common Rule to studies conducted through the FDA and several others stated it would be useful to harmonize the regulations across agencies. One government agency assumed that DHHS would not be recommending that Subpart D be extended to other Common Rule signatory agencies. One respondent noted DHHS's inability to impose its regulatory requirements for research involving children on other agencies.

Several respondents expressed concern that DHHS may discourage pediatric research by erecting additional barriers and administrative hurdles.

Many respondents expressed a desire to further engage in more robust discussions about these issues in the future, and the need to include a broad range of stakeholders in the discussions.

Several respondents emphasized the need to study the safety and efficacy of drugs in children.

Several respondents noted that the competence and ethical conduct of the investigators are important safeguards for children involved in research.

Regarding subject confidentiality, several respondents were concerned about parents being informed of research findings, particularly in sensitive research such as adolescent sexual activity and drug abuse.

One respondent suggested that OHRP should have sufficient staff expertise in pediatrics, should establish an independent pediatric workgroup, and should consider commissioning reports from the Institute of Medicine on specific pediatric research questions.

One respondent suggested that guidance state that clinical care takes precedence over research decisions.

FINDINGS

(1) Major Findings:

(a) The current DHHS regulations under Subpart D of 45 CFR Part 46 are sound, effective, and well-crafted, and when implemented properly by IRBs and investigators, provide adequate and appropriate protections for children of all ages and maturity levels participating in research conducted or supported by DHHS. Furthermore, these regulations are robust and flexible, and as such, are useful and appropriate for regulating all types of research involving children as subjects, including biomedical and behavioral research. Historically, problems and concerns related to research involving children generally have resulted from a failure to implement the existing regulations appropriately and consistently, not from fundamental deficiencies of the regulations.

(b) There are a number of complex issues inherent in both the conduct of research involving children and the interpretation of the provisions of the regulations under Subpart D of 45 CFR Part 46 that have contributed to the inconsistent implementation of the regulations. As a result, there is a clear need for DHHS to provide detailed guidance relevant to these complex issues to all parties engaged in the conduct and oversight of research involving children, including IRB members, investigators, institutional officials, and sponsors of research. Such guidance should enhance the level of consistency with which the regulations are applied and help ensure that the additional protections intended under the regulations are achieved for all children involved as subjects in research supported or conducted by DHHS.

(c) Specific terms and concepts within the regulations under Subpart D of 45 CFR Part 46 for which further guidance is most needed from DHHS include: (i) the meaning of "the prospect of direct benefit for the individual subject" [see 45 CFR 46.405]; (ii) the parameters for defining "a minor increase over minimal risk" [see 45 CFR 46.406(a)]; (iii) the meaning of "reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations" [see 45 CFR 46.406(b)]; (iv) the meaning of "disorder" and "condition" [see 45 CFR 46.406(c)]; (v) the parameters for defining "generalizable knowledge . . . which is of vital importance for understanding or amelioration of the subjects' disorder or condition" [see 45

CFR 46.406(c)]; and (vi) the appropriate procedures for recruiting children into research and providing them and/or their parents with some type of payment (financial or otherwise).

(d) The DHHS National Human Research Protections Advisory Committee (NHRPAC) provides an appropriate forum for broad public discussions of the complex issues related to the conduct of research involving children and the provisions of the regulations under Subpart D of 45 CFR Part 46. NHRPAC advice resulting from these discussions should play an important role in DHHS' formulation of the guidance needed regarding the interpretation and implementation of Subpart D.

(2) Additional Findings:

(a) Under DHHS regulations at Subpart A of 45 CFR Part 46, *minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Many have strongly recommended that when interpreting the definition of *minimal risk* for research involving children as subjects conducted or supported by DHHS, IRBs should apply an absolute standard under which "daily life" is interpreted to mean the daily life of healthy children in the general population, and that standard should be applied to all research conducted or supported by DHHS that proposes involvement of children as subjects, regardless of the expected health and socioeconomic status of the children. This interpretation may be particularly appropriate given that children are a vulnerable population and unable to provide legally effective voluntary consent. However, consensus on this interpretation has not been established.

Based upon the diverse comments received regarding the interpretation of *minimal risk*, and the critical importance of this interpretation to the overall effectiveness of applying the regulation, it would be premature to adopt an absolute standard without further discussion that fully engages all of the relevant parties, including both Federal and private organizations, and the public, before definitive guidance on this point is issued.

(b) The current definitions of *assent* and *parental permission* are appropriate and well-understood and should remain unchanged. Furthermore, the procedures and requirements under Subpart D of 45 CFR Part 46 for obtaining, documenting, and waiving the assent of children involved as subjects in research and the permission of their parents are adequate and do not require modification.

(c) There is no need for the Secretary to establish DSMBs or similar mechanisms to review adverse events associated with research involving children conducted or supported by DHHS. The DHHS regulations at Subpart A of 45 CFR Part 46 require that in order to approve any research an IRB must ensure, among other things, that (i) risks to subjects are minimized; and (ii) when appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects. When appropriate to ensure that risks to subjects are minimized for a given research protocol under review, an IRB has the authority to require establishment of a DSMB to monitor the research. For serious or life threatening conditions, an IRB may consider recommending a DSMB for planned interim monitoring and stopping rules to permit early termination of a study. For many types of research involving children as subjects, establishing a DSMB would not be necessary to ensure adequate protection of the subjects. A determination about whether a particular research study warrants oversight by a DSMB should be made by the responsible IRB, with input from the investigators and study sponsor. For certain types of research, a funding agency or research institution or sponsor may require creation of a DSMB. Beyond that, the determination of the need for a DSMB should be made by the responsible IRB.

(d) The current DHHS regulations under Subparts A and D of 45 CFR Part 46 have provisions that adequately address the issue regarding payment (financial or otherwise) that may be provided to children involved in research as subjects or their parents. In particular, under the regulations an IRB must ensure that parental permission is always sought under circumstances that minimize the possibility of coercion or undue influence. As such, in order to approve research, the IRB must ensure that the amount, type and schedule of any payment does not increase the possibility of coercion or undue influence for parents whose permission is being sought for their children to participate in research. The regulations should not be modified to prohibit such payments. Instead, additional guidance needs to be developed by DHHS regarding this issue.

RECOMMENDATIONS

DHHS recommends that the regulations under Subpart D of 45 CFR Part 46 not be modified at this time.

DHHS should provide detailed guidance relevant to the complex issues inherent in both the conduct of research involving children and the interpretation of the provisions of the regulations under Subpart D of 45 CFR Part 46 to all parties engaged in the conduct and oversight of research involving children. Guidance regarding the interpretation and implementation of Subpart D should be developed with input from the DHHS National Human Research Protections Advisory Committee (NHRPAC). Such guidance should include:

(1) Clarification for interpretation of terms and concepts of Subpart D of 45 CFR Part 46 such as “minimal risk,” “the prospect of direct benefit for the individual subject,” “a minor increase over minimal risk,” “disorder,” “condition,” and the appropriate procedures for recruiting children into research.

(2) Instructions to IRBs regarding the interpretation and application of the definition of minimal risk for research involving children as subjects conducted or supported by DHHS.

(3) Direction regarding payment (financial or otherwise) that may be provided to children involved in research as subjects or their parents, under circumstances that minimize the possibility of coercion or undue influence.

The Honorable Richard Cheney
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