

INTRODUCTION

The National Human Research Protections Advisory Committee, established in June 2000, is charged with providing advice and recommendations to the Secretary, Assistant Secretary for Health and the Director of the Office for Human Research Protections [OHRP] on issues of concern relative to the protection of human subjects. These issues may be identified by canvassing the research community, by generating committee discussion, and by learning from OHRP issues that they are addressing and would like input on, such as matters directed to OHRP by the Assistant Secretary for Health, other federal entities or the congress itself.

In October 2000, the Public Health Service Act was amended with respect to children's health that resulted in the Children's Health Act of 2000 [P.L. 106-310]. The Act addresses a number of issues such as prevention research, pediatric research, childhood malignancies, adoption awareness and so on. Section 1003 of the Act calls for the review of regulations title 45 CFR Part 46, Subpart D, by the Secretary of HHS, six months from the enactment of the Act, and asks that any modifications necessary to ensure the adequate and appropriate protection of children participating in research be considered and report the findings of the Secretary to Congress.

The Secretary has asked the Office for Human Research Protections to undertake this review and OHRP has asked NHRPAC to provide input on these complex issues. NHRPAC, in turn, established a children's workgroup to review the existing regulations and provide a report to the committee as a whole for presentation at the April 9-10 meeting. The workgroup has met once and made a good faith effort to deliberate over these issues and provide guidance, but given the limited amount of time from the establishment of the workgroup to the actual NHRPAC meeting further in-depth work needs to be conducted.

BACKGROUND

Although research is critical to understanding growth, development and disease in order to enhance the future health and well being of children, research studies in children have been less than sufficient to meet the need. The lack of critical research in the past has had a negative impact on the physical, emotional and social health of children. For a long time human subject studies were done primarily on adults and most commonly on males. The information obtained was either targeted towards men or extrapolated for women and children. Drugs efficacious in adults were in turn administered to children in an effort to identify potential treatment for the same or similar diseases or conditions. Physicians prescribed drugs for children where there had been no prior studies in this population, hoping for benefit while knowing little about appropriate dosages or the potential for toxicity and risk.

Children as a study population are indeed quite different from adults – they have unique diseases and vary dramatically in size, development, metabolism, and social environment. Research in

children also provides additional challenges in the informed consent process. Historically, there have been some significant abuses of children as research subjects and there are valid concerns about the importance of protecting children who are the subjects of research and obtaining their assent to participation when appropriate and the permission of their parent(s) or guardian.

The Report and Recommendations in 1977 on Research Involving Children by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research laid the groundwork for present federal regulations (45CFR Part 46 Subpart D) aimed at providing protections for children as the subjects of research. The report argued for the importance of research involving children while creating the expectation that prior to conducting research in children sufficient evidence from animal studies and work with adults will generally have been amassed.

In recent years, both the FDA and the NIH recognized the importance of encouraging research in children. The FDA has developed a policy to extend patent exclusivity to drug companies for an additional six months if they increase the number of protocols focused on research in children. The NIH has created the expectation that children will be subjects in research studies whenever appropriate. Both agencies have made a concerted effort to increase the number of experimental protocols conducted on children to yield new and important information impacting on the health and well being of children. While the numbers of children participating in research studies are increasing it is important to assure that the regulations for protecting children as research subjects are sufficient and that the processes through which the regulations are implemented are conscientiously applied and monitored.

Federal regulations place a large responsibility on Institutional Review Boards (IRBs) to review proposed research studies involving children to ensure adequate protections concerning risks, an appropriate informed consent process, and on-going monitoring of the research. IRBs, however, are only one part of the research enterprise which can play a role in protection of human subjects. Research funders, industry, institutions, investigators and the public share the responsibility for assuring research is performed in an ethical manner.

This workgroup was charged with review of one part of this process, adequacy of the regulations concerning children in the Common Rule, the federal regulations which govern human subjects protections in federally funded research and in particular, 45CFR Part 46 Subpart D. The workgroup benefitted from the report of another panel which was convened to review specific research proposals covered under section 407 of the regulations. The 407 panel provided important recommendations about that review process as well as helpful insights into other aspects of Subpart D.

The workgroup, while examining 45CFR 46 Subpart D in its entirety, focused its review on the questions posed in section 1003 (b) of the Children's Health Act of 2000:

In conducting the review under subsection (a), the Secretary of Health and Human

Services shall consider–

- (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.*

GENERAL IMPRESSION

The workgroup initiated the task of reviewing the adequacy of the children's regulations with a deliberate discussion of whether the existing regulations satisfied the intended goal of the protection of children involved as subjects of research. After considerable discourse the workgroup agreed that the existing regulations are sound, and have worked well. However, there is a need for clarification of the regulations to increase the usefulness and uniformity of the application of the regulations in order to benefit the subjects of research and at the same time to educate those having the responsibility to interpret and apply the regulations.

Since performance and review of research involving children requires specific expertise, knowledge and experience, the workgroup concluded that investigators and IRBs must be adequate to the task. Institutions should create policies to assure that research involving children is conducted by investigators with adequate knowledge and experience and in settings appropriate for children. IRBs may be vested with the responsibility for enforcing such policies. IRBs must also have sufficient expertise and knowledge of the regulations to evaluate research

involving children. IRBs that review research involving children should include members with a broad range of relevant expertise including appropriate unaffiliated community members with interest in issues related to children.

The workgroup discussed the applicability of the regulations to social science research in addition to biomedical research. The workgroup concluded that the regulations, when properly applied, were useful and appropriate for regulating social science and other non-biomedical research involving children. There is, however, a need to clarify issues concerning the exempt and expedited status of such research and concerns about confidentiality and privacy protections.

The workgroup understood that there have been a number of criticisms of various definitions in the regulations as too non-specific and open to broad interpretation. The group believes that increasing uniformity of the application of the regulations would be beneficial but concluded that IRBs need some level of flexibility to interpret regulations within a clear framework. This can best be accomplished by clarifying the definitions and providing realistic, comprehensible examples that would provide a level of guidance by illustration without necessarily suggesting that all similar situations would be treated identically. Illustrations can be useful tools to assist IRBs in interpreting the regulations and to facilitate functioning without being overly prescriptive.

ANSWERS TO SPECIFIC QUESTIONS

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

Over the last thirty years, there has been increasing interest in research involving the smallest children as subjects, premature infants, as well as the largest children, adolescents. The present regulations adequately address the protection of all children as subjects of research but particularly need to be clarified in regard to adolescent assent and consent. Legally emancipated minors may be treated as adults in regard to research participation, but there has been some controversy concerning assent and consent for mature adolescents who might participate as research subjects. This is particularly important because there are circumstances in older adolescents in which it might not be in the interests of the adolescent to inform the parent about an illness or behavior which is under study. In addition, as argued in the original National Commission Report, many believe that adolescents should be allowed to consent to research without parental involvement in areas in which they may legally consent to treatment. Such areas include treatment for sexually transmitted diseases and pregnancy. Under the existing regulation section 408 allows IRBs to make such a determination under certain circumstances. The Society for Adolescent Medicine has provided helpful guidance to IRBs in this area [Journal of Adolescent Health, 1995; Vol. 17(Nov)].

It is incumbent upon the IRB to make a determination as to whether the protocol is one in which the interests of the adolescent would not be served by informing the parent and requesting

parental permission for the adolescent to participate. This review and determination should be done thoughtfully and be based on the characteristics of the disease, behavior, or population of adolescents which makes this relevant. Furthermore, the IRB must assure protection of the adolescent's interests through appropriate procedural safeguards which might include: an independent assessment that the adolescent has the capacity to make an informed decision, an individual, independent from the research team, available to counsel the teenager, and adequate monitoring of the consent process. The IRB may wish to invoke differing levels of procedural safeguards dependent on the level of risk in the research study.

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

The workgroup concluded that the definition of minimal risk in the regulations is helpful and sound. "Minimal risk" is defined at 45 CFR 46.102(i) as meaning 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." Essentially, the workgroup concluded that minimal risk includes the risks, discomforts, and indignities which are the socially acceptable risks in the daily lives of average healthy children during their normal routines of going to school, visiting the doctor or dentist for routine care, or playing at home or with friends.

The workgroup agreed with the following interpretation of the concept of minimal risk devised by the 407 panel that was convened earlier:

"Daily life" is interpreted to mean the daily life of healthy children in the general population. A risk that is of an uncommon type may nonetheless be no greater in probability and magnitude of harm and discomfort than are the more familiar risks of daily life. For example, routine diagnostic radiographs obtained on a single occasion would not *automatically* be considered to be of greater than minimal risk.

In evaluating whether a given procedure or intervention qualifies as "minimal risk," an IRB should consider whether the risks presented are comparable to the risks that parents may ordinarily allow their children to experience in the course of their everyday lives.

The workgroup concluded that minimal risk should be considered an absolute standard. It recognized that a minor increment over minimal risk as described in section 406 of the regulations is a relative standard. The category of minor increment over minimal risk is applicable to children with a disorder or condition which place them in a group other than an average healthy child. This concept incorporates both the determination of the magnitude of the risk as a small increment over socially acceptable risk for the child and the experiential qualifier of experiences "reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations."

The workgroup recognized that there are many children who appear to be healthy but are subject to a condition which warrants study. The concept of a relevant condition addresses those aspects

of the environment that impact on the child, such as the biologic, environmental, social, emotional, and behavioral determinants of the child's well being. Thus, on the one hand poverty might be considered a relevant social condition worthy of careful scrutiny, and on the other hand, a genetic or family predisposition to a disease or disorder might be a relevant biologic or social condition which places a specific child outside the purview of normal average healthy children for these purposes.

(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:

The process of obtaining informed consent/assent in human subjects research is complex and difficult but remains the cornerstone of protection of the rights and interests of research subjects. There are several special concerns when dealing with children. The regulations describe the obligation of the investigator to obtain the assent of the child subject when appropriate. The workgroup concluded that a child's assent must be commensurate with the child's developmental level, which varies not only with age but considerably from child to child of the same age because of a multiplicity of factors such as maturity, cultural, environmental, sociological, and other factors. Therefore it is critical that the level and complexity of the explanation provided must be tailored to the specific maturity of the child. This is why it is important that the assent process be clarified.

The process of obtaining assent is based on the concept of respecting children as persons. The researcher/healthcare provider is demonstrating respect when providing information about the research tailored to the capacity of the individual child to understand. In instances where the research is not intended to benefit the child and the child has the capacity to understand what will transpire, active assent is required. The level of assent is tied to the maturity level of the child—assent discussions with young children can contain relevant information in simple language and request permission to proceed with the research without including extensive and complicated explanations of all risks and benefits. On the other hand, assent documents in older children and adolescents must be more thorough and may even use the same language as is used in the informed consent document for the parent(s). Requirements relative to assent differ depending on the degree to which the research is intended to benefit the child as described in section 408. Assent of the child need not be obtained when the research is intended to benefit the child, but respect for the child obligates the research team to, at a minimum, inform the child as would be appropriate in all clinical settings. For older children and adolescents the assent of the child should be sought even if the research is intended for the direct benefit of the subject because of the important role the child will play in compliance with the research procedures.

The informed consent of the parent(s) or guardians is an important part of assuring the protection of the interests of children in research. The signature on the form documents that a process has occurred but adequate time, information and effort must be extended to ensure the highest level

of understanding possible during the actual informing process.

The workgroup reviewed the requirements in sections 406 and 407 and concluded that at times the obligation to have both parents consent may create an undue and unnecessary burden on a single parent or create problems for the child. The group agreed that permission of both parents may be desirable and should be encouraged but there are circumstances when this may not be possible or appropriate. If, in fact, it appears not to be in the interests of a specific child to involve the other parent, investigators and IRBs may use the language of section 408 to make a determination that the other parent is "not reasonably available" and proceed with the research based on the signature of just one parent.

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

The workgroup reviewed these definitions in the regulations and concluded that the concepts of direct benefit and generalizable knowledge are generally well understood. There is need, however, to clarify the concept of direct benefit as regards placebo controlled trials and the term "condition" as described above in answer to question (2).

The workgroup concluded that placebo controlled trials may be considered in the category of permissible research with direct benefit to individual subjects when the trial is designed in an ethical manner. In general, the use of a placebo controlled trial is acceptable when it is not known if a new therapy is beneficial and there is no existing standard efficacious treatment. Such trials examine both efficacy and toxicity of the active treatment. Even in the instance where there is a standard treatment the use of placebo controlled trials can be ethical depending on the seriousness of the disorder under study, the risks of the standard treatment, and the natural history of the disease. The prospect of direct benefit to individual subjects may be possible because a subject might be randomized into the active arm, or the treatment, if proven effective, may be available in a cross over design or at the end of the initial study. Individual IRBs will need to review placebo controlled protocols carefully, but may determine that some level of risk above minimal is acceptable for the potential of benefit of participating in such a trial.

Another important aspect of IRB review of placebo controlled trials relates to what constitutes a placebo. For example, a saline injection in a child that creates discomfort may be compared to the effect of the injection of an active substance. In certain circumstances this may be an acceptable design.

(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 issue of incentives for participation in research is a troubling one because there can be a fine line between appropriate reimbursement for time and appreciation for participation on the one hand and coercion on the other. A major concern is the potential for abuse and the legitimate

question of how to assess what is undue and coercive and what is permissible. The workgroup agreed that reimbursement for expenses, time and travel to child and family and simple token gifts to children for participation may be appropriate. However, compensation beyond that level should not be permitted. For example, a parent may be compensated for travel or time lost from work and children may receive small gifts of appreciation for participation. Such gifts are acceptable but should rarely be cash and should not be conditioned upon study completion or time enrolled in the study. Appropriate gifts might be a gift certificate to a bookstore or other store that shows the child the value of learning. More importantly, the IRB should review and approve the plan for reimbursement and incentives for each protocol. The workgroup voiced particular concern about the coercive potential of gifts especially in the case of an adolescent consenting without parental involvement. IRBs should give careful scrutiny to incentive plans in such cases and discourage compensation above simple reimbursement for time and travel.

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

This is also an area of concern to IRBs because of the vulnerable position in which many families and children find themselves. Parents of children who are critically or chronically ill may seek experimental treatments in the hope that cure or amelioration of disease will occur. IRBs must assure that the informed consent documents are clear and accurate concerning the potential for benefit to the subjects and investigators are obligated to provide information in an honest manner without creating inappropriate hope for benefit from the research study. In specific cases the IRB may need to create a process of consent monitoring in order to assure that investigators are not inadvertently misinforming parents or research subjects.

This issue of “therapeutic misconception” in research is most troubling in the case of Phase one trials of new medications for serious and life-threatening diseases. Phase one trials generally have a very low likelihood or no potential for benefit to individual subjects of the research. Such trials are basically to determine the toxicity profile for a new drug or therapeutic intervention. However, such studies are extremely important to children in order for new therapies to be introduced for serious diseases. The workgroup concluded that if the potential subjects of such research are sick children for whom standard treatments have failed to offer the hope of cure, the consent process reveals an accurate description of the protocol and potential for benefit, and the alternative options including palliative care are offered, then the IRB may approve such studies.

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

The use of waivers of informed consent for research involving incapacitated subjects in emergency situations is a relatively new process. The workgroup is not aware of its use in children and believes it is unlikely that it will become common in research involving children. There is a need to clarify the concept of “community consultation” in the regulations but this concern is not specific to children.

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

The workgroup concluded that incidents of breach of compliance with the regulations that might require notification to the subjects/parents must be evaluated on a case-contextual basis. The IRBs need to be informed about or directly observe the breaches of the regulations by investigators and then make an individualized assessment of the correct /appropriate course of action. The workgroup agreed that truth telling is generally appropriate but the impact of the breach must be assessed in order to justify disclosure. It was noted that the concept of “materiality” is relevant here. There was some sense that the wisdom of community members on the IRB might play an important role in judging the value of notification to a research participant or suggest what the community standard might be.

Another aspect of non-compliance relates to a breach by the IRB itself. The workgroup agreed that there is a need for monitoring and accountability of IRBs. In order to accomplish this task there is a need for development of new outcome measures, assessment methods and review processes. This notion must be considered in addition to the present suggestions for prospective credentialing of IRBs.

(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:

The workgroup believes that IRBs and investigators involved in research with children are in general compliance with the regulations. There are, however, little data to support that belief because there are no outcome studies except the process measures that are revealed through paper audits, etc. This speaks to the need for the development of monitoring and accountability standards and assessment methods.

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

The appropriateness of recruitment practices for enrolling children in research studies are closely associated with the discussion above regarding payment and incentives. The two issues are inextricably entwined and thus require careful monitoring by the IRB. The workgroup believes that it is the responsibility of the IRB to assure the benefits and risks of research projects are fairly distributed throughout the population at risk. The IRB has the responsibility for determining that the processes for recruitment are fair in each protocol. As is current practice, IRBs must review all print and media advertisements and set standards for appropriate recruiting practices.

ADDITIONAL ISSUES

(A)Section 46.407 – Research not otherwise approvable.

The workgroup believes that this section of the regulations is an important method to enable review and approval of research proposals not otherwise approvable through the other sections of the regulations. The workgroup believes the recent report of the 407 panel is extremely helpful in clarifying the process for such review. Once the 407 process is clarified, IRBs may feel more comfortable in recommending proposals for national review that could not otherwise be approved locally.

(B) Data Safety Monitoring Boards (DSMBs) and Other Forms of Monitoring:

The workgroup agreed that DSMBs are an excellent mechanism to assure safety particularly in complex multi-center trials. It strongly advocated for the use of monitoring as a previously underused procedural safeguard. Funders, IRBs and investigators should all recognize the power they have to require or incorporate monitoring as part of certain studies. Relationships between DSMBs and IRBs need further clarification and evaluation. The ability of DSMBs to aggregate data and adverse events in a periodic manner throughout an ongoing study can play an important role in patient protection.

(C) Adequacy of IRB Functioning and Oversight:

The workgroup concluded that IRBs are performing the tasks of protocol review and approval for research involving children in a reasonable manner, but there is a need for additional monitoring of research studies by IRBs and meaningful oversight of the IRBs themselves. Credentialing of IRBs is a start in the right direction, but on-going monitoring and accountability is needed. The costs of performing the myriad tasks for which IRBs are responsible must be measured and methods to provide adequate compensation need to be developed.

CONCLUSION

The workgroup on research involving children agreed that the regulations for the protection of children as research subjects (45CFR 46, Subpart D) are sound, have worked in the past and appear to be working now. The problem is not that the regulations themselves are inadequate or require revision but rather that the children who are potential subjects of research and the institutions and investigators who are subject to the regulations could benefit significantly from clarification of several aspects of the regulations. Clarification of the regulations including specific illustrative examples would increase the quality and uniformity of IRB functioning. The workgroup recommends a series of 'memoranda' of clarification that would each address a particular aspect of the existing regulations and is prepared to assist in the development of such documents. The group believes that one comprehensive memorandum would be too overwhelming because too many disparate issues would need to be addressed. At this juncture, the workgroup recommends that a series of explanatory memoranda be developed and promulgated by the Office for Human Research Protections which would address a broad spectrum of issues, such as:

- what constitutes adequate expertise on the IRB when child research is considered
- minimal risk and minor increment over minimal risk—clarification of definitions, examples, etc.,
- adolescent assent, consent and parental involvement
- assent of children
- placebo controlled trials in children
- phase I trials in children
- recruitment and incentives in pediatric research
- the role of DSMBs and the relationship to individual IRBs
- the 407 process.

Children's Workgroup - Members

Alan Fleischman, M.D., Chairman

John Abramson, M.D.

Myron Genel, M.D.

Christine Gleason, M.D.^

Gilman Grave, M.D./Judith Whalen, M.P.A.

Susan Kornetsky, M.P.H., C.I.P.*

Felice Levine, Ph.D.^

Mary Faith Marshall, Ph.D.

Robert "Skip" Nelson, M.D.*

Rosemary Roberts, M.D.

Don Rosenstein, Ph.D.

Susan Weiner

Kate-Louse Gottfried, J.D., M.S.P.H. - participant/staff

^participated via conference call

*not present at the meeting but submitted written comments in response to the material distributed in advance of the workgroup meeting for review.

Other Workgroup Members – Not present at this meeting

James Leckman, M.D.

Jonathan Moreno, Ph.D.

Robert Murray, M.D.

ERRATA: CHILDREN'S WORKGROUP REPORT

Background section, paragraph 4. Sentence 2 should be deleted as it is incorrect. Consider the following: The Food and Drug Administration Modernization Act of 1997 allows sponsors to qualify for an additional six months of marketing exclusivity to be attached to existing exclusivity and patent protection for the product provided that the sponsor conducts the pediatric studies requested by FDA.