Sheet 10: RESEARCH INVOLVING CHILDREN *

1. INTRODUCTION

The mandate of Institutional Review Boards (IRBs) is to protect the rights and safeguard the welfare of human research subjects. Children are considered a vulnerable research population because their physical and intellectual capacities are limited and special ethical and regulatory considerations are involved when investigators design and IRBs review research involving children. Title 45 CFR Part 46, Subpart D provides for "Additional Protections for Children Involved as Subjects of Research" and may be obtained by calling OHSR, 301-402-3444. For Clinical Center policy, see Medical Administrative Policy (MAS) #92-5 (may be obtained by calling 301-496-5939).

In March, 1998, the NIH issued Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. Intended to foster the increased participation of children in research, the Policy and Guidelines mandate that children must be included in all human subjects research conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

2. DEFINITIONS

Assent means a child's affirmative agreement to participate in research. Failure to object should not be construed as assent.

Benefit is a valued or desired outcome.

Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under applicable law of the jurisdiction in which the research will be conducted. Generally the law considers any person under 18 years old to be a child.

Risk is the probability of harm (physical, emotional, social or economic). Both probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only minimal risk.

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. A list of procedures which may be reviewed through an expedited review procedure, if the IRB Chair or his designee consider them minimal risk, are provided in 45 CFR 46.110 and the NIH Standard Operating Procedures for IRBs Attachment 5-8, found on the OHSR website, http://ohsr.od.nih.gov. Also, see Assessing probable risks/discomforts at 3. below.

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

3. INVESTIGATOR AND IRB CONSIDERATIONS

An IRB reviewing research involving children must consider the benefits, risks, and discomforts of the research and assess their justification for children's participation in light of the benefits to the child-subject(s) or to society as a whole. In calculating the risks and benefits, the IRB should consider the circumstances of the subjects under study, the magnitude of risks or discomforts that may accrue from research participation and the potential benefits the research may provide to the subject or class of subjects.

The Federal regulations permit four categories of research involving children. The categories are determined by the degree of risk and prospect of benefit to the participating child-subject. **For any protocol involving children, the IRB, in**

consultation with the Principal Investigator (PI), is responsible for determining in which of the four categories of research the study belongs and for documenting in the minutes the rationale for its choice. Therefore, it is desirable for the PI to address these issues directly in the protocol in a section entitled "The ethical and regulatory considerations concerning the involvement of children" in which he/she identifies which of the categories the study fits into and the rationale for this categorization.

The four categories of research which may be approved by IRBs are:

Category 1: research that does not involve greater than minimal risk to children (see *Assessing probable risks/discomforts*, below).

Category 2: research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child-subject.

Category 3: research involving greater than minimal risk and no prospect of benefit to the individual child-subject. In order to approve research in this category, an IRB must determine that the risk of the research represents no more than a minor increase over minimal risk; that the intervention or procedure presents experiences to the child-subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations; and the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for understanding or amelioration of the disorder or condition.

Category 4: research not otherwise approvable under one of the above categories but the IRB determines that the study presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. In these cases the IRB will forward the research for review by the Deputy Director for Intramural Research (DDIR). If he/she agrees, the study will be forwarded to the Secretary of HHS who may approve the research after consultation with a panel of experts. The panel must determine 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 that the research will be conducted in accordance with sound ethical principles.

In all cases, the IRB must determine that adequate provisions have been made for soliciting permission of the parents or legal guardians and the assent of the children.

Assessing probable risks/discomforts: An important aspect of IRBs' considerations of research involving children is an evaluation of what constitutes "minimal risk." Procedures which generally present no more than minimal risk to healthy children include: urinalyses, small amounts of blood obtained by venipuncture, electroencephalography (EEG), allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. However, the assessment of the probability and magnitude of harm or discomfort may be different in sick children and may vary depending on the diseases or conditions that the children may have. For example, obtaining research blood samples from a very ill and anemic child may present more than minimal risk to the child. On the other hand, an IRB may consider that children suffering from chronic illnesses who are accustomed to invasive procedures are placed at minimal risk by involvement in similar research procedures, in contrast to children who have not had such experiences. The IRB must also consider the extent to which research procedures would be a burden to a child-subject, regardless of whether the child is accustomed to the proposed procedures.

Procedures that exceed minimal risk may be difficult to define in the abstract, but should not be difficult to identify on a case-by-case basis. Higher risk procedures might include biopsy of internal organs, spinal taps, or the use of drugs whose risks to children have not yet been established. Behavioral interventions likely to cause psychological stress also may exceed

minimal risk.

Assessing possible benefits: In assessing the possible benefits of research participation, the IRB should consider the variability in health status of potential subjects. For example, a potential subject might be a normal, healthy child, or a child who has been exposed to a disease or toxin (e.g., chicken pox, lead) where it is known that a percentage of the children exposed will experience untoward consequences. A child might be in the early stages of disease (e.g., HIV infection) or may suffer from the disease or other significant medical or psychiatric disorders. Thus the IRB must take into account the current health status of the child-subjects and the likelihood of progression to a worsened state without research intervention.

4. PERMISSION AND ASSENT

When children or minors are involved in research, IRBs are required to make provisions for the assent of the children and the permission of the parents.

Because children have not reached their full intellectual and emotional capacities and are unable to give legally valid informed consent, involving them in research requires the permission of their parents or legal guardians. The IRB must determine whether the permission of both parents is required. However, in some cases, such as child abuse or treatment of venereal disease, parental permission may not be appropriate. See MAS #92-5, 3(d) or 45 CFR 46 Subpart D for more information.

Although children are not capable of giving legally valid consent, they may be able to assent or dissent from participation. Out of respect for children as developing persons, they should be asked whether or not they wish to participate in research, particularly if they can comprehend and appreciate what it means to be a volunteer for the benefit of others and the research is not likely to benefit them directly. Taking into account such factors as the nature of the research, and the age, status and medical condition of potential subjects, the IRB must determine for each protocol, whether all or some of the children are capable of assenting to participation. There is no requirement that assent be sought at a specific age, but that it be sought when in the judgment of the IRB, the children are capable of providing assent. See MAS #92-5, 3(d) or 45 CFR 46 Subpart D for more information.

5. REMUNERATION/COMPENSATION

If compensation is to be paid, a section should be included in the consent document to be signed by the parent and in the assent document, if inclusion in the assent document is considered appropriate by the IRB.

6. WARDS OF THE STATE

When conducting research involving wards of the state, additional requirements may be applicable as discussed in MAS# 92-5 or 45 CFR 46.409.

7. FOR MORE INFORMATION

A checklist of issues for IRBs to consider in research with children is posted on the NIH Pediatric Staff website at http://www.cc.nih.gov/ccc/pedweb/pedsstaff/index2.html. A list of NIH intramural pediatricians who are available to serve as ad hoc IRB consultants for review of protocols involving children is attached.

If you have questions about the design and conduct of research involving children, you may ask your Laboratory, Branch or Section Chief or your IRB Chair. Also, the OHSR staff is available to help you and may be reached at 301-402-3444 (FAX 301-402-3443).

Attachment

* Much of this text has been taken directly from Protecting Human Subjects, Institutional Review Guidebook 1993, Chapter 6, "Children and Minors," issued by the NIH's Office for Human Research Protections (OHRP).