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Subject: Vulnerable Populations
Division: IRB
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IRB Policy 109.3: CHILDREN

Policy

The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations are in place for reviewing research involving children.

DHHS regulations at 45 CFR 46, subpart D and FDA regulations at 21 CFR 50, subpart D provide additional protections pertaining to biomedical and behavioral research involving children as subjects. Research that is contrary to the rights and welfare of child-subjects is prohibited.

Definition

Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted", 45 CFR 46.402(a).

Permitted Categories for Research with Children

Federal regulations require the IRB to classify research involving children into one of four categories and to document its discussions of the risks and benefits of the research study. Three of the four categories may be approved by the IRB. The fourth category requires review and approval from the Secretary of HHS. The four categories of research involving children are as follows:

1. 45 CFR 46.404 - Research not involving greater than minimal risk to the children.

   To approve this category of research, the IRB must make the following determinations:
   a) the research presents no greater than minimal risk to the children; and
   b) adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

2. 45 CFR 46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

   To approve research in this category, the IRB must make the following determinations:
   a) the risk is justified by the anticipated benefits to the subjects;
   b) the relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches; and

c) adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

3. 45 CFR 46.406 - Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition.

   In order to approve research in this category, the IRB must make the following determinations:
   a) the risk of the research represents a minor increase over minimal risk;
   b) 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;
   c) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition; and
   d) adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

4. 45 CFR 46.407 - Research that the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406 but 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.

   If the IRB believes that the research meets the requirements of 45 CFR 46.407, it may refer the protocol to HHS for review. The research may proceed only if the Secretary, HHS, or his or her designee, after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following an opportunity for public review and comment, determines either:

   a) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or
   b) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; the research will be conducted in accordance with sound ethical principles; and adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408

Analysis of Risks and Benefits

The IRB review of research involving children as subjects will consider the benefits, risks, and discomforts inherent in the proposed research and assess their justification in light of the expected benefits to the child-subject or to society as a whole. In calculating the degree of risk and benefit, the IRB will weigh the circumstances of the subjects under study, the magnitude of risks that may accrue from the research procedures, and the potential benefits the research may provide to the subjects or class of subjects.

Central to the IRB's consideration of research involving children is the determination of what constitutes minimal risk. Procedures that usually present no more than minimal risk to a healthy child include: urinalyses, obtaining small blood samples, EEGs, allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. The assessment of the probability and magnitude of the risk, however, may be different in sick children and may vary depending on the diseases or conditions the subjects may have. For example, obtaining blood samples from a hemophiliac child may present more than minimal risk to the child. On the other hand, the 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 will also consider the extent to which research procedures would be a burden to any child, regardless of whether the child is accustomed to the proposed procedures.

Procedures that exceed the limits of minimal risk may be difficult to define in the abstract, but should not be too difficult to identify on a case-by-case basis. Riskier 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 may also exceed minimal risk.

In assessing the possible benefits of research intervention, the IRB will consider the variability in health statuses among potential subjects. For example, a potential subject might be a normal, healthy child, or a child who has been exposed to a disease or a toxin (e.g., meningococcus or lead) where it is known that a percentage of the children exposed will actually experience untoward consequences. A child may also be in an early state of disease, e.g., an HIV-infected child, or may actually suffer from disease or other significant medical condition. Thus the IRB will take into account the current health status of a child and the likelihood of progression to a worsened state without research intervention.

Risk Determination	**Benefit Assessment**	**IRB Action**
Minimal	With or without direct benefit	Approvable
Greater than minimal risk*	Potential benefit to child	Approvable
Greater than minimal risk*	No direct benefit to individual, but offers general knowledge about the child's condition or disorder	Approvable case-by-case
Greater than minimal risk	No direct benefit to child, but offers potential to, "understand, prevent, or alleviate a serious problem affecting the health and welfare of children"	Not approvable**
* Risk may not be more than a minor increase over minimal risk, consent of both parents required under normal circumstances. **Approval to proceed with this category of research must be made by the Secretary of the HHS with input from selected experts, and following opportunity for public review and comment.		

Child Assent and Permission by Parents or Guardians

When children or minors are involved in research, the regulations require the assent of the child or minor and the permission of the parent(s), in place of the consent of the subjects.

Given that children have not reached their full intellectual and emotional capacities and are legally unable to give valid consent, involving children in research requires the permission of their parents or legally authorized representatives. The IRB will determine whether the permission of both parents is necessary, and the conditions under which one parent may be considered "not reasonably available" (examples of circumstances in which parental permission may be inappropriate are discussed below). In addition, the IRB will determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Category 1, minimal risk research, or Category 2, research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. Where research is covered by Categories 3 and 4, and permission is to be obtained from parents, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

The IRB must determine for each protocol - depending on such factors as the nature of the research and the age, status, and condition of the proposed subjects - whether all or some of the children are capable of assenting to participation. Where appropriate, the IRB may choose to review on a case-by-case basis whether assent should be sought from given individual subjects. While assent is not required to be sought from children starting at a specific age, assent will be sought when, in the judgment of the IRB, the children are capable of providing their assent, taking into account the ages, maturity, and psychological state of the children involved. Children age 10 and above should sign assent to participate in the research; however, if circumstances warrant, the researcher may ask a child below the age of 10 to sign assent taking into consideration the child's level of maturity, age, and psychological state.

When the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, the IRB may determine that the assent of the child is not necessary. Additionally, in such circumstances a child's dissent, which should normally be respected, may be overruled by the child's parents, at the IRB's discretion. When research involves the provision of experimental therapies for life-threatening diseases such as cancer, however, the IRB will be sensitive to the fact that parents may wish to try anything, even when the likelihood of success is marginal and the probability of extreme discomfort is high. Should the child not wish to undertake such experimental therapy, difficult decisions may have to be made. In general, if the child is a mature adolescent and death is imminent, the child's wishes should be respected.

When the IRB determines that the assent of the child is required, it will also determine that the provisions for obtaining and documenting assent are adequate. The child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity, and condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if he or she agrees to participate.

For some research activities, the IRB may require that either an IRB member or an advocate for the child be present during the assent and permission procedures to verify the child's understanding and to support the child's preferences. The IRB may also require that the parent(s) or a close family member be present during the research, especially if a young child will be exposed to significant discomfort or inconvenience, or if the child will be required to spend time in an unfamiliar place.

The requirement for parental permission may be inappropriate in some cases. Examples include research involving older adolescents who, under applicable law, may consent on their own behalf for selected treatments (e.g., treatment for venereal disease, drug abuse, or emotional disorders). In other research (e.g., research on child abuse or neglect), there may be serious doubt as to whether the parents' interests adequately reflect the child's interests. In these types of cases, the IRB will consider the development of alternative procedures, on a case by case basis, for protecting the rights and interests of the children asked to participate, including, perhaps, the court appointment of special guardians.

Parental permission may sometimes be insufficient to protect the child's interests. In cases involving transplants (e.g., of bone marrow or a kidney) between minor siblings, the parents' concern for the afflicted child may interfere with their consideration of the best interests of the healthy donor. Therefore, the IRB may consider other alternatives, such as asking for court review of the parents' decision.

The IRB will consult legal counsel about the applicability of any state laws affecting consent for the proposed research. The IRB will make itself aware of the age of majority in the state as well as laws or court decisions that might limit the right of parents to consent on behalf of their children in certain circumstances. Age and conditions of emancipation will differ from state to state. In some states the age at which a child can give consent to medical care differs depending on the medical condition involved (e.g., venereal diseases). The federal regulations require that all research activities must comply not only with the regulations but also with the law of the state in which they are performed.

Exemption From Review

Research involving children as participants may be exempt. The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Wards of the State

The federal regulations providing special protections for children include additional limitations on some research involving children who are wards of the state or any other agency, institution, or entity. Where the research involves greater than minimal risk to the subjects with no prospect of direct benefit to individual subjects, the research must either be:

- Related to their status as wards; or
- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

The IRB will require, for each child who is a ward, appointment of an advocate in addition to any other individual acting on behalf of the child as a guardian or in loco parentis.

The IRB will be particularly concerned with the involvement of HIV-infected children who are in foster care, but who are also not wards. Many of these children are from racial or ethnic minorities. The IRB will give special attention to groups of children such as these who, while they need special protections, should not be denied the opportunity to participate in research that may potentially be of benefit to them.

Finally, whenever institutionalized children might be involved in research, care should be taken to ensure that they are not included as participants simply because of their availability to the investigator.

Applicable Regulations and Guidelines

45 CFR 46, Subpart D
21 CFR 50, Subpart D
OHRP Guidance - Special Protections for Children as Research Subjects
OHRP Research with Children FAQs