

Issues Related to the Participation of Children in Research

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In order to improve children's health, it is necessary to include children as research subjects. However, children are a vulnerable population, so special efforts must be made to protect their rights. Why is it not possible to simply apply to children the knowledge gained through research in adult populations? The answer is that children are not miniature adults. As we know from treating pre- and post-transplant children and from pediatric donor management, children may respond differently to clinical as well as social-behavioral interventions. Further, from a research standpoint, conclusions from a study cannot be considered relevant to a population unless members of that population were included as research subjects.

The Federal Government defines a child as a person who has 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; however the actual age limit varies across the country and across funding agencies. For example, in a 1998 policy, the National Institutes of Health (NIH) considered a child to be a person under the age of 21.

Surprisingly, in the 1950s and 1960s child health research was more advanced than adult health services research. With the advent of Medicare, adult studies became more prevalent when Medicare data became available to researchers. In recent years, the Federal Government has placed increasing emphasis on learning what works to improve children's health. For example, the Children's Health Act of 2000 authorized expanded research for a wide variety of childhood health problems. In fact, it is expected that children be included in research unless scientific and ethical reasons are presented not to include them. Acceptable exclusionary circumstances include:

- 1) The research topic to be studied is irrelevant to children.
- 2) There are laws or regulations barring the inclusion of children in the research.
- 3) The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant.
- 4) A separate, age-specific study in children is warranted and preferable.
- 5) Insufficient data are available in adults to judge potential risk in children.
- 6) Study designs aimed at collecting additional data on pre-enrolled adult study participants; e.g., longitudinal follow-up studies that did not include data on children.
- 7) Other special cases justified by the investigator and found acceptable to the Institutional Review Board (IRB).

The Government entrusts responsibility for review and monitoring of research to authorized IRBs at organizations where research is conducted. One of the main mechanisms by which children in research are protected is through stringent procedures for IRB review of studies involving children. IRBs may approve three categories of research involving children as subjects:

- 1) Research not involving greater than minimal risk to the children; these studies must meet the following criteria:
 - the research presents no greater than minimal risk to the children; and
 - adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.
- 2) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research; in these studies:
 - the risk is justified by the anticipated benefits to the subjects;

- 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
 - adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.
- 3) 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; for these studies:
- the risk of the research represents a minor increase over minimal risk;
 - 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;
 - 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
 - adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

A fourth category of research requires a special level of HHS review beyond that provided by the IRB. In such studies, the IRB may refer the protocol to HHS for review if the IRB believes it does not meet the conditions of 45 CFR 46 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.

In educational settings where children are the subjects, research projects may be considered exempt, after initial IRB review, if only educational tests and/or passive observation of behavior are permitted. In these cases, investigators cannot interact with subjects. Clinical research and research involving donation consent processes provide more challenge.

From a practical perspective, it is important to consider what we as researchers can do with regard to involving children in research. First and foremost, do a thorough assessment of the risk/benefit ratio. Plan the project methodology and activities to reduce the risk for the child participants (and all participants) as much as possible. Risk must be assessed in various ways, including physical, emotional, and privacy domains. Enroll a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. Recruit appropriate project personnel for working with children and understanding their special needs.

In the project protocol (the document describing the research study that is presented to the IRB for review), describe plans for including children and justification for selecting or excluding a specific age range of child participants, or discuss the reason(s) for excluding children as participants in the research. If children are included, address how many subjects will be enrolled into the study for each group or condition-specific subgroup. Describe the expertise of the investigative team for dealing with children at the ages included. Also, describe the appropriateness of the available facilities to accommodate the children. Many IRBs require a section in the protocol titled, "Participation of Children" to address these issues.

Consent issues also must be addressed. The general concept that parents provide proxy consent for their children to participate often is not as straightforward as it seems. Ordinarily, one or both of the child's parents must give permission (consent), and the child would provide assent. Assent is an affirmative agreement to participate in research – mere failure to object should not be construed as assent.

For children living with foster parents, and for children considered to be 'emancipated,' researchers should seek legal guidance about the law in the state(s) where the research is being conducted. For example, in some states, neither foster parents nor youth services agencies can provide the informed consent to enroll a foster child in a research study – only a birth parent or a

person adjudicated as an adoptive parent can provide that informed consent in these jurisdictions.

For emancipated minors, the provisions that permit a minor to be considered emancipated vary depending upon the circumstance, and a minor can be considered emancipated for one purpose (for example, for obtaining birth control), but not for others. A wise guideline is that, unless the minor has been emancipated by court order, which the investigator should confirm by requesting a copy of the order, a minor should not be considered emancipated for purposes of consenting to participation in a research study.

Researchers must consider the full implications of the child's participation in the study to assure that the best interests of the child are not in conflict with the interests of the researchers, or even with the parents, who are providing consent. It is vital to make certain that risk is minimized to the greatest extent possible