DETERMINATION OF RISK FOR RESEARCH STUDIES INVOLVING CHILDREN
10/13/2014

DHHS regulations limit research involving children to those activities that meet one of four categories of research. These categories (specified in 45 CFR 46 Subpart D) are based on the level of risk and potential for benefit to the individual participant. Equivalent categories appear in the FDA regulations at 21 CFR 50 Subpart D, and are to be applied to all FDA-regulated clinical investigations that will include children as participants.

I. Research not involving greater than minimal risk (45 CFR 46.404). See equivalent category at 21 CFR 50.51 if applicable.

When the IRB finds that no greater than minimal risk to children is presented, the IRB may approve the proposal only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

II. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405). See equivalent category at 21 CFR 50.52 if applicable.

If the IRB finds that more than minimal risk to children is presented by an intervention or procedure but that the intervention or procedure holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, the IRB may approve the research only if the IRB finds that:

- the risk is justified by the anticipated benefit to the subjects;
- the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth below.

III. 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 (45 CFR 46.406). See equivalent category at 21 CFR 50.53 if applicable.
If the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, the IRB may approve the research only if the IRB finds that:

- the risk represents a minor increase over minimal risk;
- 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;
- 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; and
- adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth below.

IV. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407). See equivalent category at 21 CFR 50.54 if applicable.

If the IRB does not believe the research proposal meets any of the requirements set forth above, it may still approve the application but only if:

- 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
- the Secretary of the Department of Health and Human Services *, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
  
  - 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 below.

* FDA regulations at 21 CFR 50.54 provide for reporting to the FDA Commissioner in circumstances when this research category applies.
A. For Research Regulated by FDA

FDA does not consider the administration of a placebo to a child to offer a prospect of direct benefit to the recipient. (Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products – Federal Register 78(38):12937-12951) Consequently, for a study of a drug or biologic (whether investigational or FDA-approved) versus a placebo, with no other therapy permitted (standard of care and/or known effective treatment is withheld), the placebo recipient would be viewed as having no prospect of direct benefit from participating in the study. In such a circumstance, the risks in the placebo control group should present no more than minimal risk or a minor increase over minimal risk. The placebo control arm of such a study must be approvable under either 21 CFR 50.51 or 21 CFR 50.53, or the clinical investigation must be referred for review under 21 CFR 50.54. Those in the arm that receive the investigational product often would be viewed as having the prospect of direct benefit, and that portion of the study could be approvable under 21 CFR 50.52.

However, in a study where one study drug or study biologic is given in addition to standard therapy specified by the protocol (with drugs and doses delineated) compared with a placebo given in addition to standard therapy specified by the protocol (with drugs and doses delineated), the placebo recipient would be viewed as having the prospect of direct benefit from the standard therapy, and the study would be approvable under 21 CFR 50.52. Also those in the arm that receive the investigational product and the standard therapy would be viewed as having the prospect of direct benefit, and that portion of the study could also be approvable under 21 CFR 50.52.

With respect to the criteria that must be met for approval under 21 CFR 50.53, the inclusion of children without the disorder or condition under study would not meet the requirement of 21 CFR 50.53(c) that “the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition.”

B. Requirements for Permission by Parents or Guardians

The Federal regulations present specific requirements for obtaining permission from parents or legal guardians that are based on the level of risk and potential for benefit to the individual participant. The investigator must make adequate provisions for soliciting the permission of each child's parents or legal guardian as declared by the IRB (45 CFR 46.408(b), and 21 CFR 50.55(e) if applicable).

I. Research not involving greater than minimal risk (45 CFR 46.404). See equivalent category at 21 CFR 50.51 if applicable.

Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research in this category.
II. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405). See equivalent category at 21 CFR 50.52 if applicable.

Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research in this category.

III. 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 (45 CFR 46.406). See equivalent category at 21 CFR 50.53 if applicable.

Research approved under this category requires that, when parental permission is to be obtained, both parents must give 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.

IV. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 407). See equivalent category at 21 CFR 50.54 if applicable.

Research approved under this category requires that, when parental permission is to be obtained, both parents must give 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.

C. Waiver of Parental or Legal Guardian Permission

If the research protocol is designed to study conditions or participants for which parent or legal guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children), an investigator may request that the IRB waive the consent requirements described above, provided that both of the following conditions are met:

- an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and
- the waiver is not inconsistent with Federal, State, or local law.

The choice of an appropriate mechanism (for example, appointing a child advocate or an assent monitor) for protecting children participating in research would depend upon the nature and purpose of the activities described in the research plan, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.
The requirement for parental or guardian permission also may be waived under the circumstances in which consent may be waived under 45 CFR 46.116.

Note that for FDA regulated research, no such waiver of parental permission is permitted.

D. Documentation

Permission by parents or guardians shall be documented in the same manner as required for other participants. When the IRB determines that assent of a child is required, it shall also determine whether documentation is required.

E. Assent of Children

Assent is a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed to be assent.

The investigator must make adequate provisions for soliciting the assent of a child participant when the children are capable of providing assent. In determining whether children are capable of assenting, the investigator should take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular research protocol, or for each child. Unless otherwise specified by the investigator and approved by the IRB, the investigator will solicit the assent of children 6 years of age or older. 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.

F. Waiver of Assent

The assent of children is not a necessary condition for proceeding with the research if the IRB determines that either of the following is true:

- The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- The intervention or procedure involved in the research holds 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.

If some of the children age 6 and above would not be able to provide meaningful assent, the investigator will indicate how they will be identified. The IRB will determine and document whether their selection is justified.

The requirement for assent of the child participant also may be waived under the circumstances in which consent may be waived under 45 CFR 46.116.

For FDA regulated research, the requirement for assent of the child participant may be waived according to 21 CFR 50.55(d).
G. Child's Dissent

The IRB may request that the investigator include a description of behaviors that will be viewed as indicators that the child does not wish to participate in the research (such as crying, moving away from the investigator, or being unwilling to complete tasks). Therefore the investigator may not rely solely on the absence of verbalized objection as the basis for deciding that assent has been given.

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 a child's dissent, which should normally be respected, may be overruled by the child's parents or legal guardian.

Finally, even where the IRB determines that the children are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived for adults.

H. Independent Risk/Benefit Assessment by the Chair of Pediatrics

The investigator must consult with the Chair of Pediatrics of the Duke University School of Medicine, or his/her designee, for an independent assessment of the level of risk and the level of benefit to the child that is posed by the research. The Chair or his/her designee is asked to record the outcome of this assessment using the Pediatric Risk Assessment Form, which will be included by the investigator in the completed eIRB application that is submitted for IRB review.

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