

**UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER
INSTITUTIONAL REVIEW BOARD
REVIEW OF RESEARCH – ADDITIONAL PROTECTIONS FOR CHILDREN**

I. PURPOSE

To document the procedures used by University of Tennessee Health Science Center Institutional Review Board for the review of studies involving children.

II. SCOPE

This SOP applies to the IRB administrative staff, IRB members and investigators.

Personnel Responsible:

IRB administrative staff, members, and investigators.

III. BACKGROUND

IRBs are obligated to ensure that the rights and welfare of subjects are adequately protected. Children who are research subjects possess special vulnerabilities. These vulnerabilities relate to the increased susceptibility of children to harm (e.g., anxiety due to separation from parents or inexperience with medical procedures), as well as their limited or absent ability to make informed and voluntary decisions about research participation. Therefore, additional protections are afforded children as research subjects.

Research with children must satisfy the regulatory requirements of 45 CFR 46 Subpart D, “Additional Protections for Children Involved as Subjects in Research,” and 21 CFR 50 Subpart D, “Additional Safeguards for Children in Clinical Investigations,” as well as the general requirements of 45CFR46, Subpart A (the Common Rule). In addition to the requirements outlined in SOP #03 (Review of Research), the UTHSC IRB shall determine that research with children satisfies the additional requirements outlined in Subpart D of the HHS and FDA regulations.

The latter regulations delineate permissible research approvable by the local IRB based on three basic categories of risks and benefits: research involving no more than minimal risk, research involving more than minimal risk but offering the prospect of direct benefit, and research involving more than minimal risk without the prospect of direct benefit.

In addition, the investigator must usually obtain both the written permission of the parents or legally authorized representative and the child’s assent before the child

may participate in the study. A child's mere failure to object is not assent. Federal regulations do not require that assent be sought from children starting at a particular age, but specify that assent should 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. UTHSC IRB policy is that assent must be obtained from all children ages 8 and older who are determined to be capable of providing assent.

Assent is a process initiated by a researcher to share information about a particular study with a child or minor adolescent subject. The basic value underlying this process is to acknowledge the minor as an individual deserving of respect. During the assent process, one or more of the following will be achieved: the minor can feel included in the process, or can feel at least partially informed, or can fully understand the purpose and requirements of the research. The extent of participation of the child in the process will be determined by the age and developmental status of the minor, relevant legal statutes, cultural contexts, type of research being done, local IRB policies, health status of the minor, and the potential for therapeutic benefit. The ultimate outcome of the process is agreement or disagreement by the minor to participate in the study.

The intent of the assent process is undermined in situations where the option of dissent does not exist. Thus, it is disrespectful to the minor to initiate an assent process if the minor does not have a right to refuse to participate in the study. The researcher may judge the clinical situation to be such that an assent process should not be initiated. In such situations described below, the rationale for not initiating the assent process must be documented.

In Accordance With:

45 CFR 46 subpart D; 21 CFR 50 subpart D; OHRP Guidance on Written IRB Procedures, 1/15/07.

OHRP Children's Special Issues Page located at
<http://www.hhs.gov/ohrp/children/>.

OHRP Guidance on the Section 407 Review Process located at
http://www.hhs.gov/ohrp/children/guidance_407process.html.

OHRP FAQs on Research With Children located at
<http://www.hhs.gov/ohrp/faq.htm>

Compliance with this policy also requires compliance with state or local laws or regulations that provide additional protections for human subjects.

DEFINITIONS

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

Children are persons who have not attained the legal age for consent to treatment or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

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

Guardian means an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

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.

IV. PROCEDURES

1. When reviewing clinical studies involving children that require full board review, UTHSC IRB will have a pediatrician and / or other voting member who has expertise, experience and training in the care of children present when the study is discussed.
2. When reviewing clinical studies involving children, UTHSC IRB will only approve research studies falling into one of the following categories:
 - a. Research not involving greater than minimal risk to the research participant (45CFR46.404; 21CFR50.51).
 - b. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject. Research in this category is approvable provided (a) the risk is justified by the anticipated benefit to the subject; and (b) the relationship of risk to benefit is at least as favorable as any available alternative approach (45CFR46.405; 21CFR50.52).
 - c. Research involving greater than minimal risks with no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided: (a) the risk represents a minor increase over minimal risk; (b) the 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; and (c) the intervention or procedure is likely to yield

- generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition (45CFR46.406; 21CFR50.53).
- d. Research not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children (45CFR46.407; 21CFR50.54). When a research study is approvable only under this category, the IRB will request additional review by a panel of experts convened by the Secretary of HHS or the Commissioner of the FDA. Final approval will be contingent upon a finding by the expert panel that the study is approvable in accord with 45CFR46.407 or 21CFR50.54.
 - e. Children who are wards of the State or any other agency, institution, or entity can be included in research approved under (2c) or (2d) only if (i) such research is related to their status as wards; or (ii) the research is conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. If research is approved under this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.
 - f. The category under which the study is approved will be appropriately documented in the minutes of the IRB meeting.
3. The UTHSC IRB will only approve studies that satisfy the following requirements for assent and permission:
 - a. Permission of one parent is sufficient for research approved under 2(a) and (b) above. For research approved under 2(c) and (d) above, permission of both parent(s)/guardians is required, 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 if consistent with State law (45 CFR 46.408(b); 21CFR50.55(e)(2)).
 - b. The UTHSC IRB will require that each child aged 8 or older provide assent, provided that the investigator determines that the child is capable of assent by evaluating the child's level of maturity, psychosocial and emotional capacity, as well as the nature of the study. The assent process is a vital component of the investigator's ongoing relationship with the minor. Thus, adequate provision must be made for engaging those minors capable of participating in the process. Clinical judgment should be utilized to adapt the process and content to the minor's age, developmental

and social maturity, culture, and experience in the medical setting.

Essential components of the assent process are:

- i. An ongoing, open discussion of the research study, including risks, benefits, procedures, and alternatives, appropriate to the minor and the study;
 - ii. Ample opportunity for the minor to ask questions and to have them answered;
 - iii. An explanation that the minor's participation is voluntary and that the subject can decline to participate;
 - iv. Formally obtaining the minor's assent or dissent; and
 - v. Documentation of the assent process.
- c. **Exceptions to the Assent Requirements:**
- i. **Exceptions for Specific Research Studies**
The IRB recognizes that certain research studies involve subjects who are not capable of giving assent. The IRB can waive the requirement for obtaining assent in such cases. In addition, when the IRB has determined that the research offers the prospect of direct benefit for the subjects (approved under 45CFR46.405), and when the research intervention is important to the health or well-being of the child and it is only available in the context of the research, the assent of the minor is preferred, but not required.
 - ii. **Exceptions for Individual Subjects**
There are two clinical situations in which the PI may make an exception to the requirements for seeking assent in studies for which the IRB has required assent for participation in that study. First is the situation of a minor subject who is incapable of providing assent because of a lack of adequate cognitive or emotional maturity, cultural contexts, the health status of the minor, or other factors that interfere **with the minor's ability to decide whether or not to participate in the research**. Second is the situation in which the minor subject has an urgent or emergent condition for which potentially lifesaving treatment is only available in the context of the research study and parental permission has been obtained. In either of these two situations, investigators will use their professional judgment to determine whether the minor is incapable of providing assent, or whether the study has the potential to directly benefit the subject using a treatment that is only available in the context of the research study. If the applicable conditions obtain, then the requirement for an investigator to seek assent may be waived, provided that adequate documentation is made in the medical or research record. Even in these two situations, it is preferable that the minor has as complete an understanding of the research as possible.
 - iii. **Documentation of Exceptions to the Assent Requirements**
The Principal Investigator should document the reasons for not obtaining assent in studies where the IRB has not waived this

- requirement or indicated in writing that obtaining assent is optional for participating in the research.
- d. Even if the child is capable of assenting, the IRB may waive the requirement under the same conditions for which consent may be waived under 45CFR46.116(d). The waiver conditions are not applicable, however, for studies subject to FDA regulations for the protection of human subjects.
 - e. If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not reasonable (neglected or abused children), permission may be waived if an appropriate mechanism for protecting the children is substituted and the waiver is not inconsistent with local, state or federal laws.
 - f. The documentation of assent will vary by the age of the minor. Unless it is specified otherwise in the approval letter, research with very young children (<8 years old) requires only that parental permission is secured and that appropriate information is given to the minor about the research in the same way that procedures would ordinarily be explained to a young child. For minors between the ages of 8–13, documentation of assent to participate is required using a “short form” assent document. For older adolescents (age ≥ 14 years), a single form that both the minor and the parents sign is adequate unless the Committee has specified differently in the approval letter.