

**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 45 CFR 46, Subpart A (the Common Rule).

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 parent or legal guardian 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; 21 CFR 56; OHRP Guidance on Written IRB Procedures (07/01/2011).

Special Protections for Children as Research Subjects

<http://www.hhs.gov/ohrp/policy/populations/children.html>

Children Involved as Subjects in Research: Guidance on the HHS 45 CFR 46.407 ("407") Review Process

http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html

Research with Children – FAQ

<http://answers.hhs.gov/ohrp/categories/1570>

Research Involving Vulnerable Populations (Video)

http://www.youtube.com/watch?v=SqRw6FevuXg&feature=player_embedded

Additional Protections for Children

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm19111.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 legal guardian(s) to the participation of their child or ward in research.

Parent means a child’s biological or adoptive parent.

Legal Guardian means an individual who is authorized by a court under applicable state or local law to consent on behalf of a child to general medical care. The term “legal guardian” as used here does not include non-custodial parents, grandparents, adult siblings, step-parents or other adult family members, unless such individuals are authorized by a court of law to make decisions about general medical care for the child.

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 (45 CFR 46.404; 21 CFR 50.51).
 - 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 (45 CFR 46.405; 21 CFR 50.52).
 - 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 (45 CFR 46.406; 21 CFR 50.53).
 - d. Research not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children (45 CFR 46.407; 21 CFR 50.54). 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 45 CFR 46.407 or 21 CFR 50.54.
 - 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 for studies requiring full board review, and in the initial approval letter for studies requiring expedited and exempt review.
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 parents/legal 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); 21 CFR 50.55(e)(2)); or when there is only one legal guardian.
 - b. For research approved under 2(c) and (d) above, the following procedures should be followed to determine the reasonable availability of an absent parent/legal guardian and to secure his/her permission by telephone:
 - i. The absent parent/legal guardian should be considered not reasonably available if unable to be reached by phone within the timeframe necessary to secure permission for study participation.
 - ii. If the absent parent/legal guardian is available by phone, then the consent document should be sent to him/her by a convenient mode of communication (fax, e-mail, etc.). The consent interview may be conducted over the telephone when the absent parent/legal guardian can read the consent form as it is discussed. Study procedures may not be initiated until the signed consent form (signed by the absent parent) is returned by facsimile (or approved alternative method discussed below) to the investigative site. The consent form with the original signature of the absent parent/legal guardian should be mailed or brought to the investigative site at the earliest opportunity. The IRB will also permit the use of alternative communication technologies in FDA-regulated studies, such as e-mail, mail, or videoconference, provided that the consent form is sent to the absent parent/legal guardian prior to the consent interview, the absent parent/legal guardian can read the consent form as it is discussed, and an image of the signed consent form is returned to the investigative site prior to the initiation of study procedures.
 - iii. The steps in the effort to determine reasonable availability, to contact the second parent/legal guardian, and to secure his/her permission should be carefully documented in the research record. Careful

- documentation requires sufficient narrative that an auditor would be able to tell what efforts were made, how it was determined whether the second parent/legal guardian was reasonably available, and if he/she was available, how permission was obtained.
- iv. Securing permission by telephone must be approved by the IRB as an alteration of consent made in the electronic research application. (See the SOP entitled, “Informed Consent,” for further information on the use of telephone consent procedures.)
 - c. 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, family dynamics, 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.
 - d. 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 45 CFR 46.405), 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.
- e. 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 45 CFR 46.116(f) (previously 45 CFR 46.116(d) of the pre-2018 Common Rule). The waiver conditions are not applicable, however, for studies subject to FDA regulations for the protection of human subjects.
- f. If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or legal 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.
- g. 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 the assent discussion page at the end of the UTHSC IRB Main Consent Form template (<http://www.uthsc.edu/research/compliance/irb/researchers/consent-forms.php>). For older adolescents (age ≥ 14 years), a single consent form that both the minor and the parent or legal guardian sign is adequate unless the Committee has specified differently in the approval letter.

- h. If a minor between the ages of 14 and 17 is cognitively capable of assenting to his/her participation in the research study but cannot physically sign the assent line on the consent page (for example, due to paralysis), he/she can verbally indicate that he/she assents and can have his/her parent or legal guardian sign the assent line for him/her. This situation should be explained and documented in the assent/consent discussion notes in the research record.
 - i. If a person's role as custodial parent or legal guardian for the child was initially uncertain or was challenged by another individual, it is recommended that the research record include a notation and/or documentation of how it was determined that the individual providing permission is the child's custodial parent or legal guardian.
4. When a child reaches the age of 8 while enrolled in a research study, then assent should be obtained from the child subject using the assent discussion page of the consent form(s), and/or according to the assent process described in the IRB-approved application and protocol for the study. Please note that this is required only in circumstances where there are still interactions (including all communications such as phone calls) or interventions (such as blood draws at study visits) with the subject after he/she reaches 8 years of age.
5. When a child subject reaches the age of majority while enrolled in research study, then the subject should be consented as an adult. The consent process and the documentation of consent should be implemented in accord with the provisions of SOP: Informed Consent. Please note that this is required only in circumstances where there are still interactions (including all communications such as phone calls) or interventions (such as blood draws at study visits) with the subject after he/she reaches 18 years of age.
6. If the parent or legal guardian loses or transfers authority to make health care decisions on behalf of a child who is participating in research, then the new legally authorized representative must be identified and provide permission for the child's continued participation in the study. If a child becomes a ward of the state due to the aforementioned loss or transfer of parental or guardian rights, the stipulations in IV.2.e. (above) apply and the IRB must be notified immediately if the study has not been approved for the inclusion of children who are wards of the state as subjects.
7. The consent form for pediatric subjects should be formatted in accord with the UTHSC IRB Main Consent Form template (<http://www.uthsc.edu/research/compliance/irb/researchers/consent-forms.php>). This includes, as applicable, adding the assent signature line for

pediatric subjects age 14-17 years old, the parent(s)/legal guardian(s) signature lines, the assent discussion page for pediatric subjects age 8-13 years old, and the initials line for the parent/legal guardian at the bottom of each page except the signature pages.

8. When any UT faculty, staff, students, residents, or fellows are participating in projects involving minors that require review and approval by the Institutional Review Board (IRB), they must comply with the University of Tennessee Safety policy 0575 (Programs for Minors), which can be found at http://policy.tennessee.edu/safety_policy/sa0575/ .