University of Kentucky
IRB Policy on Children in Research

D22.0000

If you are proposing research involving individuals under the age of 18, read the requirements described below, and select appropriate categories in the IRB application.

Children are considered a vulnerable research population because their intellectual and emotional capacities are limited, and they are legally incompetent to give valid consent. Special procedures and considerations are, therefore, required by federal regulations for the review of research involving children. See ORI's Summary of Children Regulations: IRB Review of Research Involving Children for a summary of the federal regulations governing research involving children.

Whenever feasible, appropriate studies should be conducted on animals, adults, and older children before young children are involved as research subjects.

The Institutional Review Board (IRB) is required to consider the degree of risk inherent in the proposed research and the methods for obtaining the assent of the children as well as the permission of parents or guardians. The IRB's policy with respect to obtaining permission from the parents or guardians and assent from children is specified below:

1. Parental permission must be obtained if the research involves children under the age of 18 unless the individuals are legally emancipated or the IRB waives the requirement. A written form must be used to document parental permission. The permission process and form must include the elements of informed consent set forth in federal regulations and outlined in the informed consent template included in the IRB expedited and full review applications. The parental permission form should be written from the perspective of a parent being informed about what their child is being asked to experience (i.e., "Your child is being asked…", "Your child will…").
2. Subjects 6 years of age or older should be involved in the decision to participate in a research project unless the requirement for assent is waived (see below for conditions of waiving assent).

   The Investigator should at a minimum provide an explanation to the children about the proposed research procedures in language appropriate to the child's age, maturity, and condition (i.e., assent script). See the ORI Informed Consent/Assent webpage for instructions and a sample assent form containing appropriate elements.
3. Unless the requirement is waived by the IRB, signatures are required on the assent for subjects aged 12-17. The child should be given an explanation, at a level appropriate to the child's age, maturity, and condition, of the procedures to be used, their meaning to the child in terms of discomfort and inconvenience, and the general purpose of the research. In most cases, a written assent form should be used to document assent. A copy of the assent form must be submitted to the IRB for review. The form should include a simplified version of the elements of informed consent (see ORI Informed Consent/Assent webpage for instructions and a sample assent form containing appropriate elements).
4. For clinical research, individuals under the age of 18 may possibly be considered emancipated in accordance with state law. For a complete definition of emancipated minors, see the section on *Emancipated Individuals* in the Informed Consent SOP. Legal counsel will make a determination whether subjects in a study meet state requirements for being legally emancipated. Investigators should contact David Kinsella in Legal Counsel at (859) 257-6361 or david.kinsella@uky.edu before submitting the IRB application to the IRB.

Federally Mandated Categories:

Federal regulations specify that the conditions for approval of research involving children vary in accord with the following four federally mandated categories of research based on the degree of potential risk and benefit:

1. Research does not involve greater than minimal risk[i];
2. Research involves greater than minimal risk but presents the prospect of direct benefit to the individual subjects[ii];
3. Research involves greater than minimal risk, and no prospect of direct benefit to an individual subject, but is likely to yield generalizable knowledge about the subject's disorder or condition; or

4. Research does not fall under Category 1, 2, or 3 listed above; however, the research presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

The investigator selects the applicable category and addresses the federal requirements by completing the IRB expedited and full applications. The IRB applies federal regulations when conducting reviews of studies involving children. The IRB may approve only those clinical investigations that satisfy the criteria described in Categories 1, 2, and 3. Should the research fall under Category 4, a report must be sent to the applicable federal agency for review and the IRB may not independently approve the research.

Guidance Regarding FDA Associated Studies*:

Children should not be enrolled in clinical investigations unless their participation is necessary. For example, for products that are being developed for use in adults and children, if effectiveness in adults can be extrapolated to children, then adult studies ought to be used to minimize the need to collect effectiveness data in children (this is unlikely for neonates which would likely need a separate study). Further, clinical investigations involving children should be designed to maximize the amount of information gained and minimize the number of subjects involved. Additionally, as with all human subject research, studies need to ensure an equitable selection of subjects.

IRBs should consider the cumulative risk if more than one non-therapeutic procedure is planned and should ensure that procedures be performed at a high-volume center with dedicated pediatric sedation service, rigorous scientific justification for non-therapeutic procedures, a description of risk minimization if there is a sedation procedure in the protocol, children with chronic conditions are carefully monitored or excluded, non-therapeutic procedures are terminated if complications arise or sedation is inadequate, sedation not withheld if the purpose is solely to avoid risk, and that clear communication occurs with both the subjects and their parents to include formal assent/consent as applicable.

A placebo control arm of a pediatric clinical trial must be categorized under either Category 1, 3, or 4. FDA has indicated that the administration of a placebo would not meet Category 2 because it would not offer a prospect of direct benefit. In addition, the FDA does not consider the concept of enhanced safety monitoring or follow-up provided to subjects in a placebo arm to constitute a prospect of direct benefit. In a study that has one arm meeting Category 3 and another arm meeting Category 1 or 2, the protections included under the more stringent Category 3 would be applied to the entire study (e.g., provisions to solicit permission of both parents/guardians).

Intravenous catheters placed solely to administer a placebo and not needed for clinical management or routine clinical care should be considered part of the risk assessment. Further, a peripheral intravenous catheter should be considered minimal risk or a minor increase over minimal risk, whereas a central intravenous catheter should be generally considered to exceed the minor increase over minimal risk threshold in regard to placebo administration. However, further consideration of risk regarding central intravenous access devices may be necessary for studies in which the length of the study may cause issues for participants where peripheral venous access is painful and/or traumatic and assent and consent have been obtained for placement.

https://www.fda.gov/media/107320/download

Placebo-controlled drug trials requiring injections or infusions administered over the course of one or two years have been justified as a minor increase over minimal risk depending on whether appropriate risk mitigation strategies are included as part of the protocol. For example, in a placebo-controlled study lasting 2 years, one could use a 2:1 randomization or cross-over after an appropriate interval to mitigate the risk associated with receiving a placebo over a prolonged period.

https://www.fda.gov/media/114640/download

[i] Examples of minimal risk interventions may include blood draws, physical exams, chest X-rays, MRIs without contrast or sedation, or surveys.

[ii] Potential harm should be transient, reversible, and severe pain should be extremely small or nonexistent. The setting and experience level of the investigator may impact this evaluation. Examples of *minor increase over minimal risk* interventions are urine collection via catheter, bone marrow aspirate with topical pain relief, MRIs with contrast or sedation, single lumbar punctures, single muscle biopsy, or administering a single dose of an investigational drug with adequate safety information.

Whereas, large organ biopsies, such as liver or kidney biopsies, when done for research purposes only have been considered to exceed a minor increase and should not be done in children unless the procedure is performed as part of routine clinical care for their condition.

Additionally, to offer the prospect of direct benefit, any dose planned for use should have the potential to have therapeutic effects based on available scientific information. Adaptive designs involving titration may help in establishing/achieving sufficient dosing.

*Some information in this section is based on non-finalized guidance from FDA.

Federal regulations also have additional requirements for studies that involve children who are wards of state.

See the Summary of Children Regulations (Subpart D) for a detailed description of the regulatory categories and conditions of approval.

Additional requirements may apply when research with children is supported by or involves other federal agencies (e.g., Department of Education, Environmental Protection Agency). For summary guidance and IRB checklists for other federal agencies, see the Federal Agency Specific Requirements section of the IRB Survival Handbook.

Waiver of Assent and/or Parental Permission:

The IRB may waive its requirements for obtaining or documenting assent if the IRB determines:

1. Capability of the child is limited such that (s)he cannot be reasonably consulted;
2. The children are not capable of providing assent based on the age, maturity, or psychological state); or
3. The research intervention or procedure(s) involved hold 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 investigation; or
4. a) the research involves no more than minimal risk to the participants; and
   b) the waiver will not adversely affect the rights and welfare of the participants; and
   c) the research could not practicably be carried out if assent was required; and
   d) when appropriate, pertinent information is provided after participation.

If the IRB determines any of the above criteria are met and waives the requirement for obtaining assent, the IRB determines and documents which children are not required to assent.

The IRB regulatory requirements for waiving parental/guardian permission are summarized below.

1. The IRB may waive the requirements for parental/guardian permission in non-FDA regulated studies if the conditions outlined in 45 CFR Subpart D 45.408(c) or 45 CFR 46.116(e)(f) are met. (See ORI/IRB Informed Consent SOP).
2. IRB cannot waive parental/guardian permission for FDA-regulated studies that are greater than minimal risk, except for research meeting the regulatory category of Emergency Research (21 CFR 50.24). The IRB may consider criteria for waiver of parental/guardian permission in Category 1 only.

3. The IRB may determine that permission of one parent is sufficient if the research is not greater than minimal risk (Category 1) or greater than minimal risk but presents the prospect of direct benefit to individual subjects (Category 2).
4. For all other risk categories of research (Category 3 and 4), permission of both parents or guardians are required unless one parent is not reasonably available, deceased, unknown, legally incompetent, or when only one parent has legal responsibility for the care and custody of the child. Parental permission documents should be formatted to accommodate both signatures.

Exemptions

The IRB may determine that some research involving children can be exempt from the federal policy for the Protection of Human Subjects. Research that involves children and falls into categories under 45 CFR §46.104 (Category 1,4,5,& 6) may be found to be exempt. However, the exemption category under 45 CFR §46.104 (Category2), pertaining to survey or interview procedures or observations of public behavior, does not apply to research involving children, except for research involving public behavior when the Investigator does not participate in the activities being observed. In addition, the exemption category under 45 CFR §46.104(Category3) benign behavioral interventions, does not apply to interventions involving children.

State Law

State and local laws must be followed when they provide additional protections beyond those provided by federal regulations. For assistance with applying state law to research involving children, contact the University of Kentucky's legal counsel at (859) 257-2936.

For research conducted outside the state of Kentucky, the Principal Investigator (PI) is responsible for identifying the applicable state law(s) to determine which individuals are "children" or "guardians". The PI should contact legal counsel if unable to identify applicable state law(s). The PI provides the information to UK legal counsel for review and determination prior to approval by the IRB.

Definitions for "child/children", "legally authorized representative", "emancipated", "guardian", "assent", and "permission" are included in the IRB/ORI Informed Consent Standard Operating Procedure (SOP) on the ORI website.