

Research Involving Children

Children are considered a vulnerable population in the research context. The Common Rule (45 CFR 46) and FDA regulations (21 CFR 50) include Subpart D: Additional Protections for Children as Research Subjects. Subpart D establishes risk-benefit categories for research involving children. Only research that fits into one of the first three categories may be approved by an IRB; a fourth category requires the approval of the Secretary of the Department of Health and Human Services.

Subpart D also specifies requirements for obtaining the permission of parents for the child's participation in research, and establishes expectations for obtaining the assent of children who are deemed capable of providing assent.

Who is a child (and who is not)?

In order to decide whether or not the additional protections of Subpart D apply, the IRB must first determine if any of the subjects will be children.

The definition of who is a child is determined by state laws. In Colorado, as in most states, the age of majority is 18 years. In most cases this means that research enrolling persons in Colorado who are under the age of 18 must comply with all of the requirements of Subpart D.

However, there are some situations where minors may consent to their own treatment prior to turning 18. If a minor can consent to a clinical treatment or evaluation under Colorado State law without parental permission, and the research closely relates to the care for which they have provided clinical consent, COMIRB may determine that the minor can provide informed consent for the research without requiring parental permission, and that Subpart D does not apply to the research.

For example, since an adolescent can seek treatment for an STD without parental consent, COMIRB may determine that minors can consent to participate in some STD research without the requirement for parental consent. Generally, that research would have to be closely related to the STD treatment they are seeking and not include significant additional research procedures unrelated to the clinical treatment sought or include research interventions posing more than minimal risk. For example, if an adolescent seeking STD treatment were to be asked to donate a biological specimen for future unspecified research, COMIRB would require parental permission for that donation.

45 CFR 46.402, 21 CFR 50.3

Definitions

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

Assent means a child's affirmative agreement to participate in research. Acquiescence is not evidence of assent.

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

Parent means a child's biological or adoptive parent.

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

*The FDA definitions use the term "clinical investigation" instead of research.

Subpart D Protections: Risk-Benefit Categories

Subpart D categorizes research that is approvable by an IRB by the level of risk and prospect for direct benefit.

§46.404 (§50.51): Minimal Risk

When the risks of the research are not greater than minimal, any child, regardless of health status, may participate. Waiver of consent and waiver of documentation of consent are also limited to research that is minimal risk.

Parental Permission and Assent Requirements for 404 Studies: Permission of a single parent and assent of the child (if applicable) are required for research approved under §46.404.

§46.405 (§50.52): Greater than Minimal Risk with a Prospect for Direct Benefit

Research offers a prospect for direct benefit when there is a possibility that participants will directly benefit from the research procedures or interventions, based on prior research, pre-clinical data, or the expertise of the investigators and the IRB. This includes potential benefits from study monitoring and diagnostic procedures that may contribute to the subject's care or well-being.

The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

Parental Permission and Assent Requirements for 405 Studies:

Permission of a single parent and assent of the child (if applicable) are required for research approved under §46.405.

§46.406 (§50.53): Greater than Minimal Risk without Prospect for Direct Benefit, but likely to yield generalizable knowledge about the subject's disorder or condition

If the research activity or a component of the research is purely for research purposes and is not for the participants' direct benefit, federal regulations require the research to satisfy additional conditions that are not otherwise necessary for other research:

- The risks to subjects are not more than "a minor increase over" minimal risk.
- The research 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 researchers are likely to gain generalizable knowledge which is of "vital importance" for the understanding or amelioration of the subjects' disorder or condition.

This category of research is limited to children with a disease or condition. For example, healthy controls cannot be studied under this category.

Parental Permission and Assent Requirements for 406 Studies:

Permission of both parents and assent of the child (if applicable) are required for research approved under §46.406. If one parent is not reasonably available, the consent of a single parent may suffice.

§46.407 (§50.54): Research that is not Otherwise Approvable which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Children
If the IRB determines that the research does not fit into §§46.404, 405 or 406 and determines that the research could possibly be approved under §46.407, the only way for the research to proceed is if the Secretary of Health and Human Services determines that it meets the criteria of §46.407.

The Secretary requests the FDA's Pediatric Subcommittee to review the proposal and make a determination. The Pediatric Subcommittee could either find that the research fits into one of the other 3 categories, or that the research meets the requirements of §46.407 or that the research is not approvable.

Referrals for a 407 determination are quite rare.

Parental Permission and Assent Requirements for 407 Studies:

Permission of both parents and assent of the child (if applicable) are required for research approved under §46.407.

Wards of the State

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 CFR 46.404 and 45 CFR 46.405 (or 21 CFR 50.51 and 21 CFR 50.52).

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 and 45 CFR 46.407 (or 21 CFR 50.53 and 21 CFR 50.54) only if such research is:

- related to their status as wards; OR
- conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as participants are not wards (45 CFR 46.409 or 21 CFR 50.56).

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward, in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis*. For more information, please refer to COMIRB policies.

Assent Requirements

For more information about the requirements for assent of child participants, please refer to COMIRB's Assent Guidance.

Minors as Parents

Unless parental permission is waived, any minor parent can give permission for their child to participate in research but the parent/guardian of the minor parent must give permission for the minor parent to participate in research (if it does not fall within one of the categories above for which minors can consent as an adult).

Contact COMIRB

If you have any questions, please contact [COMIRB](#). We are happy to answer your questions and to schedule a meeting with you to discuss your study. COMIRB also holds [office hours](#) with pediatric IRB Chairs twice a month.