In addition to other responsibilities assigned to IRBs under this part {45 CFR 46} [21 CFR 50.50], each IRB shall [must] review research [clinical investigations involving children as subjects] covered by this subpart {Subpart D, Additional Protections for Children Involved as Subjects in Research} [D] and approve only research [clinical investigations] which [that] satisfy{ies}[y] the conditions [criteria described in §50.51, §50.52, or §50.53 and the conditions] of all applicable sections of this subpart [D].” 45 CFR 46.403 {HHS}, 21 CFR 50.50 [FDA]

In general, the Institutional Review Board (IRB) does not approve research involving children if the research and its objectives can be met by using adults. When the research can only be appropriately conducted using children, special consideration must be given to safeguarding their interests and to protecting them from harm. Additional provisions of the federal regulations on human subject research govern research involving children (45 CFR 46 subpart D, 21 CFR 50 subpart D), and the IRB follows such requirements or equivalent protections. When research involves children, the IRB follows subpart D of the DHHS regulations or equivalent laws or regulations to approve an appropriate parental permission and child assent process.

**Definitions**

The following definitions are pertinent to research with human subjects involving children. When circumstances arise in research conducted outside of Michigan, the IRB will consult with the Michigan State University (MSU) Office of the General Counsel on other state laws (e.g., child, guardian, legally authorized representative).

**Assent:** “A child's affirmative agreement to participate in research [in a clinical investigation]. Mere failure to object should not, absent affirmative agreement, be construed as assent.” 21 CFR 50.3(n), 45 CFR 46.402(b) [FDA]

**Child:** “Persons who have not attained the legal age for consent to treatments or procedures involved in the research [clinical investigations], under the applicable law of the jurisdiction in which the research [clinical investigation] will be conducted.” 21 CFR 50.3(o), 45 CFR 46.402(a) [FDA]
In Michigan, a child is a person who has not:
1. Yet reached the age of 18; and
2. Been emancipated by court order; and
3. Been emancipated by operation of law under any of the following circumstances:
   a. Marriage
   b. Active duty with the armed forces of the United States

Michigan law states that an emancipated minor has the rights and responsibilities of an adult (with certain exceptions), including the right to authorize his or her own preventive healthcare. Although it is a reasonable inference, Michigan law does not explicitly state that emancipated minors may consent to participation in research. Thus, the IRB, with input from the MSU Office of the General Counsel, may choose not to approve research that relies solely on the consent of an emancipated minor.

Emancipated: A legal status conferred upon persons who have reached the age of 18 or who have not yet attained the legal age of competence as defined by state law (for such purposes as consenting to medical care), but who are entitled to treatment as if they had, by virtue of assuming adult responsibilities, such as marriage or serving on active duty in the military, or by virtue of a court order.

Guardian: “An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.” 45 CFR 46.402(e), 21 CFR 50.3(s) [FDA]

In Michigan, a guardian is a person who has accepted a:
1. Written parental appointment to be a guardian and there are no surviving, capacitated parents with parental rights; or
2. Court appointment to be a guardian.

For purposes of the U.S. Department of Health and Human Services (DHHS) regulations (45 CFR 46), a guardian does not include a limited guardian unless the limited guardianship expressly allows the guardian to consent to medical care.

For purposes of the U.S. Food and Drug Administration (FDA) regulations (21 CFR 50, 21 CFR 56), a guardian does not include a limited guardian unless the limited guardianship expressly permits the guardian to consent to participation in research.

Parent: “Child's biological or adoptive parent.” (45 CFR 46.402(d), 21 CFR 50.3(p)

Permission: “Agreement of parent(s) or guardian to the participation of their child or ward in research [a clinical investigation].” 45 CFR 46.402(c), 21 CFR 50.3(r) [FDA]

Classification
Research involving children is classified into four categories of research. The IRB determines which category the research qualifies for and that the research meets the corresponding requirements within the category.
Each category requires that parental permission and child assent be obtained in accordance with 45 CFR 408 or 21 CFR 50.55. For parental permission and child assent requirements, see the Human Research Protection Manual (HRPP) Manual 6-4-C “Parental Permission and Child Assent.”

**Not greater than minimal risk: 45 CF 46.404 and 21 CFR 50.51.**

{HHS will conduct or fund research in which} / [Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if] the IRB finds that

[a] no greater than minimal risk to children is presented, {only if the IRB finds that}

[b] adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408 [§ 50.55]. 45 CFR 46.404 {HHS}, 21 CFR 50.51 [FDA]

**Greater than minimal risk but presenting the prospect of direct benefit to individual subjects: 45 CFR 46.405, 21 CFR 50.52.**

{HHS will conduct or fund research in which the IRB finds that} / [Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which] more than minimal risk to children is presented by an intervention or procedure that 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, [may involve children as subjects] only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) 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

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408 [§ 50.55]. 45 CFR 46.405 {HHS}, 21 CFR 50.52 [FDA]

**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, 21 CFR 50.53.**

{HHS will conduct or fund research in which the IRB finds that} [Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which] 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 that is not likely to contribute to the well-being of the subject, [may involve children as subjects] only if the IRB finds that:

(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;
(c) 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

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408 [§ 50.55]. 45 CFR 44.406 {HHS}, 21 CFR 50.53 [FDA]

Not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children: 45 CFR 46.407, 21 CFR 50.54.

{HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:}

[If an IRB does not believe that a clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of § 50.51, § 50.52, or § 50.53, the clinical investigation may proceed only if:]

(a) the IRB finds that the research [clinical investigation] presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) the Secretary [The Commissioner of Food and Drugs], 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} determine[d]{s} either:

   (1) that the research [clinical investigation] in fact satisfies the conditions of §46.404, §46.405, or §46.406, [§ 50.51,§ 50.52, or § 50.53] as applicable, or

   (2) [That] the following [conditions are met]:

      (i) the research [clinical investigation] presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

      (ii) the research [clinical investigation] will be conducted in accordance with sound ethical principles; [and]

      (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408 [§ 50.55]. 45 CFR 46.407{HHS}, 21 CFR 50.54 [FDA].

Wards
There are additional requirements if the research falls under the 45 CFR 46.406 / 21 CFR 50.53 or 45 CFR 407 / 21 CFR 50.54 categories and involves wards. 45 CFR 46.409(a), 21 CFR 50.56.

If the research involves children who are wards of the state or any other agency, institution, or entity, they can be included in the research only if the research is:

“(1) Related to their status as wards” 45 CFR 46.409 (a), 21 CFR 50.56(a) or
(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.” 45 CFR 46.409 (a), 21 CFR 50.56(a)

If the research involving wards falls into one of the above categories, appointment of an advocate is also required.

“If the research [clinical investigation] is approved under paragraph (a) of this section, the IRB shall [must] require appointment of an advocate for each child who is a ward, [(1) The advocate will serve] in addition to any other individual acting on behalf of the child as guardian or in loco parentis. [2] One individual may serve as advocate for more than one child. [3] The advocate shall [must] 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 [clinical investigation] and [The advocate must not be] who is not associated in any way (except in the role as advocate or member of the IRB) with the research [clinical investigation], the investigator(s), or the guardian organization.” 45 CFR 46.409 (b), 21 CFR 50.56(b) [FDA]

Review and Documentation
Review and approval of research involving children follows the procedures as required by the level of review. See HRPP Manual 8-2 “Expedited Review Procedure” and/or 8-3 “Full Board Review Procedure” for policies and procedures on review and documentation required for research involving children.

Additional Considerations
For research studies subject to the requirements of the U.S. Department of Education and the U.S. Environmental Protection Agency, see the following sections of the HRPP Manual:
2-2-B U.S. Environmental Protection Agency
2-2-D U.S. Department of Education