

# Human Research Protection Program Policies & Procedures



## Children as Research Subjects

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### Background:

Children are considered a vulnerable research population and, as such, require additional protections when they are potential research subjects. DHHS and FDA regulations at 45 CFR 46 Subpart D and 21 CFR 50 Subpart D codify safeguards for children as research subjects and requires IRB review in accord with the provisions of Subparts D. The regulations defer to state law regarding the age at which minors may consent to research. In Oregon, a person under 18 years old is considered a “minor” and may not legally give consent, although for medical care and certain other treatments, there are certain exceptions for emancipated and self-sufficient minors. Oregon state law is silent regarding minors consenting to their own participation in research.

### Scope:

This P&P covers research that recruits or enrolls individuals under the age of 18. Note: the National Institutes of Health include individuals up to the age of 21 as minors, however by State law and OHSU policy, individuals 15-21 are considered adults for the purposes of medical decision-making.

### Policy:

- I. The OHSU IRB must review research covered by 45 CFR 46, Subpart D and 21 CFR 50, Subpart D and approve only research that satisfies the conditions of all applicable sections.
- II. The IRB will determine that, when Subpart D applies, consent and/or assent must be obtained unless the requirements for waiver and assent are met per §46.408 and/or §46.116.
  - A. The OHSU IRB will apply the State law related to the age at which individuals under the age of 18 may seek care without parental consent. (See section on Oregon State Law below)
    1. In Oregon, the laws generally apply to medical care, substance abuse treatment and reproductive health care.
    2. For research involving activities that are not specifically indicated in the Oregon State laws, individuals under the age of 18 are considered minors.
  - B. When children cannot legally give consent, informed consent must be obtained from parents (“parental permission”), or the legally appointed guardian.
  - C. When, in the judgment of the IRB, the children are capable of providing assent the IRB may determine that assent is required, that adequate provisions are made for soliciting the assent of the children, and whether and how assent must be documented. Generally, children aged 7

to 17 may be asked to give their assent to participation, unless they are legally able to provide consent for themselves.

- III. All studies involving children will receive ward of the state review when wards are likely to be involved or at the request of the research team.
- IV. The IRB will determine the category of review for each study, upon initial review and when modified. The category will be documented in the IRB minutes and on the approval communication.

**Procedures:**

- I. **Proposed research involving children must satisfy requirements per the Common Rule and the additional requirements under Subpart D – Additional Protections for Children Involved as Subjects in Research.** 45 CFR §46.401 through 409 (& FDA 21 CFR 50.50 through 56)
  - A. Subpart D permits the IRB to approve 3 categories of research involving children as research subjects & 1 additional category that requires a special committee review.
  - B. At each review the IRB will make a categorical determination regarding the child category. All exemptions and expedited reviews are §46.404 – qualify as no greater than minimal risk.
  - C. **The categories are as follows:**
    - 1. **45 CFR §46.404 (21 CFR §50.51) Research not involving greater than minimal risk.** To approve this category of research, the OHSU IRB must make the following determinations:
      - a. the research presents no greater than minimal risk to children; and
      - b. adequate provisions must be made for soliciting the assent of the children and the permission of their parents or guardians per 45 CFR §46.408.
    - 2. **45 CFR §46.405 (21 CFR §50.52) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects.** To approve research in this category, the IRB must make the following determinations:
      - a. risk is justified by the anticipated benefits to the subjects;
      - b. the relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches; and
      - c. adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in DHHS regulations at 45 CFR 46.408.
    - 3. **45 CFR §46.406 (21 CFR §50.53) Research involving greater than minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.** To approve research in this category, the IRB must make the following determinations:
      - a. the risk of the research represents a minor increase over minimal risk;
      - b. the intervention or procedure presents experiences to the child 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 subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition; and
  - d. adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in the DHHS regulations 45 CFR 46.408.
4. **45 CFR §46.407 (21 CFR §50.54) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.** This fourth category of research requires a special level of governmental review beyond that provided by the IRB. If the IRB believes that the research does not meet the requirements of 45 CFR 46.404, 405 or 406 (or the corresponding FDA protections), but finds that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, it may refer the protocol to DHHS or FDA for "407 or 54 review". The research may proceed to the Secretary of DHHS after consulting with a panel of experts and following an opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 405, or 406; or (2) that the research satisfies the following:
- a. the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
  - b. the research will be conducted in accordance with sound ethical principles; and
  - c. adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in DHHS regulations at 45 CFR 46.408.
5. **Research that is not federally funded but meets the requirements for §46.407 Panel Review.**
- a. The review will be sent the study for review by the appropriate federal agency, or
  - b. The OHSU IRB will convene a local 407 panel for review, or
  - c. The review will be sent to another ethical review body established for child review.

## II. CF. 45 CFR §46.409 Requirements for Child Wards in Research

- A. Children who are wards of the State (agency or institution) can be included in research under §46.406 or 407 only if the research is:
  - 1. Related to their status as wards; 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)(1)&(2).
- B. Special protections for wards apply to two categories of research:
  - 1. If the research involves greater than minimal risk and has no prospect of direct benefit to the individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition per §46.406; or

2. research is not otherwise approvable but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children per §46.407.
- C. Investigators must make provisions for a child advocate for each child who is a ward of the state per §46.409. The advocate must be appointed for each child in addition to any other individual acting on behalf of the child as a guardian or in loco parentis. Whenever institutionalized children might be involved in research, care should be taken to ensure that they are not included simply because of their availability.

**III. FDA Requirements** Generally, FDA's regulations parallel those requirements in the Common Rule Subpart D. To determine whether the FDA's regulations apply to the proposed research see 21 CFR 50.1 Scope. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.1>

- A. If the IRB determines that FDA regulations apply to the proposed research study and the IRB determines that the clinical investigation does not meet the requirements parallel to §§46.404, 405, or 406 it may proceed only if through an FDA Panel process which parallels that of the 407 Panel review process.
- B. FDA & OHRP Joint Review Process: The process for IRB referrals of proposed clinical investigations that are both DHHS-conducted or supported and FDA-regulated will function in essentially the same manner as the process for FDA-only referrals. The FDA's Subcommittee will make its recommendations to both the Secretary of DHHS and the Commissioner of FDA.

**IV. §46.408 Requirements for Consent and Assent.** [See additional information in OHSU policy on consent to research.]

- A. **Documentation.** Permission by parents or guardians shall be documented per 46.117 and when the IRB determines that assent is required, it shall also determine whether and how assent must be documented. 45 CFR 46.408(d) & (e).
- B. **Parent/Guardian Consent.** Permission from parent(s) or guardian(s) must be obtained prior to enrolling a child in research. The IRB may determine that parental consent is not required if the child is not considered a minor under State law (see IV.C below). Since this is a vulnerable population, justification must be provided for not seeking consent of the parents. Parental consent typically involves a discussion that covers all of the elements of informed consent and having the parent(s) or guardian sign an informed consent document that looks like the typical adult research consent document, except that the document is not directed to the parent as a participant in research. This permission must meet the requirements for informed consent found in 46.116 (See policy on elements of consent).
  1. The permission of one parent may be sufficient for research to be conducted under 46.404 or 46.405.
  2. Where research is covered by 46.406 and 46.407 and permission is to be obtained by parents, both parents must give their permission unless:
    - a. One parent is deceased, unknown, incompetent, or not reasonably available; or
    - b. Only one parent has legal responsibility for the care and custody of the child. (46.408(b))

- C. **Consent of Minors:** Under Oregon law, minors may consent to participation in research without parental or guardian permission (i.e., as if adults) if legally emancipated and in certain treatment circumstances.
1. **Any Type of Research:** OHSU interprets laws regarding emancipated minors and married minors as authorizing a minor to consent to research as an adult does. This applies for any type of research.
    - a. **Emancipates Minors:** Parental consent is not necessary if the minor is emancipated. ORS.419B.558. Proof of entry of Judgment of Emancipation is required.
    - b. **Married Minors:** Per ORS 109.520, all persons shall be deemed to have arrived at the age of majority upon their being married and thus parental consent is not necessary when the minor is married. Proof of marriage is required.
  2. **Research Involving treatment:** Oregon law does specify the age at which individuals under age 18 may seek medical care without parental consent. OHSU interprets these laws as authorizing certain minors to consent to research involving specific types of medical treatment. The allowances are as follows:
    - a. **General Medical, Dental & Prenatal Care:** People 15 years of age or older may give consent to hospital care, medical or surgical diagnosis or treatment by a physician dentist, or nurse practitioner without the consent of a parent or guardian. (ORS 109.640). This includes prenatal care. A plan for parental involvement for the treatment must be included, unless there are clinical or legal reasons not to involve the parents. These reasons may be study-specific or subject-specific. The IRB will determine whether such reasons exist due to the nature of a particular study. Subject-specific determinations should be made by study staff at the time of consent.
    - b. **Mental Health and Chemical Dependency:** People 14 years or older may consent for outpatient diagnosis or treatment of mental or emotional disorder or chemical dependency, excluding methadone maintenance, by physician, psychologist, nurse practitioner, social worker or community health worker. (ORS 109.675) A plan for parental involvement for the treatment must be included, unless there are clinical or legal reasons not to involve the parents. These reasons may be study-specific or subject-specific. The IRB will determine whether such reasons exist due to the nature of a particular study. Subject-specific determinations should be made by study staff at the time of consent.
    - c. **Sexually Transmitted Infections:** People of any age may consent to the provision of hospital, medical or surgical care related to the diagnosis or treatment of a venereal disease. Public health reporting requirements apply and the participant must be informed of these. (ORS 109.610)
  3. **Birth Control:** People of any age may consent to obtaining birth control information and services. A physician or nurse practitioner may provide birth control information and services to any person without regard to age (ORS 109.610 and 109.640)**Parental Notification** – Oregon allows for disclosure to the parents of the non-emancipated minor’s consent in cases of mental health or chemical dependency treatment and general medical and dental care. If parents are going to be advised on the child’s consent to care, then the plan must be described in the protocol and addressed in the consent form.

- D. Assent of the Child:** The IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of assenting. See 45 CFR 46.408; 21 CFR 50.55. See policy on “Obtaining Assent from Children for Research Participation”
- E. Waiver of Consent.** The requirement for permission from parent(s) or guardian(s) or consent of a legally consenting minor may be waived if:
- a. The provisions for a waiver of some or all of the elements of informed consent in 46.116 are met (See policy on consent); OR
  - b. A research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) and an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted. The choice of an appropriate mechanism depends upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status and condition. 46.408(c). AND
  - c. The waiver is not inconsistent with Federal, State or local law.
- F. Assent Not Required Or Waived.** An investigator may request that the IRB not require assent in one or more of the following three circumstances, including FDA regulated protocols:
- a. The IRB determines that the children are not capable of assenting, after taking into account the ages, maturity, and psychological state of the children involved, either for all the children or for each child.
  - b. The IRB determines that the intervention or procedure involved in the research holds 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 research.
  - c. Even if the IRB determines that assent is appropriate, it may waive the requirement if the customary conditions for waiver or alteration of consent are satisfied (45 CFR 116 or 21 CFR 50.55(d)).
- G. Minors and Pregnancy:**
1. Research conducted on minors where they will be tested for pregnancy must inform subjects who are younger than 15 that if they are found to be pregnant, their parents will be told so that they can access prenatal care. (ORS 109.650)
  2. The following statement should be included in consent forms for such studies: *“Parents or guardians of a child participating in this study will be told the results of the child’s pregnancy test if the child is younger than 15. If the child is 15 or older the pregnancy test result will be released to the child. It will be up to her whether or not it is released to the parent or guardian. However, if the investigator believes that the child is not receiving adequate medical care for the pregnancy, he will refer the subject to a place where she can get the proper care.”* This statement may be omitted with approval of the IRB when this situation is unlikely to occur and the nature of the research warrants discretion.
- H. Children who reach Age of Majority During Research Trials**
1. Studies that include children who might reach the age of majority during the course of the study (including long-term follow up) should also submit an “Age of Majority Short

Form”, This consent should be offered to subjects upon reaching the Age of Majority and should include relevant details about their ongoing participation in the trial.

2. Studies that are closed to enrollment when subjects reach the Age of Majority should not re-open to enrollment, but rather simply obtain consent from the subjects as part of their ongoing treatment and/or follow-up.

## **Definitions**

### **DHHS Definitions:**

1. Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under state law. 45 CFR §46.402(a).
2. Assent means a child’s affirmative agreement to participate in research. 45 CFR §46.402(b).
3. Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research. 45 CFR §46.402(c).
4. Parent means a child’s biological or adoptive parent. 45 CFR §46.402(d).
5. Guardian means 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).
6. Minimal Risk – A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed 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. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination. IRB Guidebook, Chapter VI, Special Classes of Subjects.

### **FDA Definitions per 21 CFR 50.3.**

1. Ward means a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.
2. Clinical Investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA. It does not include experiments that are subject to the provisions of part 58 of this chapter, regarding non-clinical laboratory studies.
3. Test Article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, or electronic product.
4. Permission means the agreement of parent(s) or guardian to the participation of their child or ward in clinical investigation. Permission must be obtained in compliance with 21 CFR 50, Subpart B, and must include the elements of informed consent per §50.25.

5. Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. Here, a Guardian also means an individual who is authorized to consent on behalf of a child to participate in research.

**Oregon State Law:**

See Age of majority [http://www.oregon.gov/BCSW/pdfs/Age\\_Of\\_Majority.pdf](http://www.oregon.gov/BCSW/pdfs/Age_Of_Majority.pdf)

1. A minor 15 years of age or older may give consent to hospital care, medical or surgical diagnosis or treatment by a physician licensed by the Board of Medical Examiners for the State of Oregon, and dental or surgical diagnosis or treatment by a dentist licensed by the Oregon Board of Dentistry, without the consent of a parent or guardian, except as may be provided by ORS 109.660.
2. A minor 15 years of age or older may give consent to diagnosis and treatment by a nurse practitioner who is licensed by the Oregon State Board of Nursing under ORS 678.375 and who is acting within the scope of practice for a nurse practitioner, without the consent of a parent or guardian of the minor. ORS 109.640.
3. Any physician or nurse practitioner may provide birth control information and services to any person without regard to the age of the person. ORS 109.640.
4. A minor 14 yrs or older may obtain, without parental knowledge or consent, outpatient diagnosis or treatment of mental or emotional disorder or chemical dependency, excluding methadone maintenance, by physician, psychologist, nurse practitioner, social worker or community health worker. ORS 109.675.
5. Disclosure to minor patient's parents without minor's consent - A hospital or any physician, nurse practitioner or dentist as described in ORS 109.640 may advise the parent or parents or legal guardian of any minor of the care, diagnosis or treatment or the need for any treatment, without the consent of the patient, and any hospital, physician, nurse practitioner or dentist is not liable for advising the parent, parents or legal guardian without the consent of the patient. ORS 109.650.
6. Emancipation – the juvenile court may enter judgment of emancipation where the minor is at least 16 years of age .... ORS 419B.558.
7. Minor means any person who has not attained 18 yrs of age. ORS 125.005(6).
8. Age of Majority at the age of 18 yrs, ORS 109.510; or all persons shall be deemed to have arrived at the age of majority upon their being married according to law. ORS 109.520.
9. Guardian means a legal guardian, person appointed by a court of law to act as guardian of a minor or a legally incapacitated person. Oregon Administrative Rule (OAR) 309-114-0005(4).

**Authority**

- I. This procedural requirement is required by 45 CFR §46 Subpart D.

- II. Safeguards for Children in Clinical Investigations per 21 CFR §50 – identical to 45 CFR §46 Subpart D – except “clinical investigations” replaces the term “research”.
- III. Requirements by ORS 109.610 through 672 –Oregon laws articulating the rights of minors to consent to medical treatment rather than consent to research.
- IV. Additional ED Protections for Children in Research per 34 CFR §97 – which parallels the 45 CFR §46 Subpart D & applies to all research involving children as subjects conducted or supported by the Department of Education.
- V. Children’s Health Act of 2000: “On October 17, 2000, the Children’s Health Act of 2000 (P.L.106-310) was enacted, amending the Public Health Service Act. The Act contains provisions to address a number of issues related to children’s health, including vaccine injury, organ transplantation, pregnant mothers and infants, newborn and infant hearing screening, and pediatric research. Section 1003 directs the Secretary of Health and Human Services (DHHS) to conduct a review of the regulations under 45 CFR Part 46, Subpart D - Additional DHHS Protections for Children Involved as Subjects in Research, within 6 months of the Act’s enactment. That evaluation should consider if any modifications are necessary to ensure the adequate and appropriate protection of children participating in research and its findings reported to Congress by April 17, 2001.” *See Children’s Health Act of 2000, Report to Congress 5/01, pg 1, Purpose.*
- VI. Protection of Pupil Rights Amendment (PPRA) “applies to programs that receive funding from the U.S. Department of Education (ED). PPRA is intended to protect the rights of parents and students in two ways:
  - A. It seeks to ensure that schools and contractors make instructional materials available for inspection by parents if those materials will be used in connection with an ED-funded survey, analysis, or evaluation in which their children participate; and
  - B. It seeks to ensure that schools and contractors obtain written parental consent before minor students are required to participate in any ED-funded survey, analysis, or evaluation....” 34 CFR Part 98.
- VII. Family Educational Rights and Privacy Act Regulations (FERPA) protects student’s privacy for educational records. Such records cannot generally be released or accessed without parental consent. It applies to all educational institutions that receive funding from the Federal Department of Education. 34 CFR Part 99.

## References & Additional Information

**Report to National Human Research Protections Advisory Committee (NHRPAC) from the Children’s Workgroup, circa 2002:** OHSU has not adopted this view, but refers to this recommendation as guidance in the categorization of research of “minor increase over minimal risk” per 45 CFR §46.406.

1. Minor Increase Over Minimal Risk means risks that are a little more than minimal and pose no significant threat to the child’s health or well-being; and are commensurate with the risks of interventions or procedures having been experienced or expected to be experienced in the lives of specific children with a specific disorder or condition. The fact that children may experience invasive procedures with considerable risk and discomfort during the care and

treatment of a disease does not justify risks greater than a minor increase over minimal in a research study that provides no prospect of direct benefit to the individual subjects

- **Examples of minor risks:** taking a history; psychological testing; classroom observation; blood or saliva collection; vision or hearing testing; and X-ray studies.
  - **Examples of minor increase over minimal risks:** urine collection via catheter; lumbar punctures; biopsies and bone marrow aspirates.
  - **Examples of more than minor increase over minimal risks:** urine collection via suprapubic tap and organ biopsies.
  - **Procedures whose level of risk may range depending on variables such as age of subject; substance injected; prior experience of subject (for purpose of determining assent/permission; length of procedure time; sedation required or not; nature of psychological questions:** indwelling catheters; SC or IM injection; NG tube insertion; MRI; psychological interview or observations.
  - For specific guidance see NHRPAC's Report, Tables 1-2 & Examples 1-4.  
<http://www.hhs.gov/ohrp/nhrpac/documents/nhrpac16.pdf>
2. Condition means situations that may jeopardize the health of children, interfere with optimal development, or adversely affect well-being in later years.
  3. Disorder or Condition - refers to a characteristic of the group of potential research subjects, and implies that this characteristic can be understood more broadly than simply a specific disease or diagnostic category. We interpret the concept of disorder or condition as relating to a specific characteristic which describes a group of children, a physical, social, psychological, or neuro-developmental condition affecting children, or the risk of certain children developing a disease in the future based on diagnostic testing or physical examination. **Examples:** prematurity, infancy, adolescence, poverty, living in a compromised physical environment, institutionalization, or having a genetic predisposition to future illness are some of the disorders or conditions of children that can, under the appropriate circumstances, warrant permissible research that presents levels of risk that are a minor increase over minimal without the prospect of direct benefit. Obesity can be considered a condition that warrants study because of its association with development of Type II DM and other serious diseases.
  4. Prospect of direct benefit is not defined in the regulations. Direct benefit is usually considered to be medical/psychological benefits from research procedures only. Payments for participation in research or added psychological or medical interventions should not be considered a benefit.