Public Health Division
Children Participation in Research

When a proposed research project includes children, regardless of the funding, the Public Health IRB (PH IRB) elects to apply 45 CFR 46 Subpart D, "Additional Protections for Children Involved as Subjects in Research". **By regulatory definition, 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 in which the research will be conducted.** Generally, the federal law considers any person under 18 years of age to be a child. However, the age of consent for most medical procedures in Oregon is 15. ORS Chapter 109 Rights of Minors at 109.640 – 109.697 should always be referenced.

In accordance with these mandated protections, the PH IRB will take into account the benefits, risks and discomforts, and their probability as it relates to the inclusion of children in the research. To justify their partaking, the circumstances of the children who may be enrolled in the study will be assessed; their health status, age, and ability to understand the context of the research and what exactly their participation will entail. Potential benefits, not only to the participants themselves, but to other children with the same disease or condition and to society as a whole will too be assessed by the PH IRB.

In addition to Full Board and expedited reviews, most of the exemption categories at 45 CFR 46.104(d) may also be applied to research involving children as human subjects in the same way that they apply to research involving adults.

Routes of Review

The PH IRB may approve the study protocol and its inclusion of children in accordance with any of the three following categories:

- **45 CFR 46.404**: Research not involving greater than minimal risk, only if 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 .
- **45 CFR 46.405**: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. The PH IRB may approve such research if it finds:
    a. The risk is justified by the anticipated benefit to the subject;
    b. The relation of risk to the anticipated benefit is at least as favorable as any available alternative approach; 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.
- **45 CFR 46.406:** Research involving 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. The PH IRB may approve such research if it finds:
    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 settings;
    c. The intervention or procedure is likely to yield generalizable knowledge about the participant's disorder or condition which is of vital importance for the understanding or amelioration of the participants' 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.

If the PH IRB believes the proposed research and its inclusion of children does not meet one of the three categories listed above, it may reference 45 CFR 46.407.

- **45 CFR 46.407**: Research not otherwise approvable which presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. The PH IRB may approve such research if it finds:
    a. The research will be conducted in accordance with sound ethical principles; and
    b. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 46.408.

Federally Funded Studies and 407 Consideration

For any non-HHS conducted or supported research, if the PH IRB finds its inclusion of children to be permissible in accordance with 45 CFR 46.407, the research may begin after official PH IRB approval is received. However, in order for the PH IRB to approve HHS-conducted or supported research involving children in accordance with 46.407, additional federal mandated steps must first be taken.

Certification to the HHS Secretary, through OHRP, that the research has been reviewed and meets the criteria of 46.407 must be submitted by the PH IRB for "407 consideration". The Secretary, after consultation with a panel of experts in pertinent disciplines and following opportunity for public review and comment, will make a decision. More information can be found in the OHRP *Children as Research Subjects and the HHS "407" Process* guidance document.

In all cases, OHRP will confer with the FDA to determine if FDA regulations under 21 CFR 50.54 also apply. In cases where FDA regulations do apply, OHRP has delegated its authority to FDA to convene a panel of experts to both review the research and to advise the Secretary.

Informed Consent Process

In pediatric research, the informed consent process includes two elements: parental or guardian permission and child assent, where "assent" means a child's affirmative agreement to participate in research and *not* their mere failure to object. In all cases where required, the PH IRB must determine that adequate provisions have been made for soliciting the assent of children and the permission of their parent(s) or guardian(s). As Oregon state law is silent on this issue in regard to human subject's research, as stated above, the Public Health Division may extrapolate from state law regarding the age of minor consent for care without parental consent. ORS 109.640 and ORS 109.675 specifically, will be referenced. The PH IRB may allow children at least 15 years of age (14 for mental healthcare related research) to consent to research for themselves, without parental consent if:

- There is the potential of direct benefit to the child;
- Procedures involved in the research are not substantially different in their risks or benefits from existing treatment for which the minor would by state law be able to consent;
- Parental consent is not in the best interest of the child, is extremely difficult to obtain or would not be possible to obtain; and
- The research otherwise meets the federal requirements for research with children.

In all other cases, the PH IRB will determine whether the children to be enrolled in the study are capable of giving assent to participate by keeping their age, maturity, condition, and psychological state in mind. The PH IRB will also determine how assent must be documented, considering factors such as literacy and mental development. As a general rule, children seven years of age or older are considered capable of giving assent. The following guidelines are suggested:

- Age 7 - 9: A simple oral description of the child's involvement is given to the participant and verbal assent requested. The procedure may be documented on the informed consent form by the presence of the signature of a witness.

- Age 10 - 17: A more complete oral description of the research is given to the participant, along with written assent using age-appropriate terminology.

As in any consent process, the primary concern is that the participant is able to understand the explanation that is presented. A minor's dissent to participate in or withdraw from the research should be respected and honored unless the research provides access to a therapeutic intervention that is not otherwise available.

When parental/guardian permission is sought, the PH IRB will determine whether permission of one or both is necessary. If the research involves greater than minimal risk and no prospect of direct benefit to the children who are participants or is not otherwise approvable under the categories listed above, both parents/guardians must give their permission unless one is deceased, unknown, incompetent or not reasonably available, or when only one has legal responsibility for the care and custody of the child.

Mandatory Reporting

Even if a minor provides information in confidence, appropriate authorities must be notified if there are health or safety concerns regarding a minor child or vulnerable adult. Such concerns include disclosure of abuse, neglect, or imminent harm to the minor or another person. Certain health and social service professionals in Oregon are legally required to report these types of health and safety concerns, including all state employees. If children and/or vulnerable adults are to be included in a research project, all informed consent forms must include Mandatory Reporting language notifying them of this possibility.

Waiver of Informed Consent and Assent

Even where the PH IRB determines that the subjects are capable of assenting, a waiver of assent may be granted under the same circumstances in which consent may be waived in accordance with 46.116 of Subpart A. Further, the requirement for parental/guardian permission described in 46.116 and 46.408(b) may too be waived if:

- The provisions for a waiver of some or all of the elements of informed consent in 46.116 are met; **or**
- 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);

- An appropriate mechanism for protecting the children who will participate as subjects in the research is substituted. This mechanism dependent upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the subjects, and the subjects age, maturity, status, and condition; **and**
- The waiver is not inconsistent with Federal, State or local law.

The most frequent example for which such waivers would be granted is for studies limited to retrospective review of existing medical records.

Parental/guardian permission is not considered necessary if the minor is married as per Oregon law they are deemed to have arrived at the age of majority (ORS 109.520) nor if the minor is emancipated (ORS 419B.558).

Pregnant Minors

ORS 109.640 sets the age of consent without parental/guardian permission for medical care, including family planning and sexual and reproductive health, at 15 years. Therefore, if a minor-subject participates in a research project in which they will be tested for pregnancy, if younger than 15, they must be informed prior to participation that if positive, their parents will be told of the result so they can access prenatal care.

Minors as Prisoners

When a minor is also considered a prisoner, 45 CFR 46, Subpart C, "Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects" and the Public Health Division Policy on Prisoners in Research will also be applied. Juvenile prisoners are an especially vulnerable population and must be afforded additional protections. Due to their confinement, juvenile prisoners may be exploited as research participants because of their ready availability, dependent status, and possible diminished capacity to consent. As such, the PH IRB will consider this type of research on a case-by-case basis. A clear rationale for conducting this type of research must be included in any application material sent to the PH IRB.

Wards

Wards of the state may participate in research if the research:

- involves no more than minimal risk; or
- presents greater than minimal risk but presents the prospect of direct benefit to the participant on the same basis as it would other minors.

Just as with all minors, children who are wards of the state may participate in research with greater than minimal risk not offering the prospect of direct benefit but holding the likelihood of producing generalizable knowledge about the subject's disorder or condition. However, there are special stipulations with a wards participation. They may participate in research approved under 46.406 or 46.407 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 subjects are not wards.

For greater than minimal risk research meeting the latter two categories of admissible research including wards of the state, the PH IRB will require appointment of an advocate for each child, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. The advocate shall be someone who has the background and experience to act in, and agrees to act in, the best interest 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, or the guardian organization.

Applicable Regulations:
45 CFR 46, Subpart D
21 CFR 50, Subpart D
ORS Chapter 109