CHAPTER 15

IRB Review of Research Involving Children

DHHS regulations 45 CFR Part 46, Subpart D and FDA Regulations are 21 CFR 40 Subpart D require special protections for research involving children. Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted.

The significant issues for the IRB to consider when reviewing research involving children include:

- *The risk / benefit analysis to determine compliance with permitted regulatory categories*
- *Consideration of Assent requirements and,*
- *Required parental consent based on the nature and risk of the proposed research*

Definitions:

- **Assent**: an affirmative agreement to participate in a clinical investigation. Failure to object should not, absent affirmative agreement, be construed as assent.
- **Children:** Persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigation under the applicable law of jurisdiction in which the research will be conducted.
- **Parent**: A child's biological or adoptive parent.
- Ward: 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.
- **Guardian:** Individual who is authorized under applicable state or local law to consent on behalf of a child to medical care. [legally authorized representative]

1. **Risk – Benefit Analysis and Subpart D Requirements**

    a. The IRB will make the specific findings and determinations required under federal regulations when reviewing research involving children. IRB records will reflect the IRB's understand and justification for the risk and benefits posed by the approved research involving children.
    b. Based in part on the IRB's risk/ benefit analysis, the IRB must find that the proposed research falls within one of the following four categories:
        i. Research not involving greater than minimal risk,
        ii. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants.,
        iii. Research involving greater than minimal risk and no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participants' disorder or condition, and
        iv. Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health and welfare of children.
    c. Each category stipulated specific criteria that must be found satisfied before the proposed research can be approved. As needed the IRB will utilize the resources provide by identified or ad hoc consultants in these reviews.

2. **Reasonable Expectation of Benefit**

    The IRB requires strong justification for the involvement of children in greater that minimal risk research that holds out little reasonable prospect of direct therapeutic benefit to the individual child. The

assessment of and strength of the child's assent or dissent will be given serious consideration of greater weight as the child more closely approaches the age of majority.

3. Consent Requirements for Research Involving Children

a. Not Greater than Minimal Risk
    i. Assent of the child and permission of at least on parent / legally authorized representative.
b. Greater than Minimal Risk and Prospect of Direct Benefit to the Individual Subjects
    i. Assent of child and permission of at least one parent / legally authorized representative,
    ii. Anticipated benefit justifies the risk, and
    iii. Anticipated benefit is at least as favorable as that of the alternative approached to treatment.
c. Greater than Minimal Risk with no Prospect of Direct Benefit to the Individual Subject, but likely to Yield Generalizable knowledge about the Subject Disorder or Condition.
    i. Assent of child and permission of both parents / legally authorized representative,
    ii. The risk represents a minor increase over minimal risk. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical or education interventions.
    iii. The intervention is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition.
d. Not Otherwise Approvable but Presenting an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting Children.
    i. Assent of Child and permission of both parents/ legally authorized representative.
    ii. IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
    iii. The DHHS Secretary or the FDA Commissioner approves, after consultation with a panel of experts in pertinent disciplines and following public comment.

4. Assent of the Child

a. DHHS regulations at 45CFR 46.408 (a) and FDA regulations at 21CFR 50.55 require that the IRB take the following specific actions concerning the assent of child participants:
    i. The IRB must determine that adequate provisions are made for soliciting assent of the child when, in judgement of the IRB, the child is capable of providing assent.
    ii. In determining when children are capable of providing assent, the IRB must take into account the ages, maturity, psychological state of the children involved and, relying on the determination of the investigator conducting the consent/ assent process, as well as the actual cognitive ability of the child to effectively participate in and understand this process.
    iii. The assent of the child is not necessary if the IRB or the consenting investigator determines that the capability of the child is so limited that they cannot be reasonably consulted.
    iv. The assent of the child is not necessary if the IRB determines that the research holds out the prospect of direct benefit that is only available in the context of the research.
    v. The IRB may waive assent if:
        - The research is no more than minimal risk to subjects
        - The waiver will not adversely affect subjects' rights and welfare
        - The research could not practicably b carried out with out the waiver,
        - Where appropriate, subject will be provided with pertinent information after participation, for example in social and behavioral research where mild deception is involved.
    vi. The IRB must determine whether and how assent must be documented.

- The IRB will determine and document that assent is a requirement of all, some, or none of the children in a study, or consideration of the capacity of the child by the consenting investigator. The IRB will document the rationale for this determination in meeting minutes.
- Documentation of assent may vary depending on the child's level of cognitive and emotional maturity. The IRB will also make recommendations regarding the mode of documentation.

5. Parental / Legally Authorized Representative Permission

a. In accordance with DHHS and FDA requirements, the IRB will determine that adequate provision have been made for obtaining and documenting parental / legally authorized representative permission for the participation of children in research.
b. In the absence of the child's parents, permission for the involvement of the child in research may be obtained from the child's legal guardian(s) or others to the extent authorized under the laws of the state in which the research takes place.

6. Legal Capacity of Minors to Consent for Health Services, Procedures and Research: Waiver of Parental Content

South Carolina Code of Laws – Title 63-Chapter 5 -Legal Status of Children, defines the conditions for waiver of parental consent. The circumstances that allow this waiver are limited. If there is consideration of requesting such a waiver, the investigator must consult with the HRPP office. The HRPP office on consultation with Prisma Health General Council will provide a final determination to the request.

7. Re-Consent at Age of Majority

Unless the Institutional Review Board (IRB) determines that the requirements for obtaining informed consent can be waived, the investigators should seek and obtain the legally effective informed consent, as described in 45 CFR 46.116, for the now-adult subject for any ongoing interactions or interventions with the subjects. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject. However, the IRB could approve a waiver of informed consent under 45 CFR 46.116(d), if the IRB finds and documents that the required conditions are met.

Similarly, if the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of "human subjects research" (for example, it involves the continued analysis of specimens or data for which the subject's identity is readily identifiable to the investigator(s)), then it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects. The IRB may consider, if appropriate, a waiver under 45 CFR 46.116(d) of the requirements for obtaining informed consent in order for the subjects to continue their participation in the research. In this case the Age of Majority Addendum can be utilize for consent for continued participation in protocol follow up activities without any clinical intervention.

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/children-research/index.html