IRB Tip Sheet: Inclusion of Children in Clinical Research

Regulatory Definition of Children

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

Levels of Risk

When reviewing research that enrolls children, the IRB must apply the additional protections that are specified in 45 CFR part 46, Subpart D: Additional Protections for Children Involved as Subjects in Research. These additional requirements place limitations on the approvability of research procedures and interventions beyond those applied to adults.

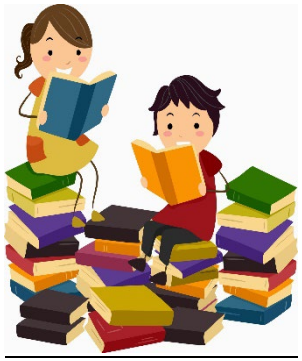
- The justification of the inclusion of children should be included in the written protocol.
- The IRB must consider the potential benefits, risks, and discomforts of the research to children and assess the justification for their inclusion in the research.
- If procedures are not described in a way that allows the risk level to be assessed, then the IRB can request further information be added to the protocol.
- Importantly, the benefit assigned to a procedure or intervention, must be a result of that same procedure. The risk of one procedure cannot be balanced by the benefit of a separate unrelated procedure or intervention.
- If both unaffected and affected children are to be enrolled, the protocol should clearly delineate which procedures will be done on each population.
- **All categories of research with children require that adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians unless this requirement is waived by the IRB.**

Permission – Assent – Waivers

Subpart D allows for various conditions and waivers by the IRB of parental/guardian permission and child assent, depending on the nature of the research activity and the maturity of the child.

Parental / Guardian Permission
Permission is the agreement of parent(s) or guardian to the participation of their child or ward in research. Signature requirements: ▪ **One parent signature:** Sufficient for research to be conducted under §46.404 or §46.405. ▪ **Two parents' signatures:** Required for research to be conducted under §46.406 or §46.407 unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. Of note, if the research contains **any** procedures determined by the IRB to be greater than minimal risk without a prospect of direct benefit, the IRB must require 2 parent signatures. This is true even if the same study includes interventions that have a prospect of direct benefit. ▪ **Wards of the State or other institutes:** Special requirements under §46.409 for participating in research under §46.406 or §46.407 include limits to types of research performed and the appointment of an advocate to act in the child's best interest.
Assent of the Child
Assent is a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. ▪ In the protocol, the PI should propose at what age a child is capable of providing assent. How assent is obtained should be based on the type and complexity of the research, and the population being enrolled. Children too young to assent should still have the research explained to them in terms appropriate to their level of understanding and maturity. ▪ The complete plan for obtaining written/verbal assent needs to be included in the protocol for IRB review/approval.
Waivers Specific to Children
The IRB requires child assent unless it can be appropriately waived, or if the child is not capable of providing assent. If an investigator wishes for the IRB to waive assent for some or all of the participants, this should be described in the protocol and the conditions under which the waiver will apply. ▪ Circumstances where assent can be waived: o if the capability of some or all of the children is so limited that they cannot reasonably be consulted. o if the intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research. o if the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults. Parental Permission may be waived if permission is not a reasonable requirement to protect the child such as with neglected or abused children. An appropriate substitute mechanism must be identified, such as a child advocate or an assent monitor.

Levels of Risk in 45 CFR part 46, Subpart D: Additional Protections for Children Involved as Subjects in Research

§46.404 Research not involving greater than minimal risk	• **Minimal Risk** means that the probability and magnitude of harm or discomfort anticipated in the 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 • *Examples of Minimal Risk Activities:* Physical assessment, small volume routine venipuncture for blood collection, non-invasive specimen collection (urine, saliva, hair, etc.), non-contrast MRI without sedation, a single skin biopsy of < 3mm • The regulations only permit healthy children to participate when research involves no greater than minimal risk
§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects	• The IRB must find that the protocol meets the following points: ○ The risk is justified by the anticipated benefit to the subjects ○ The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches
§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 IRB must find that the protocol meets the following points: ○ The risk represents a minor increase over minimal risk ▪ *A **minor increase over minimal risk** is a procedure which the risks or discomforts are temporary and not severe. Examples of this include an MRI with contrast, a CT scan, a biopsy of a superficial lymph node* ○ 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 ○ 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
§46.407 Research 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 does not believe that a proposed research activity fits any of the three categories, but that it does present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB may forward that proposed activity to the Secretary of HHS for review under conditions identified in section 407 of the regulations. • The following conditions must be met: ○ The 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 ○ The Secretary of HHS, 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 determined that a certain group of conditions are met. Details of this process are available in the OHRP Guidance: Children as Research Subjects and the HHS "407" Process

Additional Resources - OHRP Guidance: Information on Special Protections for Children as Research Subjects and OHRP Research with Children FAQs