GUIDELINE FOR ENROLLING CHILDREN AS PARTICIPANTS IN RESEARCH

Children are a special population and research involving children is subject to additional regulatory requirements at 45 CFR 46 Subpart D.

If you will enroll children as a population to enroll in your study, then these regulations apply to your protocol.

Start by reviewing the OHRP Research with Children FAQs and Policy 402.

What is a child?

"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 (45 CFR 46.402(a)).

For research conducted at an NIH site, an adult is anyone 18 years or older, unless the child is legally emancipated. For research conducted at NIH sites the determination of whether a child is legally emancipated must be in conjunction with the Office of General Counsel. Please consult with OHSRP prior to enrolling a minor that you think may be legally emancipated.

What about state law?

In the United States the legal age of adulthood is a matter of state and local law. This means that who is legally considered a child may vary from state to state; in a large majority of states eighteen years of age is the legal age of adulthood, but this is not true in every state, locality, or territory. Also, there may be exceptions to who is considered a child and additional laws in places that define emancipated minors. The definition of "children" also takes into account the particular treatments or procedures involved in the proposed research; for example, in some places individuals who are sixteen years of age may legally consent to certain medical treatments, and so if the involvement of human subjects in a proposed research activity consists of these treatments, then they may be considered as adults for that purpose. If a proposed activity includes something for which the subject has not yet reached the legal age of consent, however, that person must be considered a child. Please consult with OHSRP prior to enrolling a "child" as an "adult" based upon the consideration that they may be able to provide consent for clinical purposes.

What is minimal risk for research with children?

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. 45 CFR 46.102(i) (pre-2018 Common Rule), 45 CFR 46.102(j) (2018 Common Rule) and 21 CFR 50.3(k) (FDA regulations).

What does this mean for my protocol?

When reviewing research that enrolls children, the IRB must apply the additional protections that are specified in 45 CFR 46 Subpart D. These additional requirements place limitations on the approvability of research procedures and interventions that are over and above those that are applied to adults. These limitations depend on the following:

- whether or not the minor is healthy or affected with the disease or condition under study,
- whether the research procedure is minimal risk or greater than minimal risk

- whether the research procedure offers the prospect of direct benefit to the minor.

The IRB reviewers must be able to clearly understand what procedures are being done on each population being enrolled. Therefore, the protocol must clearly describe what procedures will be performed on children. If both unaffected and affected children are to be enrolled, the protocol should clearly delineate which procedures will be done on each population. Providing this in a table format may facilitate review.

In writing a protocol that includes children, it is important to understand the distinctions below and to provide sufficient information to the IRB that addresses the points discussed below, so that the IRB can assess whether the research is approvable.

Unaffected children

The regulations permit *only minimal risk interventions* be conducted on healthy children. Thus, when enrolling siblings of minor probands as controls, for example, no research procedures may be performed that are considered by the IRB to be greater than minimal risk. Examples of minimal risk procedures include 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. Please contact the IRB Office if you want consultation on whether a specific research procedure is minimal risk.

Affected children

Children that are affected by, or at risk for, the disease or condition under study may undergo research procedures that are minimal risk or greater than minimal risk, with some limitations based upon whether the procedure(s) offers the subject the prospect of direct benefit.

Research procedures that are greater than minimal risk with a prospect of direct benefit

If the research procedure offers the prospect of direct benefit to the research subject, then it is permissible for the IRB to approve that procedure if the following additional conditions are met:

- 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; and
- Parental consent and assent of the minor is obtained.

Direct benefit is a tangible positive outcome that may be experienced by the subject and is a result of the research intervention or procedure. In studies of a new therapy, typically the benefit of the investigational agent is the possible amelioration of the disease or its symptoms. However, in a natural history study, research procedures generally do not have therapeutic intent, and therefore may not offer the prospect of direct benefit to the subject. For example, if the protocol requires a CT scan every 6 months, and the only use of that scan is to collect research endpoint data (e.g., size of a lesion etc.), then the scan does not have prospect of direct benefit for the subject. However, if the results of the CT scan are used in a way that is likely to enhance the health and well-being of the subject, for example, by leading to a meaningful change in therapy, then the IRB may consider that procedure as offering the prospect of direct benefit.

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. In the example of the CT scan above, the benefit is the diagnostic

information obtained from the scan. However, if the results of the scan were not used diagnostically, the risk of that scan could not be weighed against some other potentially beneficial procedure in the protocol.

Research procedures that are greater than minimal risk without a prospect of direct benefit

The IRB may only approve a greater than minimal risk procedure that does not offer the prospect of direct benefit, if it finds the following:

- 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, 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; and
- Parental consent and assent of the minor is obtained.

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.

Parental signature requirements

If the research contains interventions that are only minimal risk, or greater than minimal risk with a prospect of direct benefit, the IRB can determine signature from either 1 or 2 parents are sufficient.

However, if the research contains <u>any</u> procedures determined by the IRB to be greater than minimal risk without a prospect of direct benefit, the IRB <u>must</u> require 2 parent signatures. This is true even if the same study contains interventions that have a prospect of direct benefit.

Assent

The IRB expects that the investigator will submit a proposal in the protocol describing which age groups will be able to provide assent, and which will not. This 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.

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. The IRB requires child assent unless it can be appropriately waived, or if the child is not capable of providing assent.

The regulations at 45 CFR 46.408(a) identify three types of circumstances where the IRB may determine that waiver of children's assent is appropriate:

1. if the capability of some or all of the children is so limited that they cannot reasonably be consulted;
2. 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.

3. if the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either 45 CFR 46.116(c) or 45 CFR 46.116(d).

The regulations do not require documentation of assent, so there is no need to request a waiver of documentation of assent. If your plan is to obtain assent remotely or to obtain assent verbally or using an online document, you should describe this plan in your protocol. If you will be using any written materials, you should submit those for IRB review.