For any protocol involving children, the IRB must determine which of the four categories of research apply to that study, if any. OHRP recommends that the IRB document the rationale for this choice.

The HHS regulations at 45 CFR part 46, subpart D permit IRBs to approve three categories of research involving children as subjects:

1. 45 CFR 46.404**- Research not involving greater than minimal risk to the children.**

To approve this category of research, the IRB must make the following determinations:

the research presents no greater than minimal risk to the children; ***and*** adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

2. **45 CFR 46.405- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.**

To approve research in this category, the IRB must make the following determinations:

the risk is justified by the anticipated benefits to the subjects;

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***

adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

3. **45 CFR 46.406- Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition.**

In order to approve research in this category, the IRB must make the following determinations:

the risk of the research represents a minor increase over minimal risk;

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;

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***

adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

A fourth category of research requires a special level of HHS review beyond that provided by the IRB.

4. **45 CFR 46.407- Research that the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406, but 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.**

If the IRB believes that the research does not meet the requirements of 45 CFR 46.404, 46.405, or 46.406, 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 HHS for review. The research may proceed only if the Secretary, HHS, or his or her designee, after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) 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, 46.405, or 46.406, or (2) the following:

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 research will be conducted in accordance with sound ethical principles; ***and***

adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.