Risk Levels in Pediatric Human Subjects Research

Unlike risk level determinations in research involving adults, which are either minimal risk or greater than minimal risk, research involving pediatrics can fall into one of four different pediatric risk level determinations.

"When reviewing research with children as subjects, in addition to ensuring adherence to the general regulatory requirements of 45 CFR part 46, Subpart A, the IRB also must consider the potential benefits, risks, and discomforts of the research to children and assess the justification for their inclusion in the research. In assessing the risks and potential benefits, the IRB should consider the circumstances of the children to be enrolled in the study-for example their health status, age, and ability to understand what is involved in the research-as well as potential benefits to subjects, other children with the same disease or condition, or society as a whole. For any protocol involving children, the IRB must determine which of the four categories of research apply to that study, if any." *Children: Information on Special Protections for Children as Research Subjects*

The HHS regulations at 45 CFR part 46, subpart D permit IRBs to approve three categories of research involving children as subjects: *Children: Information on Special Protections for Children as Research Subjects*. One category falls under the categorization of minimal risk, while the remaining 2 categories fall under the categorization of greater than minimal risk.

45 CFR 46.404- Research not involving greater than minimal risk to the children. (FDA 21 CFR 50.51) ("Risk level 1")

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.

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. (FDA 21 CFR 50.52) ("Risk level 2")

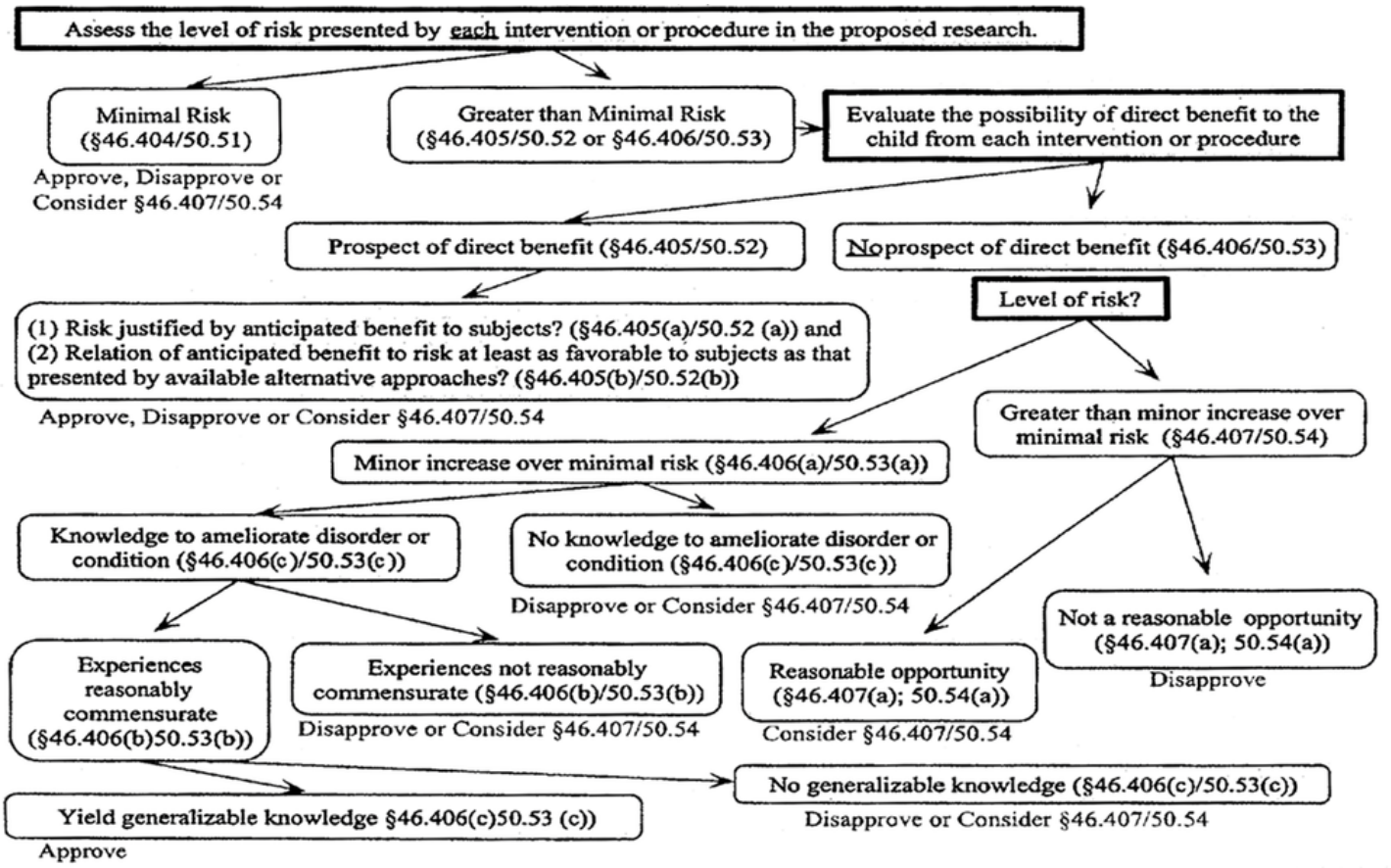
To approve research in this category, the IRB must make the following determinations:

- 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.

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. (FDA 21 CFR 50.53) ("Risk level 3")

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.

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. ("Risk level 4")

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.

For more information on the HHS 45 CFR 46.407 review process see OHRP Guidance, Children Involved as Subjects in Research: Guidance on the HHS 45 CFR 46.407 ("407") Review Process

Practical effect of the pediatric risk level determination

Research that falls into any of the categories of greater than minimal risk is reviewed by the full, convened IRB committee (not eligible for exempt or expedited review)

- Research that falls into any of the categories of greater than minimal risk does not qualify for certain waivers (waiver of consent, waiver of documentation of consent)
- Research that falls into "Risk level 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.) carries with a **regulatory** requirement that permission of both parents is obtained, unless one parent is "deceased, unknown, incompetent, not reasonably available."(45 CFR 46.408)
    - "In general, permission should be obtained from both parents before a child is enrolled in research. However, the Institutional Review Board (IRB) may find that the permission of one parent is sufficient for research to be conducted under 46.404 or 46.405. When research is to be conducted under 46.406 and 46.407 permission must be obtained from both parents, 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."(HHS Research with Children FAQs)
    - **Note:** the IRB always has the latitude to require 2 parent permission for any study, but in the case of risk level 3, the IRB has a regulatory obligation to require 2 parent permission
    - "Once the IRB determines which regulatory provision applies to the research under review, reference is then made to 46.408 and/or 50.55 which sets out the requirements relating to the permission of the parent or guardian. The permission of one parent is sufficient for the first two categories (46.404, 46.405, 50.51,50.52). For research falling under 46.406/50.53, if permission is to be obtained from parents, permission must be obtained from both parents **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." Attachment D - Parental Permission in Research involving Children; SACHRP Recommendation

If the study involves procedures that are greater than minimal risk and determined by the convened board to require two parent signatures the investigator must be aware that:

1. There is this regulatory requirement.
2. Plan accordingly regarding logistics to ensure that this requirement is met when obtaining parental permission.

Note: while a risk level determination by an IRB of 46.406/50.53 requires, per regulation, that both parents to provide permission (unless one is not able based on the criteria above), the IRB does have the leeway to require two parent permission for **any** human subject research project. Investigators must review all communications/approval letters carefully to understand what determinations were made and any additional requirements of the IRB of record.

Even when two parent permission is not required by the IRB or by regulation if both parents are involved in the child's life it is strongly recommended that both parents are involved in the discussion and provide permission.

If both parents are aware and in agreement to the child's participation

- There is a better chance of compliance/cooperation with the protocol.
- There is less chance of withdrawals after participation has begun if a second parent is not in agreement.
- This is in line with respect for persons in obtaining permission.

"There exists a broad, varied, and inconsistent spectrum of opinion as to what may be considered an appropriate determination whether a parent is or is not reasonably available. Generally, IRBs do not review the circumstances of whether a second parent is reasonably available for each enrolled subject; this is a task for the investigator. The IRB determines the requirement for parental permission at the time of IRB review of the research, based on the regulatory category that is most appropriate to the nature of the research under review and with regard to the entire population of prospective subjects. It is not until the investigator meets the parent (s) and child and discusses the particulars of the research and enrollment that information about the availability of both parents becomes apparent. While the IRB may certainly be consulted by investigators for guidance on a particular situation, it is ultimately the responsibility of the investigator to adequately assess, document, and decide whether a parent is not reasonably available given the specific facts and circumstances of each situation, including the level of that second parent's participation

in the life of the child." It can be tricky trying to determine whether a second parent is or is not reasonably available.

The Secretary's Advisory Committee on Human Research Protections (SACHRP) provides expert advice and recommendations to the Secretary of HHS on issues pertaining to the protection of human subjects in research. This committee has recommendations available for these situations.

Component analysis for pediatric risk level

In 1978, the National Commission stated, "To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively." Component analysis recognizes that each intervention may have different risks and may or may not offer direct benefit to study participants.

In studies involving multiple interventions and/or placebo, applying component analysis can help IRB members understand the different levels of risk associated with each intervention. When there are different cohorts of subjects receiving different interventions or a placebo, this analysis can help an IRB determine the appropriate pediatric risk level for each cohort.

"Each research procedure in a treatment study must be evaluated independently in terms of potential benefits and risk to the subject (i.e. component analysis). Different procedures in a single trial may be approved or disapproved under different Subpart D standards."

The committee suggests that the primary investigator should present supporting information for each procedure and intervention, regarding pediatric risk, in any given protocol in a clear and concise manner to facilitate review. SACHRP provides an example of how to present this:

Research Procedure	Prospect of Direct Benefit		No Prospect of Direct Benefit		
	Intervention	Monitoring	404: Minimal Risk	406: Minor Increase over Minimal Risk	407: Requires HHS Secretary Approval

This type of risk analysis may lead to different Sub Part D risk determinations being applied to different procedures/interventions or cohorts within the same study. The

thinking behind this is that this can lead to the greatest protection for children participating in research.

Appendix B: Recommendations regarding risk in research involving children. SACHRP Recommendations.

Component Analysis: FDA Presentation to the Secretary's Advisory Committee on Human Research Protections. Robert 'Skip' Nelson, MD, PhD