Enrolling Children (including Adolescents) in Clinical Research Policy Job Aid

Risk categories:
There are three risk/benefit categories of research involving children that an Institutional Review Board (IRB)/Ethics Committee (EC) of record can approve:

Risk Category	Risk	Required Actions
Research not involving greater than minimal risk (45 CRF 46.404 and 21 CFR 50.51)	The risks of the research are no more than minimal.	i. Permission from one parent/guardian may be sufficient if consistent with local IRB/EC approved procedures, unless the requirement to obtain parental/guardian permission is waived. ii. Adequate provisions are made for soliciting the assent of child- participants, unless the requirement to obtain child assent is waived.
Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants (45 CFR 46.405 and 21 CFR 50.52)	i. More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual participant or by a monitoring procedure that is likely to contribute to the participant's well-being; ii. The risk is justified by the anticipated benefit to the participants; and, iii. The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.	i. Permission from one parent/guardian may be sufficient if consistent with local IRB/EC approved procedures, unless the requirement to obtain parental/guardian permission is waived. ii. Adequate provisions are made for soliciting the assent of child- participants, unless the requirement to obtain child assent is waived.

Risk Category	Risk	Required Actions
Research involving greater than minimal risk and no prospect of direct benefit to individual participants but likely to yield generalizable knowledge about the participant's disorder or condition (45 CFR 46.406 and 21 CFR 50.53)	i. More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is not likely to contribute to the well-being of the child; ii. The risk represents a minor increase over minimal risk; iii. The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; and, v. The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition.	A site must have established written procedures that ensure adequate provisions are in place for: i. Soliciting permission from both parents or guardians in accordance with local IRB/EC-approved procedures unless (a) one parent is deceased, unknown, incompetent, or not reasonably available, or (b) when only one parent has legal responsibility for the care and custody of the child, (c) unless the IRB/EC has waived the requirements for obtaining parental or guardian permission. ii. Soliciting the assent of child participants, unless the requirement to obtain child assent is waived. iii. Enrolling wards of the state or any other agency, institution, or entity (e.g., orphans) with the appropriate documentation that: a. Recognizes the status of the individual child as a ward; b. Ensures communication of that status to the responsible IRB/EC; and c. Confirms the IRB/EC appointment of an advocate for the child/ward, in addition to any other individual acting as guardian or in loco parentis. See 45 CFR 46.409 and 21 CFR 50.56 for additional information on the role of the advocate.

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Research not otherwise approvable (45 CFR 46.407 and 21 CFR 50.54)	This category designation is given by an IRB/EC that believes the research does not meet the conditions under 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.	Sites will receive a notification from DAIDS Protocol Registration Office (PRO) to confirm the IRB's/EC's pediatric risk/benefit category designation. The DAIDS PRO review process will be stopped until the risk/benefit category designation is confirmed. The site Primary Investigator (PI), Investigator of Record (IoR), or designee should contact the IRB/EC Chair or designee to confirm that the IRB/EC intended to select the risk/benefit category 45 CRF 46.407 and that the IRB/EC plans to move forward with the subsequent required steps: i. If the risk/benefit category designation 46.407 was mistakenly selected, the site must request written documentation from IRB/EC with the corrected risk/benefit category designation. A copy of the relevant portion of the IRB/EC meeting minutes, signed and dated by the IRB/EC Chair or designee, documenting the IRB's/EC's risk/benefit category discussion and designation can be provided to the DAIDS PRO to meet the written documentation requirement. Sites must provide the documentation with the corrected risk/benefit category designation to DAIDS PRO in-order for the submission process to continue.

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		ii. If the IRB/EC confirms their decision of the 46.407 risk/benefit category selection, a special level of U.S. Health and Human Services (HHS) review is required beyond that provided by the IRB/EC. The PI/IoR/designee should also confirm with the IRB/EC Chair or designee when a request for special ".407" review will be submitted to HHS. Sites can refer to the May 26, 2005 Guidance, "Children as Research Subjects and the HHS "407" Process." Study enrollment at the site and the DAIDS PRO review of a site's registration submission will be stopped pending a determination from the Secretary, HHS or his/her designee. Note: If the research is also subject to the U.S. Food and Drug Administration (FDA) regulations under 21 CFR 312 (or 812), the FDA's regulatory requirements at 21 CFR 50.54 must be met.