Summary Table on Subpart D, 45 CFR 46 and 21 CFR 50: Additional DHHS Protections for Children Involved as Subjects in Research; Additional Safeguards for Children in Clinical Investigations (FDA)

The Common Rule includes Subpart D: additional protections for children as research subjects. Subpart D - Additional Protections for Children Involved as Subjects in Research establishes risk-benefit categories for research involving children. To permit combining the two regulations into one table, the wording below does not in all places follow the exact paragraph numbering and wording of the regulations. FDA-regulated clinical investigations must follow the FDA regulations.
Note: the FDA refers to "clinical investigations" rather than "research." Direct links to the regulations for exact wording are provided.

Permissible Research with Children			
45 CFR 46 (OHRP), 21 CFR 50 (FDA)	**Category**	**Requirements** The IRB must determine the following before children may be involved as subjects:	**Parental Permission**
46.404, 50.51	Research not involving greater than minimal risk[1]	Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 46.408 and 50.55.	Permission from one parent may be sufficient
46.405, 50.52	Research involving greater than minimal risk[1] but presenting the prospect of direct benefit[2] to the individual subjects	a. The risk is justified by the anticipated benefit to the subjects; b. 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 c. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 46.408 and 50.55.	Permission from one parent may be sufficient
46.406, 50.53	Research involving greater than minimal risk[1] and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the	a. The risk represents a minor increase over minimal risk; b. 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; c. 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	Permission must be obtained from both parents

	subject's disorder or condition	d. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 46.408 and 50.55.	
46.407, 50.54	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children	a. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and b. The Secretary of DHHS or Commissioner of Food and Drugs for the FDA, 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 either: 1. That the research in fact satisfies the conditions of 46.404 and 50.51, 46.405 and 50.52, or 46.406 and 50.53, as applicable, OR 2. The following: i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children; ii. The research will be conducted in accordance with sound ethical principles; iii. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 46.408 and 50.55.	Permission must be obtained from both parents

1. *"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," 45 CFR 46.102
2. "*The prospect of direct benefit"* means the intervention or procedure holds out the possibility of direct benefit to the individual subject, or the study involves a monitoring and diagnostic procedures that may contribute to the subject's care or well-being." 45 CFR 46.405, 21 CFR 50.52

Requirements for Assent of Children		
45 CFR 46 (OHRP), 21 CFR 50 (FDA)	**Category**	**Requirements** The IRB must determine the following before children may be involved as subjects:
46.408, 50.55	Requirements for assent by children	• The IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of assenting. • In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research or clinical investigations under a particular protocol or for each child, as the IRB deems appropriate.
	Documentation of assent	• When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.
	Waiver of assent	• The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines: o that the capability of some or all of the children is so limited that they cannot reasonably be consulted, or o that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. • Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement for minimal risk research in which consent may be waived under 46.116, or in which assent may be waived under 50.55. See COMIRB Guidance on waiving consent and waiving documentation of consent.

Requirements for Parental Permission		
45 CFR 46 (OHRP), 21 CFR 50 (FDA)	**Category**	**Requirements** The IRB must determine the following before children may be involved as subjects:
46.408, 50.55	Requirements for permission by parents or guardians	• The IRB must determine that adequate provisions are made for soliciting the permission of each child's parents or guardians. Both DHHS and FDA regulations qualify this requirement by referring to regulations for informed consent found in 45 CFR 46.116 and 21 CFR 50. In other words, the rules for parental permission are the same as those for informed consent. • Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research under 46.404 or 46.405 or clinical investigations under 50.51 or 50.52. • Where research is covered by 46.406 and 46.407 and clinical investigations are covered by 50.53 and 50.54 and permission is to be obtained from parents, "both parents must give their permission 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."
	Documentation of permission	• Permission by parents or guardians shall be documented in accordance with and to the extent required by 45 CFR 46.117 or 21 CFR 50.27. In other words, the rules for documenting parental permission are the same as those for documenting informed consent.
	Waiver of permission	• Parental permission may be waived for minimal risk research satisfying criteria in 46.116 or in FDA Guidance. • In addition, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided that: o an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and o the waiver is not inconsistent with Federal, State, or local law. • If the children can legally consent for themselves without parental permission under Colorado law, parental permission will not be required for the research. See Guidance for Research Involving Children.
	Waiver of documentation of parental permission	• Documentation of parental permission may be waived for research satisfying criteria in 46.117 or 56.109(c).