

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)

For all research studies involving children, the investigator should make an initial determination of the appropriate risk category. As required by the regulations of DHHS's Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA), the IRB will make the final determination of category and document the determination. 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. Significant differences between the two regulations are noted; FDA-regulated clinical investigations should follow the FDA regulations. Note that the FDA refers to "clinical investigations" rather than "research." Direct links to the regulations for exact wording are provided.

45 CFR 46 (OHRP), 21 CFR 50 (FDA)	Category	Explanation The IRB must find [<i>and document (FDA)</i>] the following before children may be involved as subjects:	Permission/Assent
46.404 , 50.51	Research or clinical investigation 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 <i>may be</i> sufficient
46.405 , 50.52	Research or clinical investigation involving greater than minimal risk ¹ but presenting the prospect of direct benefit ² to the individual subjects	<ul style="list-style-type: none"> 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. <i>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.</i> 	Permission from one parent <i>may be</i> sufficient
46.406 , 50.53	Research involving greater than minimal risk ¹ and no prospect of direct benefit ³ to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition	<ul style="list-style-type: none"> 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 d. <i>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.</i> 	Permission must be obtained from both parents if they have custody and are reasonably available
46.407 , 50.54	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the	<ul style="list-style-type: none"> 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 [<i>Commissioner of Food and Drugs (FDA)</i>], 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: 	Permission must be obtained from both parents if they have custody and are reasonably available

	<p>health or welfare of children</p> <p><i>(very rarely used)</i></p>	<ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> 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. <i>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.</i> 	
<p>46.408, 50.55</p>	<p>Requirements for assent by children</p> <p>Waiver of assent</p>	<ol style="list-style-type: none"> a. 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. b. 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. c. The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines: <ol style="list-style-type: none"> 1. that the capability of some or all of the children is so limited that they cannot reasonably be consulted, or 2. 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. d. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement 	
		<p><i>DHHS regulations, 45 CFR 46.408:</i> under circumstances in which consent may be waived in accord with 46.116 of Subpart A.</p>	<p><i>FDA regulations, 21 CFR 50.55:</i> if it finds and documents that: (1) The clinical investigation involves no more than minimal risk to the subjects; (2) The waiver will not adversely affect the rights and welfare of the subjects; (3) The clinical investigation could not practicably be carried out without the waiver; and (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.</p>

46.408, 50.55	Requirements for permission by parents or guardians	<p>e. The IRB must determine that adequate provisions are made for soliciting the permission of each child's parents or guardian. <i>[DHHS regulations qualify this requirement by saying "The IRB shall determine, in accordance with and to the extent that consent is required by 46.116 of Subpart A, that adequate provisions...." This allows parental permission to be waived in DHHS studies. Parental permission cannot be waived in FDA-regulated studies. See next part of table below.]</i></p> <ol style="list-style-type: none"> 1. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient <i>[if consistent with state law (FDA)]</i> for research to be conducted under 46.404 or 46.405 or clinical investigations under 50.51 or 50.52. 2. 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." 	<i>Requirements for permission of the parent or assent of the child if the study falls under:</i> 46.404 & 46.405, or 50.51 & 50.52 IRB may find that permission of one parent is sufficient 46.406 & 46.407, or 50.53 & 50.54 Permission must be obtained from both parents if they have custody and are reasonably available
	Waiver of permission	<p><i>[For non-FDA-regulated studies only:]</i> In addition to the provisions for waiver contained in §46.116 of Subpart A, 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:</p> <ol style="list-style-type: none"> 1. an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and 2. the waiver is not inconsistent with Federal, State, or local law. <p><i>[Parental permission cannot be waived in FDA-regulated studies; the corresponding paragraphs are not included because the FDA does not consider that it regulates any studies for which waivers of parental permission are appropriate. However, in California some minors can consent for themselves; see Children and Minors in Research.]</i></p>	
	Documentation of permission	<p>f. 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.</p>	
	Documentation of assent	<p>g. When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.</p>	

46.409, 50.56	Wards	<p>a. Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 46.406 or 46.407 or clinical investigations under 50.53 and 50.54 only if such research or clinical investigations are:</p> <ol style="list-style-type: none"> 1. related to their status as wards ; OR 2. conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.” <p>b. If the research or clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.</p> <ol style="list-style-type: none"> 1. The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis. 2. One individual may serve as advocate for more than one child. 3. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research. The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the research or clinical investigation, the investigator(s), or the guardian organization.” 	<p><i>Requirements for permission or assent if the study falls under:</i></p> <p><i>46.406 & 46.407, or 50.53 & 50.54</i> Permission must be obtained from both child advocate and any other individual acting on behalf of the child as guardian or in loco parentis</p>
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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,” 45CFR46.102

²For this paragraph, “*the prospect of direct benefit*” exists in research involving child subjects where “more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject’s well-being.” 45 CFR 46.405, 21 CFR 50.52

³For this paragraph, “*no prospect of direct benefit*” exists in research involving child subjects where “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 subject, or by a monitoring procedure that is not likely to contribute to the subject’s well-being.” 45 CFR 46.406, 21 CFR 50.53

NOTE: The FDA expects that component analysis will be used when determining the child risk category for a clinical investigation. This means that each research intervention or procedure will be evaluated separately to determine whether it does or does not hold out the prospect of direct benefit to the enrolled child.