

Research with Children

Frequently Asked Questions:

- [Question 1](#): Does research involving children include special requirements?
- [Question 2](#): How do the human subject research regulations define “children”?
- [Question 3](#): What categories of research involving children can an Institutional Review Board approve?
- [Question 4](#): What research involving children may an Institutional Review Board refer to the HHS Secretary for special review under 45 CFR 46.407?
- [Question 5](#): When should an Institutional Review Board (IRB) or institution request a “407” review for research involving children as subjects?
- [Question 6](#): What materials must be submitted to the Office for Human Research Protections with a request for a 407 review for research involving children?
- [Question 7](#): Are the exemptions different for research involving children?
- [Question 8](#): What is parental permission in the context of research involving children?
- [Question 9](#): Can parental or guardian permission for research involving children be waived?
- [Question 10](#): How should parental permission for research involving children be documented?
- [Question 11](#): Do both parents need to provide permission for their child to participate in research?
- [Question 12](#): What is child assent, and how do the requirements vary with the age of the research subjects?
- [Question 13](#): When does child assent have to be obtained for research and can it be waived?
- [Question 14](#): How should child assent for research participation be documented?
- [Question 15](#): Do parental permission and child assent for research involving children have to occur at the same time or in any particular order?
- [Question 16](#): What happens when there is disagreement between a child and his/her parents about research participation?
- [Question 17](#): If by law a child is able to consent to treatment without parental permission, can they also consent to participate in research related to that treatment?
- [Question 18](#): What happens if a child reaches the legal age of consent while enrolled in a study?
- [Question 19](#): Are there special regulatory requirements for research involving children as subjects who are also wards?
- [Question 20](#): When must an advocate be appointed to oversee a child’s enrollment in research?
- [Question 21](#): What is the role of an advocate in research involving children?
- [Question 22](#): Who may be advocates for children involved in research that are wards and how should they be appointed?

Question 1: Does research involving children include special requirements?

Yes, [Subpart D](#) of the HHS regulations at 45 CFR part 46 provides additional protections for children participating in human subjects research. Investigators conducting HHS-supported research must comply with the requirements of subpart D, as well as other subparts. The IRB must determine that all requirements of subparts A and D have been met. If the research involves pregnant minors, then the requirements of [subpart B](#) must be met and if the research involves incarcerated minors then the requirements of [subpart C](#) must be met.

Subpart D's additional protections include:

- a. requiring IRB review of some research activities involving children that would be exempt if the research subjects were adults;
 - b. use of parental permission and child assent instead of the procedures for obtaining informed consent used for research involving adults;
 - c. conditions for IRB approval of proposed research activities in three categories depending on the level of risk and other specified features of the proposed research activity;
 - d. review by the Secretary for research that an IRB finds not approvable under any of the three categories; and,
 - e. additional conditions for certain research activities involving children who are wards of the State or any other agency, institution, or entity
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- a. [Altering the Exemption](#): Subpart D widens the range of research activities requiring IRB review by reducing the scope of the exemption in [45 CFR 46.101\(b\)\(2\)](#) regarding research activities involving education tests, survey or interview procedures, or observation of public behavior, if the subjects are children. The exemption of research activities involving survey and interview procedures is eliminated. The exemption is also narrowed for research involving observation of public behavior, by eliminating the exemption of any research involving observation of public behavior if the investigator will participate in the activities being observed.
 - b. [Parental Permission](#) and [Child Assent](#): Subpart D uses parental permission and child assent instead of the procedures for informed consent used for research involving adults. In general, one or both parents or a guardian must be provided with the information ordinarily required for informed consent, so that they may decide whether to allow the child to participate, and children capable of assent must also express their willingness to participate. Subpart D allows for various conditions and waivers of parental permission and child assent, depending on the nature of the research activity and the maturity of the child.
 - c. [Categories of Approvable Research](#): Subpart D requires the reviewing IRB to identify the level of risk, the potential for direct benefits to the subjects, and other specified features of the research during the approval process. Depending on the level of risk and other specified features of the research activity, there are three categories under which the IRB can approve research involving children.
 - d. [Secretarial Review](#): If the IRB does not believe that a proposed research activity fits any of the three categories, but that it does present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB may forward that proposed activity to the HHS Secretary for review under conditions identified in section 407 of the regulations.
 - e. [Wards](#): Subpart D also sets additional conditions for research involving children who are wards of the State or any other agency, institution, or entity if the research is approved under two of the categories of approvable research: it limits the kind of research activities approved under these two categories in which children who are wards can participate, and it requires the appointment of an advocate to act in the best interests of the child.

Question 2: How do the human subject research regulations define “children”?

The human subject research regulations define “children” as follows:

“Children” are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted ([45 CFR 46.402\(a\)](#)).

In the United States the legal age of adulthood is a matter of state and local law. This means that who is legally considered a child may vary from state to state; in a large majority of states eighteen years of age is the legal age of adulthood, but this is not true in every state, locality, or territory. Also, there may be exceptions to who is considered a child and additional laws in places that define emancipated minors. The definition of “children” also takes into account the particular treatments or procedures involved in the proposed research; for example, in some places individuals who are sixteen years of age may legally consent to certain medical treatments, and so if the involvement of human subjects in a proposed research activity consists of these treatments, then they may be considered as adults for that purpose. If a proposed activity includes something for which the subject has not yet reached the legal age of consent, however, that person must be considered a child.

Question 3: What categories of research involving children can an Institutional Review Board approve?

Three of the four categories of human research involving children may be approved by an Institutional Review Board (IRB). The four categories differ from one another according to the level of risk involved, the prospect of direct benefit to the research subjects, and the anticipated research findings. For all four categories, the proposed research activity must satisfy the requirements for [parental or guardian permission](#) and child [assent](#). Depending on the category, additional conditions must be met in order for the IRB to approve the research activities. The three categories approvable by an IRB are:

- a. Section 404 of the regulations allows the IRB to approve research if the IRB finds that the risks of the research are no more than minimal.
- b. [Section 405](#) of the regulations allows the IRB to approve research if the IRB finds that:
 - o 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;
 - o the risk is justified by the anticipated benefit to the subjects; and,
 - o the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.
- c. [Section 406](#) allows the IRB to approve research if the IRB finds that:
 - o 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 well being of the child;
 - o the risk represents a minor increase over minimal risk;
 - o 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; and,
 - o 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.

The fourth category of approvable research involving children is identified in [Section 407](#), and requires the IRB to make certain findings and refer the proposed research activity to the Secretary of HHS for further review and approval.

Classifying a particular activity into one of these categories involves, among other things, determining whether the proposed research involves “minimal risk” to the subjects. The regulations rely on the definition of “minimal risk” provided in Subpart A of the regulations, as follows:

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\(i\)](#)).

Determining that a research activity presents no more than minimal risk involves comparing the possible harms or discomforts experienced in normal daily life or during routine physical or psychological examinations or tests with the possible harms or discomforts that will be faced by subjects as a consequence of research participation. The nature of the harms or discomforts (e.g., physical, psychological, legal) should be considered, as well as the chances that they will occur and the seriousness of their impact if they were to happen. Depending on what kind of experience(s) are involved in participation in a specific research activity, it may be easier to compare the anticipated experience of participation in research to the possible harms or discomforts of daily life, or to the possible harms or discomforts of a routine physical or psychological examination or test. Including measures to prevent or decrease the likelihood of harm or discomfort from the research may affect whether the proposed research activity involves no more than minimal risk.

Question 4: What research involving children may an Institutional Review Board refer to the HHS Secretary for special review under 45 CFR 46.407?

The regulations at [45 CFR 46.407](#) allow the Institutional Review Board (IRB) to refer HHS-conducted or -funded research to the HHS Secretary for consideration if the IRB finds that the research does not meet the conditions for approval under the other three categories of research involving children. If an institution’s IRB does not believe the proposed research meets the requirements of 45 CFR 46.404, 46.405, or 46.406 of subpart D, but finds and documents 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 (in accordance with HHS regulations at 45 CFR 46.407(a)), the IRB or other appropriate institutional official may submit the protocol and supporting materials to the Office for Human Research Protections (OHRP) for HHS consideration under the provisions of 45 CFR 46.407(b). Before submitting a protocol to OHRP, the IRB must determine that, in addition to meeting the requirements of 45 CFR 46.407(a) and other applicable sections of subpart D, the proposed research also meets all of the requirements of 45 CFR part 46, subpart A, except those requirements modified by Subpart D.

After receiving recommendations from a panel of experts and following an opportunity for public comment, the Secretary may approve the research under either one of two conditions:

- 1) The Secretary finds that the research is actually approvable under one of the first three categories of research, despite the IRB's finding to the contrary; or
- 2) the Secretary concurs with the IRB's findings that the research is not allowable under the other three categories and determines that the research presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting children's health or welfare, and, in addition, determines that the research will be conducted in accordance with sound ethical principles and that adequate provisions are made for soliciting the assent of children and permission of their parents or guardians as discussed in [46.408](#).

The Secretary may conditionally approve research under 46.407 providing specific stipulations are met.

You may wish to view the following related questions and answers:

[Question 5](#): When should an IRB or institution request a "407" review for research involving children as subjects?

[Question 6](#): What materials must be submitted to the Office for Human Research Protections with a request for a 407 review for research involving children?

See OHRP's guidance on the 407 review process at: http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html.

Question 5: When should an Institutional Review Board (IRB) or institution request a "407" review for research involving children as subjects?

Once an IRB determines that a protocol does not meet the requirements of 46.404, 46.405, or 46.406 for approval of research, but does meet the requirements for review under [45 CFR 46.407\(a\)](#), the institution or the Institutional Review Board may request that the Office for Human Research Protections (OHRP), on behalf of the Secretary, HHS, conduct a 46.407 review.

Question 6: What materials must be submitted to the Office for Human Research Protections with a request for a 407 review for research involving children?

For OHRP to determine whether a 407 review for research involving children should proceed, the institution must submit the following documents/information to the Office for Human Research Protections (OHRP) in both written and electronic (if available) forms:

- a. IRB documentation of required findings under [45 CFR 46.407](#) that the proposed research does not meet the requirements of 46.404, 46.405, or 46.406, but presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
- b. Institution name, institution assurance number, and IRB name.
- c. Institutional contact's name, title, phone number, fax number, mailing address, and email address.
- d. Title of protocol, and name of principal investigator(s).
- e. HHS application number and name of funding agency.
- f. Relevant HHS grant application or proposal.

- g. Most current version of protocol and grant application submitted to and reviewed by the IRB and modified by the principal investigator if required by the IRB.
- h. Most current version of parental permission/assent documents submitted to and reviewed by the IRB and modified by the principal investigator if required by the IRB.
- i. Relevant IRB minutes and correspondence.

Hard copy versions of the materials should be sent to:

Division of Policy and Assurances
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

OHRP will provide the submitting institution with instructions for transmitting documents electronically. See OHRP's guidance on the 407 review process at http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html.

Question 7: Are the exemptions different for research involving children?

One of the six exemptions of research involving human subjects is narrowed in scope by Subpart D's additional protections for research involving children. The other five exemptions apply to research involving children as human subjects in the same way that they apply to research involving adults.

The narrowed exemption is the exemption at [45 CFR 46.101\(b\)\(2\)](#), which generally applies to research involving educational tests, interviews or survey procedures or observation of public behavior, if the data are recorded without individual identifiers, or if disclosure of the recorded responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to their financial standing, employability, or reputation. Where children will be involved as research subjects, however, the use of survey or interview procedures is eliminated from this exemption, and so is research involving the observation of public behavior if the investigators participate in the activity being observed.

In other words, the only research activities involving children that may fall under this exemption are those involving educational tests or observation of public behavior where the investigators do not participate in the activity being observed. To be exempt, these activities must also meet the condition that the data are recorded without individual identifiers, or the condition that disclosure of the recorded responses would not place the subjects at risk of criminal or civil liability or be damaging to their financial standing, employability, or reputation. Otherwise, all the requirements of the human subjects regulations apply.

Question 8: What is parental permission in the context of research involving children?

By definition, children are unable to provide informed consent to participate in research, although they might be able to give their [assent](#). The IRB should determine that unless parental permission can be waived adequate provisions are made for soliciting the permission of the parent(s) or legal guardian(s). The regulations define "permission" at 46.402(c) as the

“agreement of parent(s) or guardian to the participation of their child or ward in research.” The term “parent” means a “child's biological or adoptive parent.” The term “guardian” means “an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.”

You may wish to view the following related questions and answers:

- [Question 9](#): Can parental or guardian permission for research involving children be waived?
[Question 10](#): How should parental permission for research involving children be documented?
[Question 11](#): Do both parents need to provide permission for their child to participate in research?

Question 9: Can parental or guardian permission for research involving children be waived?

Yes, under certain circumstances. An Institutional Review Board (IRB) may waive the requirements for obtaining parental or guardian permission if it makes and documents the findings under either [45 CFR 46.116\(c\) or \(d\)](#).

In addition to the provisions for waiver contained in 46.116(c) and (d), if the IRB determines that a research protocol is designed to study conditions in children or 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 parental permission requirements provided that an appropriate mechanism is in place to protect the children, and provided that the waiver is not inconsistent with federal, state, or local law ([45 CFR 46.408\(c\)](#)). The choice of an appropriate substitute mechanism (for example, appointing a child advocate or an assent monitor) for protecting children participating in research would depend on the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition ([45 CFR 46.408\(c\)](#)).

Question 10: How should parental permission for research involving children be documented?

Permission by parents or guardians shall be documented in accordance with and to the extent required by [46.117 of subpart A of 45 CFR part 46](#). Essentially, parental permission should be documented in a manner similar to that used to document informed consent. An Institutional Review Board (IRB) may find that waiver of documentation of informed consent is appropriate under the HHS regulations at 46.117.

Question 11: Do both parents need to provide permission for their child to participate in research?

It depends. 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.

Question 12: What is child assent, and how do the requirements vary with the age of the research subjects?

“Assent” is defined by the regulations as follows:

“Assent” means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. ([45 CFR 46.402\(b\)](#)).

This means the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the Institutional Review Board (IRB) is charged with taking into account the ages, maturity, and psychological state of the children involved. The IRB has the discretion to judge children’s capacity to assent for all of the children to be involved in a proposed research activity, or on an individual basis.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.”

You may wish to view the following related questions and answers:

[Question 13:](#) When does child assent have to be obtained for research and can it be waived?

[Question 14:](#) How should child assent for research participation be documented?

Question 13: When does child assent have to be obtained for research and can it be waived?

The Institutional Review Board (IRB) is responsible for deciding whether child assent is required in proposed research activities. The IRB should require child assent unless it can be appropriately waived, or if the child is not capable of providing assent.

The regulations at 45 CFR 46.408(a) identify three types of circumstances where the IRB may determine that waiver of children’s assent is appropriate:

1. if the capability of some or all of the children is so limited that they cannot reasonably be consulted;
2. if the intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research.

3. if the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either [45 CFR 46.116\(c\)](#) or [45 CFR 46.116\(d\)](#).

Question 14: How should child assent for research participation be documented?

The HHS regulations do not require documentation of assent. The Institutional Review Board (IRB) has the discretion to determine the appropriate manner, if any, of documenting child assent. Based on such considerations as the child's age, maturity, and degree of literacy, the IRB should decide what form of documentation, if any, is most appropriate. If adolescents are involved in research where a consent form would have been used if the subjects were adults, it would generally be appropriate to use a similar form to document an adolescent's assent.

If young children are involved who are as yet unable to read, documentation should take a form that is appropriate for the purpose of recording that assent took place. The IRB may also decide that documentation of assent is not warranted.

Question 15: Do parental permission and child assent for research involving children have to occur at the same time or in any particular order?

The HHS regulations do not specify the order in which parental or guardian permission and child assent should be sought. Therefore, Institutional Review Boards (IRB) have the discretion to determine the appropriate order given the research and the context in which it will be conducted.

In general, parental or guardian permission should be sought before seeking the assent of a child, particularly in more than minimal risk research, unless the requirement for obtaining parental or guardian permission can be waived. There might be some cases, however, involving minimal risk research, where it would be reasonable to seek child assent prior to seeking parental permission.

For example, a school-based study of minimal risk (e.g., investigating children's responses to music), could be posed to children in the school setting. Children could be asked if they wanted to participate and if so, sent home with a request for parental or guardian permission. In all cases, except when the requirement for obtaining parental or guardian permission can be waived, parental or guardian permission, even if sought after child assent is provided, is required before the child can be enrolled in the study.

Question 16: What happens when there is disagreement between a child and his/her parents about research participation?

If a child is capable of assent and the Institutional Review Board (IRB) requires that assent be sought, it must be obtained before the child can participate in the research activity. Thus, if the child dissents from participating in research, even if his or her parents or guardian have granted permission, the child's decision prevails.

However, the regulations state at [45 CFR 46.408\(a\)](#) that the IRB may waive the assent requirements if the intervention or procedure involved in the research holds out the prospect of

direct benefit that is important to the health or well-being of the children and is available only in the context of research. Conversely, if a child assents to participate in research, and parental permission has not been waived by the IRB, the permission of the parents or guardian is also required before the child can be enrolled in the research.

Question 17: If by law a child is able to consent to treatment without parental permission, can they also consent to participate in research related to that treatment?

HHS regulations at 45 CFR 46.402(a) define “children” as “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.” If research on a specific treatment involves solely treatments or procedures for which minors can give consent outside the research context (under applicable state and local laws, for example, research on sexually transmitted diseases or pregnancy), such individuals would not meet the definition of children as defined at 45 CFR 46.402(a). Thus, subpart D would not apply to the research and parental permission (or waiver thereof) is not a consideration for these minors. Under these circumstances, minors may provide their own informed consent.

Question 18: What happens if a child reaches the legal age of consent while enrolled in a study?

The Office for Human Research Protections (OHRP) notes that informed consent should be viewed as an ongoing process throughout the duration of a research project. When a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age of consent to the procedures involved in ongoing research, the subject’s participation in the research is no longer regulated by the requirements of [45 CFR part 46.408](#) regarding parental or guardian permission and subject assent.

Unless the Institutional Review Board (IRB) determines that the requirements for obtaining informed consent can be waived, the investigators should seek and obtain the legally effective informed consent, as described in [45 CFR 46.116](#), for the now-adult subject for any ongoing interactions or interventions with the subjects. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject. However, the IRB could approve a waiver of informed consent under 45 CFR 46.116(d), if the IRB finds and documents that the required conditions are met.

Similarly, if the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of “human subjects research” (for example, it involves the continued analysis of specimens or data for which the subject’s identity is readily identifiable to the investigator(s)), then it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects. The IRB may consider, if appropriate, a waiver under 45 CFR 46.116(d) of the requirements for obtaining informed consent in order for the subjects to continue their participation in the research.

Question 19: Are there special regulatory requirements for research involving children as subjects who are also wards?

The HHS regulations at 45 CFR part 46, subpart D provide additional protections for children who are also wards of the State or any other agency, institution, or entity. These special protections for wards apply to two categories of research:

- a. [research approved by an IRB under 45 CFR 46.406](#); or
- b. [research approved in accordance with the requirements of 45 CFR 46.407](#) that requires a special level of HHS review beyond that provided by the Institutional Review Board (IRB).

As set out in [45 CFR 46.409](#), before children who are wards of the State or any other agency, institution, or entity can be included in either of the two categories of research referenced above, the research must meet the following conditions:

- a. the research must be either related to the children's status as wards; or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards; and
- b. the IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

One individual may serve as advocate for more than one child, and must 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 should represent the individual child subject's interests throughout the child's participation in the research. The HHS regulations further require that the advocate not be associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

Question 20: When must an advocate be appointed to oversee a child's enrollment in research?

HHS regulations at [45 CFR 46.409](#) require appointment of an advocate for each child who is a ward of the State or any other agency, institution, or entity, for the following two categories of research:

- a. research approved by an Institutional Review Board (IRB) under 45 CFR 46.406; or
- b. research approved under 45 CFR 407 that requires a special level of HHS review beyond that provided by the IRB.

You may wish to view the following related questions and answers:

[Question 3:](#) What categories of research involving children can an Institutional Review Board approve?

[Question 4:](#) What research involving children may an Institutional Review Board refer to the HHS Secretary for special review under 45 CFR 46.407?

[Question 21:](#) What is the role of an advocate in research involving children?

[Question 22:](#) Who may be advocates for children involved in research that are wards and how should they be appointed?

Question 21: What is the role of an advocate in research involving children?

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child throughout the duration of the child's participation in the research. This includes ensuring that to the extent possible, the child understands what will be required of him or her during the research, and that if capable, the child provides his or her assent to participate.

Acting in the best interests of the child could include evaluating the ongoing impact of the research study on the child. The advocate should represent the individual child subject's interests throughout the child's participation in the research. This added protection is intended to ensure that the ward, who is particularly vulnerable, is not exploited, coerced, or subjected to undue influence or harm in the course of the research. HHS regulations further require that the advocate not be associated in any way (except in the role of advocate or member of the Institutional Review Board (IRB)) with the research, the investigator(s), or the guardian organization.

Question 22: Who may be advocates for children involved in research that are wards and how should they be appointed?

Each institution is likely to rely on a different process for appointing an advocate. In some cases it might be a member of the Institutional Review Board (IRB), a representative from an institution's health advocacy or ombudsman's office, or a case worker, social worker, or counselor responsible for the child's rights and welfare.

In some cases, state law or local practice might dictate who is responsible for appointing the advocate. In any case, the appointment should be made by a party or individual with no interest in or affiliation with the research being conducted. Investigators and IRBs should consult with their institution to determine the policies in procedures in place locally. IRBs should review and approve the process for appointing advocates.