

Wayne State University Human Investigation Committee	
Subject	Vulnerable Participants: Children as Research Participants
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Approvals	Original Approval SC: 03/16/05; Administrative Approval 05/02/05; Revised Administrative Approval 11/08/06; Revised Draft 12/07; General Counsel 03/14/08; Administrative Approval 09/30/10, Administrative Approval 03/07/11

Background

In accordance with its dedication to the highest levels of research integrity, all research at Wayne State University is conducted in compliance with the principles of the Belmont Report and other ethical codes of conduct for research, such as the Declaration of Helsinki and the Nuremberg Code, and are consistent with Good Clinical Practice (GCP) guidelines. Wayne State has made a commitment to conduct *all* research, regardless of sponsorship, under these principles and all relevant local, state, federal and international regulations in order to provide the same high level of protection for all human participants.

In addition to the protection provided under the Common Rule (45 CFR 46), federal regulations (45 CFR 46 subpart D) provide additional protection for children involved in research such as obtaining assent from the child and obtaining the permission of the parents/guardians for the child to be enrolled in the research protocol. More specific provisions are based on the degree of risk involved in the proposed research and the nature and degree of anticipated benefit(s).

Most of the Exemptions applicable to research involving adults (45 CFR 46.101) also apply to children. However, the exemption at 45 CFR 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply when children are involved, except for research involving the observation of public behavior when the investigator(s) does not participate in the activities being observed (see also, *Obtaining Permission from a Legally Authorized Representative or Guardian When the Subjects are Unable to Give Consent*).

For **Department of Energy**-regulated research, investigators are required to follow Department of Energy (DOE) requirements for the protection of personally identifiable information by completing and complying with the requirements of the "Checklist for IRBs to Use in Verifying that Human Subject Research Protocols are in Compliance with DOE Requirements."

For research sponsored by the **Department of Defense (DoD)**, the DoD applies the provisions in 45 CFR 46, Subparts B, C, and D for the protection of vulnerable classes of subjects. For further information, please see DoD Directive 3216.02 for research conducted or supported by a DoD component (an organizational entity within the DoD).

For research sponsored by the *Environmental Protection Agency* (EPA), the following guidance applies:

- EPA prohibits research involving the intentional exposure of pregnant women, nursing women, or children to any substance.
- EPA requires application of 40 CFR 26 Subparts C and D to provide additional protections to pregnant women and children as participants in observational research, i.e., research that does not involve intentional exposure to any substance.
- EPA policy requires submission of IRB determinations and approval to the EPA Human Subjects Research Review official for final review and approval before the research can begin.
- For research not conducted or supported by any federal agency that has regulations for protecting human research participants and for which the intention of the research is submission to the EPA, the EPA regulations protecting human research participants apply, including:
 - EPA extends the provisions of the 40 CFR 26 to human research involving the intentional exposure of non-pregnant, non-nursing adults to any substance.
 - EPA prohibits the intentional exposure of pregnant women, nursing women, or children to any substance.

Research involving children must not be conducted by VA investigators while on official duty or at VA or approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer (1200.05 48).

Definitions

Assent – The child’s affirmative agreement to participate in the research. Mere absence of an objection should not be construed as assent.

Children – *Definitions of “child” vary in different states and countries.*

DHHS: defines 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 [45 CFR 46.402(a)].

FDA: defines children as “persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted” (21 CFR 50.3(o)).

In Michigan, a child is an individual who:

- has not yet reached the age of 18
- has not been emancipated by court order; and
- has not been emancipated by operation of law under any of the following circumstances:
 - marriage
 - active duty with the armed forces of the United States

Emancipated Minor (Michigan law) – A person who has not reached the age of 18 but has been granted the status of adulthood by a court order or other formal arrangements. Michigan law states that an emancipated minor has the rights and responsibilities of an adult (with certain exceptions), including the right to authorize his or her own preventative healthcare. Although not stated, it is a reasonable inference under Michigan law that emancipated minors may consent to healthcare procedures involving research. The IRB may choose not to approve research that relies solely on the consent of an emancipated minor and may apply protections similar to the protections of Subpart D even though Subpart D does not apply to such individuals. Thus the IRB, with input from the Office of the General Counsel, may choose not to approve research that relies solely on the consent of an emancipated minor. There are no conditions under which a child below the age of 16 can be considered emancipated.

Emancipation – In Michigan, children 16 years of age or older may be emancipated under the following circumstances only:

1. Without a court order – only **one** of the following need apply:
 - a. When a minor is married; or
 - b. When a minor is on duty with the U.S. armed forces;
 - c. Or for purposes of consenting to routine non-surgical medical care or emergency medical treatment when the minor is in custody of a law enforcement agency and the minor's parents or guardian cannot be located; or
 - d. For purposes of consenting to his or her own preventative health care or medical care including surgery, dental care, or mental health care, except vasectomies or any procedure related to reproduction, during the period when the minor is a prisoner under the department or corrections or the period when the minor is a probationer residing in a special alternative incarceration facility, but only if the parent or guardian cannot be located by the department of corrections.
2. By court order whereby the court will issue an Emancipation Order if it determines that emancipation is in the best interest of the minor and the minor is able to establish **all** of the following:
 - a. The minor's parent or guardian does not object to the emancipation or if the parent or guardian does object, the parent or guardian is not supporting the minor; **and**
 - b. The minor is at least 16 years of age; **and**
 - c. The minor is a Michigan resident; **and**
 - d. The minor has demonstrated the ability to manage his or her financial affairs, including proof of employment or other means of support; **and**
 - e. The minor has the ability to manage his or her personal and social affairs, including but not limited to housing; **and**
 - f. The minor understands his or her rights under the act as an emancipated minor.

Guardian (DHHS) – An individual who is authorized under state or local law to give consent on behalf of a child for general medical care.

Guardian (FDA) – An individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of Subpart D, a guardian is also an individual who is authorized to give consent to participate in research on behalf of a child.

Guardian (Michigan law) – A person who has accepted:

- a written parental appointment to be a guardian to exercise care and custody decisions over a minor and there are no additional and capacitated parents or persons with care and custodial rights; *or*
- appointment from a court to exercise care and custody decisions over a minor.

For purposes of the **DHHS** regulations, a guardian does not include a limited guardian unless the limited guardianship expressly allows the guardian to consent to medical care.

For purposes of the **FDA** regulations, a guardian does not include a limited guardian unless the limited guardianship expressly permits the guardian to consent to participation in research.

Legally Authorized Representative (FDA) – An individual or judicial or other body authorized under applicable law to give informed consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

Legally Authorized Representative (DHHS) – An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

Minimal Risk – 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.

Minor – A youth who has not yet reached the legally sanctioned age of majority.

Permission – The agreement of parent(s) or a legal guardian to the participation of the child in research.

Parent – A child's biological or adoptive mother or father or legal guardian.

HIC Policy/Procedures

Research Conducted Outside of Michigan

If a protocol may involve children outside of Michigan, then the Principal Investigator must verify that the outside jurisdiction's definition of a "child" and any applicable laws or regulations concerning research involving children as participants. Supporting documentation (e.g., copies of national, state, or local law, or the opinion of legal counsel) must be included with the protocol submitted to the IRB. Research must comply with the regulations (local, state, or federal) that hold them to the highest level of protection of human participants.

The review of all pertinent laws and regulations by the committee will be documented in the case record and meeting minutes.

Determination of Category of Risk

In all proposed research studies the IRB must determine, at the time of approval, which category of risk applies to the research study. The IRB is guided by and recognizes **three categories** of risk, in accordance with the pertinent Code of Federal Regulations (CFR) sections. Each category considered both the degree of risk and benefit to the research participant. Based on the degree of risk and benefit to the child, a WSU IRB must approve the research and simultaneously assign one of the following risk categories to the research:

Category 1: Research not involving greater than minimal risk (45 CFR 46.404).

Adequate provisions are made for parents/guardians to give parental permission (i.e., informed consent) and for the child to give assent, as appropriate, to participate in the research study.

Category 2: Research involving greater than minimal risk but with a potential for direct benefit to the individual participants (45 CFR 46.405).

1. The risk is justified by the anticipated benefit to the participants, *and*
2. The relationship of the benefit(s) to the risk is at least as favorable to the participant as that presented by available alternative approaches, *and*
3. Adequate provisions are made for parents/guardians to give parental permission (i.e., informed consent) and for the child to give assent, as appropriate, to participate in the research study.

Category 3: Research involving greater than minimal risk and with no prospect of direct benefit to the child, but likely to yield generalizable knowledge about the child's disorder or condition, will be considered on a case by case basis by the IRB (45 CFR 46.406). Children can only be approved for these studies when:

1. The additional risk represents only a minor increase over minimal risk,
2. The intervention or procedure must present an experience to the child that is reasonably commensurate with those that are inherent in their actual or expected medical or dental condition, social situations, or educational situations,
3. The intervention or procedure must be expected to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or treatment of the disorder or condition in children, and
4. Adequate provisions are made for both parents/guardians to give parental permission (i.e., informed consent) and for the child to give assent.

Enrolling children in research

Enrollment of children in a research protocol requires consideration of the following steps for obtaining permission from the parent(s) and the assent from the child.

➤ *Parental Permission*

In most circumstances in research which includes children as participants, permission of the child's parent(s) or guardian and the assent of the child are required before research can commence. Permission must be documented in the record in accordance with federal regulations [45 CFR 46.117 and/or 21 CFR

50.52]. In category 1 or category 2 research, the IRB may determine that the permission of only one parent or the guardian is required, if consistent with laws/regulations in the jurisdiction in which the research is conducted. The circumstance for obtaining only one signature must be documented in the study records and the minutes. When the research involves greater than minimal risk without direct benefit to the child (level 3) the written consent of both parents or the child's guardian is required, 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 [45 CFR 46.408(b)].

Parental permission may be waived or altered in accordance with the criteria as described in the HIC "Waiver or Alteration of Requirement to Obtain Informed Consent Checklist". When parental permission is waived, an appropriate mechanism for protecting the children who will participate as participants in the research will be substituted. In other cases, such as child abuse or sexually transmitted disease, parental permission may not be appropriate.

For research sponsored by the Department of Defense (DoD), if the research participant meets the definition of "experimental subject", waiver of consent is prohibited unless a waiver is obtained from the Secretary of Defense. However, if the research participant does not meet the definition of "experimental subject", the IRB may waive the consent process if deemed appropriate.

For research sponsored by the Department of Education, see the subheading below.

The PI must submit an adequate plan to evaluate whether children involved in the research are capable of assenting. The IRB will review the plan and determine if the plan is sufficient to determine whether the children to be involved in the research are capable of assenting, taking into account the age, maturity, and psychological state of the children. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or 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, the assent of the children is not a necessary condition for proceeding with the research. Even when the IRB determines that the subjects are capable of giving assent the IRB may still waive the assent requirement under circumstances in which consent may be waived. The circumstance for waiving the assent requirement must be documented in the study records and the meeting minutes (see Informed Consent Options policy).

For minimal risk research studies regardless of the benefit (category 1), the parental permission from one parent/guardian may be determined to be sufficient by the IRB. The determination and results must be documented in the study record and meeting minutes.

For research involving greater than minimal risk but with the potential of benefit to the child (category 2), parental permission of one parent/guardian may be determined to be sufficient by the IRB. The determination and results must be documented in the study records and meeting minutes.

For research involving greater than minimal risk and no prospect of direct benefit to the child but likely to yield generalizable knowledge about the child's disorder or condition (category 3), both parents or the legal guardian must give permission. Only one parental signature is required when one parent is deceased, unknown, incompetent, not reasonably available, or if only one parent has

the legal responsibility for the care and custody of the child. This should be documented in the research records. Where there is disagreement between the two parents, the child may not be enrolled in the research study.

In certain types of research with children, the term “passive consent” may have been used. For example, a notice may have been sent to the parents that their child would be asked to participate in a research project conducted in the school setting unless the parent called a certain number or returned a post card. The investigator then assumed that because he/she did not hear from the parent, the parent had given “passive consent” (i.e., waived consent) for their child to participate in the research activity. From an IRB perspective, that term actually referred to a “waiver” of parental permission with the assent obtained from the child. Investigators who wish to utilize this concept should: 1) request a “waiver” of parental permission with an information sheet sent home via 1st class mail to parents; and 2) obtain assent from the child.

➤ **Child Assent Procedures:**

Parental permission of parents/guardians and the assent of the child must be obtained before research may commence. Regulations require that “adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the age, maturity, and psychological state of the children involved.” (See Participant: Types of Informed Consent and the Consent Process Policy/Procedure.)

- In making this determination, the IRB must determine and document whether assent is a requirement of some, all, or not of the children.
- When the IRB determines that assent is not a requirement, the IRB must determine and document the following:
 - The children are not capable of providing assent based on the age, maturity, or psychological state.
 - The capability of the children is so limited that they cannot reasonably be consulted.
 - 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 child and is available only in the context of the research.
 - The assent can be waived using the criteria for waiver of the consent process.

As an ethical standard, the IRB committee recommends that oral assent be obtained for children between the ages of 7 and 12 and written assent be obtained for children ages 13 and older. However, the IRB may deviate from this recommendation based upon a request and adequate justification from the investigator.

The Principal Investigator must submit an evaluation plan to determine the capacity of the child to understand the assent process. The method of evaluation should be one that is accepted for use in the field of medicine/research that is being addressed in the study. The results of the evaluation must be documented in the medical and/or research record.

The IRB must determine if the evaluation of capacity plan is sufficient.

Under 45 CFR 46.408(a), the IRB may approve the waiver of assent when:

1. The IRB or reviewer, using the expedited procedure, must determine that children are capable of providing assent. When children are not capable of providing assent, assent does not have to be waived.
2. The intervention or the procedure in the study holds out a prospect of a direct benefit that is important to the health or well-being of the children and is only available in the context of the research study; *or*
3. The IRB or a reviewer, using the expedited procedure must determine that the waiver criteria, as described in the HIC "Waiver or Alteration of Requirement to Obtain Informed Consent Checklist" are satisfied.

For *minimal risk research studies where there is no benefit to the child (category 1)*, assent from the child should be obtained as appropriate depending upon the age and mental status of the child.

For *research involving greater than minimal risk but with a potential of benefit to the child (category 2)*, assent from the child should be obtained as appropriate depending upon the age and mental status of the child. However, assent may be waived by the IRB when there is benefit to the child that may only be available from the research study. An information sheet can be used to provide information about the study to the child, when appropriate.

For *research involving greater than minimal risk with no prospect of benefit to the child but with the prospect of yielding generalizable knowledge about the child's disorder or condition (category 3)*, assent should be obtained as appropriate depending upon the age and mental status of the child.

In general, a child's dissent should be respected. Ordinarily, a disagreement between parent(s) and the child may be because the child is depressed, the parents have unrealistic hopes, the child may have different goals and outcomes from the parents, or the real prospects may have been misunderstood. Every effort should be made to reach consensus between parent(s) and child. However, when the research offers the child the possibility of direct benefit important to his/her own health and may be available only through research (category 2 research as stated above), the parent's wishes generally prevail over the child's dissent. As a rule of thumb: a "no" from a child (unless it involves category 2 research), overrides a "yes" from a parent, but a "yes" from a child does not override a "no" from a parent unless the IRB has waived the requirements for parental permission.

Research Sponsored by the Department of Education

Following are specific requirements for research that is sponsored fully or in part by the U.S. Department of Education. The research must include:

- A process to comply with the Family Educational Rights and Privacy Act (FERPA).
- A process to grant exceptions to parental/student consent to release student records for research. This responsibility may be delegated to the IRB or another individual or component of the Organization (e.g., a FERPA committee).
 - An educational agency or institution may disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to develop, validate, or administer predictive tests; administer student aid programs; improve instruction.

- A school district or postsecondary institution that uses this exception is required to enter into a written agreement with the Organization or investigator conducting the research that specifies:
 - The determination of the exception;
 - The purpose, scope, and duration of the study;
 - The information to be disclosed;
 - That information from education records may only be used to meet the purposes of the study stated in the written agreement and must contain the current requirements in 34 § 99.31(a)(6) on re-disclosure and destruction of information.
 - That the study will be conducted in a manner that does not permit personal identification of parents and students by anyone other than representatives of the Organization with legitimate interests.
 - That the Organization is required to destroy or return all personally identifiable information when no longer needed for the purposes of the study.
 - The time period during which the Organization must either destroy or return the information.
 - That education records may be released without consent under FERPA if all personally identifiable information has been removed, including:
 - The student's name and other direct personal identifiers, such as social security number of student number.
 - Indirect identifiers, such as the name of the student's parent or other family members; the student's or family's address, and personal characteristics or other information that would make the student's identity easily traceable; date and place of birth and mother's maiden name.
 - Biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting.
 - Other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.

- A process to comply with the Protection of Pupil Rights Amendment:
 - For research funded by the U.S. Department of Education: No student shall be required, as part of any research project, to submit without prior consent to surveys, psychiatric examination, testing, or treatment, or psychological examination, testing, or treatment, in which the primary purpose is to reveal information concerning one or more of the following:
 - Political affiliations
 - Mental and psychological problems potentially embarrassing to the student or his/her family.
 - Sex behavior and attitudes.
 - Illegal, anti-social, self-incriminating and demeaning behavior.
 - Critical appraisals of other individuals with whom the student has close family relationships.
 - Legally recognized privileged and analogous relationships, such as those of lawyers, physicians, and ministers.

- Religious practices, affiliations, or beliefs of the student or student's parent.
 - Income, other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under a program.
- Prior consent means:
 - Prior consent of the student, if the student is an adult or emancipated minor; or
 - Prior written consent of the parent or guardian, if the student is an un-emancipated minor. Schools and contractors obtain prior written parental consent before minor students are required to participate in any ED-funded survey, analysis or evaluation.
- For research not funded by the U.S. Department of Education: The IRB must verify compliance with U.S. Department of Education regulations that schools are required to develop and adopt policies in conjunction with parents regarding the following:
 - The right of parents to inspect, upon request, a survey created by a third party before the survey is administered or distributed by a school to students.
 - Arrangements to protect student privacy in the event of the administration of a survey to students, including the right of parents to inspect, upon request, the survey, if the survey contains one or more of the same eight items of information noted above.
 - The right of parents to inspect, upon request, any instructional material used as part of the educational curriculum for students.
 - The administration of physical examinations or screenings that the school may administer to students.
- Access to instructional material used in a research or experimentation program must meet the following requirements.
 - All instructional material—including teachers' manuals, films, tapes, or other supplementary instructional material—which will be used in connection with any research or experimentation program or project must be available for inspection by the parents or guardians of the children engaged in such research.
 - Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.
 - Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.

Research sponsored by the Environmental Protection Agency (EPA)

HIC Policy for IRB review of research conducted or supported by the EPA:

- Research involving intentional exposure of pregnant women or children to any substance is prohibited and not approved by the IRB.
- Research intended for submission to the EPA involving intentional exposure of pregnant women or children to any substance is prohibited and not approved by the IRB.
- The IRB must review observational research involving pregnant women and fetuses using 40 CFR 26 and 45 CFR 46 Subpart B.
- The IRB must review and approve observational research involving children that does not involve greater than minimal risk only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 40 CFR 26.406.

- The IRB may review and approve observational research involving children that involves greater than minimal risk but presenting the prospect of direct benefit to the individual participants if the IRB finds and documents that:
 - The intervention or procedure holds out the prospect of direct benefit to the individual participant or is likely to contribute to the participant's well-being.
 - The risk is justified by the anticipated benefit to the participants.
 - The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.
 - Adequate provisions are made for soliciting the assent of the children and permission of their parent or guardians, as set forth in 40 CFR 26.406.

IRB Submission

When enrolling children into research it is necessary to address the risk category level (category 1 through 3) of the protocol and the informed consent and assent requirements. This is addressed in the Medical/Behavioral Protocol Summary Form Appendix C.

For children ages 7-12, parental permission forms should have a line for oral assent and should be signed by the person obtaining the assent. A copy of the oral assent and the script to be used to obtain oral assent should be submitted with the submission of the protocol.

For children ages 13-17, written assent must be obtained from the subject child by a document that is written at an appropriate reading level for the child. If the parental permission form is written at a grade level that is understandable for children ages 13-17, then it is acceptable to add a signature line for the child's written assent and use the one form for both the children and parents. However, separate assent and parental permission forms may be required because the language in the parental permission form is so complex that the child may not be able to understand the parental permission/assent form.

All parental permission forms, child assent forms, information sheets, and description of oral assent documents are required to be submitted to the IRB and require IRB review and approval prior to use. Submission of a research protocol that involves children that does not include any of these documents will result in the protocol being tabled because the IRB would then be unable to assess and the prospective participant would likewise be unable to assess the protocol's risk/benefit ratio.

References

45 CFR 46 subparts B, C, and D
45 CFR 46.101
45 CFR 46.101(b)(2)
40 CFR 26 Subparts C and D
1200.5 Appendix D-5 (VA Research)
45 CFR 46.402(a)
21 CFR 50.3(o)
45 CFR 46.404, 405, 406
45 CFR 46.117
21 CFR 50.52
45 CFR 46.408 (a) and (b)
DoD Directive 3216.02