



## Special Categories of Research: Children

### Content Applies To

Mayo Clinic Human Research Protection Program

Research for which the Mayo Clinic IRB is the IRB of Record

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### Purpose

Federal regulations protecting adults in research also apply to children with two additional conditions: first, adequate provision must be made for soliciting the assent of children; second, the permission of their parent(s) or guardian(s) must be obtained.

This procedure describes the special categories of research involving children; provisions for soliciting the assent of children and permission of their parent(s) or guardian(s); regulations regarding wards of the state or other agencies; determining when children reach the legal age of consent; and determining whether a prospective research subject is a child according to applicable State laws; and the applicable State laws associated with the limitations of a guardian to consent for a minor child participating in research.

### Policy

The Mayo Clinic Office for Human Research Protection - Institutional Review Board (IRB) reviews research involving children and only approves research which satisfies the requirements of 45 CFR 46 Subpart D - *Additional Protections for Children Involved as Subjects in Research* or equivalent protections as allowed by law. The IRB determines:

- If assent is required

- Whether and how assent must be documented and
- Any limitations to the above

## Key Terms

**Assent:** A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

**Children:** Persons who have not attained the legal age for consent to treatments or procedures involving research, under the applicable law of the jurisdiction in which the research will be conducted

**Guardian:** 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.

**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.

**Parent:** A child's biological or adoptive parent.

**Permission:** The agreement of parent(s) or guardian(s) to the participation of their child or ward in research.

## Categories of Research Involving Children

1. **Research Not Involving Greater than Minimal Risk:** The IRB may approve research in which the IRB finds that no greater than minimal risk to children is presented, 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.
2. **Research involving Greater Than Minimal Risk and has the prospect of direct benefit to the individual subjects:** The IRB may approve research in which the IRB finds that greater 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, only if the IRB finds that:
  - The risk is justified by the anticipated benefit to the subjects;
  - 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
  - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.
3. **Research involving greater than minimal risk and has no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition:** The IRB may approve research in which the IRB finds that greater 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 which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

- The risk represents a minor increase over minimal risk;
  - 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;
  - 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
  - Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.
4. **Research Not Meeting Category 1-3 Requirements:** The IRB generally may not approve research that does not meet the requirements of Categories 1-3 above. However, the IRB may approve the research only if:
- The IRB 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; **and**
  - The Secretary of the Department of Health and Human Services (DHHS), 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:
    - The research in fact satisfies the requirements of §46.404, §46.405, or §46.406, as applicable, **or**
    - The following:
      - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
      - The research will be conducted in accordance with sound ethical principles; and
      - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

### **Adequate Provisions for Soliciting the Assent of Children**

In addition to the determinations required above (i.e. Categories of Research Involving Children), the IRB determines whether 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. The IRB will also determine whether and how assent will be documented.

### **Determining Whether Children are Capable of Assent**

In determining whether children are capable of assenting, the IRB will take into account the ages, maturity, and psychological state of the targeted children involved. This judgment may be made for all children to be involved in research under a particular

protocol, or for each child, as the IRB deems appropriate. When the IRB determines that assent is required, it will also determine whether and how it should be documented.

### **Use of Assent - Guideline**

- Assent is usually required for research involving minors 7 years of age or older
- 7-12 years of age – use a written assent document
- 13-17 years of age – consider the study complexity and the subject's reading level to determine when to:
  - Use an assent document for signature (perhaps supplemented with additional oral information), or
  - Use the consent document for providing information and for signatures of parent(s) and minor subject.

### **Waiver of the Assent Requirement**

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 where the IRB determines that the subjects are capable of providing assent, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with 45 CFR 46.116.

### **Adequate Provisions for Soliciting Permission of Parents / Guardians**

In addition to the determinations based on requirements in this document, the IRB will determine that adequate provisions are made for soliciting the permission of each child's parents or guardians. Where parental permission is to be obtained, the IRB may either find that the permission of one parent is sufficient for research to be conducted or that permission is to be obtained from both parents.

- If the research is minimal risk for the minor subject (Category 1 above) then permission from at least 1 parent or guardian must be obtained.
- If the research is greater than minimal risk, but presenting the prospect of direct benefit to the minor subject (Category 2 above), permission from at least 1 parent or guardian must be obtained.
- If the research is greater than minimal risk and has no prospect of direct benefit to the minor subject, but may yield generalizable knowledge about the subject's disorder or condition (Category 3 above) or fits within Category 4 above, then permission from both parents must be obtained. Note: When required by the IRB, 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.

## **Conditions in Which Parental Permission May Not be Feasible**

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 requirement for permission, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is consistent with Federal, State, or Local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition. This waiver of parental or guardian permission does not apply to research regulated by the FDA.

## **Waiver of Parental/Guardian Permission for Public Demonstration Projects**

The IRB may approve a procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain parental or guardian permission provided the IRB finds and documents that:

- The research is conducted by or subject to the approval of state or local government officials.
- The research or demonstration protocol is designed to study, evaluate, or otherwise examine:
  - Public benefit of service programs.
  - Procedures for obtaining benefits or services under those programs.
  - Possible changes in or alternatives to those programs or procedures.
  - Possible changes in methods or levels of payment for benefits or services under those programs.
- The research cannot practicably be carried out without the waiver or alteration.
- The research is not FDA-regulated

## **Wards of the State or Other Agency**

Children who are wards of the State or any other agency, institution, or entity can be included in research that presents minimal risk (Category 1 above) or greater than minimal risk with a prospect of direct benefit (Category 2 above) approved in accordance with the requirements of this policy.

Children who are wards of the State or any other agency may participate in research under Categories 3 and 4 above only if the convened IRB finds and documents that such research is:

- Related to their status as wards;
- Or
- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as participants are not wards.

If the convened IRB determines the conditions for inclusion of children who are wards in Category 3 and 4 research are met, the IRB shall 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. 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 and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the Investigators, or the guardian organization.

## **Exemptions**

- The exemptions specified in 45 CFR 46.101(b) and the IRB document *Exempt Human Subjects Research* apply to research involving children with one exception.
- The exemption at 45 CFR 46.101(b)(2) for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.
- Only the IRB may determine which activities qualify for exempt review.

## **Investigator Responsibilities**

- For IRB review, the Investigator describes the target population for the research and provides justification for inclusion of children as potential subjects, or the justification for exclusion of children as potential subjects in cases in which the benefit of research has been established. The Investigator includes a description of the intended method for obtaining assent and parental permission.
- Mayo Clinic investigators must submit the following to the Mayo Clinic Pediatric & Adolescent Research Committee via the IRB electronic system prior to IRB review:
  - All greater than minimal risk new applications and related modifications involving participants who are less than 18 years of age.
  - Minimal risk new applications and related modifications involving participants who are less than 18 years of age and involving prospectively collected tissue at the time of surgery.
- Provide a description (via the IRB application) on how assent by children will be obtained and documented, or submit a request for a waiver of assent.
- Identify in the plan, if a case by case assessment of the children is anticipated, how it will be determined whether it is appropriate to obtain assent from the child.
- Provide a description to the IRB (via the IRB application) on how permission by the parent(s) or guardian(s) will be obtained and documented, or submit a request for a waiver of parental/guardian permission.
- Comply with the IRB requirements for obtaining and documenting the assent from the minor subject(s) and the permission of parent(s) or guardian(s).

- Submit to the IRB a modification request if planning to enroll a ward of the State into a study and await IRB review and approval before enrollment.

When assent is required by the IRB, the investigator shall also:

- Assess the developmental level of each child and
- Provide as appropriate to the child, an explanation of the research procedures in language understood by the child, a description of any risks, discomforts, or inconveniences that the child might experience, and assurance that the child can withdraw from the study at any time.

The investigator may delegate the activities of planning and facilitating the assent process to authorized personnel. Authorized personnel are those who are listed on the IRB electronic application for the approved study and designated for involvement in the consent process. It is the investigator's responsibility to ensure that delegated activities are performed by authorized and qualified staff in accordance with policies and procedures on the assent process.

## **IRB Responsibilities**

- The IRB reviews the proposed research according to all applicable IRB Policies, taking into consideration the additional requirements for involvement of children in research.
- Using the *Subpart D Determinations - Additional Protections for Children Involved as Subjects in Research* document as a guide, the IRB discusses and documents in its determination whether additional protections necessary for this population are adequate.
- The IRB determines whether children are capable of providing assent, taking into account the age, maturity, and psychological state of the children targeted for the study population. This determination may apply to all children involved in the study, or on a case-by-case basis, as deemed necessary by the IRB.
- The IRB determines whether documentation of assent is required, and how it should be documented.
- The IRB determines whether permission from one or both parents is required.
- If applicable, the IRB reviews and provides a determination to the Investigator about the appointment of an advocate to act in the best interest of the child who is a ward.

## **Determining Whether a Prospective Research Subject is a Child**

Federal regulations place limitations on the types of research that can be approved to include children, and the processes for approving that research. (45 C.F.R. 46 Subpart D; 21 C.F.R. 50 Subpart D).

Further, when research has been approved to include children, federal regulations describe who must provide informed consent before a child can be enrolled in the research, and provide requirements for obtaining the assent of the child. (45 C.F.R. 46.408; FDA 21 C.F.R. 50.55.). Office of Human Research Protections (OHRP) and Food and Drug Administration (FDA) regulations state that the determination of whether

an individual is a child is to be determined by “applicable law” (45 C.F.R. 46.402(a); 21 C.F.R. 50.3(o)), which typically means state or local statutes, regulations or cases.

### **Applicable Law - Arizona**

The following is a brief description of the “applicable law” in Arizona:

Under Arizona law, a person is generally considered to be a child until reaching the age of 18 years. In such instances, the child may not participate in research unless informed consent is provided by the child’s parent(s) or guardian, as provided in Mayo IRB policies.

While there are no research-specific exceptions for determining whether a person is a child, there are certain limited situations in which a person younger than 18 years old may become an “emancipated minor” under Arizona law. In such cases, the person may be treated the same as an adult for purposes of determining who may provide informed consent to participate in research. These situations include the following:

1. The person is at least 16 years old and has been declared emancipated by a court in Arizona, or can document emancipation from another jurisdiction in the United States;
2. The person is married, or has been married;
3. The person is presently in the military service of the United States;
4. The person is homeless (living away from parents and lacking a fixed nighttime residence; or living in a supervised shelter designed to provide temporary accommodations, a halfway house, or a place not designed for or ordinarily used for sleeping by humans);
5. The person is seeking treatment for sexually transmitted diseases, and the research procedures relate to diagnosis or treatment of sexually transmitted diseases;
6. The person is at least 12 years old and under the influence of a dangerous drug or narcotic or is suffering withdrawal symptoms; and the research relates to substance abuse treatment;
7. The person is seeking HIV testing, and the research procedures involve HIV testing, if a physician determines that the minor is mature and has the capacity to provide consent; or
8. The person is seeking contraception or pregnancy-related care, and the research procedures relate to contraception or pregnancy-related care.

### **Applicable Law - Florida**

Under Florida law, a person is generally considered to be a child until reaching the age of 18 years. In such instances, the child may not participate in research unless informed consent is provided by the child’s parent(s) or guardian, as provided in Mayo IRB policies.

While there are no research-specific exceptions for determining whether a person is a child, there are certain limited situations in which a person younger than 18 years old may become an “emancipated minor” under Florida law. In such cases, the person may



treated the same as an adult for purposes of determining who may provide informed consent to participate in research. These situations include the following:

1. The person has been declared emancipated by a court order;
2. The person is married, or has been married;
3. The person is unmarried but pregnant, and the research procedures relate to the diagnosis or treatment of pregnancy; or
4. The person is seeking treatment for sexually transmitted diseases, and the research procedures relate to diagnosis or treatment of sexually transmitted diseases.

### **Applicable Law - Minnesota**

Under Minnesota law, a person is generally considered to be a child until reaching the age of 18 years. In such instances, the child may not participate in research unless informed consent is provided by the child's parent(s) or guardian, as provided in Mayo IRB policies.

While there are no research-specific exceptions for determining whether a person is a child, there are certain limited situations in which a person younger than 18 years old may become an "emancipated minor" under Minnesota law. In such cases, the person may be treated the same as an adult for purposes of determining who may provide informed consent to participate in research. These situations include the following:

1. The person has been declared emancipated by a court order;
2. The person is married;
3. The person is living apart from his or her parents and managing his or her own financial affairs;
4. The person has given birth;
5. The person is seeking treatment for pregnancy and associated conditions; sexually transmitted diseases; or alcohol and other drug abuse, and the research procedures relate to those conditions.

### **Limitations of a Guardian to Consent for a Minor Child Participating in Research**

The following is a description of the 'applicable law' in Arizona, Florida and Minnesota.

#### **Arizona**

Arizona law does not expressly adopt any limitation as to the duties of a guardian concerning authorization of consent for research involving health care procedures. Because Arizona statutes (Arizona Revised Statute § 14-5312) define a guardian of a minor as having the powers and responsibilities of a custodial parent regarding the ward's support, care, and education, any existing limitations on a guardian to consent to a minor's involvement in research will only reflect those placed upon a custodial parent. The statute further states that a guardian should maintain sufficient contact with the ward to know of the ward's capacities, limitations, needs, opportunities and physical and mental health. As such, the researcher should be advised that no extra limitations are

placed on a guardian's authority to provide informed consent for a minor involved in health care research.

Arizona law (Arizona Revised Statute § 14-5312) provides a guardian of an incapacitated person with the same rights that a parent has respecting a parent's unemancipated minor child. A guardian may give consent necessary to enable the ward to receive medical care, counsel, treatment or service. A researcher is therefore advised that a guardian would not be limited in providing informed consent for a minor involved in health care research.

## **Florida**

Florida law does specifically address certain limitations placed on a guardian's ability to consent on another's behalf for specific procedures (both for health maintenance and experimental treatments). Under Florida Statute 394.4598, unless the guardian advocate has sought, and received, express court approval in a proceeding separate from the proceeding to determine the competence of the patient to consent to medical treatment, the guardian advocate may not consent to:

- Abortion.
- Sterilization.
- Electroconvulsive treatment.
- Psychosurgery.
- Experimental treatments that have not been approved by a federally approved institutional review board in accordance with 45 C.F.R. part 46 or 21 C.F.R. part 56.

As Florida Statute 394.4598 covers mental health treatments alone, no limitation appears to exist with regard to a guardian's authority to consent to experimental treatments without a court order if they do not involve treatments concerning a minor's mental illness.

## **Minnesota**

Minnesota law (524.5-102 subd. 5) defines a guardian as a person who has qualified as a guardian of a minor or incapacitated person pursuant to appointment by a parent or spouse, or by the court, and includes a limited, emergency, or temporary substitute guardian but not a guardian ad litem.

Like its Florida counterpart, Minnesota has limited a guardian's power to approve some health care treatments for a minor. Minnesota law (Minn. Stat. § 524.5-207) requires approval by court order before a guardian may give consent for psychosurgery, electroshock, sterilization, or experimental treatment of any kind. Because the text of Minn. Stat. § 524.5-207 directs the reader to a separate regulation covering developmentally disabled wards (Minn. Stat. § 524.5-313), it is likely that any express restriction on a guardian's authority to consent to any kind of experimental treatments be limited only to those treatments involving mental illness alone. As a result, Minnesota law remains silent as to any limitations placed on a guardian to provide informed consent for research involving those health care procedures and treatments not encompassing mental health.

## Children Who Reach the Legal Age for Consent

- Informed consent should be viewed as an ongoing process throughout the duration of a research project.
- When a child who was enrolled in a research study 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 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.
- 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), then it would be necessary for the investigator to obtain the informed consent of the now-adult subjects. The IRB may consider, if appropriate, a waiver or alteration 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.

## Legal Counsel

Legal counsel is available to assist the Mayo Clinic Institutional Review Board (IRB), researchers, and study teams regarding the

- Applicability of federal and state laws involving human subjects research,
- Resolution of any legal issues related to research regulations involving human subjects, and the
- Resolution of conflicts among applicable laws within (or outside) the jurisdiction where the organization resides.
- Contact information for Mayo Clinic Legal Counsel is available on the Legal Department website: <http://intranet.mayo.edu/charlie/legal/>.

## Related Documents

[Subpart D Determinations - Additional Protections for Children Involved as Subjects in Research](#)

[Exempt Human Subjects Research](#)

[Informed Consent and the Research Subject](#)

## References

[45 CFR 46](#) - *Protection of Human Subjects*

[45 CFR 46 Subpart D](#) - *Additional Protections for Children Involved as Subjects in Research*

[45 CFR 46.402 \(a\)](#) *HHS Policy for Protection of Human Research Subjects - Definitions*

[45 CFR 46.116](#) *General requirements for informed consent*

[45 CFR 46.409](#) *Wards*

## **Effective Date**

March 15, 2017

## **Revision History**

<b>Date</b>	<b>Synopsis of Change</b>
March 15, 2017	Scheduled review. Fixed broken link in fourth bullet under Legal Counsel heading.