SOP		
Department	**Title**	**Dates**
Research Integrity and Protection	Research Involving Children	Effective: 10/25/2017
		Approved: 6/21/2017
ID		Last Revised: n/a
IRB-SOP-908		Expiration: n/a

PURPOSE

This procedure explains and establishes the responsibilities of the Investigator and IRB in assuring additional protections are in place when involving children in research. Federal Regulations (45 CFR 46.111(b), 21 CFR 56.111(b)) require IRBs give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The Ascension Wisconsin IRB considers children to be a vulnerable population, in accordance with 45 CFR 46, Subpart D and 21 CFR 50, Subpart D. These regulations impose added responsibilities that depend on the degree of risk involved in the research and the extent to which the research is likely to benefit the subject or relate to the subject's illness. The regulations also set forth requirements for obtaining permission from parents and guardians, and, except under certain circumstances, assent by the children themselves.

SCOPE

This SOP applies to all research conducted at Ascension Wisconsin that involves children, as defined in this SOP, as possible human subjects. The Ascension Wisconsin IRB imposes additional protections on research involving children, in accordance with 45 CFR 46, Subpart D and 21 CFR 50, Subpart D, regardless of funding source, unless otherwise outlined in the Ascension Wisconsin Flexibility Policy. Research involving minors that is supported by the Department of Defense cannot be determined to be exempt.

DEFINITIONS

Advocate An individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the research. The Advocate is not associated in any way (except in her/his role as advocate or member of the IRB) with the research, the investigators, or the guardian.

Assent Agreement by an individual not competent to give legally valid informed consent (i.e. a child or cognitively impaired person). Ex: to obtain consent for research involving a child between the ages of 7 and 17, an assent form written in language understandable to the child is signed by the child, and a separate Child Consent form is read and signed by the parent(s) or legally authorized representative allowing the child to participate.

Children Persons who have not attained the legal age of consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. In Wisconsin, “children” are generally those persons under the age of 18 years (WSA 48.02(1d), 48.02(2)). Wisconsin state statues and case law, allow for minors with “majority” status to consent to their own medical care in certain circumstances such as emancipated minors or a minor seeking care for drug addition, testing or treatment for sexually transmitted diseases, or mental health care; Subpart D is not applicable in these cases.

Emancipated minors An emancipated minor, under Wisconsin law, includes (1) a married, widowed or divorced person who is at least 16 years old, (2) a minor who has given birth, (3) a minor emancipated by court order, (4) a minor emancipated by parental consent, and (5) a minor living on his or her own who is not supported by parents. (WSA 48.375(2)(e), 765.02(2), 895.037(1)(c)). Emancipated minors are able to give legal consent to treatments or procedures involved in research.

Guardian An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. In Wisconsin a "Guardian" of a minor means that the individual has the duty and authority to act in the best interests of the minor, subject to residual parental rights and responsibilities, to make important decisions in matters having a permanent effect on the life and development of the minor and to be concerned with his or her general welfare. (s. 48.02 (8)) Under Wisconsin law, in addition to a parent, a court-appointed "guardian" for an un-emancipated child under the age of 18 has the authority to consent to major medical, psychiatric and surgical treatment. [Wis. Stat. 48.023(1)].

Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. In considering the risks of a study involving children:

- Ascension Wisconsin interprets minimal risk in relation to the normal experiences of average, healthy, normal children.
- When evaluating risk, focus on the equivalence of potential harm or discomfort anticipated in research with the harm or discomfort that average, healthy, normal children may encounter in their daily lives or experience in routine physical or psychological examinations/tests.
- Consider the risk of harm or discomfort in relation to the ages of the children to be studied.
- Assess the duration, as well as the probability and magnitude, of potential harm or discomfort in determining the level of risk.

Parent A child's biological or adoptive parent.

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

Ward A child who is placed in the legal custody of the State or other agency, institution or entity, consistent with applicable Federal, State and local law. 21 CFR 50.3(q). This definition includes children placed in foster care.

PROCESS

1. **Safeguards, Considerations and IRB Review**
   - **1.1.** Any investigator who proposes to include children in research must complete the related applicable section of the IRB application including an initial determination of the risk/benefit category for the research, whether they feel assent may be obtained, or other safeguards are necessary. The IRB and/or designated member will review this information, including the requirements for assent and parental permission, as part of the protocol review process.
   - **1.2.** When any protocol involves the use of children as research subjects, an IRB member or consultant with appropriate expertise will be assigned to complete the review.
   - **1.3.** The IRB/designated reviewer will make a final determination as to the level of risk, the potential for direct benefits to the children and other specified features of the research in order to specify the category of research under which the IRB can approve the involvement of children. The following information describes the permissible risk categories for research that involves children.
     - **1.3.1.** Research not involving greater than minimal risk, if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. Consent from one parent is sufficient. (45 CFR 46.404; 21 CFR 50.51)
     - **1.3.2.** Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects, only if risk is justified by the anticipated benefit (45 CFR 46.405; 21 CFR 50.52.), where:
       - 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 the permission of their parents or guardians, as set forth below. Consent from one parent or guardian is sufficient.

1.3.3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406/21 CFR 50.53), where:

- 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 that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth below. Consent must be obtained from both parents if they have custody and are reasonably available.

1.3.4 Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem that affects the health or welfare of children, which the IRB does not believe meets the above requirements of this section, only if:

- The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem that affects the health or welfare of children; and
- The Secretary of the Department of Health and Human Services or the Commissioner of the Food and Drug Administration, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following the opportunity for public review and comment, has determined that either:
  i. The research satisfies the above requirements of this section, as applicable, or
  ii. The following: (1) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem that affects the health and welfare of children; (2) The research will be conducted in accordance with sound ethical principles; (3) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. Consent must be obtained from both parents if they have custody and are reasonably available.

1.4. The IRB will document the rationale for the risk/benefit assessment, and assent and parental permission; for protocols reviewed at a convened meeting. This will be included in the minutes.

1.5. The final letter of approval sent to the investigator will indicate the final risk/benefit determination and parental permission, assent or other requirements.

2. Special Procedures for Wards of the State

2.1. If children who are Wards are to be included in any research study, the investigator must provide the IRB with detailed information about the proposed permission/assent process, as well as the identity and authority of individuals who will provide permission for the Ward subjects, including method to be used to determine changes in guardianship (45 CFR 46.402; 21 CFR 50.55).

2.2. If the investigator does not initially anticipate the inclusion of Wards in the study, but the circumstances change or a situation arises where the investigator wishes to include a Ward, an amendment must be submitted so that any required regulatory requirements may be fulfilled.

2.3. Children who are Wards of the State may be included in:

2.3.1. Research that presents minimal risk. (45 CFR 46.404; 21 CFR 50.51)

2.3.2. Research that presents greater than minimal risk with a prospect of direct benefit. (45 CFR 46.405; 21 CFR 50.52.)

2.3.3. Research that presents greater than minimal risk with no prospect of direct benefit but is likely to yield generalizable knowledge; or research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, only if the IRB determines and documents that such research is: 1) related to the children's status as Wards; or 2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as participants are not Wards. (45 CFR 46.409(a); 21 CFR 50.56(a))

2.4. If Wards are to be included in research with no prospect of direct benefit the IRB shall appoint an advocate for each child who is a Ward. The advocate may serve in addition to any other individual acting on behalf of the child as guardian. One individual may serve as advocate for more than one child. The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the research. The advocate must not be associated in any way (except in the role of advocate or member of the IRB) with the research, the investigator(s), or the guardian organization. (45 CFR 46.409(b); 21 CFR 50.56(b)).

2.5. Since these situations are complex, investigators who wish to enroll Wards should contact the IRB and Office of General Counsel for guidance in complying with all Federal and State regulations pertaining to the inclusion of Wards in research.

3. Consent Process for Research Involving Minors

3.1. In addition to the *SOP: Obtaining Informed Consent for Research* and *SOP: Documentation of Informed Consent for Research*, there are special considerations and requirements for the informed consent process sand documents when involving minors as subjects.

3.2. Parental Permission

3.2.1. The IRB must 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 IRB is responsible to determine whether permission should be obtained from one or both parents.

3.2.2. The IRB will require permission to be obtained from both parents unless:

- One parent is deceased, unknown, incompetent, not reasonably available;
- Only one parent has legal responsibility for the care and custody of the child; or
- The study poses no more than minimal risk or more than minimal risk but offer the prospect of direct benefit to the individual subject (45 CFR 46.404 & 405), and the IRB specifically determines that the permission of one parent is sufficient.

3.2.3. Waiver of Parental or Guardian Permission

3.2.3.1. The IRB may waive or alter the elements of parental permission if it finds that the criteria at 45 CFR 46.116(d) are satisfied.

3.2.3.2. The IRB may waive documentation of parental permission if it finds the criteria at 45 CFR 46.117(b) are satisfied.

3.2.3.3. The IRB may also waive parental permission if a research protocol is designed to study conditions 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, for example, appointing a child advocate or an assent monitor.

3.2.3.4. The IRB cannot waive or alter the elements of parental permission if the study is FDA regulated or if the research is federally-supported and involves the use of newborn dried bloodspots collected on or after March 18, 2015.

3.2.4. Investigators conducting research involving Wards should also refer to the SOP: Obtaining Consent from a Legally Authorized Representative (LAR).

3.3. Assent from Children

3.3.1. Although the regulations state that children are unable to provide legally effective informed consent to participate in research, some might be able to give their assent. The IRB must review the proposed plan for assent and determine that adequate provisions are made for soliciting the assent of the children, when appropriate.

3.3.2. When determining whether children are capable of assenting, the IRB should take 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.

3.3.3. The IRB may waive or alter the elements of assent in accordance with 45 CFR 46.116(d), even if they determine that a child is capable of providing assent.

3.3.4. Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. The plan should include obtaining affirmative agreement from the child unless the capability of the child is so limited that the child cannot reasonably be consulted or the IRB determined that assent was not a requirement.

3.3.4.1. In general, a child's dissent should be respected and effort should be made to reach consensus between the parent(s) and the child. However, when the research offers the possibility of direct benefit important to his/her own health and may be available only through research, the parent(s) wishes generally prevail over the child's dissent. A child's assent, however, cannot override the unwillingness of a parent to provide parental permission.

3.3.5. When considering the plan for obtaining assent, the Investigator and IRB should consider:

3.3.5.1. The assent process should include a thoughtful discussion with the child regarding participation in the research and should illustrate respect for the child and convey the essential information the child requires, in a manner the child can understand, in order to make a decision about participating in the research.

3.3.5.2. If the child is under the age of 7, typically no assent form is required.

3.3.5.3. If the child is 7-17 years of age, a child assent form is usually required. The form should be brief and study specific, with language that is appropriate to the child's maturity and age. It may be appropriate to have more than one assent, depending on the age range of children involved.

3.3.5.4. In some cases, additional steps may be necessary to make it easier for the child to ask questions and not feel coerced by a parent/guardian. For example, it may be appropriate to spend time with the child/adolescent alone, without the parent/guardian present, or have a space for only the child to sign the assent form.

3.4. Consent from Children who Reach the Age of Maturity while Participating in a Study

3.4.1. When a child who was enrolled in research with parental or guardian permission reaches the legal age of consent, the subject's participation in the research is no longer regulated by the requirements regarding parental or guardian permission and subject assent, including this policy and 45 CFR 26.408 or 21 CFR 50.55.

3.4.2. The investigators should seek and obtain the legally effective informed consent for the now-adult subject for any ongoing interactions or interventions with the subjects, unless the Institutional Review Board (IRB) determines that the requirements for obtaining informed consent can be waived, in accordance with 45 CFR 46.116 and 21 CFR 50.20, .25.

3.4.3. 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 to seek and obtain the informed consent of the now-adult subjects. The IRB may consider waiver of the requirements for obtaining informed consent in order for the subjects to continue their participation in the research, if appropriate and the study is not FDA regulated.

REFERNCES
45 CFR 46, subpart D

RELATED MATERIAL
None

REVISION HISTORY

Version #	Date Revised	Reason for/Brief Description of Change	Revised By
01	4/11/2017	New- Initial Integration Update	J. Blundon