AAH RSPP GUIDANCE
Vulnerable Population

PURPOSE
The purpose of this document is to provide guidance to researchers on additional safeguards to protect the rights and welfare of vulnerable population who may have limited autonomy and/or at risk for coercion and undue influence. The federal regulations specify certain groups being vulnerable which include pregnant women, human fetuses, and neonates, prisoner, and children.

In addition to the populations covered by subparts B (pregnant women, human fetuses, neonates), C (prisoners), and D (children), the AAH IRBs will consider the need for additional protections when reviewing research involving other groups who may be subject to coercion or undue influence, either temporarily or permanently. These other potentially vulnerable populations may include, but are not limited to, AAH employees, students, individuals who are decisionally incapacitated, non-English speaking, educationally or economically disadvantaged, and the elderly.

This guidance is specific to vulnerable populations under subparts B, C, and D. However see the notations below on other important aspects of inclusion of vulnerable populations in HSR conducted at AAH. See also, RSPP Guidance: Employees as Research Subjects and RSPP Guidance: Surrogate Decision Makers/Legally Authorized Representatives (LAR) in Human Subject Research for information on the inclusion of these specific subject populations in your research.

NOTE the following:

- The AAH IRB is not constituted to review research that involves prisoners. If such research is to be conducted at AAH, or if an enrolled subject becomes a prisoner while an active participant, the research study will need to be ceded to an external IRB that is constituted to review this type of research.
- Per AAH system policy 2467, only when Human Subject Research is funded by the U.S. Department of Health and Human Service (DHHS), will the requirements of Advocate Aurora Health’s Federal Wide Assurance (FWA) – including the additional protections found in subparts B, C and D of 45 CFR 46 – be met. Human Subject Research not regulated by federal regulation will be reviewed and approved by the AAH IRB in accordance with the requirements of DHHS regulations except that the requirements at Subparts B-D of 45 CFR 46 may be incorporated, as the IRB determines appropriate, on a study-by-study basis.
- In the state of Wisconsin, if research is being conducted on inpatients that are being treated for mental illness, developmental disabilities or alcohol or drug abuse, the IRB must assign a consent monitor who has the authority to be present during the consent
process and to dis-enroll subjects whose rights under Wisconsin Statutes 51.61 have been violated or who withdraw their consent.

Definitions of italicized words can be found in the AAH RSPP Glossary.

PREGNANT WOMEN, HUMAN FETUSES, NEONATES (SUBPART B)

Pregnant women represent a vulnerable population when involved in human subjects research and require additional safeguards because of additional health concerns during pregnancy and the need to avoid unnecessary risk to the fetus.

What protections and safeguards must I include in my protocol and/or consent in which pregnancy is coincidental to subject selection or pregnant women are a targeted subject population?

Include the following if applicable:

• a statement that the particular treatment or procedure may involve risks to the subject and/or her fetus or nursing infant that are unforeseeable;
• the risks to the fetus or nursing infant due to the mother’s participation in the study.
• if there is a need to advise nonpregnant subjects to avoid pregnancy or nursing for the time during or following the research;
• if there is a need for the researchers to advise subjects to immediately contact them should they become pregnant;
• whether the potential risk is sufficient to justify requiring either excluding pregnant women from the research or requiring specific methods of contraception during and following participation in the research.

What are the considerations of the IRB in research involving evaluating pregnant women or fetuses?

The IRB will take into consideration the following:

• Whether the research is directed to the mother’s or fetus’ health and the risks to the woman and the fetus.
• Where scientifically appropriate, that preclinical studies and clinical studies have been conducted and there is data to support the inclusion of pregnant women, fetuses, and neonates.
• The risk of the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus. If there is no direct prospect of benefit, the IRB will consider if the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
• There must be no inducements, monetary or otherwise, offered to terminate a pregnancy. Individuals engaged in the research will have no part in any decisions as to the timing, method, procedures used to terminate a pregnancy.
• Individuals engaged in the research must have no part in determining the viability of a neonate.
• Any risk is the least possible for achieving the objectives of the research.

When is consent required from the pregnant woman?
Consent of the pregnant woman solely is obtained when the research holds out:
• The prospect of direct benefit to the pregnant woman,
• The prospect of direct benefit to both the pregnant woman and the fetus, or
• No prospect of benefit for the woman or the fetus when risk to the fetus is no greater than minimal and the purpose the research is the development of important medical knowledge which cannot be obtained by any other means.

The need for consent from the pregnant woman will be documented in the IRB meeting minutes or on a Primary Reviewer checklist if the study is approved under expedited review. The IRB approval letter will also document the IRB’s requirement for consent.

When is consent required from both the pregnant woman and the fetus’s father?
Consent from both the pregnant woman and the fetus’s father is required when the research holds out prospect of direct benefit solely to the fetus, except that the father’s consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

The need for consent from the pregnant woman and the fetus’s father will be documented in the IRB meeting minutes or on a Primary Reviewer checklist. The IRB approval letter will also document the IRB’s requirement for consent.

What if the pregnant woman is a minor?
The Common Rule generally requires informed consent from those who participate in research studies. Although Illinois and Wisconsin law specifically addresses consent for medical treatment of a pregnant minor, it does not separately address consent for participation in a research study that involves medical treatment. In the absence of specific law or regulations addressing consent for research, most institutions, including AAH, follow the local law for consent to medical treatment when determining legally effective informed consent for research studies under the Common Rule.

When may neonates be included in research?
Neonates of uncertain viability may be included in research if all of the following conditions are met:
• Where scientifically appropriate, pre-clinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;
• Each individual providing consent is fully informed regarding the reasonable foreseeable impact of the research on the neonate;
• Individuals engaged in the research will have no part in determining the viability of the neonate;
• The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
• The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent’s legally authorized representative is obtained in accord with the regulations, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

The need for consent from the pregnant woman and/or the fetus’s father will be documented in the IRB meeting minutes or on a Primary Reviewer checklist. The IRB approval letter will also document the IRB’s requirement for consent.

Non-viable neonates may be included in research after delivery if all of the following conditions are met:
• Where scientifically appropriate, pre-clinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;
• Each individual providing consent is fully informed regarding the reasonable foreseeable impact of the research on the neonate;
• Individuals engaged in the research will have no part in determining the viability of the neonate;
• Vital functions of the neonate will not be artificially maintained;
• The research will not terminate the heartbeat or respiration of the neonate;
• There will be no added risk to the neonate resulting from the research;
• The purpose of the research is the development if important biomedical that cannot be obtained by any other means; and the
• The legally effective informed consent of both parents of the neonate is obtained unless one parent is unable to consent because of unavailability, incompetence, or temporary incapacity and the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not be permissible under the regulations.

The need for consent from the pregnant woman and/or the fetus’s father will be documented in the IRB meeting minutes or on a Primary Reviewer checklist. The IRB approval letter will also document the IRB’s requirement for consent.
ENROLLMENT OF PRISONER SUBJECTS (SUBPART C)

NOTE: AAH IRB is not constituted to review research involving prisoners. If your proposed research will involve subjects that fall under the regulatory definition of “prisoner” or if an enrolled subject becomes a prisoner while an active participant, the research study will need to be ceded to an external IRB that is constituted to review this type of research. Contact the RSPP office for more information.

Potential research subjects who are prisoners are at increased risk for coercion and/or undue influence as a result of their incarceration. To ensure that their participation in research is uncoerced and voluntary, additional protections are afforded this population. [See OHRP guidance: Prisoner Research FAQs]

This guidance applies to whether the research involves individuals who are prisoners at the time of enrollment in the research, who become prisoners after they are enrolled in the research, or their status as prisoners is incidental to the research.

What are the additional regulatory considerations for research involving prisoners?

- The exemptions that generally apply to certain types of research involving human subjects do not apply to research involving prisoners;
- The IRB must include a prisoner or a prisoner representative;
- In order to approve research involving prisoners, the IRB must find that the proposed research falls into one of the permissible categories of research;
- the institution must certify to OHRP that an IRB has reviewed the proposal, and receive OHRP authorization prior to initiating any research involving prisoners; and
- A waiver informed consent is certain emergency research is not applicable to research involving prisoners.

What are the categories for permissible research involving prisoners?

- Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
- Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
- Research on conditions particularly affecting prisoners as a class (e.g. vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults);
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health and well-being of the participant. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research,
the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research.

What happens when a current research subject becomes a prisoner while in a research study?
If a subject becomes a prisoner, or the discovery of subjects with prisoner status as incidental to the research, after enrolling in a research study which was not approved for prisoner participation, the investigator is responsible for reporting the event in writing to the IRB per RSPP SOP #7 (UP Submission Requirements) and #8 (Review of UPs).

If the study was not previously reviewed and approved by the IRB in accordance with the requirements of Subpart C, all research interactions and interventions with, and the obtaining of identifiable private information must cease until all of the requirements under subpart C have been satisfied with respect to the relevant protocol. In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chair may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.

At the earliest opportunity after receiving the investigator’s notice or otherwise becoming aware of the Prisoner status of a subject, the IRB should review the protocol again with a Prisoner Representative as a member of the IRB.

GUIDANCE FOR THE ENROLLMENT OF CHILDREN (SUBPART D)

Children are considered by the federal regulations as being vulnerable to coercion. To safeguard their interests and protect them from harm, additional regulatory protections exist for research involving children. [OHRP Guidance: Research with Children FAQs]

Can a minor consent for themselves in research?
Minors cannot consent for themselves to participate in a research study as they have not reached the legal age of consent. [See Aurora system policy 189: Informed consent – informed refusal] The permission of the parent(s) and or legal guardian of the child is obtained in most research studies.

If a minor has been adjudicated as emancipated minor by an Illinois or Wisconsin court with jurisdiction over the minor, the minor would also be able to consent to medical treatment and research relating to treatment and/or research under Illinois and Wisconsin law.

Do I need to obtain parental permission from one or both parents?
Subpart D defines four categories of research involving children that specifies the number of parental signatures required for each category.
Category 1: Research not involving greater than minimal risk (45 CFR 46.404; 21 CFR 50.51)

- The research presents no more than minimal risk to the children; and
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or legal guardians as set forth at 46.408. Permission of one parent is permitted if approved by or the IRB may require the permission of both parents unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for care and custody of the child.

Category 2: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child (45 CFR 46.405; 21 CFR 50.52)

- The research presents more than minimal risk to the children by an intervention or procedure that holds out the prospect of direct benefit for the individual child, or by a monitoring procedure that is likely to contribute to the child’s well-being;
- The risk is justified by the anticipated benefit to the child;
- The relation of the anticipated benefit to the risk is at least favorable to the children as that presented by available alternative approaches; and
- Adequate provisions are made for obtaining the assent of the child and permission of their parents or legal guardian. Permission of one parent is permitted if approved by the IRB or the IRB may require the permission of both parents unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for care and custody of the child.

Category 3: Research involving greater than minimal risk and no prospect of direct benefit to the individual child, but likely to yield generalizable knowledge about the child’s disorder or condition (45 CFR 46.406; 21 CFR 50.53)

- Greater than minimal risk is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual child, or by a monitoring procedure which is not likely to contribute to the well-being of the child;
- Risk represents a minor increase over minimal risk;
- Intervention or procedure presents experiences to subjects that are reasonably commensurate with those intent in their actual or expected medical, dental, psychological, social, or educational situations;
- Intervention or procedure is likely to yield generalizable knowledge about the subject’s 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 obtaining the assent of the child and permission of their parents or legal guardian. Permission of both parents is required unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for care and custody of the child/minor.

Category 4: Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407; 21 CFR 50.54). For research where the IRB finds that the research does not meet the
requirements set forth in categories 46.404, 46.405, or 46.406 as described above, the IRB may approve the research only if:

- The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, alleviation of a serious problem affecting the health or welfare of children; and
- If Federally funded or under the purview of the FDA, the Secretary of DHHS or, if applicable, FDA Commissioner, after consultation with a panel of experts in pertinent disciplines and following an opportunity for public review and comment, has determined either:
  - That the research in fact satisfies the conditions of categories 46.404, 46.405, or 46.406; or
  - The research presents a reasonable opportunity to further the understanding, prevention, 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 and guardians. Permission of both parents is required unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for care and custody of the child.

The category of research involving children along with the need for parental permission, and from one or both parents, will be documented in the IRB meeting minutes or on a Primary Reviewer checklist. The IRB approval letter will also document the IRB’s determination of research category for research with children, and the requirement for parental permission from one or both parents.

**Should assent be obtained from children to participate in a research study?**

When children are involved in research, the regulations require investigators to obtain the child’s agreement to take part in the study unless the child’s capacity is limited or compromised due age, maturity, and/or psychological state. This is known as assent. Generally, IRBs require that the assent of a minor child be sought when the child is seven years of age or older, unless the child’s decision-making capacity is impaired.

The need for assent from the child will be documented in the IRB meeting minutes or on a Primary Reviewer checklist. The IRB approval letter will also document the IRB’s requirement for assent.

**How is assent documented?**

If the child is not old enough or cannot document their agreement in writing, the child should verbally indicate their willingness to participate. Documentation of the child’s assent should be recorded using the checkbox on the parental permission document, and within medical record.
Older children may document their assent in writing (by the printing or signature of their name) in an assent document that is appropriate for their age/reading level. If the subject population includes a wide range of ages it may be necessary to use more than one assent document to accommodate different ages/reading levels.

The RSPP Office has a parental permission template available on the [RSPP website](#), as well as multiple assent document templates that may be used to create age appropriate assents for the research study.

**Can I get a waiver of assent?**

The IRB may grant a waiver of assent if the IRB determines and provides protocol specific information documenting that:

- Children are not capable of providing assent based on their age, maturity, or psychological state;
- The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- 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 research.

The IRB’s granting of a waiver of assent will be documented in the IRB meeting minutes or in a Primary Reviewer checklist. The IRB approval letter will also document the issuance of a waiver of assent in the study.

**Can I get a waiver of parental permission?**

The IRB may waive the requirement for obtaining parental permission from parents or guardians when the research does not fall under FDA regulations and it meets the criteria for a waiver:

- The research involves no more than minimal risk;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not practicably be carried out without the waiver or alteration; and
- Whenever appropriate, subjects will be provided with additional pertinent information after participation.

The IRB’s granting of a waiver of parental permission will be documented in the IRB meeting minutes or in a Primary Reviewer checklist. The IRB approval letter will also document the issuance of a waiver of assent in the study.

**What happens if the child does not assent, but the parent or guardian gives parental permission?**

When assent is required by the IRB, the decision of the child assenting is binding. This means that the child cannot be included in the research if he/she does not provide assent.
What happens if the duration of the child’s participation in research may continue after turning 18 years old?
Informed consent is 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 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 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.

What happens if the enrolled child becomes a ward of the state during research participation?
Should a child become a ward of the state during research participation, permission from child protective services or the appointed guardian will need to be obtained for the child to continue in a research study that involves an intervention. If the study is a medical record review only, permission from the parent that was obtained prior to the change in custody is still applicable. AAH Research Legal counsel may be obtained should this situation occur.

REQUIREMENTS
- Common Rule Regulations 45 CFR 46, subparts B, C, D
- FDA regulation: 51 CFR 50
- AAH System Policy: 2467, 189
- AAH RSPP SOPs: 5-8
- State Law: WI statute - §51.61