

6.0 Vulnerable Subjects in Research

6.1 Policy

The following procedures describe the requirements for involving vulnerable subjects in research under the purview of the Pennington Biomedical Research Center IRB.

6.2 Involvement of Vulnerable Populations

When some or all of the subjects in a protocol are likely to be vulnerable to coercion or undue influence, the investigator should include additional safeguards to protect the rights and welfare of these subjects. Some of the vulnerable populations that might be involved in research include individuals who are children, pregnant women, fetuses, neonates or economically or educationally disadvantaged, adults who lack the ability to consent, students, employees or homeless persons.

Additional requirements for IRB oversight of research involving vulnerable subjects can be found at 45 CFR part 46, which includes the following: subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research; and subpart D - Additional Protections for Children Involved as Subjects in Research. Pennington Biomedical Research Center does not review research under Subpart C - Research Involving Prisoners.

DHHS-funded research that involves any of these populations must comply with the requirements of the relevant subparts. Research funded by other federal agencies may or may not be covered by the subparts.

Under Pennington Biomedical Research Center FWA, the subparts only apply to DHHS-funded research and research funded by another federal agency that requires compliance with the subparts (FDA regulations include Subpart D, which applies to all FDA-regulated research). The following policies and procedures, which are based on the subparts, apply to all research regardless of funding. The individual sections describe how the subparts apply to DHHS-funded research.

6.3 Definitions

Vulnerable population (or “vulnerable subjects”): This includes the following classes of potential or actual research subjects: children, pregnant women, cognitively-disabled persons, or economically or educationally disadvantaged persons.

6.4 IRB Responsibilities

- The IRB reviews the investigator's justifications for including vulnerable populations in the research to assess appropriateness of the research proposal.
- The IRB must ensure that additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects as needed at the time of initial review of the research proposal.
- The IRB shall continue to review research at intervals appropriate to the degree of risk and determine whether the proposed research continues to fulfill criteria for approval. Information reviewed should include the number of subjects considered as members of specific vulnerable populations.
- The IRB needs to carefully review the DSMB plan for all research involving vulnerable subjects.
- The IRB should be knowledgeable about and experienced in working with populations who are vulnerable to coercion and undue influence. If the IRB requires additional qualification or expertise to review a protocol, it should obtain consultation.

6.5 Procedures

6.5.1 Initial Review of Research Proposal

The following steps are relevant with respect to initial review of a research proposal:

- The investigator is responsible for identifying the enrollment of potential vulnerable subjects in the research proposal and provide the justification for their inclusion in the study. The investigator is responsible for identifying patients who are at risk for impaired decisional capacity as a consequence of psychiatric illness, and who are being asked to participate in a research study with greater than minimal risk.
- The IRB evaluates the proposed plan for consent of the specific vulnerable populations involved. If the research involves adults unable to consent, the IRB evaluates the proposed plan for permission of legally authorized representatives.
- The IRB evaluates and approves the proposed plan for the assent of subjects.
- The IRB evaluates the research to determine the need for additional protections.
- The investigator should provide appropriate safeguards to protect the subject's rights and welfare, which may include the addition of an independent monitor. The independent monitor is a qualified individual not involved in the research study who will determine the subject's capacity to provide voluntary informed consent.

- The IRB assess the adequacy of additional protections for vulnerable populations provided by the investigator.

6.5.2 Continuing Review and Monitoring

At continuing review, the investigator should identify the number of vulnerable subjects enrolled and any that needed an independent monitor in the progress report.

6.6 Research Involving Pregnant Women or Fetuses

6.6.1 Definitions

Delivery: means complete separation of the fetus from the woman by expulsion, extraction, or any other means.

Fetus: is the product of conception from the time of implantation until delivery. [DHHS 45 CFR 46.202(c); LA R.S. 40:1299.35.1].

Pregnant: is the period of time from confirmation of implantation until expulsion or extraction of the fetus. [DHHS 45 CFR 46.202(f)].

6.6.2 Research Not Funded by DHHS

For research not funded by DHHS, no additional safeguards are required by the regulations and there are no restrictions on the involvement of pregnant women in research where the risk to the fetus is no more than minimal risk.

Pregnant women or fetuses may be involved in research not funded by DHHS involving more than minimal risk to fetuses if all of the following conditions are met:

- Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
- The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;
- Any risk is the least possible for achieving the objects of the research;
- If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accordance with the provisions for informed consent;
- If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accordance

with the provisions for informed consent, 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;

- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- For children who are pregnant, assent and permission are obtained in accordance with the provisions of permission and assent (see section [6.8.3.2](#));
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- Individuals engaged in the research will have no part in determining the viability of a neonate.

Regulations & Guidance: DHHS 45 CFR 46.204.

6.6.3 Research Funded by DHHS

For DHHS-funded research, 45 CFR subpart B applies to all research involving pregnant women. According to 45 CFR subpart B, pregnant women or fetuses may be involved in research funded by DHHS if all of the following conditions are met:

- Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses.
- The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal risk and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
- Any risk is the least possible for achieving the objects of the research;
- If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal risk and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accordance with the provisions for informed consent.

- If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accordance with the provisions for informed consent, 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.
- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in section 6.8.3.2;
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- Individuals engaged in the research will have no part in determining the viability of a neonate.

6.7 Research Involving Neonates

6.7.1 Definitions

Neonate: means newborn. [DHHS 45 CFR 46.202(d)].

Neglect: neglect of neonate means a medical finding by a Louisiana licensed physician that a neonate either is dependent upon or suffers from withdrawal symptoms from an illegal controlled dangerous substance. It also includes a medical finding by a physician that a neonate suffers from an illness, disease or condition attributable to the exposure of the newborn, in utero, of an illegal CDS.

Non-Viable Neonate (or “Non-Viable Fetus”): is a fetus ex utero that, although living, is not able to survive to the point of independently maintaining a heartbeat and respiration. [DHHS CFR 46.202(e)].

Viable Neonate (or “Viable Fetus”): means a fetus that is able, after delivery, to survive to the point of being able to independently maintain a heartbeat and respiration (given the benefit of available medical therapy). [DHHS 45 CFR 102(c) & (l); 45 CFR 46.202(h)].

6.7.2 General Requirement Regarding Research Involving Neonates

Neonates of uncertain viability and non-viable neonates may be involved in research if all of the following conditions are met:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;
- Each individual that's providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate; and
- Individuals engaged in the research will have no part in determining the viability of a neonate.

The requirements of neonates of uncertain viability or non-viable neonates (see below in this section) have been met as applicable.

Regulations & Guidance: DHHS 45 CFR 46.205(a).

6.7.3 Neonates of Uncertain Viability

Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met.

The IRB determines that:

- 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 accordance with the provisions of permission and assent, 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 IRB Chair will have the IRB determine and document individuals providing consent are fully informed regarding the reasonably foreseeable impact of the research on the neonate.

Regulations & Guidance: DHHS 45 CFR 46.205(b).

6.7.4 Non-Viable Neonates

After delivery, non-viable neonates may not be involved in research covered by this subpart unless all of the following additional conditions are met:

- 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 of important biomedical knowledge that cannot be obtained by other means; and
- The legally effective informed consent of both parents of the neonate is obtained in accordance with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.
- However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a non-viable neonate will suffice to meet the requirements of this paragraph, except that 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 non-viable neonate will not suffice to meet the requirements of this paragraph.
- The IRB Chair will have the IRB determine and document individuals providing consent are fully informed regarding the reasonably foreseeable impact of the research on the neonate.

Regulations & Guidance: DHHS 45 CFR 46.205(c).

6.7.5 Viable Neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accordance with the requirements of IRB review process and research involving children. [DHHS 45 CFR 46.205(d)].

6.7.6 Research involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accordance with any applicable federal, state, or local laws and regulations regarding such activities.

If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research participants and all pertinent sections of this document are applicable. [DHHS 45 CFR 46.206].

6.7.7 Research Not Otherwise Approvable

6.7.7.1 Research Not Funded by DHHS

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 pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the IRB will consult with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, and law). Based on the recommendation of the panel, the IRB may approve the research based on either:

- That the research in fact satisfies the conditions of Section 6.6, 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 pregnant women, fetuses or neonates;
 - The research will be conducted in accordance with sound ethical principles; and
 - Informed consent will be obtained in accordance with the provisions for informed consent and other applicable sections of this document.

Regulations & Guidance: DHHS 45 CFR 46.207.

6.7.7.2 Research Funded by DHHS

DHHS-funded research that falls in this category must be approved by the Secretary of DHHS. 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 pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

Newborns are only considered neonates until they are determined to be viable (able to survive outside of the uterus). Once they are determined to be viable, they are considered children; the IRB will follow guidelines from section 6.8 Research Involving Children.

6.8 Research Involving Children

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with subpart D of 45 CFR 46 (applicable to DHHS-funded research) and subpart D of 21 CFR 50 (applies to FDA-regulated Research involving Children).

Regulations & Guidance: FDA 21 CFR 56.109(h); 21 CFR 56.111(c)].

6.8.1 Definitions

Assent: means a child's affirmative agreement to participate in research. Mere failure of a child to object may not, absent affirmative agreement, be construed as assent.

[FDA 21 CFR 50.3(n)].

Child: are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. [DHHS 45 CFR 46.402(s); FDA 21 CFR 50.3(o)].

According to Louisiana Law, the legal age for consent for treatment or medical procedures is 18 years or older. [LA Children's Code 116; LA R.S. 40:1095]. Louisiana law is silent with respect to the legal age to consent with respect to research. For purposes of these SOPs, any person who is under the age of 18 generally is unable to consent for him/herself. Several important exceptions exist under Louisiana law that effectively treat children as adults and gives them the capacity to consent to their own medical care and to participate in research. They include the following: for a child to receive medical and/or surgical care at a hospital and/or to receive physicians' services [LA R.S. 40:1095]. This may or may not overlap with the proposed research; if a child is emancipated by marriage. Regardless of age, a child is fully emancipated upon his or her marriage [LA Children's Code Art 379]; if a child is judicially emancipated. This requires a court order for child older than 16 years of age [LA Children's Code Art 366 and 1922];

If a child is emancipated by authentic act this requires a child older than 16 years of age and the child's parents to execute a written document of emancipation, signed before two witnesses and a notary [LA Children's Code Art 368]; if a child seeks to be treated for venereal disease [LA R.S. 40:1065.1]; and if a child seeks to be treated for drug abuse [LA R.S. 40:1096].

Because Louisiana law does not specifically address consent of children with majority status to research, the institution's IRB will review issues of consent related to enrollment of these children in research on a case-by-case basis.

Guardian (or legal guardian): means an individual who is authorized under applicable state or local law to consent on behalf of a child to (a) general medical care when general medical care includes participation in research; or (b) to participate in research. [DHHS 45 CFR 46.402(e); FDA 21 CFR 50.3(s); LA. Children's Code 116(12.1) (a) (i) (b)]. A guardian of a minor retains the duty and authority to (1) act in the best interests of the minor, subject to residual parental rights and responsibilities (if any); (2) make important decisions in matters having a permanent effect on the life and development of the minor; and (3) to be concerned with the minor's general welfare. For research conducted in jurisdictions other than Louisiana, the research must comply with the laws regarding guardianship in all relevant jurisdictions where the research will take place.

Health Agent: is an authorized representative legally acting for a person pursuant to a Durable Power of Attorney for Health Care (Medical Power of Attorney) or other legal document permitted within a jurisdiction that allows a person to appoint another person(s) to make medical decisions for the patient if the patient should become temporarily or permanently unable to make those decisions for himself/herself. Any adult (18 or older) can be granted this power. [LA R.S.40:1299.53(A) (13)].

Legally Authorized Representative: is an individual, judicial, or other body authorized under applicable law to consent or otherwise provide permission on behalf of a subject, either prospectively or during the course of research, to the subject's participation in the procedure(s) involved in the research. [DHHS 45 CFR 46.102(c); FDA 21 CFR 50.3(l)]. For the purposes of this document, a legally authorized representative includes a person appointed as a health agent, a court-appointed legal guardian of the person, as well as next-of-kin in the following order of priority unless otherwise specified by applicable state law: the subject's spouse; adult child(ren) of subject (18 years of age or older); parent of subject; adult sibling(s) of subject (18 years of age or older); grandparent(s) of subject; or adult grandchild(ren) of subject (18 years of age or older). If there is more than one person within the above named class, the consent shall be given by a majority of those members of the class available for consultation. [LA R.S. 40:1299.53] legally authorized representative should not be confused with legal guardian.

Minor: means any person under the age of 18 years. [LA Children's Code Art 116]. Do not confuse the definitions of minor (pertaining to a person's age) with child/children (pertaining to a person's ability to assent).

Parent: means a child's biological or adoptive parent.

[FDA 21 CFR 50.3(p)].

6.8.2 Allowable Categories

Research on children must be reviewed and categorized by the IRB into one of the following groups:

1. Not greater than minimal risk: research on children not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., minimal risk). This includes adequate provisions are made for soliciting the assent of children and the permission of their parents or legal guardians as set forth in section 6.8.3.
2. Greater than minimal risk: research on children involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject.
 - 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 children and the permission of their parents or legal guardians as set forth in section 6.8.3.
3. Greater than minimal risk and no prospect of direct benefit: research on children involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
 - 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 to the understanding of amelioration of the subjects' disorder or condition; and
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or legal guardians as set forth in section 6.8.3.
4. Research Not Otherwise Approvable: research on children not otherwise approvable which presents an opportunity to understand, prevent, or alleviate

serious problems affecting the health or welfare of children. Federally-funded research in this category must be approved by the DHHS Secretary, and requires consent of either both parents and the legal guardian. FDA-regulated research in this category must be approved by the FDA Commissioner. For non-federally funded research, the IRB Chair will consult with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, or law) and following opportunity for public review and comment, determine either:

- That the research in fact satisfies the conditions of the previous categories, 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
 - Informed consent will be obtained in accordance with the provisions for informed consent and other applicable sections of this document. Adequate provisions are made for soliciting the assent of children and the permission of their parents or legal guardians as set forth in section 6.8.3.

Regulations & Guidance: DHHS 45 CFR 46.404; 45 CFR 46.405; 45 CFR 46.406; 45 CFR 46.407.

6.8.3 Parental Permission and Assent

6.8.3.1 Parental Permission

Since a child cannot consent for him/herself, the IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or legal guardian, as documented in the consent (the sample minor document can be found at www.pbrc.edu/HRPP/Forms)

Consent should be obtained as follows in this order of priority: mother and father [LA Children's Code Art 216] or adoptive foster parents [LA R.S. 40:1299.55]. The right first rests with married parents of the child. If they consent, comply with their wishes (subject to the assent requirements below). If they do not agree, the father's choice prevails [LA Children's Code Art 216]. A power of attorney from the child's parents to another adult [LA Children's Code Art 216 The court recognized tutor [LA Children's Code Art 246 and 253]; or a power of attorney from the child's tutor to another adult [LA R.S. 9:951].

For research conducted in jurisdictions other than Louisiana, the research must comply with the laws regarding the legal age of consent in all relevant jurisdictions. The institution's legal department will provide assistance to the IRB office and investigators with regard to the laws in other jurisdictions.

Parents or legal guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in Policy 5.

In addition to the requirements under Louisiana law, the IRB may find that the permission of one parent is sufficient for research to be conducted under FDA categories CFR 21.51 or 50.52 45, or under HHS categories CFR 46.404 or 45 CFR 46.405. Consent from both parents is required for research to be conducted under categories CFR 21. 50.52 or 50.52, or under HHS categories 45 CFR 46.406 or 45 CFR 46.407 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.

For research not covered by the FDA regulation, the IRB may waive the requirement for obtaining consent from a parent or legal guardian if: The research meets the provisions for waiver in Policy 5 or if the IRB determines that the research protocol is designed for conditions or a subject population for which parental or legal guardian permission is not a reasonable requirement to protect the subjects (e.g., neglected or abused children) provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with federal, state or local laws. 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.

For research that involves no more than minimal risk or more than minimal risk with the prospect of direct benefit to the individual children, the IRB determines whether:

- The permission of both parents 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, or the permission of one parent is sufficient.

- For research that involves more than minimal risk without the prospect of direct benefit to the individual children, the IRB determines that the permission of both parents 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.

Parental permission may not be waived for research covered by the FDA regulations.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by HRPP Policy 5.

Regulations & Guidance: DHHS 45 CFR 46.408

6.8.3.2 Assent from Children

Because assent means a child's affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the IRB is charged with taking into account the ages, maturity, and psychological state of the children involved.

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

The IRB presumes that children ages 9 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script should be obtained from children 9 -11 years of age. Written assent using a written

document for the children to sign may be sought for older children. This opportunity can be extended to children at age 7, provided the child's age and maturity level enables the child to comprehend the nature of the research activity.

At times there may be inconsistency between parent permission and child assent. Usually a "no" from the child overrides a "yes" from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual exceptions to these guidelines (such as when the use of an experimental treatment for a life threatening disease is being considered). The general idea, however, is that children should not be forced to be research subjects, even when their parents' consent to it.

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.

The IRB will determine and document that assent is a requirement of: all children, some children or none of the children. When the IRB determines that assent is not a requirement of some children, the IRB determines and documents which children are not required to assent.

6.8.3.2.1 Determination by the IRB Assent is not a Requirement

When the IRB determines that assent is not a requirement for some or all children, the IRB determines and documents one or more of 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.
- Assent can be waived using the criteria for waiver of the consent process.

6.8.3.2.2 Determination by the IRB Assent is a Requirement

When the IRB determines that assent is a requirement, the IRB determines whether:

- Assent will be documented.
- If so, the process to document assent.

Even when the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances detailed in the Waiver of Informed Consent section of Policy 5.

Regulations & Guidance: DHHS 45 CFR 46.408.

6.8.3.3 Consent from Pregnant Minors

A minor may consent to medical care or the administration of medication by a hospital licensed to provide hospital services or by a physician licensed to practice medicine for the purpose of alleviating or reducing pain, discomfort, or distress of and during labor and childbirth. [LA R.S. 40:1095(A) (2)]. This consent shall be valid and binding as if the minor had achieved her majority, and it shall not be subject to a later disaffirmance by reason of her minority.

If research pertains to such permitted minor consent, then the minor may consent to the involved research. If not and the IRB has not waived the consent requirement, then assent from the minor is required, as well as parental permission.

6.8.4 Assent Form

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

Researchers should try to draft a form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form (Sample Child's Assent on the HRPP website) should:

- Tell why the research is being conducted;
- Describe what will happen and for how long or how often;
- Say it's up to the child to participate and that it is permissible to say no;
- Explain if it will hurt and if so for how long and how often;
- Say what the child's other choices are;

- Describe any good things that might happen;
- Say whether there is any compensation for participating; and
- Ask for questions.

For younger children, the document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

6.8.5 Children who are Wards of the State

Children who are wards of the state or any other agency, institution, or entity can be included in research involving greater than minimal risk where there is no prospect of direct benefits to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, only if 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 subjects are not wards.

If the research meets the condition(s) above, the IRB Chair will determine an advocate must be appointed by the IRB or institution for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or *in loco parents*.

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child 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 investigator(s), or the guardian organization.

Regulations & Guidance: DHHS 45 CFR 46.409.

6.9 Persons with Impaired Decision Making Capacity

The requirements in this section apply to all research involving persons with mental disabilities or persons with impaired decision-making capacity regardless of funding source.

Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

- Only incompetent persons or persons with impaired decision making capacity (as determined by licensed health care professionals who are qualified to make such determinations consistent with the scope of their license) are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
- The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the subject. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
- Procedures have been devised to ensure that subject's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health agents (appointed under Medical Power of Attorney) and next-of-kin, or legal guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest. In addition and as appropriate, if assent can be obtained by a subject/potential subject with diminished decision making capacity (versus impaired), then the investigator should obtain such assent. The determination as to whether an individual retains capacity to assent must be determined by a duly qualified health care provider, consistent with the provider's scope of licensure.
- A non-therapeutic clinical trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written consent document. Non-therapeutic clinical trials may be conducted in subjects with consent of a legally authorized representative provided the following conditions are fulfilled:
 - The objectives of the trial cannot be met by means of a trial in subjects who can give consent personally;
 - The foreseeable risks to the subjects are low;
 - The negative impact on the subject's well-being is minimized and low.
 - The trial is not prohibited by law;
 - The opinion of the IRB is expressly sought on the inclusion of such subjects, and the written opinion covers this aspect; and

- Unless an exception is justified, the trial should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in such trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

6.9.1 IRB composition

The IRB membership must include at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population. The IRB may utilize ad hoc members as necessary to ensure appropriate scientific expertise.

6.9.2 Determination of Decision-Making Capacity

The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation.

The investigator and research staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate.

For research protocols that involve subjects with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group.

For research that poses greater than minimal risk, the IRB may require investigators to use independent and qualified professionals to assess whether potential subjects have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the IRB may require that the study include a capacity assessment if there are reasons to believe that potential subjects' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research subjects with mental disorders. See the next section for details with respect to determining capacity to consent.

For research protocols involving subjects who have fluctuating or limited decision making capacity the IRB may ensure that Investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the

subject to consider the information that has been presented. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with health agent may be necessary.

It is often possible for Investigators and others to enable persons with some decisional impairment to make voluntary and informed decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent interviews, second opinions, use of independent consent observers, interpreter for hearing-impaired subjects, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision making process.

Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

In the event research subjects become incompetent or impaired in decision making capacity after enrollment, the investigator is responsible for notifying IRB staff. The investigator is responsible for developing a monitoring plan which follows the guidelines outlined above for incompetent and impaired decision making research subjects.

6.9.3 Determining Capacity to Consent

The majority of studies conducted at the institution only allow enrolling subjects who have the capacity to consent. For studies that have been approved for enrolling vulnerable populations who may lack capacity to consent, there must be someone who is able to assess capacity of each potential subject to consent. The investigator may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time. Additionally, if the reason for lack of capacity is because of mental illness then a psychiatrist or licensed psychologist must confirm this judgment and document in the individual's medical record in a signed and dated progress note.

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring: ability to evidence a choice; ability to understand relevant information; ability to appreciate the situation and its likely consequences; and ability to manipulate information rationally.

A range of professionals and methods may be utilized to assess capacity. In general the consent assessor should be a researcher or consultant familiar with dementias and qualified to assess and monitor capacity and consent in such subjects on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team and/or institution.

A person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject must then be notified. If a person objects to participating, this objection should be respected.

6.9.4 Informed Consent and Assent

Whenever the subjects have the capacity to give consent (as determined by licensed health care professionals who are qualified to make such determinations consistent with the scope of their license), informed consent should be obtained and documented in accordance with Policy 5. When subjects lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject as described below.

A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the trial to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, sign and date the written informed consent or a separate assent form. If the person objects to participating, this objection should be heeded.

Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with legally authorized representative may be necessary. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

6.9.5 Consent by Legally Authorized Representative

The regulations generally require that the investigator obtain informed consent from subjects. Under appropriate conditions, investigators also may obtain informed consent from a legally authorized representative of a subject (legally authorized representative).

This policy is designed to protect human subjects from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to persons who are incompetent, or who have an impaired decision-making capacity.

Legally authorized representative may be obtained from a court appointed legal guardian of the person or a health agent appointed by the person in a Medical Power of Attorney. For example, a subject might have designated an individual to provide consent with regard to health care decisions through a durable power of attorney and have specified that the individual also has the power to make decisions on entry into research.