6 Vulnerable Subjects in Research

When participants in research conducted under the auspices of CMU are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all of the regulatory requirements for the protection of vulnerable subjects are met and that appropriate additional protections for vulnerable subjects are in place.

The following procedures describe the requirements for involving vulnerable participants in research under the auspices of CMU.

6.1 Involvement of Vulnerable Populations

When participants in a protocol are likely to be vulnerable to coercion or undue influence, the IRB should include additional safeguards to protect their rights and welfare. Examples of the vulnerable populations that might be involved in research include children, fetuses, neonates, prisoners, or individuals with impaired decision-making capability, students, employees, or homeless persons.

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants. 45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations that also have additional requirements for IRBs.

Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D – Additional Protections for Children Involved as Subjects in Research

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 CMU's 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.

6.2 Responsibilities

1. The PI is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal. The PI is responsible for identifying participants who are at risk for impaired decisional capacity who are being asked to participate in a research study.

2. The IRB shall include representation, either as members or ad hoc consultants, individual(s) who have professional interest in or who have experience with the vulnerable populations involved in a research proposal.
3. The IRB reviews the PI's justifications for including vulnerable populations in the research to assess appropriateness of the research proposal.
4. 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.
5. Information reviewed as part of the continuing review process should include the number of participants considered as members of specific vulnerable populations.
6. For studies that do not have or are not required to have a Data and Safety Monitoring Board (DSMB) or a Data Monitoring Committee and have entered vulnerable subjects, the IRB needs to carefully review the safety monitoring plan.
7. 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.

6.3 Procedures

6.3.1 Initial Review of Research Proposal

1. The PI should identify the potential to enrol vulnerable subjects in the proposed research at initial review and provide the justification for their inclusion in the study.
2. 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.
3. The IRB evaluates and approves the proposed plan for the assent of participants.
4. The IRB evaluates the research to determine the need for additional protections and consider the use of a Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee as appropriate.
5. The PI should provide appropriate safeguards to protect the subjects' 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.
6. The IRB assesses and documents the adequacy of additional protections for vulnerable populations provided by the PI.

6.4 Research Involving Pregnant Women, Human Fetuses, and Neonates

CMU IRB does not review research on neonates or fetuses of uncertain viability.

6.4.1 Research Involving Pregnant Women or Fetuses

The following applies to all research regardless of funding source. Since, according to the CMU FWA, Subpart B of 45 CFR 46 applies only to DHHS-funded research, the funding-source specific requirements are noted in the appropriate sections.

6.4.1.1 Research Not Funded by DHHS

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

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:

1. 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 riskrisks to pregnant women and fetuses.
2. 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.
3. Any risk is the least possible for achieving the objectives of the research.
4. If the research holds out the prospect of direct benefit to the pregnant woman and/or the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
5. 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 accord 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.
6. Each individual providing consent under paragraph (4) or (5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
7. For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent.
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

6.4.1.2 Research Funded by DHHS

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

1. 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 risk to pregnant women and fetuses.
2. 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 and the purpose of the research

is the development of important biomedical knowledge that cannot be obtained by any other means.

3. Any risk is the least possible for achieving the objectives of the research.
4. 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 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 accord with the provisions for informed consent.
5. 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 accord 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.
6. Each individual providing consent under paragraph (4) or (5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
7. For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section .
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

6.4.2 Research Involving 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 accord with the requirements of IRB Review Process and Research Involving Children.

6.4.3 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 accord 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 subjects and all pertinent sections of this manual are applicable.

6.5 Research Involving Prisoners

6.5.1 Applicability

The following applies to all research involving prisoners, regardless of funding source. The requirements in this section are consistent with Subpart C of 45 CFR 46, which applies to DHHS-funded research.

Even though CMU IRB may approve a research protocol involving prisoners as subjects according to this policy, investigators are still subject to the Administrative Regulations of the [Michigan] Department of Corrections and any other applicable state or local law [See 45 CFR 46.301].

6.5.2 Composition of the IRB and Role of the Prisoner Representative

In addition to satisfying the general requirements detailed in the IRB section of this manual, when reviewing research involving prisoners, the IRB must also meet the following requirements:

1. A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB.
2. At least one voting member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.
   The prisoner representative may be listed as an alternative member who becomes a voting member when needed.
3. The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C or equivalent protections.
   The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer)
4. The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved.
   The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.
5. The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.
6. Minor modifications to research may be reviewed using the expedited procedure described below, using either of the two procedures described based on the type of modification.
7. Modifications involving more than a minor change reviewed by the convened IRB – must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).
8. Continuing review must use the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

If no participants have been enrolled, the research may receive continuing review using the expedited procedure under expedited category #8.

6.5.3 Use of Expedited Review Procedures

1. For research involving interaction with prisoners reviewed by the expedited procedure:
2. Research involving interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied.
3. The prisoner representative must concur with the determination that the research involves no greater than minimal risk.
4. The prisoner representative must review the research as a reviewer, designated by the chair, or consultant. This may be as the sole reviewer or in addition to another reviewer, as appropriate.
5. Review of modifications and continuing review must use the same procedures for initial review using this expedited procedure including the responsibility of the prisoner representative.
6. For research that does not involve interaction with prisoners (e.g. existing data, record review) reviewed by the expedited procedure:
    a. Research that does not involve interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied.
    b. Review by a prisoner representative is not required.
    c. The prisoner representative may review the research as a reviewer or consultant if designated by the IRB chair.
    d. Review of modifications and continuing review must use the same procedures as initial review.

6.5.4 Exempt Determinations

The CMU IRB does not make exempt determinations when reviewing prisoner research.

6.5.5 When a Participant Becomes a Prisoner

If a participant becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, then the following steps must be carried out by the IRB and the investigator:

1. Confirm that the participant meets the definition of a prisoner.
2. Terminate enrollment or review the research study under Subpart C if it feasible for the participant to remain in the study.
3. Before terminating the enrollment of the incarcerated participant the IRB should consider the risks associated with terminating participation in the study.
4. If the prisoner's participation cannot be terminated for health or safety reasons, then the IRB may:
    a. Allow the prisoner to remain enrolled in the study and review the research under Subpart C.

b. If some of the requirements of Subpart C cannot be met, but it is in the best interests of the participant to remain in the study, then the IRB may allow the prisoner to remain enrolled and inform OHRP of the decision along with the justification.
c. Remove the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use, or off label use.

6.5.6 Additional Duties of the IRB when prisoners are involved

In addition to all other responsibilities prescribed for IRB in the CMU Institutional Review Board and IRB Review Process sections of this manual, the IRB will review research involving prisoners and approve such research only if it finds the following:

1. The research falls into one of the following **permitted categories** [See 45 CFR 46.306]:
   a. 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 subjects;
   b. 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 subjects;
   c. Research on conditions particularly affecting prisoners as a class (e.g., research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults);
   d. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subjects.
2. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his/her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
5. The information is presented in language which is understandable to the subject population.
6. Adequate assurance exists that Parole Board will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.
7. Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences and for informing subjects of this fact.

6.5.6.1 Certification to HHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is supported by HHS shall certify to the Secretary (through OHRP) that the IRB has made the seven (7) findings required under 45 CFR 46.305(a). For all HHS conducted or supported research, CMU will send to OHRP a certification letter to this effect, which will also include the name and address of the institution and specifically identify the research protocol in question and any relevant HHS grant application or protocol. HHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its approval in writing to CMU on behalf of the Secretary under 45 CFR 46.306(a)(2).

Under its authority at 45 CFR 46.115(b), OHRP requires that the institution responsible for the conduct of the proposed research also submit to OHRP a copy of the research proposal so that OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so, which one. The term "research proposal" includes the IRB-approved protocol, any relevant HHS grant application or proposal, any IRB application forms required by the IRB, and any other information requested or required by the IRB to be considered during initial IRB review.

The above requirement does not apply to research that is not HHS conducted or supported.

6.5.6.2. Waiver for Epidemiology Research

The Secretary of DHHS has waived the applicability of 45 CFR 46.305(a)(l) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiological studies that meet the following criteria:

1. The sole purposes are:
   a. to describe the prevalence or incidence of a disease by identifying all cases, or
   b. to study risk factor associations for a disease, and
2. The IRB has approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)–(7) and determined and documented that
   a. the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
   b. prisoners are not a particular focus of the research.
3. The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a)(2).
4. The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects.
5. In order for a study to be approved under this waiver, the IRB would need to ensure that, among other things, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.

6.6 Research Involving Children

The following procedures apply to all research involving children, regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children.

6.6.1 Allowable Categories

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

1. Research 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). Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 6.7.2.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject:
   a. the risk is justified by the anticipated benefit to the subjects; and
   b. adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 6.7.2.
3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject but likely to yield generalizable knowledge about the subject's disorder or condition:
   a. the risk represents a minor increase over minimal risk;
   b. 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;
   c. adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 6.7.2.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children:
   a. federally-funded research in this category must be approved by the Secretary of Health and Human Services;
   b. FDA-regulated research in this category must be approved by the Commissioner of Food and Drugs;
   c. for non-federally-funded, non-FDA research, the IRB will consult with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on whether
      i. the research in fact satisfies the conditions of the previous categories, as applicable; or
      ii. the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
   d. the research will be conducted in accord with sound ethical principles; and

5. adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 6.7.2.

6.6.2 Parental Permission and Child Assent

6.6.2.1 Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in Section 5.5.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories (a) and (b) above. The IRB's determination of whether consent must be obtained from one or both parents will be documented in the consent checklist when a protocol receives expedited review and in meeting minutes when reviewed by the convened committee.

Consent from both parents is required for research to be conducted under Categories (c) and (d) above unless:

1. One parent is deceased, unknown, incompetent, or not reasonably available; or
2. 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

1. the research meets the provisions for waiver in Section 5.8, or
2. if the IRB determines that the research protocol is designed for conditions or a subject population for which parental or 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 law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol; the risk and anticipated benefit to the research subjects; and their age, maturity, status, and condition.

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

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 5.6 and 5.9.

6.6.2.2 Assent from Children

Because "assent" means a child's affirmative agreement to participate in research, the child must actively show his/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 has the discretion to judge children's capacity to assent for all of the children to be involved in a proposed research activity or on an individual basis.

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 7 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script should be obtained from children 7 - 11 years of age. Written assent using a written document for the children to sign may be sought for older children.

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.

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 this manual.

6.6.2.3 The Assent Form

When the IRB determines that assent is required, it will 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 should:

1. tell why the research is being conducted,
2. describe what will happen and for how long or how often,
3. say it's up to the child to participate and that it's okay to say no,
4. explain if it will hurt and if so for how long and how often,
5. say what the child's other choices are,
6. describe any good things that might happen,
7. say whether there is any compensation for participating, and
8. 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.

6.6.2.4 Children Who Are Wards

Children who are wards of the state or any other agency, institution, or entity can be included in 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, **only if such research** is:

1. related to their status as wards; or
2. 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, an advocate must be appointed 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 parentis.*

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.

6.7 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 be approved only when the following conditions apply:

1. Only incompetent persons or persons with impaired decision making capacity 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.

2. 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 participant. 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.
3. Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents, appointed under Durable Power of Attorney for Health Care (DPAHC), and next-of-kin, or 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.

6.7.1 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 a consultant as necessary.

6.7.2 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.

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.

It is often possible for investigators and others to enable persons with some decisional impairments 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.

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 surrogate consent may be.

Though competent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives.

In the event research participants become incompetent or impaired in decision making capacity after enrolment, the PI is responsible for notifying the IRB and HRPP office. The PI is responsible for developing a monitoring plan which follows the guidelines outlines above for incompetent and impaired decision-making research participants.

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring:

1. ability to communicate a choice,
2. ability to understand relevant information,
3. ability to appreciate the situation and its likely consequences, and
4. 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/she is sufficiently independent of the research team.

A person who has been determined to lack capacity to consent to participate in a research study should 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 should then be notified. If the person objects to participating, this objection should be heeded.

6.7.3 Informed Consent and Assent

Whenever the participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained and documented in accordance with Section 5 above. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject (i.e., surrogate consent) 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 research to the extent compatible with the subject's

understanding and, if possible, the subject should give their assent to participate, and sign and date the written informed consent or a separate assent form

Surrogate consent may be obtained from a legally authorized representative as described in Section 5.2.