

6.0 SPECIAL SUBJECT POPULATIONS

6.1 Children: Additional Requirements for Participation in Research

6.1.1 Definitions

- 1) Children: Persons < 18 years old
- 2) Assent: An affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
- 3) Permission: The agreement of parent(s) or guardian to the participation of their child or ward in research.
- 4) Parent: A child's biological or adoptive parent.
- 5) Guardian: An individual who is authorized under Commonwealth of Pennsylvania law or the law of another competent jurisdiction to consent on behalf of a child for general medical care.

6.1.2 Inclusion of Children in Research

Note that the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects, effective October 1998, requires that children be included in all human subject research conducted or supported by the NIH unless there are scientific and ethical reasons not to involve them. The goal of this policy is to increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders that affect adults and may also affect children. Therefore, for human subject research protocols (to be) conducted or supported by NIH and/or which involve the use of the General Clinical Research Center (GCRC), the investigators must include a description of the plans for including children and a rationale for selecting or excluding a specific age range of child participants, or an explanation of the reason(s) for excluding children as participants in the research. When children are included, the plan must also include a description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. If children (or specific age ranges of children) are to be excluded from the research study participation, the investigator must provide a justification addressing one or more of the specific exclusionary circumstances listed in this policy. For research protocols that do not involve NIH support or use of the GCRC, the investigators should address their plans for the inclusion of children (including the respective considerations listed above) and/or provide a justification for their exclusion from study participation.

The IRB addresses the appropriateness of the population studied in terms of the aims of the research and ethical standards. IRBs have the responsibility to examine ethical issues, including equitable selection of research participants in accordance with Federal Regulations (45 CFR 46). The participation of children in research is important to assure that they receive a share of the benefits of the research.

6.1.3 Permitted Categories of Research Involving Children

IRBs have special review requirements (45 CFR 46, Subpart D, Sections 401-409) to protect the well-being of children who participate in research. IRBs may approve research involving children only if one of the following specific criteria is met:

- 1) The research presents no greater than minimal risk¹ to the involved subjects. (45 CFR 46.404)
- 2) The research involves an intervention or procedure that presents greater than minimal risk to the involved children but which holds out the potential for direct individual benefit; provided that:
 - a) the risk is justified by the extent of potential benefit to the involved children; and
 - b) the relation of the potential benefit to the risk is at least as favorable to the involved children as that presented by available alternative approaches. (45 CFR 46.405)
- 3) The research involves an intervention or procedure that presents greater than minimal risk to the involved children and which does not hold out the potential for direct individual benefit; provided that:
 - a) the risk represents a minor increase over minimal risk;
 - b) the intervention or procedure presents experiences to the involved children that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; and
 - c) the intervention or procedure is likely to contribute to increased generalizable knowledge about the involved child's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition. (45 CFR 46.406)
- 4) Research not otherwise permitted which presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and which is determined by an ethics committee convened by the Secretary, DHHS, to meet this criterion and sound ethical principles. (45 CFR 46.407)

6.1.4 Permission by Parent(s) or Guardian for Children Involved in Research

6.1.4.1 Permission Requirement

The permission of the child's parent(s) or guardian must be obtained prior to participation of the child in a research study. An exception to the above requirement is a prospective determination by the IRB that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (e.g. neglected or abused children). Under this circumstance, an appropriate mechanism for protecting the children who will participate as subjects in the research must be substituted (e.g., see 6.1.7 Wards). 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 involved children, and their age, maturity, status and condition. The IRB must consider whether to require permission of both the child's parents unless:

- a) one parent is deceased, unknown, incompetent, or not reasonably available; or
- a) when only one parent has legal responsibility for the care and custody of the child.

¹Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

6.1.4.2 Documentation of Permission by Parent(s) or Guardian

The permission of the child's parent(s) or guardian must be documented by the inclusion of signature(s) on the consent form using the following statement:

PARENTAL CERTIFICATION

"I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study."

Parent Signature

Date

6.1.5 Assent by Children

6.1.5.1 Child Assent Requirements

- 1.) The written assent of children ages 14-17 must be obtained prior to their participation in a research study.
- 2.) In addition, children younger than age 14 who are developmentally able to sign the assent section should be asked to do so.
- 3.) Exceptions to the above requirements are limited to a prospective determination by the IRB that a) the capability of the children included in the study is so limited that they cannot reasonably be consulted, or b) 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 study.

6.1.5.2 Documentation of Assent

For children ages 14-17 or for younger children who are developmentally able to sign their names include the following language:

This research has been explained to me, and I agree to participate.

Signature of Child-Subject

Date

Printed Name of Child-Subject

To document obtaining the assent of a child who is unable to sign the assent section, the following Verification of Explanation statement must appear on the informed consent document (i.e., below the signature line of the parent(s) or guardian) and be signed and dated by the principal investigator or listed co-investigator.

VERIFICATION OF EXPLANATION I certify that I have carefully explained the purpose and nature of this research to (name of child) in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she provided affirmative agreement (i.e., assent) to participate in this research.

Principal/Co-Investigator Signature

Date

6.1.6 Child Abuse Statement

The following statement shall appear under the Confidentiality section of all informed consent documents involving research studies conducted on children: **“If the researchers learn that you or someone with whom you are involved is in serious danger or harm they will need to inform the appropriate agencies as required by Pennsylvania law.”** Alternate language for this statement may be used, however, the IRB must review and approve any deviations from standard language.

6.1.7 Wards

6.1.7.1 Limitations on Research Involving Wards

Children who are wards of the Commonwealth of Pennsylvania or any other agency, institution, or entity can be included in specific criteria 3) and 4) of section 6.1.3, paragraph 2 (see above) 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

6.1.7.2 Advocate for Wards Involved in Research

Research involving wards meeting the limitations defined under 6.1.7.1 and approved by the IRB requires the appointment of an adult advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as a guardian or in loco parentis.

- 1) One individual may serve as an advocate for more than one child.
- 2) The advocate shall be an adult who has the background and experience to act in, and agrees to act in, the best interests of the ward for the duration of the child's participation in the research and who is not associated in any way with the research, the investigator(s), or the guardian organization.

6.1.8 Emancipated Minors

The provisions that permit a minor to be considered emancipated vary depending upon the circumstance. In the State of Pennsylvania, a minor can be considered emancipated for one purpose (for example, obtaining birth control) but not for others. Unless a minor has been emancipated by court order, which should be confirmed by requesting a copy of the order, a minor should NOT be considered emancipated for research purposes.

6.1.9 Foster Children

Under Pennsylvania law, neither foster parents nor CYS can provide the informed consent to enroll a foster child in a research study. Only the birth parent, or a person adjudicated as an adoptive parent, can provide that informed consent. If a legal guardian provides consent, the court order or legal authorization should be copied and included in the research records with the consent document.

6.2 Pregnant Women, Fetuses, and In-Vitro Fertilization: Additional Requirements for Participation in Research

6.2.1 Definitions

- 1) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous

movement of voluntary muscles, nor pulsation of the umbilical cord.

- 2) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.
- 3) Fetus means the product of conception from implantation until delivery.
- 4) Neonate means a newborn.
- 5) Nonviable neonate means a neonate after delivery that, although living, is not viable.
- 6) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.
- 7) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.
- 8) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

6.2.2 General Requirement for Research Involving Pregnant Women and Fetuses

Pregnant women or fetuses may be involved in research only if all of the following conditions are met:

- 1) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks 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 which cannot be obtained by any other means;
- 3) Any risk is the least possible for achieving the objectives of the research;
- 4) The informed consent of the pregnant woman shall be obtained in accord with the standard regulatory provisions for informed consent if the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit to both the pregnant woman and the fetus, or no prospect of direct benefit for the pregnant woman nor fetus when 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 other means.
- 5) The informed consent of the pregnant woman and the father shall be obtained in accord with the standard regulatory provisions for informed consent if the research holds out the prospect of direct benefit solely to the fetus; except the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity, or if the pregnancy resulted from rape or incest.
- 6) Each individual providing consent under 4) or 5) above shall be 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 requirements outlined in section 6.1 of this chapter.

- 8) No inducements, monetary or otherwise, shall be offered to terminate the pregnancy.
- 9) Individuals engaged in the research shall have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- 10) Individuals engaged in the research shall have no part in determining the viability of the neonate.

6.2.3 General Requirements for Research Involving Neonates

- 1) Neonates of uncertain viability and nonviable neonates may be involved in research only if all of the following conditions are met:
 - a) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;
 - b) Each individual providing consent (see section 6.2.2, 4 and 5) is fully informed regarding the reasonably foreseeable impact of the research on the neonate;
 - c) Individuals engaged in the research will have no part in determining the viability of the neonate; and
 - d) The requirements outlined under this section, items 2) and 3) below, have been met as applicable.
- 2) Requirements for research involving neonates of uncertain viability: Until it has been determined whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions are met:
 - a) The IRB determines that:
 - (i) 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 the objectives of the research, or
 - (ii) 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
 - b) 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 standard regulatory provisions for informed consent; except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. (**Note:** For research involving viable neonates, the IRB is permitted to grant a waiver or alteration of such informed consent in accord with applicable regulatory provisions.)
- 3) Requirements for research involving nonviable neonates: A nonviable neonate may not be involved in research unless all of the following additional conditions are met:
 - a) Vital functions of the neonate will not be artificially maintained;
 - b) The research will not terminate the heartbeat or respiration of the neonate;

- c) There will be no added risk to the neonate resulting from the research;
 - d) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
 - e) The legally effective informed consent of both parents of the fetus is obtained in accord with the standard regulatory provisions for informed consent. (**Note:** the IRB is not permitted to grant a waiver or alteration of such informed consent for research involving nonviable neonates.) However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable 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. (**Note:** The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.)
- 4) Requirements for research involving viable neonates: A neonate, after delivery, that has been determined to be viable is a child and may be included in research only to the extent permitted by and in accord with the requirements outlined under section 6.1 of this chapter.

6.2.4 General Requirements for Research Involving, After Delivery, the Placenta, the Dead Fetus, or Fetal Material

- 1) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus does not constitute "human subject" research in accordance with the Federal Policy definition of "human subject".
- 2) If information associated with the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus is recorded in such a manner that living individuals (e.g., the parent(s)) can be identified, directly or through identifiers linked to such individuals, those individuals are "human subjects" of the research study and the requirement for their informed consent applies.

In some instances, federal regulations allow for tissue to be utilized without informed consent. However, as it relates to fetal tissues or organs, the Pennsylvania Abortion Control Act (18 Pa.C.S. Section 3216 - <http://www.legis.state.pa.us/WU01/LI/LI/CTS/18/00.032.016.000..HTM>) specifies that fetal tissues or organs may only be obtained for use in research subsequent to obtaining the written informed consent (i.e., for use of the fetal tissue in research) of the mother. The Pennsylvania Abortion Control Act specifies that research involving the use of fetal tissue or organs must also conform to each of the following general requirements:

- 1. No consideration of any kind (i.e., monetary or otherwise) will be offered to the mother in obtaining her consent for the research use of the fetal tissue or organs.
- 2. The mother will not be permitted to designate the recipient of the fetal tissue or organ for use in research.
- 3. All persons who participate in the procurement or use of the fetal tissue or organs will be informed as to the source of the tissue (e.g., abortion, miscarriage, stillbirth, ectopic pregnancy). Note: Any research protocol that involves an intervention derived from fetal tissue or organs must include this information as part of the informed consent document and process.
- 4. Since the Abortion Control Act prohibits the individual involved in obtaining such consent from "employing the possibility of the use of aborted fetal tissue or organs as an inducement to a pregnant woman to undergo abortion", informed consent for the research use of fetal tissue derived from an abortion will be obtained separate from, and after the decision and consent to abort has been made.

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- If researchers are obtaining fetal tissues or organs from sources outside of the University of Pittsburgh, confirmation must be provided from the outside source that the material was collected without appropriately obtained consent.

6.2.5 General Requirements for Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Pregnant Women, Fetuses, or Neonates

Research the IRB does not believe meets the requirement of sections 6.2.2, 6.2.3, or 6.2.4 may be approved only if:

- 1) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of pregnant women, fetuses or neonates; and
- 2) The Secretary, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:
 - a) The research in fact satisfies the conditions of sections 6.2.2, 6.2.3, or 6.2.4, as applicable, or
 - b) The following:
 - (i) 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;
 - (ii) The research will be conducted in accord with sound ethical principles; and
 - (iii) Informed consent will be obtained in accord with the standard regulatory provisions for informed consent unless the IRB has approved a waiver or alteration of the standard informed consent requirements.

6.3 Prisoners: Additional Requirements for Participation in Research

6.3.1 Definitions

- 1) Prisoner: The federal regulations define a "prisoner" as "any individual involuntarily confined or detained in a penal institution. This term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute; individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution; and individuals detained pending arraignment, trial, or sentencing."
- 2) Minimal Risk: For research involving prisoners, the federal regulations define "minimal risk" as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons."

6.3.2 Specific Investigator Requirements for Research Involving Prisoners

No prisoner may be involved as a subject of a research activity unless the specific requirements listed below have been **addressed by the investigator** and approved by the IRB. These requirements apply to research that specifically involves prisoners **or to research that involves a person who at a later date becomes a prisoner.**

(If a subject becomes a prisoner after enrollment in a research study the investigator should notify the IRB immediately. Either the prisoner-subject must be withdrawn from study participation; or the IRB must, at the earliest opportunity, re-review the research protocol and consent form in accordance with the listed requirements. The IRB can either (a) approve the involvement of the prisoner-subject in the research or (b) determine that this subject must be withdrawn from the research. **Note that if the subject-prisoner is withdrawn from study participation, s/he must be fully informed of the reason for such action.)**

Requirements:

- 1) The research under review represents one of the following categories of research permissible under the Subpart C, 45 CFR Part 46, regulations; i.e.,:
 - a study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study represents no more than minimal risk and no more than inconvenience to the subjects;
 - a 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;
 - research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; or research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults); or
 - research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.
- 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 magnitude that his or 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 nonprisoner 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 Board 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 boards 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; and

- 7) Where there may be a need for follow-up examination or care of participants 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 participants of this fact

6.3.3 Specific IRB Requirements for Research Involving Prisoners

When the IRB reviews a protocol in which a prisoner is a subject, the federal regulations require that at least one member of the IRB shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity.

The IRB must meet this special composition requirement for all types of review of a protocol that involves a prisoner-subject; including initial review, renewal review, protocol amendments, and reports of unanticipated problems involving risk to subjects.

If the research protocol (or research protocol renewal or modification) that is being submitted for IRB review involves a prisoner-subject notify, in advance, the IRB specifically of this situation so that the special composition requirements can be addressed. Investigators should also plan for delays in the time for IRB review as a result of the special arrangements and OPRR notifications that are necessary to comply with this special composition requirement and the additional OPRR certifications required by the federal regulations for research involving prisoners as subjects.

6.3.4 State Law Considerations

In Pennsylvania, the Department of Corrections has issued Policy Statement 2.1.2 which effectively bans the use of state prisoners in any medical experiments, cosmetic experiments, or pharmaceutical testing, with the exception for some testing involving treatment for AIDS and HIV infection.

6.3.5 Federal Bureau of Prisons

The Federal Bureau of Prisons has adopted extensive regulations for researchers seeking to use federal prisoners as research subjects. Among other things, these regulations prohibit use of prisoners within federal facilities for "medical experimentation, cosmetic research, or pharmaceutical testing." 28 C.F.R. 512.11(a)(3). In addition, strict limitations are imposed on incentives to prisoner/participants, and researchers may not promise confidentiality to subjects who reveal a future intent to engage in criminal behavior.

6.4 Persons with Decisional Impairment: Additional Requirements for Participation in Research

6.4.1 General Principles

While persons with a condition that may impair their ability to give informed consent may be enrolled in research under federal regulations and state law, special consideration must be taken in the design of the protocol and in the seeking of proxy consent. This chapter sets forth the principles that investigators and the IRB must follow in approving research involving persons with decisional impairment.

As a general rule, all adults, regardless of their diagnosis or condition, should be presumed competent to consent to participation in research unless there is evidence of serious disability that would impair reasoning or judgment. For example, mental illness, cognitive impairment or other disability alone should not disqualify a person from consenting to participate in research; rather, there should be specific documented evidence of the individual's incapacity to comprehend the voluntary nature of research participation, the nature of the research procedures, their potential risks and benefits, and their ability to make a personal judgment about the value of participation before they are deemed unable to consent.

6.4.2 General Guidelines for Research Involving Persons with Decisional Impairment

6.4.2.1 Selection of Subjects

- 1) Research involving persons with decisional impairment shall bear some direct relationship to the subject's condition or circumstances. For example, a person with decisional impairment should not be considered as a subject for a protocol that does not either involve the study or treatment of the condition that has produced their decisional impairment, or is otherwise related to the subject's condition.
- 2) Preferentially, subjects should be recruited from among non-institutionalized populations whenever possible.

6.4.2.2 Generally Accepted Categories of Research

Research involving persons with decisional impairment shall be limited to the following categories.

- 1) Research presenting no greater than minimal risk to the involved subjects.
- 2) Research involving an intervention or procedure that presents an increase over minimal risk to involved subjects, but which offers the potential for direct individual benefit to the subject.
- 3) Research involving an intervention or procedure that presents an increase over minimal risk to involved subjects and which does not have the potential for direct individual benefit; provided that the knowledge sought has direct relevance for understanding or eventually alleviating the subjects' disorder or condition.

6.4.2.3 Research Protocol Considerations

In addition to the standard research protocol requirements, the investigators should address the following items in the Human Subjects section of any research protocol involving persons with decisional impairment:

- 1) Provide a justification indicating which of the approved categories of research is being conducted in the current study (i.e., 6.4.2.2, paragraphs 1 - 3).
- 2) When it will be necessary to obtain informed consent from the subject's legally authorized representative (see Section 6.4.3), the following additional information must be addressed:
 - a) The rationale for the need to obtain proxy consent;
 - b) The criteria that will be used in determining whether a potential subject has decisional impairment sufficient to require the use of proxy consent, including any use of standardized assessment tools.
 - c) Whether any additional methods are proposed to enhance subjects' ability to achieve decisional capacity with regard to the proposed study (e.g., reading of the consent form may not be sufficient and use of other tools such as videos, educational materials, post-tests, etc. might be considered to assist potential subjects in understanding what is involved with the research.)
 - d) Who will be approached, and in what order, to provide proxy consent (see Section 6.4.3 for further information on who may provide proxy consent).
- 3) In evaluating a protocol involving the enrollment of persons with decisional impairment, the IRB shall consider requiring additional safeguards where appropriate for a given protocol. Such safeguards may

include any of the following. The protocol for each study should state which of the following safeguards are included:

- a) Use of an independent party (independent of the study investigator with appropriate expertise) to assess the capacity of a potential subject.
 - b) Use of standardized assessments of cognition and/or decisional capacity.
 - c) Use of informational or educational techniques. Because informed consent is an on-going process throughout the course of the research protocol, assessing and enhancing comprehension at each stage is essential. Tools to aid in this effort may include single sheet summaries of important information about key elements of the studies, regular opportunities for study participants and their families to ask questions, and other educational tools to enhance understanding, including use of videos demonstrating study interventions or use of post-tests documenting comprehension.
 - d) Use of an independent monitor. This monitor, who must be independent of the study investigators, will monitor the consent process to verify what information was conveyed.
 - e) Use of waiting periods. Vulnerable populations may need additional time to consider information about a research protocol. Planning built-in waiting periods into the informed consent process may be useful to increase comprehension in decisionally impaired populations and to allow involvement, where appropriate, of participants' family members.
 - f) Use of proxy consent, in accordance with the procedures set forth in section 6.4.3.
 - g) Use of assent in addition to proxy consent in order to respect the autonomy of individuals with decisional impairment.
- 4) In any protocol approved as a high risk study or which falls under category 6.4.2.2 (3) above, the protocol must include the safeguards set forth in Section 6.4.2.3 (3a), and must address which of the other safeguards contained under Section 6.4.2.3 (3) will be included, or provide an explanation of why such safeguards will not be included.

6.4.3 Consent Requirements for the Involvement of Persons with Decisional Impairment in Research

6.4.3.1 General Considerations regarding Consent and Assent

Respect for the autonomy of individuals requires that, as a general rule, all adults, regardless of their diagnosis or condition, should be presumed competent to consent to participate in research unless there is evidence of serious mental disability that would impair the individual's ability to comprehend the voluntary nature of research participation, the nature of the research procedures, their potential risks and benefits, and their ability to make a personal judgment about the value of participation before they are deemed unable to consent. In those cases where a protocol fitting into one of the categories described in section 6.4.2.2 is approved by the IRB, and proxy consent is contemplated, the following procedures must be followed. These procedures reflect Pennsylvania law regarding the federal requirement that a subject or a subject's legally authorized representative consent to any research procedure.

- 1) Persons with decisional impairment may also have been adjudicated legally incapacitated by a court decision. If such persons are considered for enrollment in a research protocol, the *only* party who may provide proxy consent is the court-appointed guardian. Under Pennsylvania law, such guardian may only provide proxy consent if the court order, appointing them guardian, specifically states that they have the authority to enroll the incapacitated person into a research protocol. For this category of subjects, a copy of the court order appointing the guardian should be attached to the informed consent document.

- 2) Persons may also, through a health care proxy appointed by a power of attorney, designate a person to make decisions for them in the event that they are subsequently incapacitated. This person may give proxy consent for enrollment of a subject in research.
- 3) If a potential subject has neither a guardian, nor a health care proxy designated, the investigator may obtain the informed consent of the subject's legally authorized representative. Pennsylvania case law supports the use of proxy consent by close relatives where a subject is unable to make decisions regarding medical care. Where neither a court-appointed guardian, nor a health care proxy exists, investigators may seek informed consent from the following individuals, in the order listed below:
 - i. Spouse;
 - ii. Natural or adoptive parent;
 - iii. Adult child;
 - iv. Adult brother or sister;
 - v. Any other available adult relative related through blood or marriage known and documented to have made decisions for the subject in prior health care settings;
- 4) Where a person is giving proxy consent, the proxy should be informed that, where possible, he/she should base his or her decision on substituted judgment, reflecting the views that the subject expressed while decisionally capable. The proxy should be fully informed on the risks, benefits and alternatives to the research, and, where the values of the subject are not known with respect to a proposed research study, the proxy should act in the best interest of the subject.
- 5) If a person with decisional impairment is capable of exercising some judgment concerning the nature of the research and participation in it, the investigator should obtain the subject's assent in addition to the consent of his/her legally authorized representative.
- 6) The verbal objection of an adult with decisional impairment should be binding. If the subject, at any time, objects to continuing in the research study, such objection should be respected.
- 7) Where the condition causing the subject's decisional impairment is of an intermittent or temporary nature, the informed consent process should include a mechanism for obtaining the subject's subsequent direct informed consent to participate in the research. If such subject, upon regaining decisional capacity, declines to continue participation in the research, such decision must be respected.

6.4.3.2 Documentation of Consent and Assent: Consent Form

- 1) Adult persons, not deemed to have decisional impairment, should read and sign the informed consent document in a standard manner.
- 2) For adult persons with decisional impairment, the investigator shall:
 - a) Document the conclusion that the subject is incapable of understanding the information presented regarding the research, to appreciate the consequences of acting (or not acting) on that information, and to make a choice;
 - b) Document the information provided to the subject's legally authorized representative regarding the cognitive and health status of the subject, the risks and benefits of the research, and the role of the proxy; and

- c) Obtain the consent and signature of the subject's legally authorized representative or guardian and the signature of a witness to this consent.

Sample Consent Form:

Patient/Subject Signature

ONLY WHEN APPLICABLE

The patient is unable to consent because:

I, therefore, consent to participation for the patient.

Signature

Date

Legal Representative

Relationship to Subject

Witness Signature

Date

- 3) To document obtaining the assent of a subject with decisional impairment to participate in the research study, the following verification of explanation statement should appear on the respective informed consent document and be signed and dated by the principal investigator, listed co-investigator, or other research staff when authorized by the IRB (e.g., in minimal risk studies where the protocol designates a member of the research team, who is not listed as a co-investigator, to obtain consent).

Sample

VERIFICATION OF EXPLANATION

I certify that I have carefully explained the purpose and nature of this research to (name of subject) in appropriate language. He/She has had an opportunity to discuss it with me in detail. I have answered all of his/her questions and he/she provided affirmative agreement (i.e., assent) to participate in this research.

6.4.3.3 Documentation of Consent and Assent: Research Record

In studies in which some or all participants may have decisional impairment, it is recommended that at the time of obtaining consent the following be documented in a note to file for the subject's research record:

- 1) Whether the subject demonstrated the ability to understand the nature of the research procedures, the potential risks and benefits, the voluntary nature of participation and to make a personal judgment about participation;
- 2) Use of any supplemental methods to enhance or evaluate decisional capacity.

- 3) A summary of the matters discussed with the subject's legally authorized representative.

6.5 Traumatized and Comatose Persons: Additional Requirements for Participation in Research

Research involving patients undergoing emergency care differs from clinical research in other settings because the patient's capacity to provide consent is often severely compromised, and decisions about participation in research may have to be made too quickly to obtain permission from the patient's legally authorized representative.

6.5.1 Informed Consent Requirements for Traumatized and Comatose Persons

6.5.1.1 Waiver of Informed Consent for Minimal Risk Research

According to DHHS Federal Policy regulations, the requirement to obtain informed consent from potential research subjects may be waived prospectively by the IRB only if each of the following conditions is met:

- 1) the risks of study participation are no greater than minimal;
- 2) the research could not reasonably be carried out without waiving the requirement for informed consent;
- 3) such a waiver would not adversely affect the subject's rights or welfare; and
- 4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

6.5.1.2 Waiver of Informed Consent for Research Conducted in Certain Emergency Conditions

In accordance with DHHS Federal Policy regulations (45 CFR 46.101(i)), the IRB may waive the requirement for obtaining and documenting informed consent for a strictly limited class of research, involving research activities that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subject's medical condition and the unavailability of legally authorized representatives of the subjects, no legally affective informed consent can be obtained. Please see Chapter 8, Section 8.8.3 for further information about this type of waiver.

6.5.1.3 Emergency Medical Care Involving Non-Approved Drugs or Devices

Note that DHHS Federal Policy regulations do not "limit the authority of a physician to provide emergency medical care to individual patients." (See 2.4 Emergency Use of Unapproved Investigational Drugs, Biologics, and Devices.)

6.6 Terminally Ill Patients: Additional Requirements for Participation in Research

Research involving terminally ill patients presents additional concerns in that potential subjects tend to be more vulnerable to coercion or undue influence, and the research is likely to present greater than minimal risk. As a result, special attention should be given to the informed consent process. The following elements must be emphasized:

- 1) Accurate information concerning eligibility for participation (i.e., diagnosis and prognosis) and risks and benefits should be conveyed clearly and in a manner that will not either engender false hope or eliminate all hope;

- 2) Patients should be fully informed of the availability of treatment alternatives; including at what point their participation in the research study should or may be terminated to permit a treatment alternative (e.g., discontinuation of participation in a drug trial to permit organ transplantation), and that an alternative may include no additional treatment.
- 3) Any costs to the patient associated with research study participation should be stated explicitly.

6.7 HIV Screening: Additional Requirements for Informed Consent

Some research protocols involve obtaining blood samples at screening to determine HIV seroprevalence or other procedures through which subjects' HIV serostatus will be discovered. In addition to ensuring that the standard elements of informed consent are adequately addressed (in particular, the confidentiality of this information and research data), potential research subjects must be informed that:

- 1) they are being tested for HIV;
- 2) if their test results are linked to personal identifiers they will be informed of the test results;

(Under the Public Health Service policy, individuals may not be given the option "not to know" their test results, either at the time of consenting to be tested or thereafter. "Special circumstance" exceptions to this policy include such compelling and immediate reasons as an indication that a given individual would attempt suicide if informed that s/he was HIV seropositive; or that extremely valuable knowledge might be gained from research involving subjects who would be expected to refuse to learn their HIV status.)

- 3) appropriate pretest counseling is available, if desired; and
- 4) appropriate posttest counseling will be provided.

See Appendix H for a sample HIV informed consent document for use in research applications. Note that the consent form for HIV testing used in the medical management of patients may not be appropriate for use in the research setting. This "clinical consent form" for HIV testing may be used in the research context only if the HIV testing is performed for the medical management of patients and the results subsequently used for determining research subject eligibility. The "clinical consent form" should not be used when the HIV testing is being performed solely for research or research screening purposes.

6.8 Research Being Conducted in Nursing Homes - Additional Requirements

For investigators conducting research studies at nursing home facilities:

The Commonwealth of Pennsylvania law specifies under 28 PA Code Section 201.29 (o): "Experimental research or treatment in a nursing home may not be carried out without the approval of the Department (i.e., PA Department of Health) and without the written approval of the resident after full disclosure. For the purposes of this subsection, "experimental research" means an experimental treatment or procedure that is one of the following:

- (1) Not a generally accepted practice in the medical community.
- (2) Exposes the resident to pain, injury, invasion of privacy or asks the resident to surrender autonomy, such as a drug study."

6.9 Research Being Conducted in State In-Patient Mental Health Facilities

According to the Patient Bill of Rights, 55 Pa. Code 5100.54 (Article VI.2(d)):

No patient shall be the subject of any research, unless conducted in strict compliance with Federal regulations on the protection of human subjects. Patients considered for research approved by the facility shall receive and

understand a full explanation of the nature of the research, the expected benefit, and the potential risk involved. Copies of the Federal regulations shall be made available to patients involved in, or considering becoming involved in, research or their advocates. Patient research conducted in State facilities or funded by State monies requires prior approval of the Deputy Secretary of Mental Health.