UNIVERSITY OF SOUTHERN MAINE
Office of Research Integrity & Outreach

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Procedure Title:	Vulnerable Subjects

1.0 Objective

1.1. To describe the policies and procedures for reviewing research involving vulnerable subjects.

2.0 Responsibility

2.1. It is the responsibility of the Office of Research Integrity and Outreach (ORIO) staff, Research Protections Administrator (RCA), Institutional Review Board (IRB), and investigators to execute this SOP.

3.0 General Description

3.1. The University of Southern Maine (USM) Institutional Review Board (IRB) gives special consideration to protecting the welfare of vulnerable subjects.

3.1.1. Vulnerable subjects include but are not limited to:

3.1.1.1. Children, minors;
3.1.1.2. Pregnant women, fetuses, human in vitro fertilization;
3.1.1.3. Prisoners; institutionalized, elderly individuals;
3.1.1.4. Military persons and students in hierarchical organizations;
3.1.1.5. Terminally ill, comatose, physically challenged;
3.1.1.6. Visually or hearing impaired;
3.1.1.7. Ethnic minorities, refugees, international research;
3.1.1.8. Individuals with impaired decision-making capacity, intellectually challenged; and/or
3.1.1.9. Economically or educationally disadvantaged persons.
3.1.1.10. Students

3.1.2. Pregnancy Women or Fetuses

3.1.2.1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-

pregnant women, have been conducted and provided data for assessing potential risks to pregnant women and fetuses.

3.1.2.2. One of the following is true:

3.1.2.2.1. 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.

3.1.2.2.2. 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.

3.1.2.3. Any risk is the least possible for achieving the objectives of the research.

3.1.2.4. For children who are pregnant, assent and permission are obtained in accordance with the regulations.

3.1.2.5. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.

3.1.2.6. Individuals engaged in the research have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.

3.1.2.7. Individuals engaged in the research have no part in determining the viability of a neonate.

3.1.3. Neonates of Uncertain Viability

3.1.3.1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provided data for assessing potential risks to neonates.

3.1.3.2. Individuals engaged in the research have no part in determining the viability of a neonate.

3.1.3.3. One of the following is true:

3.1.3.3.1. The research held 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.

3.1.3.3.2. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there is no added risk to the neonate resulting from the research.

3.1.3.4. The IRB determines whether the criteria for approval of research are met when research involves nonviable neonates. The IRB determines and documents that:

3.1.3.4.1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provided data for assessing potential risks to neonates.

3.1.3.4.2. Individuals engaged in the research have no part in determining the viability of a neonate.

3.1.3.4.3. Vital functions of the neonate are not artificially maintained.

3.1.3.4.4. The research will not terminate the heartbeat or respiration of the neonate.

3.1.3.4.5. There is no added risk to the neonate resulting from the

research.

3.1.3.4.6. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

3.1.4. Additional Protections **for Children the IRB** determines whether the criteria for approval of research are met when research involves children. The IRB determines and documents that:

3.1.4.1. Category 1:

3.1.4.1.1. No greater than minimal risk to children is presented.

3.1.4.2. Category 2:

3.1.4.2.1. More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is likely to contribute to the participant's well-being.

3.1.4.2.2. The risk is justified by the anticipated benefit to the participants.

3.1.4.2.3. The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.

3.1.4.3. Category 3:

3.1.4.3.1. More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual participant, or by a monitoring procedure, which is not likely to contribute to the well-being of the participant.

3.1.4.3.2. The risk represents a minor increase over minimal risk.

3.1.4.3.3. The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.

3.1.4.3.4. The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition.

3.1.4.4. Category 4:

3.1.4.4.1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

3.1.4.4.2. The federal agency, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determined either: [If not federally funded, the organization can substitute an equivalent mechanism.]

3.1.4.4.2.1. That the research fell into categories 1 through 3; or

3.1.4.4.2.2. 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 the research will be conducted in accordance with sound ethical principles.

3.1.4.5. The IRB determines whether the criteria for approval of research are met when research in Category 3 or 4 involves wards of the state or any other agency. The IRB determines and documents that:

3.1.4.5.1. The research is:

3.1.4.5.1.1. Related to their status as wards; or

3.1.4.5.1.2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as participants are not wards.

3.1.4.5.2. The IRB requires appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

3.1.4.5.2.1. The advocate is 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.

3.1.4.5.2.2. The advocate is not associated in any way (except in the role as advocate or member of the IRB) with the research, the researchers, or the guardian.

3.1.5. When following DHHS requirements:

3.1.5.1. When research involves pregnant women, the IRB determines that the consent of the pregnant women is required if the research holds out:

3.1.5.1.1. The prospect of direct benefit to the pregnant woman.

3.1.5.1.2. The prospect of direct benefit both to the pregnant woman and the fetus.

3.1.5.1.3. No prospect of benefit for the woman or 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.

3.1.5.2. When research involves pregnant women, the IRB determines that the consent of the pregnant woman and the father is required, 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 if the research holds out the prospect of direct benefit solely to the fetus.

3.1.5.3. When the research involves neonates of uncertain viability, the IRB determines that the consent of either parent of the neonate is required or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective consent of either parent's legally authorized representative is required, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

3.1.5.4. When the research involves non-viable neonates, the IRB determines that the consent of both parents is required, except:

3.1.5.4.1. If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the consent of one parent is required

3.1.5.4.2. If the pregnancy resulted from rape or incest the consent of the father need not be obtained.

3.1.5.5. When the research involves non-viable neonates, the IRB is not allowed to approve the consent of a legally authorized representative.

3.1.6. For Research Involving Prisoners:

3.1.6.1. For prisoners, "minimal risk" means 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.

3.1.6.2. The IRB determines whether the criteria for approval of research are met when research involves prisoners. The IRB determines and documents that:

3.1.6.2.1. The research represents one of the following categories:

3.1.6.2.1.1. Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.

3.1.6.2.1.2. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.

3.1.6.2.1.3. 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; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults).

3.1.6.2.1.3.1. For DHHS-funded research, OHRP has consulted with

appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of its intent to approve such research.

3.1.6.2.1.4. Research on practices, both innovative and accepted that has the intent and reasonable probability of improving the health or well-being of the participant.

3.1.6.2.1.4.1. For DHHS-funded research which require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after OHRP has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of its intent to approve such research.

3.1.6.2.1.5. Epidemiologic studies that meet the following criteria:

3.1.6.2.1.5.1. The sole purposes are one of the following:

3.1.6.2.1.5.1.1. To describe the prevalence or incidence of a disease by identifying all cases.

3.1.6.2.1.5.1.2. To study potential risk factor associations for a disease.

3.1.6.2.1.5.2. The research presents no more than minimal risk and no more than inconvenience to the prisoner- participants, and

3.1.6.2.1.5.3. Prisoners are not a particular focus of the research.

3.1.6.2.2. 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 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.

3.1.6.2.3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.

3.1.6.2.4. Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners.

3.1.6.2.5. Unless the researcher provides justification in writing for following some other procedures, control participants are selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.

3.1.6.2.6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole.

3.1.6.2.7. When there is a need for follow-up examination or care of participants after the end of their participation, adequate provisions are made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

3.1.6.2.8. For DHHS-funded research, indicate the individual Provost and Vice President for Academic Affairs who certifies to OHRP the duties of the IRB have been fulfilled.

3.1.6.3. For research involving prisoners reviewed by the convened IRB:

3.1.6.3.1. The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C or equivalent protections.

3.1.6.3.2. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved.

3.1.6.3.3. 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.

3.1.6.3.4. 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.

3.1.6.3.5. 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).

3.1.6.3.6. 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).

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

3.1.6.4. If you review research involving prisoners by the expedited procedure, you may use the following two options:

3.1.6.4.1. For research involving interaction with prisoners reviewed by the expedited procedure:

3.1.6.4.1.1. 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.

3.1.6.4.1.1.1. The prisoner representative must concur with the determination that the research involves no greater than minimal risk.

3.1.6.4.1.2. 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.

3.1.6.4.1.3. 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.

3.1.6.4.2. For research that does not involve interaction with prisoners (e.g., existing data, record review) reviewed by the expedited procedure:

3.1.6.4.2.1. 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.

3.1.6.4.2.2. Review by a prisoner representative is not required.

3.1.6.4.2.3. The prisoner representative may review the research as a reviewer or consultant if designated by the IRB chair.

3.1.6.4.2.4. Review of modifications and continuing review must use the same procedures as initial review.

3.1.6.5. If a participant becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C:

3.1.6.5.1. When Subpart C applies:

3.1.6.5.1.1. Confirm that the participant meets the definition of a prisoner.

3.1.6.5.1.2. Terminate enrollment or review the research study under Subpart C if it is feasible for the participant to remain in the study.

3.1.6.5.1.3. Before terminating the enrollment of the incarcerated participant, the IRB should

consider the risks associated with terminating participation in the study.

3.1.6.5.1.4. If the participant cannot be terminated for health or safety reasons:

3.1.6.5.1.4.1. Keep the participant enrolled in the study and review the research under Subpart C.

3.1.6.5.1.4.1.1. 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, keep the participant enrolled and inform OHRP of the decision along with the justification.

3.1.6.5.1.4.2. Remove the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.

3.1.6.5.2. When Subpart C does not apply, and the IRB has written procedures for providing equivalent protections:

3.1.6.5.2.1. Confirm that the participant meets the definition of a prisoner.

3.1.6.5.2.2. Decide whether it is in the best interests of the participant to remain in the study or to terminate enrollment.

3.1.6.6.2.3. Also decide whether it is feasible for the participant to remain in the study.

3.1.6.6.2.4. If it is in the best interests of the participant to remain in the study, keep the participant in the study and review the research at the next meeting of the convened IRB.

3.1.6.6.3. When IRBs do not have written procedures for research involving prisoners:

3.1.6.6.3.1. Confirm that the participant meets the definition of a prisoner.

3.1.6.6.3.2. Decide whether it is in the best interests of the participant to remain in the study or to terminate enrollment.

3.1.6.6.3.3. Also decide whether it is feasible for the participant to remain in the study.

3.1.6.6.3.4. Determine whether Subpart C applies.

3.1.6.6.3.4.1. If Subpart C applies:

3.1.6.6.3.4.1.1. Find an IRB that can review the study or refer to the federal regulations and identify a prisoner representative

so that your IRB can review the study.

3.1.6.6.3.4.2. If Subpart C does not apply:

3.1.6.6.3.4.2.1. Find an IRB that can review the study or develop written procedures for providing equivalent protections.

3.1.6.7. If a participant is incarcerated temporarily while enrolled in a study:

3.1.6.7.1. If the temporary incarceration has no effect on the study, keep the participant enrolled.

3.1.6.7.2. If the temporary incarceration has an effect on the study, handle according to the above guidance.

4.0 Procedures

4.1. Submission and Screening

4.1.1. The Principal Investigator (PI) identifies, with ORIO guidance, if required, the categories of vulnerable subjects involved in the research in the IRB application submitted to ORIO.

4.1.1.1. When research on vulnerable subjects is conducted outside the state of Maine, the PI should identify state law(s) applicable to the determination of legally authorized representatives. When the PI is a faculty, student or staff member of the University of Southern Maine, they should contact the University of Maine System Counsel to confirm their understanding of the state laws prior to submission to the IRB.

4.1.2. The PI submits a completed IRB application to the ORIO, including specific information regarding the ethical and regulatory issues pertaining to the conduct of research involving vulnerable subjects.

4.1.3. Upon receipt of the application, the ORIO staff screen the application, including the informed consent process and documentation for completeness and accuracy.

4.1.3.1. ORIO staff contact the PI for any additional information needed for a thorough review.

4.1.3.2. If it is clear to the designated ORIO staff that the application does not include the required information regarding the conduct of research involving vulnerable subjects, the designated ORIO staff contacts the PI and recommends the application be amended.

4.1.3.2.1. After screening the application, the ORIO staff sends the application to the RCA or designee.

4.1.3.2.2. The RCA or designee makes the final determination regarding whether the research involves vulnerable subjects.

4.1.4. IRB membership includes representation with expertise in selected vulnerable populations routinely reviewed by the IRB, such as children or prisoners.

4.1.4.1. The RCA or designee ensures that designated representatives review research involving vulnerable populations when necessary.
4.1.4.2. The RCA or designee requests a consultant review if additional expertise is needed. (See *HRPP-022 IRB Use of Additional Expertise*)

4.2. Protocol Review Process

4.2.1. The IRB reviewer evaluates the IRB application to determine whether the protocol includes enrollment of vulnerable subjects and whether appropriate safeguards are in place.

4.2.2. As applicable, the IRB considers the following elements when reviewing research involving vulnerable subjects:

4.2.2.1. Inclusion/exclusion criteria;
4.2.2.2. Selection or exclusion of certain groups based on perceived limitations (i.e., targeting prisoners as research subjects because they are a readily available "captive" population); and
4.2.2.3. Knowledge of applicable or local context/laws that bear on the decision-making process (i.e., emancipated individuals, legally authorized representatives, age of majority for research consent).

4.2.3. The IRB follows applicable federal and state regulations and IRB policy to assist in reviewing and approving proposed research that involves vulnerable subjects, such as but not limited to:

4.2.3.1. Pregnant women, human fetuses and neonates;
4.2.3.2. Research involving prisoners;
4.2.3.3. Research involving children;
4.2.3.4. Research involving individuals with impaired decision-making capacity
4.2.3.5. Research involving economically or educationally disadvantaged persons; and
4.2.3.6. Research involving students recruited by their professors or advisors for research participation.

4.2.4. The IRB considers each of the specific findings discussed in the IRB application forms for research involving vulnerable subjects as documented by IRB approval.

4.2.4.1. IRB approval also documents that the IRB members acknowledge and agree with the preliminary description of safeguards and the risk assessment of the protocol as described in the application by the PI.

4.2.4.2. ORIO staff document discussions of controverted issues at convened meetings in the meeting minutes.

4.2.5. Specific findings are either documented by ORIO staff in the meeting minutes or by exempt/expedited reviewers in their determinations

4.2.6. The IRB may require more frequent review (i.e., issue an approval period shorter than 12-months) for protocols involving vulnerable populations based on the nature of the research and the level of risk.

5.0 References

5.1. 45 CFR 46 Subpart B;

5.2. 45 CFR 46 Subpart C;

5.3. 45 CFR 46 Subpart D;

5.4. 21 CFR 50 Subpart D;

5.5. 34 CFR 97 Subpart D.