Institutional Review Board

University of Missouri-Columbia

Standard Operating Procedure

Additional Protections for Vulnerable Populations, International, and Non-English Speaking Participants

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1.0 Purpose

To aid in assuring knowledge and compliance of all persons involved in any aspect of human subject research by documenting the additional protections for vulnerable populations.

2.0 Scope

The SOP applies to all non-exempt human subject research falling under the purview of the University of Missouri Institutional Review Board.

3.0 Policy/Procedure

Federal Regulations require the selection of subjects to be equitable. In ensuring this requirement, the IRB takes into account the purpose and the setting in which the research will be conducted. In addition, all MU research involving human participants shall be conducted in accordance with the ethical principles and guidelines outlined in the Belmont Report. When involving potentially vulnerable populations, the IRB evaluates the appropriateness of their inclusion (or exclusion) and whether additional safeguards are necessary.

The regulations have additional requirements to protect pregnant women, human fetuses, neonates, prisoners, children, and wards. This policy also covers other potentially vulnerable populations and the considerations for protection of these populations.

The categories in the regulations are as follows:

1. **Subpart B (Pregnant Women, Human Fetuses and Neonates)**
2. **Subpart C (Prisoners)**
3. **Subpart D (Children); (Wards)**

1. Research involving Pregnant Women (45 CFR 46 Subpart B)

Pregnant women or fetuses may be involved in research if the IRB determines all the following conditions are met (45 CFR 46.204):

a. 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;
b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the pregnant 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 to develop important biomedical knowledge that cannot be obtained by any other means;
c. Any risk is the least possible for achieving the objectives of the research;
d. 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 is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of the pre-2018 requirements or the 2018 requirements, as applicable;
e. 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 informed consent provisions of the pre-2018 requirements or the 2018 requirements, as applicable, except when 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.
f. Each person providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
g. For children who are pregnant, assent and permission are obtained in accord with Subpart D;
h. No inducements, monetary or otherwise, can be offered to terminate a pregnancy;
i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
j. Individuals engaged in the research will have no part in determining the viability of a neonate.

Research involving Neonates 46.205(a)
Neonates of uncertain viability and nonviable neonates may be involved in research if the IRB determines 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 under paragraph 45 CFR 205(b)(2) and c(5) of this section 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 a neonate.
d. The requirements of 45 CFR 205(b) and (c) of this section have been met as applicable.

Neonates of Uncertain Viability 46.205(b)
Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

a) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, ***or***
b) 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
c) 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 pre-2018 requirements or the 2018 requirements, as applicable, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

Non-Viable Neonates 46.205(c)
After delivery, 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 neonate is obtained in accord with the pre-2018 requirements or the 2018 requirements, as applicable, except that a waiver and alteration provisions of the pre-2018 requirements or the 2018 requirements do not apply. However, if either parent

is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a 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. The consent of a legally authorized representative of either or both of the parents of a non-viable neonate will not suffice to meet the requirements of the paragraph.

Viable Neonates 46.205(d)
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 the pre-2018 requirements or the 2018 requirements, as applicable, and subpart D of this part.

Research Involving, after Delivery, the Placenta, the Dead Fetus or Fetal Material 46.206
Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

If information associated with material 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 policies are applicable.

Research not Otherwise Approvable for Pregnant Women and Fetuses, or Neonates 46.207
The research must present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

IRB will approve the research only if:
(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and
(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable; or
(2) 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 informed consent policies.

When such research is supported by a non-federal sponsor and not FDA regulated, MU will convene an independent panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and provide an opportunity for review and comment by the local community where the research is to be conducted before deciding whether to proceed with the research.

Missouri Law
See the statute below regarding utilizing fetal organs or tissue from an abortion:
MO Rev Stat § 188.036. Prohibited abortions, those done with intent to use fetal organs or tissues for transplant, experiments or for consideration, exceptions.

See the statute below regarding the use of any fetus or child aborted alive:
MO Rev Stat § 188.037. Experimentation with fetus, or child aborted alive, prohibited, exception.

2. Prisoners in Research (45 CFR 46 Subpart C)

The IRB recognizes that research involving prisoners raises the issue of whether the subject's situation prohibits the exercise of free choice to participate in research and whether the prisoner's confidentiality will be adequately maintained. When reviewing research with the use of prisoners, minimal risk is defined 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.

IRB staff will assure that the person designated as the prisoner representative (see Board Structure and Responsibilities SOP) reviews all materials pertaining to the research and documents determinations utilizing the reviewer checklist.

The research must fit into one of the four categories (45 CFR 306):

i. Category I: Studies of the possible cause, effects, and processes of incarceration and criminal behavior, and involves no more than minimal risk with no more than inconvenience to the subjects;
ii. Category II: Studies of prisons as institutional structures or of prisoners as incarcerated persons, and involves no more than minimal risk no more than inconvenience to the subjects;
iii. Category III*: Studies 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) provided that the study may proceed only after the HHS Secretary has consulted with appropriate

experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or

iv. Category IV*: Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the HHS Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

*Category III and Category IV: When such research is not HHS supported or conducted, the Secretarial consultation and OHRP certification is not required.

<u>In order to approve the research, the IRB must find and document that (45 CFR 46.305)</u>:

1. The research falls under one of the categories of research listed above;
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. 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 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 the Board finds 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.

The Board shall carry out such other duties as may be assigned by the Secretary. The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

For epidemiologic studies, the following must be true:

1. The sole purposes are one of the following:
   a. To describe the prevalence or incidence of a disease by identifying all cases.
   b. To study potential risk factor associations for a disease.
2. The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
3. Prisoners are not a particular focus of the research.

Research using the Expedited Procedure, the IRB may use the following two options:

1. For research involving interaction with prisoners reviewed by the expedited procedure:
   a. 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.
   b. The prisoner representative must concur with the determination that the research involves no greater than minimal risk.
   c. 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.
   d. 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.
2. 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.

Modifications and Continuing Review:

1. Minor modifications to research may be reviewed using the expedited procedure described above, using either of the two procedures described based on the type of modification. See Amendment SOP for more information.

2. Modifications involving more than a minor change initially 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.
3. 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 (if the study was approved by the full board initially).
    a. If no participants have been enrolled, the research may receive continuing review using the expedited procedure under expedited category #8. See Continuing Review of Research SOP for more information.

<u>If a participant becomes a prisoner while enrolled in a research study that was not initially reviewed according to Subpart C:</u>

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.
    a. Before terminating the enrollment of the incarcerated participant, the IRB should consider the risks associated with terminating participation in the study.
    b. If the participant cannot be terminated for health or safety reasons:
        i. Keep the participant enrolled in the study and review the research under Subpart C. If some the requirements of Subpart C cannot be met, but it is in the best interest of the participant to remain in the study, keep the participant enrolled and inform OHRP of the decision along with the justification.
        ii. 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. <u>Children in Research (45 CFR 46 Subpart D):</u>

To approve the research, the research must meet one of the following categories:

Category 1: 45 CFR 46.404 and 21 CFR 50.51
The research involves minimal risk, and adequate provisions are made to solicit the assent of the children and permission of the parents or guardians in accordance of 21 CFR 50.55 and or 45 CFR 46.408 (the IRB may find that the permission of one parent is sufficient*)

Category 2: 45 CFR 46.405 and 21 CFR 50.52
The research is greater minimal risk but presents the prospect of direct benefit to an individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being.

The IRB must find that:

i. the risk is justified by the anticipated benefit to the subject;
ii. the relation of the anticipated benefit to the risk is at least as favorable as any available alternative approach; and
iii. Adequate provisions are made to solicit the assent of the children and permission of the parents or guardians in accordance of 21 CFR 50.55 and or 45 CFR 46.408 (the IRB may find that the permission of one parent is sufficient*)

Category 3: 45 CFR 46.406 and 21 CFR 50.53
The research is greater minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

The IRB must find that:

ii. the risk represents a minor increase over minimal risk;
iii. the experience is reasonably commensurate with those in their actual or expected medical, dental, psychological, social, or educational situations;
iv. the intervention is likely to yield generalizable knowledge about the disorder or condition that is of vital importance; and
v. Adequate provisions are made to solicit the assent of the children and permission of the parents or guardians in accordance of 21 CFR 50.55 and or 45 CFR 46.408 (two parent consent is required*)

Category 4: 45 CFR 46.407 (DHHS)
Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Research that is not approvable under one of the previous categories may be conducted or funded by DHHS provided that the IRB and the Secretary, after consultation with a panel of experts, finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children. The panel of experts must also find that the research will be conducted in accordance with sound ethical principles and adequate provisions are made for soliciting the assent of children and the permission of the parents or guardians*.

When such research is supported by a non-federal sponsor and not FDA regulated, MU will convene an independent panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and provide an opportunity for review and comment by the local community where the research is to be conducted before deciding whether to proceed with the research.

Category 4: 21 CFR 50.54 (FDA)
If the proposed research is regulated by the FDA and does not meet one of the previous categories, the research may proceed only if:

(a) The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
(b) The Commissioner of Food and Drugs, 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, determines either:
(1) That the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or
(2) That the following conditions are met:
(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and
(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 50.55*.

Parental/Guardian Consent and Child Assent requirements are discussed within the MU HRPP/IRB Informed Consent Requirements SOP

Pregnancy Testing of Children/Minors

When a study involves pregnancy testing of minors, the IRB will require a provider/practitioner be listed on the study to help ensure standard clinical processes are followed for mandatory reporting and discussing pregnancy with minors and parents/guardians.

1. If circumstances lead to a suspicion of abuse (including sexual abuse) or neglect of the minor involved in the research, the mandatory reporting law must be followed. Abuse is not limited to abuse inflicted by the parent/guardian, but includes abuse inflicted by any other person. 210.115, Revised Statutes of Missouri. Statutory rape in Missouri is committed if the victim is "less than fourteen years of age." In addition to any required report to Children's Division, a positive pregnancy result in a minor under age 14 may be reported to the parent or guardian.
2. For minors aged 14 and older, the results of the pregnancy test should be shared with the minor.
3. When in the judgment of the IRB the minors can provide assent, minors aged 14 and older should authorize the pregnancy test and disclosure of a positive test to parents/guardians. The minor should be informed in certain

circumstances researchers are required to disclose the information pursuant to mandatory reporting laws.

4. Questions about reporting information about minors involved in research to parents/guardians or other third parties should be directed to the MU HRPP/IRB office.

Children as Wards (45 CFR 46.409 Subpart D)

"Child" under Missouri State law: for purposes of the foster care system is defined as any person under the age of 17 years of age and any person over seventeen but not yet 18 alleged to have committed a status offense (RSMo 211.021(2) and RSMo 211.031.1(2)) or any person under the retained jurisdiction of the juvenile courts until age of 24 years of age (RSMo 211.041)

Before Enrolling Wards of the State, the following approvals are required:

1. University of Missouri IRB; and
2. After IRB approval, the Missouri Department of Social Services, Children's Division.
    a. An application (http://dss.mo.gov/cd/info/forms/pdf/886-4454s.pdf) must be submitted to the Department of Social Services, Children's Division. The University of Missouri IRB approval letter, a copy of the consent document(s) and assent(s), and a cover letter.
    b. Send the application via email to CD.ResearchCommittee@dss.mo.gov or send via postal mail to:
    Children's Division Research Committee
    PO Box 88
    Jefferson City, MO 65103
3. Obtain concept approval to enroll Wards of the State from the Missouri Children's Division Research Committee.
4. Obtain CD local office approval for each individual Ward of the State enrolled in the study.
    a. Investigators must carefully review any conditions of approval provided in the approval documents from the Children's Division. Depending on the specific circumstances of the study, the Children's Division may require, for example, that other members of the Family Support Team be consulted and/or required to give consent for enrollment of a Ward. (This will need to be done on a child-by-child basis.)
    b. If there are any conditions of approval from the Children's Division, investigators must submit an amendment to update the approved protocol to reflect these additional requirements.

c. A listing of the Authorized Representatives of the Missouri Children's Division is available at: http://dss.mo.gov/cd/office/

Obtaining Appropriate Consent

Foster parents cannot consent for foster children (Wards of the State) in their care to participation in experimental treatments and procedures, or to participate in research.

> Foster parents **can** consent for ordinary, necessary medical treatment and medical treatment which may be reasonably necessary in a medical emergency when consultation with the Children's Division is not medically feasible under the circumstances for foster children (Wards of the State) in their care. Foster parents **cannot** consent for foster children (Wards of the State) in their care to undergo non-emergency, extraordinary medical treatments and procedures, be the subject of experimental treatments and procedures or participate in research.

Authorized Representatives of the Missouri Children's Division are those individuals designated by the Children's Division from time to time authorized to sign a research consent form to enroll a Ward of State in a human subjects research study. The ward's case manager is considered an Authorized Representative.

1. A fax signature from the Case Manager of the Missouri Children's Division is acceptable.
2. Email signature may not be acceptable, as not all MU systems comply with FDA Part 11 regulations regarding electronic signatures. See Informed Consent Requirements SOP regarding electronic signature.

A Ward was identified during the Course of a Study:

1. An Amendment must be submitted obtaining the required approvals noted above.
2. Appropriate consent must be obtained after IRB approval.

A Child Becomes a Ward during the Course of the Study:

1. An Amendment must be submitted obtaining the required approvals noted above.
2. At the time it is known that the child has become a Ward of the State, consent must be obtained from the appropriate authorized individual as noted above.

Federal Requirements for use of Wards in research 45 CFR 46.409 & 21 CFR 50.56

> Children who are wards of the state or any other agency, institution, or entity can be included in research approved under categories 46.406, 46.407, 50.53 or 50.54 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.

The IRB will require 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. One individual may serve as advocate for more than one child. The advocate shall 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.

Emergent or Life Threatening Situation (treated with an investigational drug or device):

1. There is a life-threatening emergency;
2. The IRB must approve the research and a waiver of consent in accordance with 45 CFR Part 46 and 21 CFR Part 50 (if applicable).
3. CD local office approval is necessary. Contacts for the local office can be found at: http://dss.mo.gov/cd/office/. See below for the CD letter explaining the CD procedure. For after hours and weekends, call the hotline at 573-751-3448.
4. See Investigational Test Articles and Emergency Use SOP for more information regarding emergency situations.

Additional Subject Populations - Special Considerations

1. Subjects Unable to Consent

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. See the Informed Consent Requirements SOP for additional information.

2. Students and Employees

The IRB recognizes the special concerns that may present when students and employees participate in research projects. The IRB will consider the following:

For projects involving students:

a. If extra or course credit is offered:
    - The investigator must provide a comparable (time and commitment) alternate method of credit for a student;

- The student shall not lose the extra credit if they withdraw from the study, or there is an approved proration plan; and
- Students must be assured that they will not be penalized and their grade will not be adversely affected by their decision to participate in the research.

b. If necessary to recruit his/her own students, there must be a recruitment plan utilizing a third party unassociated in an instructor-student relationship with the student.
c. In cases where regular classroom activities are also the topic of research, investigators must clarify for participants (and/or their legal guardian) those activities that are optional and distinct from required classroom activities.
d. A student's decision about participation may not affect (favorably or unfavorably) grades, potential letters of recommendation, or other opportunities or decisions made by teacher-investigators.
e. When educational records must be accessed for research purposes, the Family Educational and Rights Privacy Act (FERPA) may apply. The MU Registrar's office may be consulted as necessary to ensure all requirements are met. See the Federally Sponsored or Supported Research SOP regarding FERPA and the Protection of Pupil Rights Amendment (PPRA), if applicable.

For projects involving employees:

a. An employee cannot be required to participate in research as a condition of employment;
b. They cannot be selected solely on the basis of convenience;
c. If necessary to recruit his/her own employees, there must be a recruitment plan utilizing a third party unassociated in a supervisory relationship with the employee.
d. In cases where regular workplace activities are the topic of research, investigators must clarify for participants those activities that are optional and distinct from any mandatory workplace activities.
e. An employee's decision about research participation may not affect (favorably or unfavorably) performance evaluations, career advancement, or other employment-related decisions made by peers or supervisors.
f. Workplace conditions may make it difficult for investigators to keep participation confidential, which could pose risks to participants. In these situations, research should be conducted off-site and/or outside of regular work hours when possible.

3. <u>Elderly and Economically or Educationally Disadvantaged Subjects</u>

The IRB will make sure participants are not coerced or unduly influenced to participate in research given their potential vulnerability. The IRB will also assess the process for offering compensation to subjects, if applicable.

4. <u>International Participants</u>

MU IRB policies do not affect any foreign laws or regulations that may otherwise be applicable and that provide additional protections to human subjects of research.

For federally sponsored or supported research, where procedures differ from the DHHS regulations, department or agency heads may determine the procedures prescribed by the institution afford protections that are at least equivalent to those provided in DHHS policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements in DHHS policy. See 45 CFR 46.101 (g-i) for additional information.

Researchers should have sufficient knowledge of the local customs and traditions to carry out the research in a way that protects the rights and welfare of the participants while producing viable research results.

OHRP provides a compilation of regulations and guidelines that govern human subject's research in other countries, as well as standards from a number of international and regional organizations. [See OHRP *International Compilation of Human Subject Protections* at https://www.hhs.gov/ohrp/sites/default/files/2018-International-Compilation-of-Human-Research-Standards.pdf

Researcher Responsibilities:
When studies are conducted in other countries researchers should be knowledgeable about the local laws and customs which apply to the research, and the cultural context in which they will be working.

The researcher should consider influencing factors including, but not limited to:

- Local Laws
- Regulations
- Customs
- Socio-economic factors
- Politics
- Culture
- Language
- Literacy

These factors may affect the study design, the risks, and the consent process.

Potential Risks:
Some items to consider:

1. Methods may have increased risk when being conducted in a different country;
2. Innocuous questions may be offensive;
3. Maintaining or assuring confidentiality may be difficult; and
4. Breach of confidentiality may be dangerous for subjects.

Obtaining Informed Consent:
Informed consent is a decision to participate in research, by a competent individual who has received the necessary information; who adequately understands the information; and

who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation. In some circumstances, it may be inappropriate to document consent by using the standard written and signed consent document. The consent should be obtained in the language that is most familiar to the prospective participant.

Other factors to consider are the potential for different rules on determining who may serve as a legally authorized representative, age of majority, children as subjects and potential differences in the authority structure.

IRB Review

The IRB will review in accordance to the regulations that apply to the local area. The most stringent requirements for protection of human subjects will prevail when there are differences. The IRB office will ensure appropriate expertise and knowledge of the country(ies) either through IRB membership or consultants. The IRB will also confirm the qualifications of the researchers for conducting research in that country(ies).

Federally Funded/ FDA regulated Research

1. For federally funded research, the regulations of that sponsoring agency apply and the required federal protections must be provided. It is not sufficient to provide "equivalent" protections.
2. FDA and ICH-GCP regulations apply to international research studies utilizing drugs, devices or biologics http://www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm
3. For DHHS funded research, 45 CFR 46 applies. For other guidance by OHRP on international research, see http://www.hhs.gov/ohrp/international/

European Union General Data Protection Regulations (GDPR)

The European Union's GDPR regulates the processing (e.g. use, access, collection, recording, storage, or transmission) of all **personal data** about individuals in the European Economic Area (EEA)-based operations and certain non-EEA organizations that process personal data of individuals in the EEA, regardless of citizenship or residency status of the individual to whom the data pertains. It applies to the processing of personal information:

1. Through activities within the borders of EEA countries;
2. That is related to offering goods and services to EEA residents; or
3. That involves monitoring the behavior of EEA residents.

The following countries making up the EEA are adopting the GDPR: Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lichtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and UK

Personal Data is any information that relates to an identified or identifiable living individual. Different pieces of information, which collected together can lead to the identification of a particular person, constitute personal data.

Examples of personal data include, but are not limited to

1. A name and surname
2. A home address;
3. An email address;
4. Income and banking information;
5. An identification card number;
6. An Internet Protocol (IP) address;
7. A cookie ID;
8. Electronic location data;
9. Phone identifiers; or
10. Data held by a hospital or doctor which could uniquely identify a person.

Activities Subject to the GDPR

1. Activities involving the processing (i.e. collection) of personal data is being collected from one or more research participants **physically located** in the EEA at the time of data collection (even if the participant is NOT an EEA resident).
2. Activities involving the transfer of personal data collected under the GDPR from an EEA country to a non-EEA country.

Requirements for Data Collection and Access

The researcher is required to collect, in a transparent manner, only the minimum necessary information for the defined research purpose. When the personal data of an EU subject is collected, used, or accessed, the researcher must present certain information to the subject noted below.

Consent Process

1. Consent records, including time and date of consent, must be maintained for each subject. In the case of verbal, online, or any other type of undocumented consent, the Principal Investigator is responsible for maintaining a consent log indicating each subject (either by name or study ID number) and the date and time that they provided consent.
2. Consent must be explicit. If the consent form or consent script serves multiple purposes (e.g., a consent form that is also the recruitment email), then the request

for consent must be clearly distinguishable within the document. Furthermore, when processing is conducted for more than one purpose, consent must be obtained for each purpose.

3. Each subject has a right to withdraw consent, at any time. Each subject must be informed of this right prior to giving consent. Withdrawal of consent must be as easy as giving consent.
4. Consent must be an affirmative action. This means that opt-out procedures or pre-checked boxes indicating consent are not permitted.
5. Consent information must be provided in clear and plain language in an intelligible and easily accessible format. Consent forms using excessive jargon or that do not have separate sections with section headings will be returned for revision.
6. Consent must be freely-given. Individuals in a position of authority cannot obtain consent, nor can consent be coerced. This means that faculty members or teachers cannot obtain consent from their own students.

<u>Consent forms must contain the following information:</u>

- The identity of the Principal Investigator;
- The purpose of data collection;
- The types of data collected, including listing of special categories:
  - Racial or ethnic origin;
  - Political opinions;
  - Religious or philosophical beliefs;
  - Trade union membership;
  - Processing of genetic data;
  - Biometric data for the purposes of unique identification;
  - Health data; and/or
  - Sex life or sexual orientation information;
- The right to withdraw from the research and the mechanism for withdrawal;
- Who will have access to the data;
- Information regarding automated processing of data for decision making about the individual, including profiling;
- Information regarding data security, including storage and transfer of data;
- How long data will be stored (this can be indefinite);
- Whether and under what conditions data may be used for future research, either related or unrelated to the purpose of the current study.

Rights of Research Subjects / Data Storage

The data of individuals from the European Union must be stored in a way that enables the following rights:

1. The right to access the data, free of charge, in an accessible, comprehensible format.
2. The right to object to a particular use of that data.

3. The right to correct the data, without undue delay, in the event the individual feels that it is incorrect, incomplete, or inaccurate.
4. The right to "be forgotten," or to erase all data relating back to that person in an irreversible fashion. Parents of children and children each individually hold this right, so either of those parties can require a child's data to be deleted.
5. The right to move data; this means that the individual can ask you to transfer it to them, or to another party, in a commonly-used and machine-readable format.

The GDPR permits the retention of personal data for only as long as necessary to achieve the specific purpose for which it was collected. It must be deleted after that time. If a subject requests their previously collected data be erased, contact the IRB immediately to ensure the data has been appropriately erased.

Data Breach
If there is a data breach which could pose any risk to participants, participants must be informed of the breach without undue delay. Data breaches must be reported to the MU Office of General Counsel within 24 hours. An Event Report also has to be submitted within 5 business days to the IRB.

Coded Data vs Anonymized Data
For data to no longer considered personal data, it must be rendered anonymous in such a way that the individual is not identifiable. The anonymization must be irreversible. If a link or key exists between the data and subject identifiers (Pseudonymized data/coded data), the data is not anonymous. It is considered personal data, regardless of whether the investigator has access to the key. This is in stark contrast to US regulations protecting human subjects.

Data from Children
The GDPR defines a child (for the purposes of using or accessing personal data) as an individual under the age of 16. Parental consent is required for any personal data collected regarding a child under the age of 16. NOTE – individual member states may utilize a lower age of consent (no lower than 13 years) within their own jurisdiction.

Investigators conducting research with data from the EU must comply with the responsibilities established by the GDPR. Failure to comply with these regulations results in non-compliance, monetary fines, and reputational harm.
See the EU GDPR website for more information: https://eugdpr.org/

5. Non-English Speaking Participants

The governing principles of human subject research require that researchers not exclude subjects based solely on their inability to read, speak, or understand English.

Investigators need either to communicate directly with subjects, or to provide a reliable alternative to ensure that:

1. Study participation is voluntary, as indicated by free and truly informed consent;
2. Study schedules, procedures, and risks are accurately communicated, and subjects have ongoing opportunities to express concerns and ask questions, in order to minimize risks to subjects; and
3. There are fair procedures and outcomes in the selection of research subjects so that risks and benefits of research are shared in society.

It is the investigator's responsibility to judge the subject's comprehension of the consent information including the understanding that participation is voluntary and that the subject has the right to withdraw at any time during the study. If the investigator doubts the subject's consent comprehension, he/she should not enroll the subject in the study. The subject's autonomy must not be jeopardized due to a language barrier.

Translated documents shall be prepared after IRB review and approval of the English version. The translated documents shall be submitted via an Amendment Form for IRB review.

Consent Methods:
There are two methods for obtaining and documenting informed consent for research subjects who do not read, speak, or understand English:
1. The **preferred method** is to provide consent forms written in the subject's language.
2. For the occasional and unanticipated non-English-speaking subject, an **alternative "short form" method** is allowed [21 CFR 50.27(b)(2) and 45 CFR 46.117(b)(2)].

Preferred Method for Obtaining Informed Consent from Non-English Speaking Subjects:
1. The IRB supports the policy set forth by the Office of Human Research Protection (OHRP) and strongly encourages investigators to provide a written consent document in a language understandable to the subject.
2. If the investigator anticipates a substantial portion of eligible subjects to be non-English-speaking people, translated consent forms in the common languages should be prepared in advance.

Alternative Short Form Method for Obtaining Informed Consent from Non-English Speaking Subjects:
The alternative "short form" method for obtaining informed consent should only be used for the occasional and unexpected enrollment of a non-English-speaking subject in a study for which no consent form in the subject's language has been prepared. See Informed Consent Requirements SOP for more information.

References:

Combined Policies January 21, 2019:
Recruitment of Special Subject Populations
Approval Dates: February 16, 2001; July 23, 2002; October 2005; December 1, 2006; June 10, 2010; July 1, 2011; March 1, 2015; July 1, 2015; June 8, 2017
Transnational Research
Approval Dates: June 15, 2010; July 1, 2011; March 1, 2015; July 1, 2015; June 8, 2017
Non-English Speaking – Study Requirements
Approval Dates: July 1, 2004; June 9, 2004; December 1, 2006; February 2009; June 10, 2010; July 1, 2011; March 1, 2015, July 1, 2015; June 8, 2017
Wards of the State
Approval Dates: September 1, 2008; July 10, 2009; June 10, 2010; July 1, 2011; March 1, 2015; July 1, 2015; June 8, 2017