UNIVERSITY OF SOUTH ALABAMA

IRB SOP 507
Risks to Research Subjects

Purpose

The purpose of this Standard Operating Procedures (SOP) is to identify and analyze risks and identifying measures to minimize such risks. This SOP also serves as guidance on how to assess the risk of harm to participants in human research and what procedures should be implemented in order to minimize risk.

Scope

This Standard Operating Procedure applies to all Investigators and IRB members.

Definitions

Risk: The probability of harm (physical, psychological, social, legal, or economic) occurring as a result of participation in a research study. Both the probability and the magnitude of possible harm may vary from minimal to significant. The Federal regulations only define "minimal risk."

Minimal Risk: A risk is considered to be minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

Benefit: A valued or desired outcome; although these terms may appear straightforward, evaluations of risk and benefit are made more complex both by the subtle distinctions between therapeutic and research activities, and by evaluations of actual risks in the lives of normal and vulnerable classes of subjects (i.e., prisoners, children, cognitively impaired individuals, etc.)

Policy

1.0 Risk in Human Subjects Research

Risk is the probability of harm or injury (physical, psychological, social, legal or economic) occurring as a result of participation in a research study. Both the probability and magnitude (severity) of a possible harm may vary from minimal to significant. The magnitude of potential harm is the summative measure of its severity, duration and reversibility. Thus, a research protocol with a low probability of harm occurring, but a high severity of harm if it occurs, may be determined to be greater than minimal risk (e.g. a severe allergic reaction to a new medication, or stigmatization from unintentionally releasing HIV status of participants). Alternatively, a protocol with a high probability of harm occurring, but a low severity of harm, may be assigned minimal risk for participants (e.g. itchiness after electrode tape removal, or distress related to answering sensitive, personal questions). Federal regulations define only "minimal risk".

The IRB will consider a wide range of categories or types of risks including physical, psychological, social, economic, legal or unknown risks. In most cases these risks apply to individuals, however, risks can also apply to groups of individuals (e.g. research on alcoholism among Native Americans may be perceived as denoting a negative stereotype). A research procedure or intervention may be minimal risk to certain individuals or groups, but greater than minimal risk to others. For example, the effect on "vulnerable" populations and the specific circumstances of a protocol may change the risk/benefit ratio making the study greater than minimal risk. Many risks in social, behavioral, and educational research are often subjective from the perspective of the participant and the researcher should consider this when evaluating risks. The overall study risk is determined by the risk to the most vulnerable known members of the group

2.0 Types of Risk to Research Subjects

Physical Harms: This would consist of minor pain, discomfort or injury from a procedure, drug research or device research. The physical harm could be permanent but most are transient in nature, e.g. nausea, dizziness, headaches, muscle soreness, numbness, tingling. For all research with the potential to do physical harm investigators are encouraged to think through all risk possibilities, however rare they may seem, so that they can be resolved quickly and effectively to minimize harm to subjects. By clearly detailing procedures to address situations of physical harm, the IRB can be assured that the investigator has made efforts to minimize physical risks to the greatest extent possible.

Psychological Harms: Research may result in undesired changes in thought processes and emotion (e.g. episodes of depression, confusion, feelings of stress, guilt, loss of self-esteem, embarrassment, distress). The possibility of psychological harm may be most prevalent when the research involves an element of deception. For all research with the potential to cause

psychological harm investigators are encouraged to think through all risk possibilities, however rare, so that a course of action can be planned to quickly and effectively minimize the distress to subjects. By clearly detailing procedures to address situations of psychological harm, the IRB can be assured that the investigator has made efforts to minimize psychological risks to the greatest extent possible.

Invasion of Privacy: Participant's perception/observation of behavior considered private. When developing your research consider if the invasion of privacy involved is acceptable in light of the participants' reasonable expectations of privacy in the situation and also whether the research question of sufficient importance to justify the intrusion. Invasion of privacy can be intrusion of one's solitude or into one's private affairs, public disclosure of embarrassing private information, publicity that puts the individual in a false light to the public, or appropriation of one's name or picture for personal/ commercial advantage.

Loss of Confidentiality: Unlike physical risks related to direct interaction and data collection from the participants, the risk of breach of confidentiality concerns safeguarding information that has been given voluntarily by one person to another. Some research requires the use of medical, school or employment records. Access to such records for legitimate research purposes is generally acceptable, as long as the researcher protects the confidentiality of that information. It is important to recognize that a loss of confidentiality may result in psychological harm to individuals (in the form of embarrassment, guilt, stress, etc.) or in social harm.

Social Harms: Some invasions of privacy and breaches of confidentiality may result in embarrassment within one's business or social group, loss of employment, or criminal prosecution. Areas of particular sensitivity are information regarding alcohol and drug abuse, mental illness, illegal activities, and sexual behavior. Some social and behavioral research may yield information about individuals that could "label" or "stigmatize" the participants (e.g. as actual or potential delinquents or people with schizophrenia). Confidentiality safeguards must be strong in these instances. The IRB is especially concerned about information regarding drug and alcohol use, mental illness, sexual behavior, and illegal activities. For these situations investigators should clearly detail strong precautions to ensure that the research does not cause social, legal or economic risks to the subjects.

Economic Harms: Participation in research may result in additional costs to individuals. Any anticipated costs to research participants should be described to prospective participants during the consent process. Research may also pose direct economic risk to study subjects. Procedures billed to insurance companies may require a significant co-payment on behalf of subjects, insurance companies may refuse to pay for "investigational" therapies, subjects may be responsible for transportation costs, and subjects may lose wages during research participation. Investigators should attempt to minimize economic costs to subjects. If the research may involve additional actual costs to individuals, the anticipated costs should be described to subjects during the consent process.

Legal Harms: Many researchers find themselves in ethical and legal quandaries when presented with a subpoena, which is a legal document requesting an appearance in court. While a subpoena is not likely for most research studies, if a study is examining things like sexual abuse, drug use or criminal activity, then it may cause the participants legal harm (consequences). Legal harm can be defined as causing an interaction between the participant and the court system.

3.0 Vulnerable populations: Special considerations for risk assessment

Pregnant Women, Fetuses, and Neonates: Research related risks to this population are those that are directly or indirectly connected to the medical condition of being pregnant. Taking a survey about personal career interests is a minimal risk activity for anyone, including pregnant women. However, something like taking a new medication for acne may be minimal risk for nonpregnant adults but is greater than minimal risk for pregnant adults because it is unknown what effects the medication may have on the woman's fetus. Therefore, the only time pregnant women are considered a vulnerable population is when the intervention has the potential to influence the safety of the fetus. Surveys, questionnaires, interviews, focus groups, and various cognitive tasks are considered minimal risk to pregnant women (45CFR46 Subpart B).

Prisoners: Assessing research related risks to research participants who are incarcerated is especially challenging due to the difficulty in assuring uncoerced, voluntary participation. Federal regulations specify that research involving prisoners has additional required protections and restrictions on permitted goals and intent of the study (www.hhs.gov/ohrp/policy/prisoner.html) (45CFR46 Subpart C).

Minors: Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under applicable law of the jurisdiction in which the research will be conducted. Generally, the law considers any person under 18 years old to be a child. In assessing the risks and potential benefits, consider the circumstances of the children to be enrolled in the study - for example their health status, age, and ability to understand what is involved in the research - as well as potential benefits to participants, other children with the same condition or situation, or society as a whole (www.hhs.gov/ohrp/policy/populations/children.html) (45CFR46 Subpart D).

Significantly Disadvantaged Persons: Persons significantly disadvantaged due to mental, social, economic, or educational circumstances including the sensory and mobility challenged, cognitively impaired, the poor and the illiterate may require additional protections of their interest and welfare before allowing them to enroll in research studies. Researchers planning or anticipating significantly disadvantaged persons to be enrolled in their research should describe planned procedures for minimizing risks to the participants.

4.0 Risks/Benefit Ratio Assessment

Risk to participants must be reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result. The benefits of a study do not alter the risk classification. The risk/benefit assessment only refers to the acceptability of the risk, not the level of the risk. A study deemed greater than minimal risk cannot be classified as minimal risk just because the potential benefits are great, but the research could be approved for this reason. However, the same study may not be approvable if the risks are greater than minimal, but anticipated benefits are also minimal or lacking. In evaluating risks and benefits, the IRB will consider only those risks and benefits that are directly related to participation in the research, as distinguished from risks and benefits of procedures/interventions individuals would receive even if not participating in the research. IRB reviewers identify any anticipated risks involved with the study and classify those risks as minimal or as greater than minimal risk. Reviewers then determine whether the anticipated risks to participants are reasonable in relation to the anticipated benefits to participants, if any, and the importance of the knowledge that may reasonably be expected to result (45CFR46.111(a)).

4.1 Risks and Benefits to include in protocol

Researchers should provide detailed information in the IRB protocol about potential risks and benefits associated with the research and provide information about the probability, magnitude and potential harms associated with each risk. Please keep in mind that these risks are to be directly related to participation in the research components themselves and on the immediate or reasonably foreseeable risks. They should not be risks or benefits of procedures or interventions individuals would receive even if not participating in the study and they should not be long-range effects of applying knowledge gained in the research.

4.2 Minimizing Risk

Risks, even when unavoidable, can be reduced or managed. Precautions, safeguards, and alternatives can be incorporated into the research activity to reduce the probability of harm or limit its severity or duration. An important aspect of risk assessment is the nature and type of planned protections to minimize the probability and/or severity of potential harm to participants. A greater than minimal risk may be reduced to minimal risk if protections for research participants are judged to be adequate. For example, a breach of confidentiality of sensitive information poses a risk of serious harm, but protections such as restricted access (encrypted data storage, locked files, Certificates of Confidentiality) reduce the absolute risk significantly and may thereby render a minimal overall risk to participants. To minimize risk to study participants, consider the following:

- Provide complete information in the protocol regarding the experimental design and the scientific rationale underlying the proposed research, including the results of previous studies.
- Use procedures which are consistent with sound research design and which do not unnecessarily expose participants to risk.
- Assemble a research team with sufficient expertise and experience to conduct the research.
- Ensure that the projected sample size is sufficient to yield useful results.
- Develop inclusion/exclusion criteria that will enroll only the desired population of interest.
- Collect data from standard-of-care or methodologically appropriate procedures to avoid unnecessary risk, particularly for invasive or risky procedures.
- For studies involving an element of deception provide a thorough debriefing following completion of the study.
- Provide up to date resources for additional help/support for participants (counselors, rehab centers, etc.).
- Incorporate adequate safeguards into the research design such as an appropriate data safety monitoring plan and the presence of trained personnel who can respond to emergencies.
- Store data in such a way that it is impossible to connect research data directly to the individuals from whom or about the data pertain; limit access to key codes and store separately from the data.
- Incorporate procedures to protect confidentiality of data (e.g. encryption, codes, passwords) and follow the USA IRB Human Research Data Security Standards.
- Obtain a Certificate of Confidentiality (CoC). This legal document provides protection against compelled (legal demand) disclosure of identifying information about individuals enrolled in sensitive biomedical, behavioral, clinical or other research. CoCs are issued by the National Institutes of Health (NIH) (https://humansubjects.nih.gov/coc/index)
- Obtain HIPPA Authorization or a waiver: Depending on the construct of your research you may request access to one's personal medical records through a HIPPA Authorization form or you may request a waiver of HIPPA under very specific circumstances (see SOP: HIPAA in Research).
- Obtain FERPA Consent or waiver: Depending on the construct of your research you may request access to one's education records through a FERPA consent form or you may request a waiver of FERPA under very specific circumstances.
- Obtain signature from the Legally Authorized Representative (LAR) for potential adult participants with diminished decision-making capacity (e.g. result of trauma, mental retardation, forms of mental illness, or dementia). The LAR is an individual, judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (45 CFR 46.102(c)).

Procedures

These policies and procedures are based on: Common Rule 45 CFR 46.111(a)(1),(2); FDA 21 CFR 56.111(a)(1),(2). When reviewing the application submitted by the Principal Investigator (PI), the IRB analyzes levels of risk, ensures risks are minimized, and ensures risks are reasonable relative to anticipated benefits, before approving the proposed research.

Investigators submitting research proposals for IRB review should understand that the IRB is responsible for assessing the possible risks vs. anticipated benefits, if any, of research as one of its primary functions. In addition, once risks and benefits have been assessed, the IRB is responsible for ensuring that the risks of study participation are minimized to the greatest extent possible, while the benefits of study participation are maximized.

1.0 Identifying Potential Risks (PI Input)

When considering risks, the IRB considers only those risks associated with the research, i.e., physical, psychological, social, legal, emotional. Investigators should be aware that risks would include immediate risks of study participation, risks of randomization (especially to placebo groups in medical and pharmaceutical research), risks of breach of confidentiality, and risks of long-term effects.

For biomedical research (primarily medical and pharmaceutical research) the IRB is required to determine and differentiate between the risks associated with the research and the risks associated with standard diagnostic or therapeutic interventions or therapies subjects would undergo regardless of participation in research. The IRB does not establish or determine what constitutes “standard of care.” It is important for investigators to clearly distinguish procedures which they consider are “standard of care” from those which are conducted solely for research purposes in the protocol and the informed consent form.

Minimal Risk Much of the IRB review process is governed by the concept of “minimal risk.” Assignment of research for expedited review, approval of waiver of consent, and the conduct of research involving vulnerable research populations may be dependent upon whether the research places subjects at minimal risk or greater than minimal risk (significant risk).

2.0 Ensuring Risks Are Minimized (IRB Determination)

The IRB considers the overall level of risk to participants in evaluating the proposed research in accordance with the conditions outlined in 45 CFR 46.111(a)(1-7), 21 CFR 56.111(a)(1-7) and the ethical principles outlined in the Belmont Report. Furthermore, the IRB may consult with additional experts as needed. [45 CFR 46.111(a)(1)(i), 21 CFR 56.111 (a)(1)(i)]

When assessing risks and benefits, the IRB is required to:

1. identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in the research;
2. determine that the risks will be minimized to the fullest extent possible;
3. identify the probable benefits to be derived from the research;
4. determine that the risks are reasonable in relation to the benefits to subjects, if any, and the importance of the knowledge to be gained;
5. assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits;
6. determine intervals for periodic review (no greater than annually), and, where appropriate, determine that adequate provisions are in place for monitoring the data collected and, if the subjects are likely to be members of vulnerable populations, determine that appropriate additional safeguards are in place to protect the rights and welfare of these subjects.

The IRB examines the research plan, including research design and methodology, to determine that there are no inherent flaws that would place research participants at unnecessary risk. This includes the risk that research lacking in statistical power may not lead to meaningful results. Appropriate safeguards can also minimize risk to participants, for example: having an adequate data monitoring plan, or protecting confidentiality by using coded data. If risks are not adequately minimized, the protocol will not be approved as written.

The IRB also considers the professional qualifications and resources (including time, equipment, support services) of the research team to protect participants and minimize potential harm. Research personnel must have received appropriate training, and clinicians involved in the research must maintain appropriate professional credentials and licensing privileges.

3.0 Data Monitoring Plan (Required for Greater Than Minimal Risk Studies)

To approve research, the IRB must determine that, where appropriate, the research plan makes adequate provisions for monitoring the data to ensure the safety of research participants. (45 CFR 46.111(a)(6), 21 CFR 56.111(a)(6), 38 CFR 16.111(a)(6))

Many studies (e.g., if more than minimal risk) need a Data and Safety Monitoring Plan (DSMP):

Data Monitoring Plans and Data Monitoring Committees – NIH and NCI policies:
- NIH: Policy for Data and Safety Monitoring
- NIH: Further Guidance On Data And Safety Monitoring For Phase I And Phase II Trials
- NCI: Data and Safety Monitoring Guidelines: Essential Elements

IRB Review of the Data Monitoring Plan (See SOP: Data Safety Monitoring Plan)

In addition, periodic (usually annual) reports from the monitoring entity are submitted by the PI to the IRB at continuing review. (When a monitoring entity is used, the IRB conducting continuing review of the research may choose to rely on a current statement from the monitoring entity indicating that it has and will continue to review study-wide adverse events, interim findings, and any recent literature that may be relevant to the research.)

Whether the method of monitoring is by PI oversight or from the establishment of a DSMB, the IRB can tailor a specific timeframe for future reporting of data monitoring findings to the IRB. The IRB can set the date of continuing review for the protocol as being less than the maximum of a year, if they determine that interim reporting of data monitoring information will serve to better protect participants. Alternatively, the IRB can request a report after a specific number of participants are enrolled or after a serious adverse event has been reported.

4.0 Risks to Vulnerable Populations

The IRB is cognizant of the vulnerable nature of many participants. Food and Drug Administration (FDA) regulations and the Common Rule require IRBs to give special consideration to protecting the welfare of vulnerable participants. In order to approve research involving vulnerable populations, the IRB must determine, where appropriate, that additional safeguards have been included to protect the rights and welfare of participants who are likely to be vulnerable to coercion or undue influence, such as:

- Children (45 CFR 46 Subpart D; 21 CFR 50 Subpart D),
- Prisoners (45 CFR 46 Subpart C),
- Pregnant women, human fetuses, or neonates (45 CFR 46 Subpart B),
- Persons with mental disabilities, or
- Economically or educationally disadvantaged persons

The IRB includes among its members persons who are knowledgeable about and experienced in working with vulnerable participants. (45 CFR 46.107(a); 21 CFR 56.107(a)). When a research study involves a vulnerable population not otherwise covered by these policies, the IRB takes steps to evaluate whether additional safeguards have been included in the research to protect the rights and welfare of participants.

4.1 Children

Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted.

The IRB follows the requirements of the DHHS regulations at 45 CFR 46, Subpart D and FDA regulations at 21 CFR Part 50, Subpart D in reviewing protocols involving children. The IRB makes the findings and determinations required by the DHHS and FDA regulations related to the risks before allowing research involving children to proceed. See Chapter 12.2 for consent requirements for research involving children participants.

4.2 Prisoners

Any individual involuntarily confined or detained in a penal institution. This includes individuals:

- sentenced to such an institution under a criminal or civil statute,
- detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution,
- detained pending arraignment, trial, or sentencing.
- DHHS details special protections for research involving prisoners, who due to their incarceration may have a limited ability to make truly voluntary and un-coerced decisions about whether or not to participate as participants in research.
- [45 CFR 46, Subpart C]. The IRB will apply the standards of Subpart C to all prisoner research, whether or not DHHS-supported.

DHHS-supported research: The IRB must certify to the Secretary (of DHHS), via the Office for Human Research Protections (OHRP) that it has reviewed and approved the research under 45 CFR 46.305; additionally, the Secretary (through OHRP) must determine that the proposed research falls within permissible categories [45 CFR 46.306(a)(2)]. If biomedical or behavioral research is conducted or supported by DHHS, approval must be obtained from the Secretary of DHHS (through OHRP) before commencing research. Note: OHRP discourages expedited review of any research involving prisoners as participants.

When a previously enrolled research subject becomes a prisoner and the relevant research protocol was not reviewed and approved by the IRB (under 45 CFR 46, Subpart C) the PI should promptly notify the IRB of this event through the IRB Amendment Form. The PI should state that all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-participant will cease until the requirements of Subpart C have been satisfied with respect to the relevant protocol, unless the PI asserts that it is in the best interests of the participant to remain in the research study while incarcerated, in which case the IRB Chair may determine that the participant may continue to participate in the research until the requirements of Subpart C are satisfied. Upon receipt of notification that a previously enrolled research participant has become a prisoner, the IRB should promptly re-review the protocol in accordance with the requirements of Subpart C if the PI wishes to have the prisoner participant continue to participate in the research.

5.0 Decisionally Impaired Participants

The IRB reviews the risk-benefit analysis including the possibilities of coercion and undue influence, and must determine whether such participants should be recruited and whether support mechanisms, such as surrogate consent, are appropriate.

6.0 Pregnant Women, Human Fetuses, and Neonates

The Department of Health and Human Services (DHHS) details special protections for research involving pregnant women, human fetuses, and neonates. [45 CFR 46, Subpart B.]
Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent, in accordance with the guidance Additional Protections for Research Involving Pregnant Women, Fetuses, and Neonates.
In general, Subpart B requires that research involving pregnant women, human fetuses, and neonates should involve the least possible risk. Persons engaged in the research may have no part in the timing, method, or procedures used to terminate the pregnancy, or to determine the viability of the fetus. No inducements may be offered to terminate a pregnancy.
Four separate conditions, each with their own requirements and IRB determinations, apply to research with pregnant women, human fetuses, and neonates:

6.1 Research Involving Pregnant Women. No pregnant women may be involved as a participant in research unless either of the following conditions applies: The purpose of the activity is to meet the health needs of the mother, and the fetus is placed at risk only to the minimum extent necessary to meet such needs; OR the risk to the fetus is minimal. The mother and the father must be legally competent and provide consent, unless the purpose of the research is to meet the health needs of the mother, or the father is not reasonably available, or the pregnancy resulted from rape.

6.2 Research Directed at Human Fetuses. The IRB must find that: the purpose of the research is to meet the health needs of the individual fetus and shall be conducted in a way that will minimize risk; OR the research will pose no more than minimal risk to the fetus, and the purpose of the activity is to ascertain important biomedical knowledge that is unobtainable by other means. These activities are permitted only if the mother and father are legally competent and have given their informed consent, unless the father is not reasonably available or the pregnancy resulted from rape.

6.3 Research Involving Neonates. For research involving neonates, the IRB must distinguish between viable and non-viable neonates. Viable is defined in the

regulations as being able to survive to the point of independently maintaining a heartbeat and respiration, given the benefit of available medical therapy. If the neonate is viable, it is considered a "child" and may be involved in research to the extent permissible under 45 CFR 46, Subpart D, which is discussed later in this chapter.

• A non-viable neonate may not be involved in research unless all of the following conditions apply: The vital functions of the neonate are not artificially maintained; experimental activities that would of themselves terminate the heartbeat or respiration are not employed; AND the purpose of the research is development of important biomedical knowledge that cannot be obtained by other means. Research involving a non-viable neonate is permitted only when both parents have given their informed consent, unless one parent is not reasonably available or the pregnancy resulted from rape or incest. In the case of non-viable neonates consent by a parent's legally authorized representative is not allowed.
• A neonate of uncertain viability may not be involved in research unless one of the following conditions applies: There is no added risk to the neonate and the purpose of the research is to obtain important biological knowledge that cannot be obtained by other means; OR the purpose of the activity is to enhance the probability of survival of the individual neonate. Research involving a neonate of uncertain viability is permitted only if either parent or the parent's legally authorized representative gives their permission.

Regulated Documentation

45 CFR 46; 21 CFR 50; 21 CFR 56

University Related Documents

Investigator Checklist for Research Involving Children
Investigator Checklist for Research Involving Pregnant Women
Investigator Checklist for Research Involving Prisoners

References

SOP: Data Safety Monitoring Plan
Special Protections for Research Involving Children (DHHS OHRP)
Additional Safeguards for Children in Clinical Investigations (FDA)

HISTORY

Effective Date: October, 2018