Risks and Benefits

**Risk:** The probability and magnitude of harm 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.)

**Identifying Risks:** When considering risks, the IRB considers only those risks associated with the research methods themselves and the data generated or accessed for the research. This includes risks to primary participants and third party participants in context of their life and environment. 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 of the intervention, interaction, or use of data.

- **Physical Risks:** Some research presents risk of physical injury to subjects. Although most of these risks are transient, some adverse effects of study participation (especially those which result from medical procedures, drug research or device research) may result in permanent injury to subjects. 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 Risks:** Some research has the potential to cause undesired changes in thought processes and emotion including episodes of depression, confusion, and hallucination resulting from drugs, feelings of stress, guilt, and loss of self-esteem. As is the case with physical risks, these effects are usually transient. 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.

- **Legal:** Some research involves generating or accessing data that may reveal unlawful behavior and as a result of the research or access of data, the unlawful behaviors are more exposed, identified at all, or accessible to others through breach. In these cases, the risks to participants include possibilities of arrest, audit, deportation, incarceration, removal form home, etc. The researcher must be aware of and communicate all reporting obligations to the IRB and to participants when possible.
• **Academic Risks**: Some research involves generating or accessing data that may affect a participants academic standing, ability to get into a program, grades in a class, favor with teachers/principals, or reveal issues of cheating. The researcher must be aware of and communicate all reporting obligations regarding academics to the IRB and to participants when possible. This includes issues of power dynamics and undue influence/coercion and harm to the participants’ academic environment.

• **Medical and Insurability Risks**: Research may also pose direct medical or insurability risk to study participants. Procedures billed to insurance companies may require a significant co-payment on behalf of subjects, insurance companies may refuse to pay for “investigational” therapies, Insurance companies may refuse to provide insurance to a participant as a result of the data from a project, medical decisions could be altered or changed etc.

• **Social, Reputational, Relationships, Private Behavior**: This risk is about how the data generated or accessed could cause harm among the participants’ relationship, social network, or their reputation. What about the data could reveal something embarrassing, something betraying, or something inappropriate? Could the information result in loss of relationship or loss of credibility?

• **Economic, Financial, Employable**: This risk is about if the participants could suffer financially or at their work as a result of the study. Could a participant be fired, demoted, not promoted? Could the study identify areas that could put the subjects’ financial life at risk? Subjects may be responsible for transportation costs, and subjects may lose wages during research participation. Investigators should attempt to minimize economic costs to subjects

• **Breach of Confidentiality**: Some research proposals involve the handling of sensitive information which may result in injury to subjects through a breach of confidentiality. These breaches may result in harm such as embarrassment within a subject’s business or social group, loss of employment, criminal prosecution, removal from academic program, etc. For these situations investigators should clearly detail strong precautions to ensure that the research and handling of the data does not breach confidentiality and pose privacy risks.

**When assessing risks and benefits, the IRB:**
- 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;
- determine that the risks will be minimized to the fullest extent possible;
- identify the probable benefits to be derived from the research;
- determine that the risks are reasonable in relation to the benefits to subjects, if any, and the importance of the knowledge to be gained;
- assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits;
- 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.
- Identify the risks and benefits to primary participants and secondary/third party participants.
- Identify risks as related to data security throughout the lifecycle of the data.
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.

**Potential Risks v. Anticipated Benefits (PI Input)**
The Protocol Application requires that the PI describe the potential benefit(s) that may be gained by participants, and how the knowledge gained may benefit the participants, future participants or society. The PI must explain how these potential benefits to the participant or society outweigh the risks inherent in the research.

**Potential Risks v. Anticipated Benefits (IRB Determination)**
The IRB determines whether the risks of the research are reasonable in relation to the anticipated benefits (if any) to research participants and the importance of the knowledge that may reasonably be expected to result. The IRB bases its risk/benefit analysis on the information provided by the PI and by the expertise of its members and consultants who utilize the most current information about the risks and benefits of the interventions involved in the research.

The IRB considers only those risks that result from the research, and does not consider long-range effects (e.g., public policy implications) of applying the knowledge gained in the research. The IRB does not consider those risks and benefits that participants would receive even if not participating the research.

**Do the anticipated benefits justify the risks to the potential research subject?**
This evaluation is the major ethical judgment in reviewing research applications. In analyzing the risks and benefits of proposed research, the IRBs consider the following questions:

- What are the risks of participating in this protocol as compared to the risks of standard of therapy or everyday life?
- Are the risks adequately described in the application and protocol?
- Are there risks that might be different for children or other vulnerable populations and are these adequately described?
- If deception is used, is it adequately justified and is the debriefing plan adequate?
- Are risks minimized to the extent possible? Risks may be minimized by appropriate eligibility criteria, measures to make study procedures as comfortable as possible, study-wide monitoring of safety and data integrity, good study design, plans to handle adverse effects, using research personnel who are qualified to perform their duties, and having adequate levels of supervision.
- What will the research subject experience through study participation (number and length of study visits, procedures involved, etc.)?
- Are subjects told about the study in a way they can understand, so the participants can make an informed choice about taking part?
• Are provisions in place to maintain the privacy of the subjects and confidentiality of the data and research records?
• What are the expected benefits?
• Are risks of the research reasonable in relation to the benefits?

Minimizing Risks:

Has the research been designed to minimize risks to participants? To make this determination IRBs evaluate the following as appropriate:

• The eligibility criteria to ensure they are equitable.
• The procedures used to ensure they are not unnecessary or excessive.
• The study design to ensure it is sound, such that participants are not unnecessarily exposed to risks and any risks participants assume will result in usable information.
• The probability or magnitude of risks to see if these can be reduced by using procedures already being performed for diagnostic or treatment purposes.

Are resources necessary to protect participants? To make this determination IRBs evaluate the following as appropriate:

• The number of qualified staff or, in the case of student research, is the level of supervision to ensure it is adequate.
• The facilities and time available for the researchers to conduct and complete the research.
• The medical or psychosocial resources participants may need as a consequence of the research to ensure these will be available.
• The access to a population will allow recruitment of the necessary number of participants.

Are the risks are reasonable in relation to the anticipated benefits? This risk/benefit assessment is dependent upon prevailing community standards and case-specific determinations of risk and benefit. To make this determination IRBs evaluate the following as appropriate:

• The expected benefits (direct benefits can take the form of therapy, education, information, resources, or empowerment).
• The importance of the research to society (especially if there are no expected benefits to participants).
• The potential risks (physical, social, economic, psychological and legal harms).
• The likelihood and magnitude of any potential benefits or risks.

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

**Considerations in Reviewing Research involving Vulnerable Participants**
The IRB considers the following elements of the research plan when reviewing research involving vulnerable participants and they include this in their risks/benefits analysis:

- Strategic issues that involve inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.

- Group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable participants.

- Participant selection to prevent over-selection or exclusion of certain participants based on perceived limitations or complexities associated with those participants. For example, it is not appropriate to target prisoners as research participants merely because they are a readily available “captive” population.

- Application of state or local laws that bear on the decision-making abilities of potentially vulnerable populations. State statutes often address issues related to competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research.

- Procedures for assessing and ensuring participants’ capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable participants, the IRB verifies that such procedures are a part of the research plan. In certain instances, it may be possible for investigators to enhance understanding for potentially vulnerable participants. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a participant advocate, interpreter for hearing-impaired participants, translation of informed consent forms into languages the participants understand, and reading the consent form to participants slowly and ensuring their understanding paragraph by paragraph.

- Need for additional safeguards to protect potentially vulnerable populations. For example, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

**Other Potentially Vulnerable Participants**
The context of the research is an important consideration for the IRB when reviewing research that involves other potentially vulnerable participants such as research involving homeless persons, members of particular minority groups, or the economically or educationally disadvantaged. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of participants and the IRB takes such considerations into account. Nevertheless, research involving these participants is socially important for understanding and eventually improving adverse health and general well-being in these populations.
Data Security and Risks: Federal regulations require IRBs to determine the adequacy of provisions to protect the privacy of subjects and to maintain the confidentiality of their data. To meet this requirement, federal regulations require researchers to provide a plan to protect the confidentiality of research data.

Maintaining human subject data securely with the appropriate level of anonymity, confidentiality, or de-identification is a key factor in ensuring a low risk threshold for the participants, the researchers, and the university. As such, principal investigators (PIs) and their study teams may be required to outline the data management and security procedures.

Assessing the data security method needed: Based on the type of data involved in the study, the IRB is required to 1) assess potential risks to participants, and 2) evaluate the researchers’ plan to minimize risks. All research activities result in some type of risk and the researcher has the responsibility to mitigate the risk of improper disclosure.

What is the risk as related to data security?

- Is the data identifiable, de-identified (coded), or anonymous?
- Is sensitive information being collected that could result in harm to participants?
- What is the risk of harm to the participant or others?

What are the protections against anticipated threats or hazards (during collection, transmission, storage)?

- Encryption of data on device to protect against loss/theft of device
- Use of secure data transmission channels to protect against data interception
- Strong passwords to protect against unauthorized access
- Store data behind a secure firewall whenever possible
- Ensure strong data security controls on all storage sites

Data Transmission: The process of transmitting data is often overlooked as a risk. The plan to protect confidentiality should describe the methods to protect the data during collection and sharing both internally and externally to the University. It is advisable to utilize a secure transmission process even if the data is anonymous, coded, or non-sensitive information. If the research team develops a best practice on using a secure data transmission process, then it is less likely a data breach will occur. Email notifications are generally not secure, except in very limited circumstances, and should not be used to share or transmit research data. Text messages are stored by the telecommunications provider and therefore are not secure. Data should be encrypted when “in-transit,” and the University provides extensive guidance, software, and resources to assist researchers in this. Terms such as Secure Sockets Layer (SSL and HTTPS) or Secure File Transfer Protocol (SFTP) are indications that the data is being encrypted during transmission. Tools which can be used to encrypt files before transmission, are made available to all University faculty and staff at no cost.

Data Storage: It has become common practice to store some level of personal information in the Cloud with services such as Box, Google Drive, Dropbox, Salesforce.com, Evernote, Office365, and Amazon. Using such services can often result in cost savings; however, special attention must be paid to potential security risks, export control restrictions, and data ownership issues. Please refer to the NC State OIT guide for proper data storage.
Other Considerations:

It is important for researchers to consider and plan for issues related to the following:

- Software on computers to protect against malware
- Data security to ensure all software updates and patches are being applied
- Data collection, transmission, and storage methods employed
- Data collected is only that data necessary to answer the research question
- Codes are not stored with the corresponding de-identified data
- Encryption methods are being used on all portable devices (laptops, mobile devices, and removable storage)

Mobile Applications: Many researchers are purchasing mobile apps or building their own app to interact with study participants. Seek expert IT review and, if commercially available, purchase the app through the appropriate means and check with your Department as to how to do this so a legal and data security review is performed if necessary.

Even if the participant is asked to download a free App or provided monies for the download, the researcher is still responsible for disclosing potential risks. It is possible that the App the participant downloaded will capture other data stored or linked to the phone on which it is installed (e.g., contact list, GPS information, access to other applications such as Facebook). The researcher has the responsibility to understand known or potential risks and convey them to the study participant. Commercially available apps publish “terms of service” that detail how app data will be used by the vendor and/or shared with third-parties. It is the researcher’s responsibility to understand these terms, relay that information to participants, and monitor said terms for updates. Additionally, it is important that the researcher collect from the App only the minimum data necessary to answer the research questions.