Is it Human Subjects' Research?: Definition of "Human Subject"

This document provides information regarding the federal definition of "human subject" and what activities involving humans are regulated by the IRB. An activity may be research and involve humans, but may not meet the criteria for regulated research with human subjects as defined by the federal regulations governing research with human subjects (45 CFR 46).

The federal regulations that govern research with human subjects define a *human subject* as a living individual about whom an investigator (whether professional or student) conducting research:

- Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Furthermore, the federal regulations define the following terms:

- Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- Interaction includes verbal, non-verbal, and written communication between investigator and subject.
- Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).
    - Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
    - An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Key Points from the Federal Definition:

"Living Individual"

- The data obtained, used, studied, analyzed, or generated must be about a live person. The data can be about a primary participant or a third party participant.
    - Primary participants are people who are in the research project where the data generated or accessed is directly about their own thoughts, feelings, opinions, experiences, habits, physical/intellectual reactions, or biodata.
    - Third party participants are people whom researchers do not directly interact with, but information about them is revealed or shared throughout the research process. This makes them an individual who may be directly affected by the research procedures who also needs to be considered throughout the protections put in place through research

design. Third party participants often are involved in research when methods like photovoice or interviews are used, as well as when research on the genome is completed. The identifiable nature of the information about the third party shared when compiled with the sensitivity of the data, will directly affect the risk assessment

- For example: When a primary participant discusses someone else in an interview, survey, or focus group, the person they are referring to is considered a third party participant and must be considered as a participant during the IRB review process where risks/benefits analysis is made.
- For example: When biospecimens or information from a deceased person are used to generate information about living people, such as their biological family.

"About Whom"

- A person's physical nature or physical responses
- A person's thoughts, feelings, reactions, habits, choices, opinions, and experiences
- Information or facts about a person's private life
- A person's performance or checks in ability or understanding

Intervention

- A procedural system by which data or specimens are gathered about an individual
  - For example: Behavioral interventions such as a computer game, changes in curriculum, change in clothing, changes in interior/exterior design that affect how people interact with a space
  - For example: Collection of biospecimens
  - For example: Use of a device or drug affecting the human body
  - For example: Manipulation of the environment such as changing a person's environment to see what happens or changing their environment in a way that exposes them to or increases risks to which they would not otherwise be exposed
    - For example: request participants to put items in their home space for research purposes (when they otherwise would not).
- Observations and Recordings
  - Observations are considered an intervention because the researcher is implementing a systematic way of observing human behavior and their behavior is recorded (written, audio, video, other) where it would not have been otherwise
  - Please see the IRB guidance regarding video and audio recordings (Word document)

Interaction

- An interaction includes communication or interpersonal contact between the researcher and possible participant.
  - For example: Implementation of a survey, interview, or focus group
  - For example: Recruitment processes or consent processes

Private Identifiable Data

- Please see guidance regarding secondary data (Word document) and the nature of identifiability (Word document).
- Other laws and regulations may apply to this, such as FERPA, HIPAA, and the GDPR. Please find the IRB's guidance regarding these laws on the Policies, Rules, and Regulations page of the IRB website (opens in a new window).

Office for Human Protections (OHRP - opens in a new window) Regulated Research and What NC State University Regulates

The Office for Human Research Protections (OHRP) only regulates human subjects research funded by the federal government. Funding agencies and signatories of the "Common Rule" (aka the regulations governing research with humans, 45 CFR 46 - opens in a new window). Universities receiving federal money must adhere to OHRP's standards, however Universities are permitted to apply the federal regulations to additional projects. NC State University's regulation (10.10.03 - opens in a new window) applies the federal regulations governing research with human subjects to all research projects, regardless of funding.

- OHRP determines what needs to be regulated by asking these questions:
    - Is the project federally funded?
    - Is the project research as defined by the regulations?
    - Is the project human subjects research as defined by the regulations?
    - If the answers to the above questions are yes, then OHRP requires review of the project

- NC State University determines what needs to be regulated by asking these questions:
    - Is the project research (Google document) as defined by the regulations?
    - Is the project human subjects research as defined by the regulations?
    - Is NC State University engaged in the research (when someone associated with the research team is acting as an agent of NC State such as a faculty, staff, or student and the research is within the scope of their appointed role at NC State)?
    - If the answers to the above questions are yes, then NC State University requires IRB review and approval of the project
        - Exemption determinations are made by the NC State IRB office, not the researchers. If the study possibly qualifies for exemption, the researcher applies to the NC State IRB for that official determination.
        - A reliance or individual investigator agreements may also apply. Find information about both on the cooperative research page of the IRB website (opens in a new window). IRB review is required for all research with humans where NC State University researchers are on the research team. This is regardless of funding source.

Projects considered research involving humans subjects that require IRB approval

- Due to OHRP Regulations and the NC State University Regulation
    - Any federally funded non-exempt research involving human subjects.
    - Projects where researchers receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (i.e. awardee institutions), even where all activities involving human subjects are carried out

by employees or agents of another institution. This requires the execution of a reliance agreement (opens in a new window) among IRBs.
    - Researchers that obtain (for research purposes) identifiable private information or identifiable biological specimens from any source for the proposed research.
- Due to NC State University Regulation and IRB Convened Full Board Determination
    - Any research with humans regardless of funding source or IRB review level.
        - Any research involving human subjects includes the activities: recruitment, consent, data collection, access of data, or analysis of identifiable data.
        - NC State University applies the human subjects regulations to all research completed with human subjects.
    - Manipulation of participants' environment or experiences where the data generated is not about the participant specifically, but instead the human is used as a tool for data collection where the study could not be carried out without their participation and something unique about the individual may affect the study procedures or data.
        - For example: Studies where the researcher exposes themselves to insects such as arm in cage studies or for the collection of ticks. This is considered human subjects research because the human is acting as a tool where their body influences the data collection and they are exposed to physical risk as a result of research procedures (such as skin irritation, allergic reaction to insect bites, etc.).
        - For example: Pesticides or traps used in a person's home. This is considered human subjects research because the research could not take place outside of the human's home and the human environment and their unique space and their individual practices may influence the data collection. They are also exposed to physical and reputational risk as a result of research procedures (such as reaction to pesticide or trap, possible effects this intervention could have on use of spaces within home by people and pets, reputation regarding stigmas associated with insects in the home).
        - For example: Collection of samples from property such as well water and soil. This is most often considered human subjects research because the data collected about the property could affect the participants' welfare, reputation, or have financial consequences. This can be considered human subjects research and it can also not be considered human subjects research and it would depend on the study design, role of participant, private/public nature of the property and the risks/benefits ratio of the research to the participant.
        - For example: Implementation of citizen science projects where the people are both acting as a researcher of sorts, and also collecting data about themselves or they are manipulating their own environment for the sake of research. This includes having participants bring items from the outside environment into their home environment such as putting samples and specimens in the refrigerator.

The following projects are NOT considered research involving humans subjects and as a result do NOT require IRB approval

- When humans administer medicine to animals for animal research except when
    - There are **any procedures** that involve the human such as a survey or collection of demographics about the human, this will require IRB approval
    - The research question is about humans and not necessarily the animals, this will require IRB approval.
- Biospecimens obtained from another source (not directly from the patient) that is:
    - either/totally anonymous and unlinkable to the person who it was obtained from or is coded such that the researcher obtaining the sample does not know who it belongs to AND
    - a confidentiality agreement assures the researcher cannot learn the identity of the person who the sample was obtained from.
    - This includes the research team members inability, through design and choice, to re-identify an individual through any data combination and analysis techniques.
- Data from another source (not directly from a patient or their records) that is either:
    - totally anonymous and unlinkable to the person who it was obtained from or
    - is coded such that the researcher obtaining the data does not know who it belongs to AND
    - a confidentiality agreement assures the researcher cannot learn the identity of the person who the data was obtained from.

Appendix A

Vet School Information

How do I know if I need IRB approval as well as IACUC approval?

- If you are working with people and you ask them about their thoughts, feelings, experiences, habits, behaviors, or choices as related to their animals. Sometimes how one question in a survey or interview or interaction is phrased makes it human subjects research.
- If you are working with people and asking about their animals or farms, if any of the questions are about "why" something occurs or their "thoughts about an occurrence or choice" then this would require IRB approval.
    - "How many pigs are on the farm"
        - This is not a question that is considered human subjects research as it is about operations of a farm
    - "Why did you choose to have that many pigs on the farm"
        - This is considered human subjects research because it is asking the individual about their choice.
    - Requesting the human to provide their own demographic information, even if the rest of the questions are about operations or animals, is considered research with humans because the demographics is collecting directly or indirectly identifiable data about the human.
- If you are working with people who are completing activities as a normal part of their veterinarian treatment or student learning, if there is *anything* added to the person's normal practices as a result of the research (such as additional sensors donned or questions asked or information recorded when it otherwise would not be) then this would require IRB approval. Additionally, if you are asking a research question as related to their performance in their duties, then this would require IRB approval.
- If the question you are asking is about people, check with the IRB as it will likely need IRB review.

When humans are involved in IACUC-approved research but the IRB does not oversee the research procedures, this information should be included in the information provided to people:

- When humans are asked to apply creams or administer medicine to their animals, you should make sure to let the humans know the following:
    - If the product or activity would expose the human to any additional risk they would not normally be exposed to on an average day, what that risk is, and how to mitigate it.
    - Discuss the FDA approval status of the medicine and anything known about the medicine and its effects on humans or animals. You can check the approval status of a FDA drug for human use at the Drugs@FDA: FDA Approved Drugs database (opens in a new window).

- Discuss the procedure for administering the cream or medicine and if the participants should wear gloves or avoid the cream or medicine in some way.
- Screen out humans who have allergies or could experience an adverse reaction as a result of the medicine which may increase risk or expose participants to risks they would not normally be exposed.
- Discuss boundaries around financial obligations of what they do and do not have to pay for, including if something goes wrong with them or their animal during the course of the research activities.

Appendix B

"Humans As Tools" in Research - Questions for Consideration for Determination

What are the research questions for this project?

What are the data collection methods for this project?

What will the humans be doing in this study?

Will any of the data points collected be about

- The human's thoughts, feelings, experiences, habits, or beliefs?
- The human's physical reactions or physiology?
- The human's environment and how they interact with it or how it affects them?
- Private facts about the person?

Will this study influence or manipulate the human's environment?

Will the data collection method that the human is involved in pose the human any risk? If so, describe.

IRB Considerations: Human Factors and Environment

Identify the role of the humans in the research (Participants? Researchers? Data collection agents? Other)

- Human Subjects Involvement:
    - Is this about a living individual or a living third party?
    - Is the data obtained through interaction or intervention (physical procedures, manipulation of environment, communication or contact)?
    - Does the research affect the human's environment in any way? If so, how.
    - Is the data identifiable?
    - What are the participants' privacy expectations?

Appendix C

Examples of HSR and NHSR at NC State University where Humans are involved as "Tools"

HSR = Human Subjects Research and Requires IRB approval

NHSR = Not Human Subjects Research and DOES NOT Require IRB approval

- Humans collecting ticks: HSR
    - Participants don socks and collect ticks on the socks. Later the ticks are pulled off the socks. This is HSR because it is looking at if ticks land on certain people and not others – how the human affects the outcome of this. The tick also may bite the human and if they do, the blood from that would 1) have a negative effect on the person and 2) be about the person's physiology

- Collection of soil or water samples from a human's private property HSR/NHSR
    - There are no interactions with humans other than permission to access their property. Samples are taken from the soil or water and, when analyzed, the data reveals information that may cause harm to the participants reputation, economic standing, or even resale value of the property.
    - In some cases, this is human subjects research and in some cases, it is not. This will be dependent on any other study procedures, the private/public nature of the property, analysis of the data, and what it is likely to reveal about the participants or others.

- Arm in cage study: HSR
    - Participants don material or spray and put their arm in a cage with mosquitos. This is HSR because it is looking at if some mosquitos land on certain people and not others – how the human affects the spray or the material will affect the outcome of this. The mosquito also may bite the human and if they do, the blood from that would 1) have a minor negative effect on the person and 2) be about the person's physiology.

- Collection of animal excrement: Not HSR
    - Humans collect their pet's excrement, bag it and send it to the lab for analysis. This is not HSR because these are animal specimens, but from the specimen, they are not getting information about humans or their environment.
        - More importantly, the samples that are collected will not affect the humans environment (e.g. the stool is not stored in the fridge, the information gleaned from the excrement won't provide information about the human such as animal abuse/neglect, and researchers are not seeking information about the humans from the excrement)

- Administration of nasal spray to animals: HSR/NHSR
    - Humans administer nasal spray to their animals and answer questions about their pet's reaction. None of the questions are about humans or their choices. This is NHSR.
    - If the survey were about the humans at all (including demographics) this would become HSR and would be regulated, including what is communicated about the nasal spray and interactions with their pet.

- Collection of bird eggs: HSR
    - Participants collect bird eggs from nests outside of their living area and put them in the fridge for storage and later send. Info about the eggs and location is shared.
    - This is HSR because of how the egg is handled and placed in the refrigerator with the human's food. This affects the human's environment and humans were asked to complete a survey about the location of the eggs, therefore providing information to the researchers about the environment around the human's house

Appendix D

When it's NHSR but there are Ethical Obligations and What to Communicate to People

If you are completing research activities that involve humans, but it has been determined that the IRB cannot review or approve the protocol because it does not meet the definition for research or human subjects research, you may still have ethical obligations around transparency and communication.

Ethically, you are obligated to communicate all possible foreseeable risks to participants so that they can make an informed choice about their participation. This should include

- A discussion of what the worst-case scenario would be and the likelihood of that occurring due to your research design and risk mitigation strategies.
- A discussion regarding any type of compensation or limits related to that compensation
- In your research design, you should scientifically justify your inclusion/exclusion criteria and communicate those criteria to participants.
- A discussion around proper procedures, safety precautions, emergency procedures, reporting obligations, etc.

The IRB suggests that you create an information sheet and provide it to people who choose to help you with your research project. This form should be written at a 4th-6th grade level and include:

- Contact information for the researchers
- Description of all procedures and expectations related to the procedures
- Description of how the information from the project will be used, protected, and reported including information about identifiable data.
- Information about compensation and limits
- Detailed information about risks as related to the procedures and any mitigating circumstances related to the risks
- Additional resources as available or alternatives available
- Information about any applicable laws that may be relevant to the activity

The IRB suggests that you work with your department and the office of general counsel as appropriate when creating these forms or information that will be shared