1.8 Investigational Activities Requiring IRB Review and Approval

1.0 Purpose

The purpose of this policy is to describe the investigational activities that require IRB approval.

2.0 Policy

It is the policy of the Organization that:

- 2.1. IRB review and approval is required for research involving human subjects which falls in the following categories regardless of the funding source:
  - 2.1.1. Research conducted on the premises of any of the components of the Organization {defined in HRPP policy 1.1 Human Research Protection Program} by faculty, students, staff or other representatives of the Organization, or by any non-affiliated investigator.
  - 2.1.2. Research performed elsewhere by faculty, students, staff or other representatives of the Organization, as a part of their institutional responsibilities. However, with approval of the IO an external IRB may be accepted as the IRB of record {in accordance with HRPP policy 1.4 UNMC Ceding Review to an External IRB}.
  - 2.1.3. Research performed elsewhere by faculty, students, staff or other representatives of the Organization where the personnel are identified as being affiliated with the Organization (for example in research documents, publications, or clinical trial listings). However, with approval of the IO, an external IRB may be accepted as the IRB of record {in accordance with HRPP policy 1.4 UNMC Ceding Review to an External IRB}.
- 2.2. The IRB does not routinely review activities which do not meet the definition of human subject research, with the exception of research involving human fetal tissue and human embryonic stem cells
- 2.3. IRB review will be performed in accordance with the authorities granted by institutions within the Organization in {accordance with HRPP policy 1.2 Authority Granted to the IRB by the Organization]}.

3.0 Definitions

- 3.1. HHS Regulations
  - 3.1.1. Research is defined in the Federal Policy as, “any systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge” (45 CFR 46.102(l)). Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes.
    - 3.1.1.1. The definition of “research” in the HIPAA Privacy Rule (45 CFR 164.501) is identical to that in the Federal Policy; that is “a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.”)
    - 3.1.1.2. Systematic investigation means an activity described in a protocol which includes a set of scientific aims or objectives, procedures to pursue the objectives (for example, interventions or interactions), analysis of the data, and conclusions drawn based upon the analysis.
    - 3.1.1.3. The Belmont Report provides further clarification of “research” as follows: “… the term ‘research’ designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships).”
    - 3.1.1.4. Generalizable knowledge means conclusions, facts, or principles derived from the research which can be applied outside the specific study population and which enhance scientific or academic understanding. Generalizable knowledge usually includes one or more of the following concepts: Knowledge that contributes to a theoretical framework of an established body of knowledge; the primary beneficiaries of the research are other researchers, scholars, and practitioners in the field of study; dissemination of the results is intended to inform the field of study (though this alone does not make an activity constitute research “designed to contribute to generalizable knowledge”); the results are expected to be generalized to a larger population beyond the site of data collection; the results are intended to be replicated in other settings (after Emory University and UC Berkeley HRPP).

        - 3.1.1.5. Certain activities described in section 6.0 are deemed not to be research, as per 45 CFR 46.102(l)
    - 3.1.2. Human Subject is defined as “A living individual about whom an investigator (whether professional or student) conducting research: 1) obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens, or 2) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens” (45 CFR 46.102(e))
        - 3.1.2.1. Intervention means both physical procedures by which information or biospecimens are gathered and manipulations of the subject or the subject’s environment that are performed for research procedures. The intervention was carried out either solely or partially for the purposes of research.
        - 3.1.2.2. Interaction means communication or interpersonal contact between the PI and other study personnel with the subject. The interaction was carried out either solely or partially for the purposes of research.
        - 3.1.2.3. Private information means information about behavior(s) of the subject that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., medical record).
        - 3.1.2.4. Identifiable private information means private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
        - 3.1.2.5. Identifiable biospecimen means a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.
    - 3.1.3. Human subject research means research activities which involve human subjects.
    - 3.1.4. Engagement in Human Subject Research. The UNMC HRPP follows the OHRP guidance (October 16, 2008) in determining whether an institution is engaged in human subject research. In general, the Organization will be considered engaged in research when its employees or agents (that is, individuals who act on behalf of the institution; exercise institutional authority or responsibility; or perform institutionally designated activities) for the purposes of research obtain:
        - 3.1.4.1. Data about the subjects of the research through intervention or interaction with them; or
        - 3.1.4.2. Identifiable private information about the subjects of the research; or
        - 3.1.4.3. Informed consent of the human subjects of the research.
- 3.2. FDA Regulations
    - 3.2.1. Human Subject is defined at 21 CFR 56.012(e) as “. . . an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.”
        - 3.2.1.1. Under FDA’s current regulations governing the conduct of in vitro diagnostic device (IVD) studies, the definition of human subject includes individuals on whose tissue specimens, an IVD is used [21 CFR 812.3(p)]. However, if the specimen is not individually identifiable by the investigator or any other individuals associated with the investigation, including the sponsor, the FDA will exercise enforcement discretion with regard to the requirements for informed consent in accordance with guidance issued April 25, 2006 titled “Guidance on Informed Consent for In Vitro Diagnostic Device Studies using Leftover Human Specimens That Are Not Individually Identifiable.” The UNMC IRB will determine whether subjects can be individually identified and apply 21 CFR 50, 56 accordingly.
    - 3.2.2. Clinical Investigation is defined at 21 CFR 56.102(c) as, “…any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under Section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.” “The terms research, clinical research, clinical study and clinical investigation are deemed to be synonymous for the purposes of FDA regulations.”
        - 3.2.2.1. Experiments that must “meet the requirements for prior submission to the Food and Drug Administration under Section 505(i) of the Federal Food, Drug, and Cosmetic Act” means any use of a drug other than the use of an approved drug in the course of medical practice [21 CFR 312.3(b)].
        - 3.2.2.2. Experiments that must “meet the requirements for prior submission to the Food and Drug Administration under Section 520(g) of the Federal, Food, Drug, and Cosmetic Act” means any activity that evaluates the safety or effectiveness of a device [21 CFR 812.2(a)]. Any activity in which results are being submitted to or held for inspection for FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research [21 CFR 50.3(c), 21 CFR 56.102(c)].
    - 3.2.3. Test Article is defined at 21 CFR 56.102(l) as, “any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Act or under Sections 351 or 354-360F of the Public Health Service Act.”
    - 3.2.4. Human drugs: The primary intended use of the product is achieved through chemical action or by being metabolized by the body.
        - 3.2.4.1. A drug is defined as a substance recognized by an official pharmacopoeia or

formulary:
    - 3.2.4.2. A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
    - 3.2.4.3. A substance (other than food) intended to affect the structure or any function of the body.
    - 3.2.4.4. A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Note: See http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm for further information.
  - 3.2.5. Investigational new drug: An investigational new drug means a new drug or biological drug that is used in a clinical investigation.
  - 3.2.6. Medical devices: A medical device is “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.”
  - 3.2.7. Investigational Device: An investigational device means a device, including a transitional device, which is the object of a clinical investigation. As further defined, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.
  - 3.2.8. Food additives: In its broadest sense, a food additive is any substance added to food. Legally, the term refers to “any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food.” This definition includes any substance used in the production, processing, treatment, packaging, transportation or storage of food.
  - 3.2.9. Color additives: A color additive is any dye, pigment or substance which when added or applied to a food, drug, or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. http://www.fda.gov
  - 3.2.10. Foods: Foods include dietary supplements that bear a nutrient content claim or a health claim.
  - 3.2.11. Infant formulas: Infant formulas are liquid foods intended for infants which substitute for mother’s milk.
  - 3.2.12. Investigator is defined 21 CFR 56.102(h) as, “an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.”

4.0 HRPP Classifications of Human Subject Research

- 4.1. Biomedical Research: Biomedical Research includes all human subject research performed with intent to develop or contribute to generalizable knowledge (i.e., test a hypothesis and draw conclusions) about human biological systems and processes, including efficacy and safety of preventative, diagnostic or therapeutic methods. Biomedical research usually falls into one of two categories:
  - 4.1.1. “Therapeutic” research characterized as research which involves a drug, medical device, technique or other intervention or strategy (including non-physical means, like diet, cognitive therapy, etc.) to diagnose, treat, prevent or otherwise study a particular condition or disease
  - 4.1.2. “Non-therapeutic" research characterized as research to study normal or abnormal physical or physiologic processes (for example, gait and balance testing, biomechanical assessments).
- 4.2. Human Biological Material Research: Human Biological Material (HBM) research includes the collection and/or use of human biological specimens obtained directly from human subjects or from other sources such as a biorepository (tissue bank) for purposes of research. The full range of human biological specimens includes sub-cellular structures (e.g., DNA); cells; tissues (e.g., blood, bone, muscle, connective tissue, teeth, and skin); organs; gametes (e.g., sperm and ova); and waste (e.g., hair, nail clippings, urine, feces, saliva, and sweat).
- 4.3. Medical Records Research: Medical Records Research utilizes individual medical or clinical records with subject identifiers for both retrospective and prospective studies.
- 4.4. Behavioral and Social Science Research: Behavioral and social science research includes all research performed with intent to study behaviors, attitudes and interactions and social processes among and between individuals, groups, and cultures. Generally this category of research has no intent of producing a diagnostic, preventive, or therapeutic benefit to the subject who is not seeking nor expecting a health benefit from the research.

5.0 Activities Which Are Not Human Subject Research

- 5.1. Systematic investigation involving data or human biological materials (HBM) without investigator access to subject identifiers: A systematic investigation involving data or HBM

obtained from living individuals where (1) there are no identifiers which would allow any of the investigators to readily identify the individual, and (2) where the specimen or data was not collected specifically for the purposes of the research does not constitute human subject research under this policy. Required de-identification (i.e., the number of identifiers which must be removed) before the data or HBM is given to the investigator depends on whether or not the research is subject to HIPAA.

- 5.2. Innovative Therapy: Physicians and other health care professionals are free to engage in innovative therapy if the innovative procedure is applied solely to enhance the well-being of their patient and is based upon sound clinical judgment. However, when innovative therapy differs significantly from routine practice it should be viewed and treated as such with appropriate safeguards in place to protect the rights and welfare of the patients through formal IRB review of a promising therapy in the context of a clinical trial. Therefore, in order to validate innovative therapy, the innovative procedure should be subjected early on to IRB review as a formal research protocol.
- 5.3. Quality Improvement Activities: QI activities take place in a particular localized health care setting, their design is expected to incorporate the specific features of the setting, they are led by people who work in that setting, and they incorporate rapid feedback of results to bring about positive change for the patients in that setting. Instead of a fixed protocol implemented for a time period that may last for years, QI methods often require repeated modifications in the initial protocol as experience accumulates over time and as the desired changes engage the local structures, processes, patterns, habits, and traditions.
  It is often difficult to determine whether a particular activity constitutes QI or research; therefore, a conversation between the person designing the activity, and the IRB, is useful and encouraged.
  In general Quality Improvement activities have the following characteristics:
  - 5.3.1. The activity is intended to improve the process/delivery of care while decreasing inefficiencies within a specific health care setting
  - 5.3.2. The activity is intended to evaluate current practice and/or attempt to improve it based upon existing knowledge
  - 5.3.3. There is sufficient existing evidence to support implementing this activity to create practice change
  - 5.3.4. The activity is conducted by clinicians and staff who provide care or are responsible for the practice change in the institutions where the activity will take place
  - 5.3.5. The methods for the activity are flexible and include approaches to evaluate rapid and incremental changes
  - 5.3.6. The activity will involve a sample of the population (patients/participants) ordinarily seen in the institution where the activity will take place
  - 5.3.7. The planned activity will only require consent that is already obtained in clinical practice, and could the activity be considered part of the usual care
  - 5.3.8. Future patients/participants at the institution where the planned activity will be implemented will potentially benefit from the project
  - 5.3.9. The risk to patients/participants is no greater than what is involved in the care they are already receiving OR participating in the activity can be considered acceptable or ordinarily expected when practice changes are implemented within a health care environment.

Note: Publishing or presenting the results of a quality improvement project does not necessarily mean the activity is research. Descriptions of non-research activities (e.g., an account of the quality improvement project) are often an expected outcome of the project. On the other hand, re-analysis of the data derived from the quality improvement project in order to prove or disprove a hypothesis is research. Depending on whether or not subject identifiers are maintained, it may qualify as exempt research.

- 5.4. Program Assessment: Program assessment (or program evaluation) is a systematic collection of information about the activities, characteristics and outcomes of a specific program or model, to contribute to continuous program improvement, and/or to inform decisions about future program development https://www.cdc.gov/evaluation/php/about/?CDC_AAref_Val=https://www.cdc.gov/evaluation/. Program assessments do not constitute human subject research under this policy.
  In general, Program Assessments have the following characteristics:
  - 5.4.1. Intent of project is to evaluate a specific program, only to provide information for and about that program.
  - 5.4.2. Activities are not designed to develop or contribute to generalizable knowledge; does not involve randomization of individuals, but may involve comparison of variations in programs.
  - 5.4.3. Activities are mandated by the program, usually its funder, as part of its operations.
  - 5.4.4. Findings of the evaluation are expected to directly affect the conduct of the program and identify improvements.
  - 5.4.5. No benefit to participants expected; evaluation concentrates on program improvements or whether the program should continue. (Source: Oregon State University)
- 5.5. Case Histories: Descriptive case histories which are published and/or presented at national or regional meetings are not considered research if the case is limited solely to a description of the clinical features and/or outcome of individual patients.
  Note: When a physician or other health care professional authors a case history that is not research, ethical guidelines should, nevertheless, be taken into consideration; specifically, Informed consent should be obtained from the patient; and appropriate safeguards to protect confidentiality should be in place.

Note: If a case history involves multiple patients with concomitant analysis and correlation of data as part of a systematic investigation, it is considered research. Depending on whether or not subject identifiers are maintained, it may qualify as exempt research.

- 5.6. Student Projects: A systematic investigation conducted by a student that involves living individuals but is performed solely to meet educational requirements of a single academic course is not considered human subject research providing the results of the investigation are presented only within the confines of the classroom or similar forum and to the students, their instructors, parents/family members, or a limited number of other invited guests. This does not include presentation in a student research fair or forum, where the public are invited or have easy access.
  Note: It is recommended that the students' supervisor and/or department exert appropriate review and oversight of the project, including, for example, completion of an IRB application without submission to the IRB.
  Note: A systematic investigation conducted by a student with intent to present the results of the investigation outside of the confines of the institution does constitute human subject research.
  Note: An investigation conducted to meet educational requirements with no intent to present the results of the investigation outside of the organization, but is then re-analyzed in order to prove or disprove a hypothesis does constitute human subject research.
- 5.7. Pilot Testing: small investigations characterized as "pilot testing" prior to conduct of research are not considered human subject research provided the procedures meet the following conditions:
  - 5.7.1. Pilot testing is limited to interventions intended to test the equipment or the methodology, or to refine the parameters of the protocol, or to train the student to use the equipment.
  - 5.7.2. The pilot testing is not explicitly named as one of the aims of the research.
  - 5.7.3. The data generated from the pilot testing is not retained after the completion of the specific goals of the pilot testing (as per 5.7.1 above)
  - 5.7.4. The data generated from the pilot testing is not presented in any public format (abstract, poster, or publication) nor used as background material for a grant application or similar purpose.
  - 5.7.5. The pilot testing will only involve healthy volunteers (preferably research staff) as participants.
  - 5.7.6. The pilot testing procedures constitute no greater than minimal risk to participants.
- 5.8. Secondary research involving non-identifiable newborn screening blood spots.

6.0. Other Activities Deemed Not Research

Other activities specifically defined in 45 CFR 46.102(l) are deemed "not research." These activities include:

- 6.1. Scholarly and journalistic activities
  - 6.1.1. This includes, but is not limited to, oral history, journalism, biography, literary criticism, legal research, and historical scholarship, including the collection and use of information that focuses directly on the specific individuals about whom the information is collected. There is no attempt to perform a systematic analysis of the data in order to draw conclusions or test a hypothesis for the purpose of developing or contributing to generalizable knowledge.
  - 6.1.2. Studies using methods such as participant observation and ethnographic studies, in which investigators gather information from individuals in order to understand their beliefs, customs, and practices, and the findings apply to the studied community or group, and not just the individuals from whom the information was obtained fall with the scope of the definition of research.
- 6.2. Public health surveillance activities
  - 6.2.1. The collection and testing of information or biospecimens conducted, supported, requested, ordered, required, or authorized by a public health authority.
  - 6.2.2. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products).
- 6.3. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- 6.4. Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

7.0 Determination of When an Activity Constitutes Human Subject Research

- 7.1. Individuals should contact the ORA for guidance in determining whether or not a proposed activity constitutes human subjects research. An IRB Administrator, in consultation with the IRB Executive Chair/designee as necessary, will determine whether or not the planned activities constitute human subject research, using the OHRP Human Subject Decision Charts, the criteria in sections 4, 5 and 6 of this policy, and if necessary consultation with OHRP.
- 7.2. Once a determination is made, the investigator will be so informed.

8.0 Type of Review

- 8.1. The type of IRB review required depends upon the proposal classification:
  - 8.1.1. Full Board (FB) research will be reviewed by the IRB in accordance with HRPP policy 2.2.
  - 8.1.2. Expedited (EP) studies will be reviewed by the IRB in accordance with HRPP policy 2.3.
  - 8.1.3. Exempt (EX) research will be reviewed by the ORA in accordance with HRPP policy 2.6.
- 8.2. The IRB Administrators and/or the IRB Executive Chair/designee will use the OHRP Human Subject Decision Charts as necessary in determination of the type of review.

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