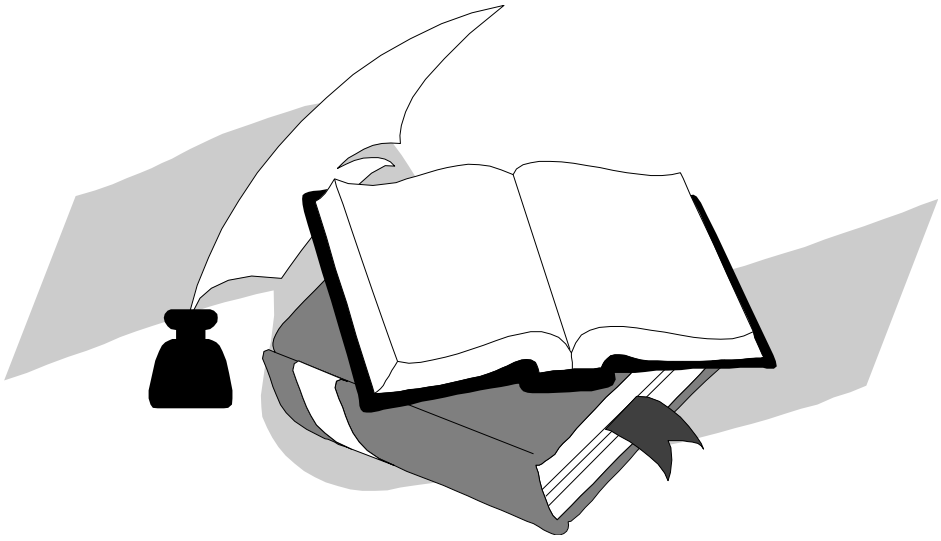
BLUE BOOK

The Guide for Preparation and Processing of Human Research



National University of Health Sciences

2023

How to Use the Guide Book

This book is a *guide* on the process of research at NUHS. Sections of the guide are designed to introduce you to the research process, provide guidance on the use of human subjects in research, and provide guidance on the use of NUHS IRB forms. Individual sections should be referred to depending on the questions of the researcher. For example, the sections on how to complete IRB forms are designed to explain important aspects of a research proposal and why they are important. However, this book is not meant to be an instruction book on how to do research.

THE REVIEW PROCESS FOR RESEARCH PROPOSALS

INTRODUCTION

NUHS Policy on Protection of Human Subjects from Research Risks
This policy was adopted by the University Board as the principle endorsement and agreement for implementation of all governmental rules and policies regarding the use and involvement of human research subjects at the University. All investigators must become familiar with the policy before undertaking any research involving human beings.

An institutional review process assures that proposals funded internally, or submitted to outside agencies for consideration for funding, are of the highest possible quality. Such a process maximizes the likelihood of external funding, as well as assures that institutional funds are expended in the most prudent and productive fashion. Furthermore, the institutional review process enables the University to remain in compliance with federal and state regulations or guidelines, as well as its own policies, regarding the protection of human or subjects from research risks. If human subjects are involved in the research, the Institutional Review Board (IRB) must review and approve the project. A flow chart of the approval process is on page 11.

This guidebook (The Blue Book) is designed to inform and guide you through the preparation of a research proposal and the institutional review process. The guidebook is divided into several different sections which address various aspects of the research process. Sections of the guide are designed to introduce you to the research process at NUHS, provide guidance on the use of human subjects in research, and provide guidance on the use of NUHS' IRB forms. Some of these sections may not be relevant for your research needs, while others may be extremely important.

I. NUHS STANDING COMMITTEES

Research Committee

It is incumbent on National University of Health Sciences to insure that research conducted either at the University, or in conjunction with another institution, by a member of the University community is of the highest quality possible. The Dean of Research reviews all proposals regardless of subject matter and signs them as the responsible institutional official. The Research Committee advises the Dean of Research on scientific merit of research proposals. The Dean of Research can ask the Research Committee to review any research proposal. Such proposals are typically those requesting financial support from the Research Department, proposals by new investigators, proposals which establish a new line of research, and proposals which are to be submitted to an outside sponsoring agency. The committee reviews the proposal for scientific merit and ensures that the work proposed is consistent with the mission and goals of the University and with all institutional policies. The committee also assists the Dean of Research in prioritizing proposals requesting institutional support, and matching new investigators or other interested researchers with experienced researchers and with individuals who share similar or complementary interests or expertise. Any individual can request Research Committee review of their proposal, or can appeal a decision by the Dean of Research to the Research Committee for funding and priority recognition. However, the Dean of Research will make the final decision related to internal funding priorities.

Institutional Review Board (IRB)

The IRB is a separate and independent body which ensures that human subjects who participate in research at the University are protected from risk. All potential research involving human subjects must be approved by the IRB, or determined to be exempt from review by the IRB according to criteria in the *University Policy*, before the research begins. This includes research on patients, students, faculty, and staff. The IRB ensures that all research using human subjects at the University complies with regulations for the protection of human subjects from research risks as defined by the United States Department of Health and Human Services Office.

Training and Education

There are requirements for training and continuing education for the IRB members, principal investigators and for other individuals working with human subjects and with animals. These requirements can be fulfilled in several ways including current literature and periodicals from relevant organizations and professional associations, as well as audiovisual materials and internet websites. The office of the Dean of Research and the Research Coordinator can assist in defining the specific requirements and maintaining the training resource's available.

II. DEFINITIONS

Established Investigator - 1) Established investigators are faculty and staff who have published results of scientific investigations in the peer reviewed literature or used similar methods in the field of the proposal; or 2) have graduate training in the methods used in the proposal and have done on-going work at NUHS in that field.

NUHS Contact Person - full time NUHS faculty member who serves as Principal Investigator, Faculty Mentor or NUHS Investigator of Record on a research project.

Principal investigator (PI) - the lead scientist for a particular well-defined science project. The PI is the person who takes responsibility for conceiving a project, directing the research, reporting to the funding agency and ensuring completion of a funded project.

NUHS Investigator of Record - If the principal investigator is not a full time NUHS faculty member, the NUHS Investigator of Record is responsible for submitting and maintaining project review to the NUHS IRB during the course of the project and to comply with all federal regulations and any additional regulations required by NUHS or state and local laws or regulations which provide additional protections for human subjects

Research - Research means a systematic investigation and use of the scientific method including experimentation, development, testing and evaluation designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration, teaching, pilot, and service programs may include research activities.

Human Subject - A human subject is a living individual (whether a member of the public, an employee of NUHS, or a student) about whom an investigator conducting research obtains data, either through intervention or interaction with the individual, or identifiable private information.

Why so many committees and so much paperwork?
IRB (and IACUC for research dealing with animals) approval are necessary because these committees and their roles are mandated by various levels of government and related University policies. Furthermore, the Office of Human Research Protections (OHRP) requires that research institutions conducting research involving human subjects set forth the procedures it will use to protect the human subjects in a policy statement, called an “Assurance”. This “Assurance” is a formal written commitment to the government to adhere to 1) widely held ethical principles, 2) the Department of Health and Human Services’ (DHHS) Regulations for Protection of Human Subjects, and 3) institutional procedures which adequately safeguard the rights and welfare of human subjects. The same sort of assurance concept and University Policy exists for research that involves animals, but these guidelines and regulations fall under the U.S. Department of Agriculture.

III. SCOPE AND PURPOSE OF THE IRB

The National University of Health Sciences has established an Institutional Review Board (IRB) to review research projects that involve human subjects. The IRB consists of representatives from a variety of scientific disciplines, non-scientists and community members. The primary functions of the IRB are to protect the rights and welfare of human subjects and to assist investigators in this process. Investigators bear the primary responsibility for ensuring that research protocols meet the standards established by federal regulations and the University.

Before a research project involving human subjects is initiated, it must first be reviewed by the Dean of Research and then reviewed and approved by the IRB. This compliance is a crucial element of the IRB process, because it is the collective effort of individual investigators in this area that ensures the integrity of NUHS as a research institution.

NUHS authorizes the investigator to decide whether or not his or her research involves human subjects as defined in the Federal Regulations for the Protection of Human Subjects, including all of its subparts. These regulations are published by the U.S. Department of Health and Human Services (HHS) at Title 45, United States Code of Federal Regulations, Part 46 (45 CFR 46). If the investigator determines that the research does not involve human subjects, the basis of that decision must be registered with the investigator's Department Head, the Dean of Research and the Research Coordinator and/or the IRB as determined by the Dean of Research. Once an investigator has completed the registration and received notification of concurrence from the Dean of Research or the IRB, the proposed research may begin without involvement of the NUHS IRB. Such a research project is considered exempt and but the Investigator must annually complete a form indicating that there have been any or no changes in the project then would thereafter require IRB review and approval.

It is important to keep in mind that research that involves persons, or the study of information about persons, but does not meet the definition of human subjects as described above, that research still may be subject to other pertinent federal, state, or local laws and NUHS rules or policies.

Ethical Principles Guiding the IRB
In 1974, the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission published the *Belmont Report,* which sets forth the basic ethical principles that guide the conduct of research with human subjects. Three principles were defined in the report as basic to the protection of human subjects: respect for persons, beneficence, and justice. The IRB and investigators are guided by these principles as follows:

- **Respect for Persons:** In consideration of respect for persons, investigators are required to seek voluntary informed consent from potential subjects. Voluntary informed consent means that subjects are given free choice to decide about participation, and that the study is fully described in terms that are easy to understand. The consent form should include adequate information about the study risks and benefits that will assist subjects in deciding whether or not to participate in the

research. There should not be pressure to participate. In addition, respect means honoring the privacy of individuals and maintaining the confidentiality of data obtained.

The principle of autonomy requires that protection be given to potentially vulnerable populations such as children, the elderly, the mentally ill, prisoners, or others in status type relationships (i.e. students). These individuals may be incapable of understanding information that would enable them to make an informed decision about research participation. Respect for minors and mentally disabled persons require taking extra precautions to protect those individuals who are immature or incapacitated, perhaps even to the extent of excluding them from participation in certain research. The extent of protection depends upon the level of autonomy the person possesses.

- **Beneficence:** The principle of beneficence requires that researchers maximize the potential benefits to subjects and minimize the risks or harm. Benefits to subjects, or generalized knowledge gained from the research, should balance or outweigh the risks.

- **Justice:** The principle of justice means that subjects are selected fairly and that the risks and benefits of research are distributed equitably. Investigators should take precautions not to select subjects simply because of the subjects' easy availability, their compromised position, or because of social, racial, gender, economic or cultural biases. Investigators should base inclusion criteria on those factors that most effectively and soundly address the research problem. Subjects should not be selected based on class, socioeconomic status, or race unless justified by the research objectives. Women have been underrepresented in certain research studies because of the risks associated with child-bearing. Now researchers must justify why women may not be included in a research population. Failure to provide scientifically sound arguments for the exclusion of one gender could be grounds for denial. An existent counselor-client or physician-patient relationship requires consideration of the potential for power-based coercion when expanding that relationship to include investigator-subject. Provisions, or adjustments, might need to be made to attempt to equalize the roles. Teacher-student relationships always carry a perception of inequalities in roles. The informed consent process should reflect the precautions taken to balance the relationship and guard against even the perception of coercion.

Federal Regulations and Review by the IRB

The IRB reviews research in accordance with the Food and Drug Administration (FDA) regulations published at 21 CFR 50 and 56, Health and Human Subjects (HHS) regulations published at 45 CFR 46, and the "Common Rule" regulations published at 45 CFR 46, Subpart A. In their review of research projects, the IRB must be assured that:

- Risks to subjects are minimized, a) by the use of procedures consistent with sound research design which do not expose subjects to unnecessary risk, and b) when

appropriate, by the use of procedures already being performed on the subjects for diagnostic or treatment purposes.

- Risks to subjects are reasonable in relation to any benefits that might be expected from taking part in a research study and to the importance of the knowledge that may result.

- Selection of subjects is fair and equitable. The IRB seeks to determine that no eligible individuals are denied the opportunity to take part in any study, particularly those from which they may benefit, based on arbitrary criteria such as sex, age, or social or economic status. NOTE: the following are justifications for excluding children:
    - Research topic is irrelevant to children,
    - Laws or regulations bar the inclusion of children in the research,
    - Knowledge being sought in the research is already available for children or will be obtained from another ongoing study and an additional study will be redundant,
    - A separate, age specific study in children is warranted and preferable,
    - Insufficient data are available in adults to judge potential risk in children,
    - Study designs are aimed at collecting additional data on pre-enrolled adult study participants, or
    - Other special cases justified by the PI and found acceptable to the IRB.

- Participation is voluntary and informed consent is obtained from each prospective subject or, where appropriate, from the subject's legally authorized representative.

- When appropriate, the research plan provides for monitoring the data collected to protect the safety of subjects.

- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

What Needs IRB Review and Approval

The IRB must review all research where the investigational procedures involve human subjects. This definition includes a wide variety of activities, such as *in vivo* and *in vitro* studies, research on medical records, and collection of data through surveys or observation, pilot studies, research using existing pathological specimens, discarded tissue or secretions, use of investigational drugs or devices and randomized trials.

The following definitions, as noted in 45 CFR 46.102 apply:

> ***Research:*** a systematic investigation, including research development, testing and evaluation, designed to develop or to contribute to generalizable knowledge.
>
> ***Human subject:*** a living individual about whom an investigator (whether professional or student) conducting research (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

A subject may be either a healthy individual or a patient. Because the above definition excludes non-living humans, research that uses autopsy materials or cadavers is not 'human subjects research' and therefore is exempt from review.

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 communication or interpersonal contact between investigator and subject.

Private information: 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: private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Identifiable biospecimen: a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Minimal Risk – A Benchmark for Review
According to Federal regulations, **minimal risk** means that the probability and magnitude of harm or discomforts anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Examples of minimal risk procedures include electrocardiograph, collection of blood by venipuncture from healthy adults who are not pregnant, moderate exercise testing, and administration of psychological tests involving a minor level of stress.

This definition of minimal risk serves as the benchmark to determine the level of review by the IRB. Minimal risk research may be either **exempt** or **expedited**. The next two sections describe the specific criteria to be used to determine whether a study is eligible for exemption or expedited review.

NUHS IRB Approval Guidelines for Off-Campus Research
Research projects external to NUHS that might want to involve NUHS faculty, staff or students as co-investigators or research subjects may take multiple forms:

- Projects that are University sanctioned for recruitment within the University community but have no IRB approval must be reviewed by the NUHS IRB (or Chair) prior to recruitment and must include a NUHS on campus investigator
- Projects that are University sanctioned for recruitment within the University community and have already been approved by another IRB should be submitted to the NUHS IRB (or Chair) along with the outside IRB approval prior to beginning recruitment
- Projects that have been approved by an external IRB and involve a NUHS faculty co-investigator must be reviewed by NUHS IRB, (or Chair) and a copy of the external IRB approval should be submitted with the application

RESEARCH that is sent directly to NUHS faculty, staff or students *may* not need any NUHS IRB approval. But direct-mail research often does turn out, in fact, to need an on campus approval and it may be prudent to simply have the primary researcher run the project through the IRB first. The NUHS IRB is committed to promoting quality research with minimal delay or other burden to the researcher while still assuring mandatory protections for human subjects.

Single IRB (sIRB) Mandate for Cooperative Research

In the 2017 revision of the Common Rule, it was decided that US institutions engaged in federally funded cooperative research must rely on a single IRB, or sIRB, to oversee the portion of the research conducted at US sites (institutions may apply for exceptions to this mandate if a single IRB is not appropriate. See CFR 45 CFR 46.114(b)(2).

Commonly, the lead PI chooses the IRB to serve as the sIRB, which could be the PI institution IRB, a co-investigator institution IRB, an IRB specified by the funding agency, or an outside, fee-based IRB. The factors considered in selecting the sIRB include IRB history, capacity, expertise, turn-around time, cost, and investigators' familiarity with the IRB process and procedures.

Regardless whether NUHS is serving as the sIRB, or ceding oversight to another IRB a letter of agreement between NUHS and the non-NUHS institution should include the following information

- The name and contact information of the lead NUHS Investigator and the name and contact information of the lead non-NUHS investigator, and indication of the lead principal investigator for the project
- The name of the sIRB organization and its FWA# and IRB#; the name of the relying organization and its FWA# and IRB#
- The title of the study and if applicable, sponsor/funding agency and grant #
- Terms of responsibility for each institution specified by ceding organization
- Signature, name, contact information of NUHS IRB Chair and non-NUHS IRB Chair

The signed letter of agreement should be submitted to both sites and kept as part of the project IRB record.

IV. CATEGORIES OF RESEARCH AND IRB REVIEW

All research is reviewed by the IRB at convened meetings unless it is "minimal risk" and qualifies for "expedited" review or for "exempt" status. The type of review a study receives depends on the risks posed to potential subjects by the research. These risks include the probability and severity of possible harm to the subjects' physical, psychological, social, legal or economic welfare.

Exempt Research (45 CFR 46.104)
Minimal risk research activities in which the only involvement of human subjects is in one or more of the following categories are exempt from review by the IRB and other requirements of federal policy. However, these must be reviewed by the Research Coordinators office and the IRB Chair to confirm their exempt status. This confirmation may also be made by IRB-designated officials or departmental review committees but it cannot be made by the investigator.

Notes to Investigators: The IRB reserves the right to request additional information and, when a higher degree of risk may be involved or if there are questions about human subject protection, the investigator may be requested to submit such proposals for expedited or full board review.

All exempt research involving human subjects must maintain an adequate standard of informed consent and confidentiality of data. In some exempt research projects, standard written informed consent should be obtained. An example would be obtaining the consent of parents for research involving educational strategies for their children.

The exempt categories that follow **do not** apply to research involving pregnant women, prisoners, mentally incompetent people and other subject populations determined to be vulnerable. Except for Category 2, they do apply to research with minors.

The following categories are established as exempt research:

1. Research, conducted in established or commonly accepted educational settings that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

   (i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

3. (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

   (A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

   (B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

   (C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

   (ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

   (iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

4. Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

   (i) The identifiable private information or identifiable biospecimens are publicly available;

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of “health care operations” or “research” as those terms are defined at 45 CFR 164.501 or for “public health activities and purposes” as described under 45 CFR 164.512(b); or

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

   (i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects

6. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level found to be safe and for a use found

to be safe, or an agricultural, chemical or environmental contaminant at or below the level found to be safe, by the federal government.

7. Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).

8. Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

   (i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);

   (ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;

   (iii) An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and (iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

Expedited Review – (45 CFR 46.110)

The Secretary of HHS has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The Secretary will evaluate the list at least every 8 years and amend it, as appropriate, after consultation with other federal departments and agencies and after publication in the Federal Register for public comment. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b)(1) An IRB may use the expedited review procedure to review the following:

(i) Some or all of the research appearing on the list described below, unless the reviewer determines that the study involves more than minimal risk;

(ii) Minor changes in previously approved research during the period for which approval is authorized; or

(iii) Research for which limited IRB review is a condition of exemption under §46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

(2) Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB

except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited procedure set forth in §46.108(b).

Principal investigators (PIs) are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

Categories one (1) through seven (7) pertain to both initial and continuing IRB review. The categories in this list apply to subjects regardless of their age, except as noted.

Research categories that can qualify for expedited review include:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met. (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.) (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger, heel or ear stick, or venipuncture as follows: (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and

effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects as noted in 45 CFR 46.104. This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects as noted in 45 CFR 46.104. This listing refers only to research that is not exempt.)

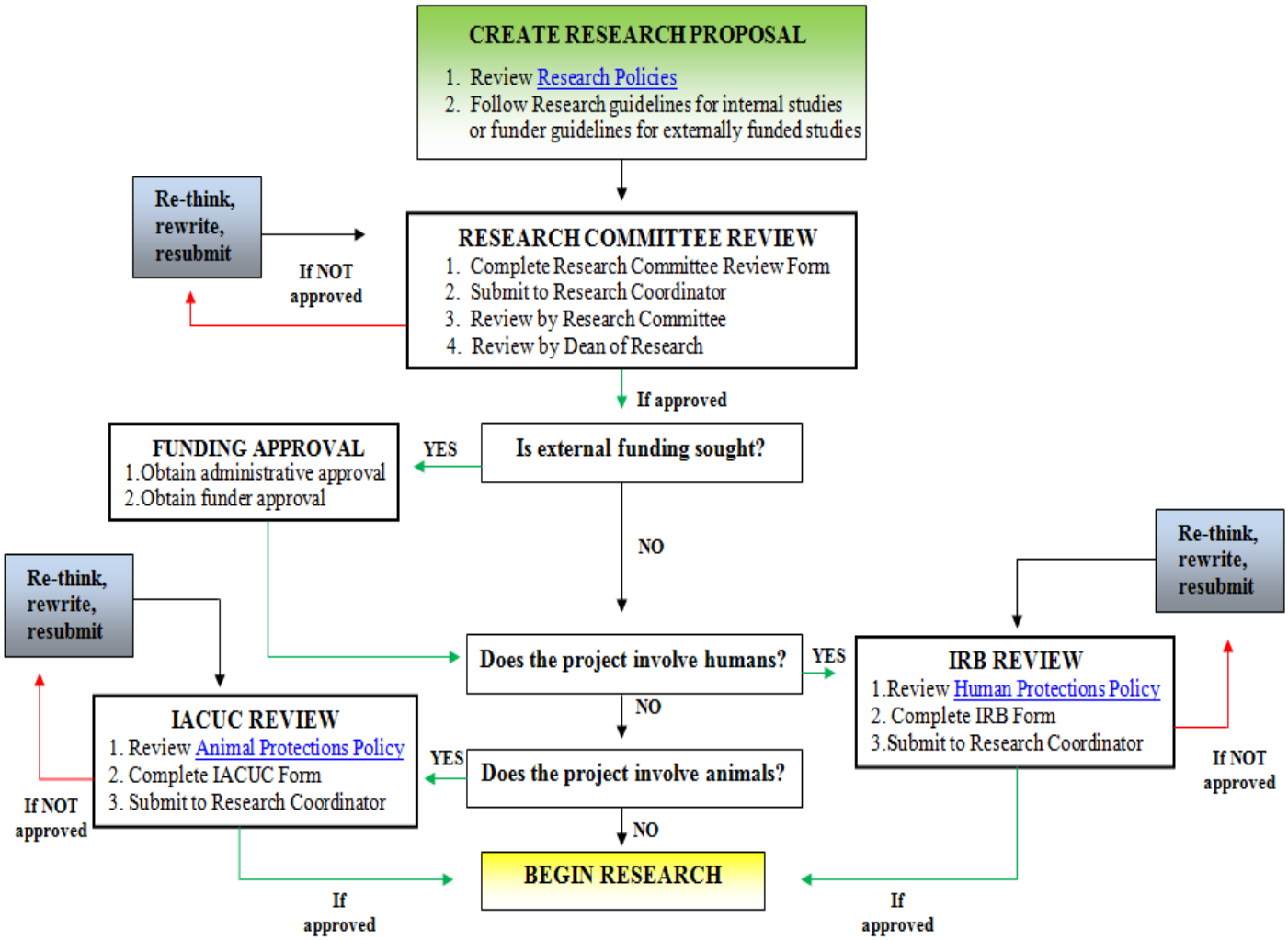
8. Continuing review of research previously approved by the convened IRB as follows: (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or (b) where no subjects have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Review at Convened Meetings
Research which presents or may present greater than minimal risk to subjects requires review at a convened meeting of the IRB.

V. SUBMISSION DEADLINES AND REVIEW PROCEDURES

Flow Chart 1: How to Submit a Research Proposal



Steps for Conducting Research at NUHS: Institutional Review

1. *Application to the RESEARCH COMMITTEE for Approval of a New Research Project* must be submitted to the Research Coordinator for review of scientific merit and budget and time commitment. In the case of proposals to outside agencies, it is the PI's responsibility to submit such a draft in time for the review to be returned and the suggestions acted upon *before the proposal is sent to the funding agencies*.

   The proposal should include the complete budget or complete budgetary information. The Dean of Research reviews the proposal and determines whether the work proposed is consistent with the mission and goals of the University, and prioritizes proposals that request institutional financial support. For example, an excellent proposal may call for a large budget, but the institution may not have the funding for such a project.

If the project involves the use of specific facilities not under the control of the PI, then the PI should obtain written approval for the use of the facilities. It is important for all departments affected by research be aware of the project and how it involves their facility even if that involvement is minor.

2. If the proposal requires review by the Research Committee, the Dean of Research will forward the proposal to the reviewers of the Research Committee along with appropriate instructions. The proposal will be reviewed by the Research Committee to determine consistency with institutional goals and the availability of resources. The Research Committee does not approve or disapprove a project. It is an advisory committee to the Dean of Research and to the PI of the project. After review by the Research Committee, the Dean of Research will sign off on the proposal. In the case of requests for institutional funding only, the Dean will notify the PI of the disposition of the request.

3. Following Research Committee review, the Dean of Research will instruct the PI about other committees who should review the proposal before the project can begin, such as the Institutional Animal Care and Use Committee (IACUC) or the Institutional Review Board (IRB).

4. The Dean of Research or the Research Coordinator will also provide the PI with the appropriate forms for each committee and instructions on how to use the forms.

5. Following review and approval by the IRB or IACUC, and with consideration of the proposed budget, the PI can begin the study.

Required Forms

For projects which fall into categories that are exempt from IRB review (see 45 CFR 46.104), a combined *Application to the Research Committee/Claim of Exemption* (Form A) is submitted to the Research Coordinator for administrative review and approved by the Dean of Research and Chairman of the IRB or his designate. For non-exempt projects *Application to the RESEARCH COMMITTEE for Approval of a New Research Project* is submitted to the Research Coordinator for review by the Research Committee and approved by the Dean of Research. Following approval, the *Application to the IRB for Approval of a Research Project* **(F**orm B) should be completed and Submitted to the Research Coordinator for projects reviewed by IRB.

Both forms contain checklists of items that should be included with the application; missing items may delay project review.

Research Committee and IRB forms and instructions are available on the NUHS website or can be obtained from the Office of the Dean of Research or the Research Coordinator.

Exempt Research

The University Policy lists the basis for determining that a project is exempt from IRB review. To obtain confirmation of exemption, submit the following to the Research Coordinator:

- A completed combined *Application to the Research Committee/Claim of Exemption* (Form A)
- A management plan for Financial Conflict of Interest
- Any questionnaires, scripts, surveys, recruitment materials used

- Informed consent document, if applicable (see the NCCIH Clinical Research Informed Consent Template an informed consent template) OR consent script/online form/incorporated document used for waiver of written consent OR information sheet for waiver or alteration of consent

This application will be reviewed by the Dean of Research; subsequently, IRB Chair or an IRB member delegated by IRB Chair will review to confirm that the protocol meets an exempt criterion. Following this review, the investigator will receive documentation of exempt status from the Research Coordinator or, alternatively, notified that the project requires full review. If determined to be exempt, no further action or IRB oversight is required, as long as the study remains the same. However, the investigator must inform the IRB of any changes – e.g., confidentiality, consent or particular changes in the risk profile – so a decision may be made whether reclassification of the research (i.e., into the expedited or full board review category) may be required. An annual report (Form F) verifying the exempt status of the project must be submitted while the project is open.

Expedited Review
The University Policy follows Federal Register for Expedited Review. An Expedited Review does not require approval of the proposal by the entire IRB at a convened meeting. Rather a project can be reviewed by the IRB Chair or an individual designated by the Chair. If the individual does not approve the project it must be reviewed by the entire IRB. An expedited review cannot disapprove a project. There is no submission deadline for minimal risk studies that meet the criteria for expedited review. To obtain expedited IRB approval of a project, submit the following to the Research Coordinator:

- An approved Research Committee application
- *Application to the IRB for Approval of a Research Project* (Form B) that contains:

  a. A management plan for Financial Conflict of Interest
  b. Characteristics of the research population (e.g., number, sex and age of subjects, racial and ethnic origin, inclusion and exclusion criteria, and justification for the use of any vulnerable subjects)
  c. Methods and procedures, including data analysis, monitoring, storage and confidentiality (attach test instruments such as surveys)
  d. Any potential risks, protection against risk(s), potential benefits and, if applicable, alternatives to participation
  e. Subject identification, recruitment and consent/assent (i.e., how subjects will be identified and recruited, the process of consent, subject competency/comprehension, any debriefing procedures, and documentation of consent/assent).
  f. Data and procedure monitoring plan and forms
  g. Financial obligations and incentives, if any (i.e., costs to the subject or incentives for participation)

- Informed consent document, if applicable (see the NCCIH Clinical Research Informed Consent Template for an informed consent template) OR consent script/online form/incorporated document used for waiver of written consent OR information sheet for waiver or alteration of consent
- Any questionnaires, scripts, or surveys used
- Subject recruitment materials (e.g., advertisements, flyers)

Completed applications will be reviewed by the IRB Chair. In most cases, approval for minimal risk research will remain in effect for one year. Please note that this approval is forwarded to the full IRB for information. If, in the rare case the IRB subsequently determines that the study requires full board review, the investigator will be notified and approval will be temporarily suspended if necessary.

Full IRB Review at a Convened Meeting
The submission deadline for full review is one week prior to next scheduled meeting, please confirm with Research Coordinator as to the next meeting date. (**Note**: The Dean of Research must sign the application form prior to submission to the IRB) Materials are required in advance so that members have sufficient time to read and process the information. If the proposal is being submitted for external support, investigators should be aware of the IRB deadline as well as the deadline for their funding agency so that problems do not occur in the submission process. **IRB review and approval may not need to have been granted before submitting the proposal to an external funding agency, but it must be obtained before beginning any research.** To obtain IRB approval of research, submit the following:

- An approved Research Committee application
- *Application to the IRB for Approval of a Research Project* (Form B) that contains:

    a. A management plan for Financial Conflict of Interest
    b. Characteristics of the research population (e.g., number, sex and age of subjects, racial and ethnic origin, inclusion and exclusion criteria, and justification for the use of any vulnerable subjects)
    c. Methods and procedures, including data analysis, monitoring, storage and confidentiality (attach test instruments such as surveys)
    d. Any potential risks, protection against risk(s), potential benefits and, if applicable, alternatives to participation
    e. Subject identification, recruitment and consent/assent (i.e., how subjects will be identified and recruited, the process of consent, subject competency/comprehension, any debriefing procedures, and documentation of consent/assent).
    f. Data and procedure monitoring plan and forms
    g. Financial obligations and incentives, if any (i.e., costs to the subject or incentives for participation)

- Informed consent document, if applicable (see the NCCIH Clinical Research Informed Consent Template for an informed consent template and checklist) OR consent script/online form/incorporated document used for waiver of written consent OR information sheet for waiver or alteration of consent
- Any questionnaires, scripts, or surveys used
- Subject recruitment materials (e.g., advertisements, flyers)

The Chair will convey one of the following four decisions of the IRB in writing to the investigator promptly after the meeting:

- **Approval:** If a study is **approved as submitted**, a letter of approval is sent to the principal investigator listing the investigator's responsibilities and stating the date and duration of approval.

The investigator is responsible for providing notification of IRB approval to funding agencies or other entities.

- **Pending:** If a study approval is **pending approval of minor revisions** (e.g., consent form changes that do not affect subject safety), a letter is sent to the principal investigator requesting these changes. **Subjects may not be enrolled in the study until the requested revisions are made.** The Chair may approve the study upon receipt of the revisions without further action by the IRB. After the Chair's approval, a letter is sent to the principal investigator listing the investigator's responsibilities and stating the date and duration of approval.

- **Tabled:** More substantive issues regarding the protocol and/or consent form must be addressed. Clarifications or requested revisions may have a significant impact on subject safety or understanding. A letter is sent to the investigator requesting that these issues be addressed. Full board review of the investigator's response is required prior to approval.

- **Disapproved:** Questions regarding the rights and welfare of the subjects are of such significance that the Board feels approval of the study is unwarranted.

  Principal Investigators may appeal a disapproval decision made by the IRB. Such appeals will be heard (either in person or in writing) by the IRB or a subcommittee of the IRB. Upon consideration of the appeal materials and/or presentation, the decision may stand (disapproved) or, if appropriate, the decision may be to approve as resubmitted, or approve after required modifications. As disapproval of studies may only be an action of the convened IRB, approval of a previously disapproved study may only be given at a convened meeting of the IRB.

VI. RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR/FACULTY SPONSOR

Research Oversight
Any part-time faculty, non-NUHS investigator, or NUHS student (undergraduate, certificate, professional, master's program or resident) can serve as principal investigator of a research project provided that the Faculty Sponsor is a full time NUHS faculty

- Faculty Sponsor is listed as NUHS Investigator of Record on IRB forms
  - Part-time faculty, non-NUHS investigator, or student is listed as Principal Investigator
- Faculty Sponsor is responsible to IRB
- Faculty Sponsor signs Faculty Assurance at end of application
- Faculty Sponsor signs Investigator Assurance at end of application

The letter of approval sent to the principal investigator states the continuing responsibilities the Investigator of Record has to the IRB while the research is being conducted. These responsibilities include:

- Conducting the research only in accordance with the protocol study design as submitted and approved by the IRB, and requesting approval of any proposed changes in the research activity.
- Reporting any unanticipated serious problems involving risks to subjects or others.
- Applying for study re-review and providing reports on the progress of the study in a timely fashion.
- Using only consent forms approved by the IRB.
- Obtaining approval of all recruitment materials (e.g., advertisements).

The procedures for carrying out these responsibilities are described below:

Proposed Changes

Amendments
Any changes to an approved protocol, consent form or research process must have IRB approval prior to implementing. The only exception is when a change is required to protect subjects from an immediate hazard, in which case the report and request are to be made promptly to the IRB. Amendments can be described on the *Request for Amendment/Modification Form*.

Amendments involving greater than minimal risk will be reviewed at a convened meeting of the board. Amendments involving minor changes will be reviewed using an expedited process. Minor changes eligible for expedited review are defined as those that do not change the risk/benefit ratio of the study, do not increase the risk presented by the study beyond the level of minimal risk, or in and of themselves do not present more than minimal risk.

When amendments impact the safety of subjects currently enrolled and participating in a study intervention (i.e. receiving experimental treatments, participating in therapy, etc.), it may be necessary to convey this information (i.e., to obtain the consent of the subjects) by means of an addendum to the existing consent form or by using a new form. The IRB may determine, for example, that such subjects must be notified of new findings or risks not noted at the time they were originally enrolled. Such notification is consistent with the view of informed consent as a

continuous process, and affords subjects the opportunity to determine whether or not they wish to continue their participation in the research. The IRB shall determine on a case-by-case basis when such notification, and its documentation, is required.

NOTE: Approval of an amendment does not extend the original project approval period.

Changing the Principal Investigator
If a principal investigator is on sabbatical leave from NUHS, an interim PI must be appointed. The IRB should be informed of this person's qualifications. If a researcher leaves NUHS permanently, the IRB should be notified both of any interim investigators and of the final replacement.

Removing Co-investigators
Often, a co-investigator has a specific role in a research project that involves direct access to subjects and/or records. Once data collection is completed, the PI may remove the co-investigator from the project's application (either by amendment to the protocol or noting change on project's annual review). Should the PI have occasion to have a post-data collection dialog with the co-investigator involving subject data, it is not always necessary to return the co-investigator to the IRB application; it is up to the discretion of the PI to determine if the co-investigator's involvement presents any risk to human that should be reviewed by IRB.

Study Closures
IRB requires continuing annual review of studies until all collection and handling of identified data is complete. IRB requires written notification that a study is completed/closed or a request to close studies that have not been initiated. Upon receipt, the IRB office will discontinue the annual review, thereby terminating study approval. If the only research activity involves use of de-identified data, the project can be closed to IRB review after Protected Health Information (PHI) and identifier keys (document that links Research ID to identifier) is given to the Research Coordinator/IRB administrator for oversight. Per NUHS policy "Institutional Review Records", research records will be retained 7 years after last review, then destroyed. Should a researcher request use of PHI after review is discontinued, IRB will decide whether IRB oversight should be re-instated with the request.

As a study progresses and the risks and benefits of participating in the study are better understood, researchers sometimes find that the study must be stopped. For example, in some placebo-controlled trials, preliminary findings may give compelling evidence that a new treatment is efficacious. It then becomes unethical to continue giving placebos. (This occurs most frequently in multisite trials in which a central statistical center receives and processes large volumes of data from several sites.) In such cases, the investigator should write to the IRB, describe the findings, and recommend suspending the placebo portion of the study. If the IRB agrees, the researcher should identify all subjects who received a placebo and invite those subjects to continue in an "open label" study in which all subjects receive the study medication or device.

Reporting Adverse Experiences and Deaths

Principal investigators are responsible for reporting to the IRB serious and unexpected adverse events that impact the safety of or risk to their subjects. These reports should be completed in a timely fashion. If an unexpected death occurs, the report should be sent to the IRB office immediately. Serious, unexpected events (e.g., treatment requiring hospitalization) are to be

reported within 48 hours. Other adverse events such as a breach of confidentiality, an error in consent documentation or unexpected complications regarding a subject should be reported to the IRB within 10 working days. The IRB can be notified at the same time as the study sponsor.

The report of the event should discuss:

- the facts of the case, including the date and a description of the subject;
- whether the event is related to the study's procedures, design or to the subject's underlying disease or condition;
- the steps that have been taken to address the problem;
- whether the event is likely to recur; and
- whether the event provides new information about the study's risks that should be conveyed to participants, in a revised consent form.

Any proposed changes in the consent form or research procedures resulting from the report are to be prepared/identified by the principal investigator and submitted with the report to the IRB for approval.

The following definitions apply:

- A **serious event** refers to any event in which the outcome is fatal or life-threatening, cause's permanent disability requires inpatient hospitalization or is a congenital anomaly, cancer, or overdose.

- An **unexpected adverse event** refers to those not identified in their nature, severity, or frequency in the current risk documents (e.g., investigator's brochure) or through clinical practice.

Based on the frequency and seriousness of adverse events, the IRB may deem it necessary to suspend or terminate a research study or studies. The IRB will involve the investigator in making such a decision. Until a decision is rendered the project will remain open, but the PI has the authority and responsibility to take such action at any time.

Events at Other Institutions
If the project is a multisite trial and the event occurred at another institution, the researcher must write a memo to the NIHS IRB describing the nature of the event, its severity, the likelihood that it will occur at NUHS, and the implications for future subjects.

Continuing Review

Institutional Review Board review is an ongoing process. Regular re-evaluation ensures that research is conducted responsibly. Even in responsibly conducted studies, a one-time review is inadequate, because risks can only be understood after research has begun, and regulations for human subject's research are constantly being refined as the risks and benefits are better understood. Unexpected developments in a project can raise questions about the conduct of the research, and new findings can raise questions about the project.

"Continuing review" refers to regularly scheduled complete reappraisals of a project. The goals of continuing review are to ensure that the risk/benefit ratio is still acceptable, that the measures taken to safeguard subjects are adequate, that the approved protocol is followed, and that the project reflects any changes that have been made in the regulations for human subject's

research since the last approval. A research project will be reviewed by IRB until data use is complete (thesis, presentation at a conference, publication, etc.).

The IRB may require changes to the protocol or revisions in the consent form if the study's risks were originally underestimated, but the converse can also occur: the investigators and the IRB may have underestimated the benefit to research subjects.

All human subjects' research, no matter what stage it is in, must be conducted under an IRB-approved research protocol. Research is considered active even if you have completed all data collection, including follow-up assessments, and identified data analysis. Revised research risk statements in the Consent Form may be necessary.

It is best to keep your research protocol active until you are confident that you have completed all analyses of the identified data generated from the study.

If your research has completed new subject enrollment and subject interactions is complete, your research may be eligible for review under expedited review procedures. Contact the chairman of the IRB to determine if the research is eligible for expedited review.

When Continuing Review is Required

Project re-review occurs at least annually, but high-risk projects sometimes require more frequent review. The terms of the review, as well as the documentation required for any special review, are delineated when approval is originally granted. The *Annual Review of an Ongoing Research Project* (Form C) is submitted annually for continuing review of expedited and full review projects; *Annual Review of an Exempt Research Project* (Form F) is submitted annually to reaffirm no change has occurred to the protocol of an exempt project.

Two months before the required date of renewal, a notice will be sent to the Principal Investigator and one month prior to renewal a second notification will be sent to the Principal Investigator. Failure to comply will result in closure of the project. The proper form or forms should be completed and submitted along with a copy of the current Informed Consent to the Research Coordinator's office. If the approval status lapses, new approval must be applied for. A lapse means that the study is no longer in compliance. Lapses in approval are extremely difficult to justify to regulatory and funding agencies. The IRB must report such lapses to the National Institutes of Health's Office of Human Research Protections and the Food and Drug Administration.

If the investigator does not respond to the final notice, the IRB will classify the study as "suspended."

What to Report

The following information is asked on the annual report:

- Co-investigator signature: A co-investigator still involved in recruiting, patient interventions or interactions, or sensitive data will sign the annual review; paper signature, fax or e-signature is acceptable. If a co-investigator's role in the project is complete, the PI can remove the co-investigator from the IRB application on the annual review report (or amendment during the approval period) and the co-investigator signature is no longer required.
- the number of subjects enrolled since the last review and the total number of subjects enrolled to date. If enrollment is not on track, an explanation is requested.

- a summary of the results of the research to date, including:
    a. any unanticipated risks or adverse outcomes
    b. any early indication that one of the treatment groups under the study is significantly better or worse than the other(s)
    c. any difficulties recruiting or retaining subjects, an explanation of the difficulties, and the number of subjects who withdrew from the study
    d. any changes to the research protocol approved since the last review
    e. any changes in study investigators since the last review
- location of identified data and de-identified data
- a copy of the consent form currently in use (as most recently approved by the IRB)

Researchers can prepare for continuing review by modifying their data collection forms and protocols to accommodate requests for this information.

Keeping Records

Researchers should maintain a file of all documents concerning the use of human subjects in research, to include original paperwork whenever possible, and a copy of everything else. The principal investigator's records should be a mirror image of the IRB's records: where the IRB holds an original, the PI should hold a copy, and vise versa.

The documents that researchers should have on file include:

- a copy of the original application submitted to the IRB, including the consent form and the research protocol
- an original of the IRB's response
- a copy of responses to IRB stipulations or requests for additional information
- the original notice of final approval
- a copy of the "Certification of Approval" sent by the IRB to any funding agencies
- copies of originals of all other correspondence with the IRB
- copies of completed *Annual Review of an Approved Research Project* forms and attachments
- the original notice of renewal of approval and certification, where applicable; and
- copies of data safety monitoring reports
- copies of inspection or audit reports

Original signed consent forms should be kept in a secure location separate from correspondence with the IRB but readily available to inspectors. Whenever a subject is a patient of the NUHS Clinics, a copy of the signed informed consent should be placed in the patient's medical chart as a precautionary measure, in case complications with the research protocol occur and emergency medical treatment is required.

IRB records are subject to inspection by federal authorities. Sanctions for incomplete or nonexistent records include suspension of funding, fines, exclusion from future funding, and suspension of laboratory access.

Commitment to Protect the Confidentiality of Research Records

New project applications submitted to the NUHS IRB must include a description of a how participant confidentiality is protected, including what information is collected, who has access to

research information and if any of the research information will be included in permanent records (medical charts, school records etc.). Records should only be retained for as long as is required, taking into account all administrative, operational, legislative and regulatory needs (including any stipulated by funding bodies), but even at a minimum, research records are kept for seven years .

The purpose of this guidance is to recommend appropriate data security measures and re-iterate the importance that researchers utilize these security measures (or comparable) to protect the identity of and/or confidential information obtained about people that participate as subjects in research.

Keeping information secure

Due to the often sensitive and confidential nature of the information created and managed during research projects it is imperative that appropriate security measures are in place and that all staff are aware of the need to keep information secure. During the research project and on its completion, it is imperative that records and data are stored in a secure and appropriate environment. The selected store should be “fit for purpose” and provide adequate space, security, access control and environmental conditions. Appropriate technical procedures should be established to ensure that instances of unauthorized access, loss or misuse of data do not occur. These procedures should apply to both on and off-campus activity and especially if staff work from home. Access to all personal data should be controlled through the use of passwords, which must be changed on a regular basis (and always when a member of staff leaves the project).

Paper records
Minimize the use of identifiable data. Avoid storing linking keys with the de-identified records. Records must be kept in locked cabinets and in locked offices or storage rooms, if unattended, access to cabinets, offices and storage rooms must be restricted to authorized personnel only.

Information should be destroyed appropriately, either using a cross-cut shredder or by using the University’s confidential shred service

Electronic records

- Where identifiable data is not a requirement of the research project, then the data should be retained in an anonymous format
- Avoid storing linking keys on network drives
- Ensure that your PC is locked whenever you are away from your desk
- Passwords should never be shared with other members of staff and should be changed on a regular basis
- Each study database should be password protected, with its own unique password and access to the password restricted to authorized personnel only

Non-compliance

Suspension of IRB Approval

Studies which have not received re-approval before the expiration date of IRB approval will be automatically suspended until re-approval is given or the study is terminated. The course of action and the timing of it may include a grace period, at the discretion of the IRB, if the circumstances are explained to the IRB prior to the expiration date.

The IRB has the authority to suspend approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any such suspension of approval shall be reported promptly to the investigator and shall include a statement of the reasons for the IRB's action. The IRB shall notify appropriate NUHS officials, and appropriate funding and/or federal officials. Such suspension will normally be made at a convened meeting of the IRB unless immediate suspension is necessary. In this case, the IRB Chair may suspend approval.

Subjects may not be enrolled and research interventions may not be conducted during the period of suspension.

Allegations of Investigator Non-Compliance

Allegations of non-compliance and alleged violations of human subject rights or welfare will be investigated by the IRB office. Depending upon the nature of the situation, the investigation may be made by one or more IRB office staff members and may also be conducted by a team consisting of IRB office staff and committee members. Results will be reported to the IRB for appropriate action (which may range from no action to study termination and/or investigator restrictions). Allegations found to have a basis in fact will be forwarded to appropriate University officials for their further action.

Required Education

IRB requires that, prior to engaging in NUHS-approved research projects involving human participants, Investigators and key personnel of the approved projects (co-investigators, staff, etc.) must undergo training. Subscription programs (e.g. CITI) satisfy training requirement; Other training materials are available from the Research Coordinator.

In addition, the IRB requires continuing education in human protection for all investigators and key personnel. Annual notices will be sent to all principal investigators regarding continuing education. It is the responsibility of the PI to provide description of the educational program and a list of the key personnel who participated in the program.

Conflict of Interest

Objectivity of researchers is essential in scientific research and the basis for public trust. The opportunity for researchers to reap financial benefits from their research or a link to industry is not always unacceptable. However, concerns are raised when financial considerations may or may appear to compromise an investigator's professional judgment and role in the design, conduct, or publication of research. Investigators participating in PHS-funded research are required to comply with the training and disclosure requirements contained in the NUHS Policy *Financial Conflict of Interest in Research*. Regardless of funding source, any conflict of interest that could affect the design, conduct, or reporting of a research project must be reported to the IRB; the IRB may consider and respond to possible investigators' financial conflicts of interest and studies may be closed, suspended, or not approved.

Clinical Trial Registration

In 2005, the International Committee of Medical Journal Editors (ICMJE) initiated a policy requiring investigators to deposit information about trial design into an accepted clinical trials registry before the onset of patient enrollment. This registration is a condition of consideration for publication in their journals (The details of this policy are contained in http://www.icmje.org/clin_trialup.htm). The ICMJE encourages editors of other biomedical journals to adopt similar policy.
The ICMJE does not advocate one particular registry, but its member journals will require authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include at minimum the data elements in the following table. Trial registration with missing fields or fields that contain uninformative terminology is inadequate. The ICMJE recommends that journals publish the trial registration number at the end of the Abstract.

Complete details for Uniform Requirements for Manuscripts Submitted to Biomedical Journals can be found in http://www.icmje.org/index.html

VII. INFORMED CONSENT

National University of Health Sciences Informed Consent Guidelines

Informed consent is one of the basic ethical obligations for researchers. Informed consent is not just a form. It is a process of information exchange that takes place between the prospective subject and the investigator, before, during and sometimes after the experiment. The amount of information that needs to be presented both in writing (i.e., the consent document and related materials) and verbally is directly related to the risk and the complexity of the procedures.

The manner and context in which information is conveyed is as important as the information itself. There must be no coercion or undue influence. Subjects must have sufficient time to decide whether or not to participate in the research and should be allowed to consult with family and/or others if needed. If consent is to be informed, the subjects must genuinely understand the research. Hence, researchers should strive to convey information to subjects, not merely disclose it to them. Subjects should be able to explain what they are being treated with and/or how they are being treated.

The investigator should have an adequate plan in place to ensure existence of an acceptable level of comprehension before consent is obtained. If children/youth and/or incompetent adults will be subjects, the investigator should also have a specific plan to assess comprehension during assent (the subject's agreement).

It is expected that the investigator will assess the subject's understanding of the research. Formal tests of understanding are not required, but investigators are expected to establish reasonable and practical plans to verify that subjects understand what they will be doing if they volunteer to participate in the research.
It is critical to the consent process that the researcher not only field questions, but also to ask questions. Asking questions can further the discussion, elicit questions from the prospective subject, prompt the prospective subject to think more carefully about the project, and help the

researcher decide whether the person has adequately understood the project. These questions need to be prepared in advance.

Useful questions are open-ended and non-directive. Rather than asking for yes or no answers, these questions ask for explanations and often can be answered in a variety of ways, and do not already contain the correct answer. Open-ended questions are often introduced with "what," "where," "how often," "when," and "please describe." Examples of open-ended questions are:

- "Describe in your own words the purpose of the study."
- "Just so that I'm sure you understand what is expected of you here, would you please explain to me what you think we're going to ask you to do?"
- "What is the possible benefit to you of taking the new experimental drug? What are the possible risks?"
- “What might be an alternative for you besides participating in this research?”
- "What more would you like to know?"

In contrast, closed ended questions tend to stop discussion instead of furthering it. Examples of closed-ended questions are:

- "Do you understand?"
- "Do you have any questions?"
- "Do you see that there are some risks to taking this drug?"

The Consent Form
The purpose of a consent form is to provide a written source of information and a place to document that a subject’s consent has been given before the start of the study. Consent forms must be signed and dated by the subject before any research procedures begin. The form serves as a baseline of information for initial presentation and a reference source during the study as well as documentation of voluntary participation.

These guidelines contain explanations and examples of text that may be used in preparing consent forms for research studies. Due to the wide variety of research projects conducted, several types of consent forms are acceptable to the IRB. A template to help develop a comprehensive informed consent and checklist for required elements can be found in the *NCCIH Clinical Research Informed Consent Template*.

The IRB reviews each form to determine that it contains required information in sufficient detail to protect the rights and welfare of human research subjects.

The following are general suggestions:

- All consent forms must be understandable to the subject population.
- Use short sentences and non-technical terms.
- An eighth-grade reading level is usually desirable for studies of the general population. Most word processors can generate ‘reading level scores.’
- Use second person (i.e., write the consent form as if you are talking to the subject).
- Project Title may be a repeat of the ‘official’ title as submitted to the IRB and grant agency, or if it assists the subjects to understand the study, it may be simplified (as long as it does not cause confusion about the study including the treatment and/or the risk).

- Use element headings and 'white-space' to improve readability in long forms.
- All scientific, medical and technical terms should be defined or explained.
- Use lists, tables and charts to show complex schedules and study designs.
- Use type no smaller than 12 point.
- Use letterhead stationery for the first page.
- Number the pages of the consent form, e.g., 1 of 3, 2 of 3, and 3 of 3.
- The version date of the consent form should appear on the bottom of the last page.
- Provide translated versions if non-English speaking populations are a target population.

Although each research study involving human subjects is unique, federal regulations and the IRB require that all consent forms contain the following information elements:

Specific Sections of an Informed Consent

Introduction
This part of the consent form must state that this is a research study and it should indicate why the person is being asked to participate. It should state which department is conducting this study. It should say that subjects should read the form carefully and instruct them to ask the investigator and/or person obtaining consent any questions that they may have before making a decision whether or not to participate. Especially for long-term studies, complex procedures, and studies with greater risk, this section should emphasize that the form contains important information and that subjects should keep their copies to refer to as the study proceeds.

The introduction is an opportunity to reinforce the voluntary nature of subjects' participation ("You are being asked to participate …", "You are invited to participate….") the introduction may be used to provide background on why the study is being conducted and its importance and the importance of subject participation. The importance, however, should not be overstated or exaggerated.

Purpose of Study
This section of the consent document must briefly and simply inform the subject of the purpose (aim/goal) of this study. It may be appropriate to inform the subjects if the study is being undertaken locally, or on a larger scale, e.g., city-wide, regionally, nationally, or internationally.

Description of Study Procedure
This section should contain a complete description of the procedures that are necessary to complete the study. All experimental procedures must be described and any related but non-experimental procedures should be stated. The subject's time commitment must be explained in terms of the length of study participation, visits required and any other activities (e.g., diaries, telephone follow-up) required for completion. Use lists, tables and charts to show complex schedules and study designs.

For clinical studies this section would include explanations about medications being given, the amount of blood drawn, invasive and/or non-invasive procedures, length of hospital stay, follow-up procedures and the like.

- All scientific/medical/technical terms should be defined or explained in lay terms.
- Avoid the use of undefined medical abbreviations such as EKG, U/A, SMA-12.

- If the study involves a randomization, then the randomization procedure should be explained along with the chances of being randomized into each group.
- If the study involves the use of a placebo, define placebo.
- If the study is double/single masked, explain the meaning to the subject. **Note**: the word 'masking' is preferable to the word 'blinding.'
- If there are explicit exclusion or inclusion criteria for the study, e.g., allergies, pregnancy, medical conditions, use of certain medications, etc. they can be included in this section. **Note**: the risk of pregnancy is not an acceptable criterion to exclude women of child-bearing age. Contraceptive measures and pregnancy testing can be used, with subject removal from the study if positive.
- Use tables and/or charts to show complex schedules.

Risks of Participation
This section should contain a sufficient description of the risks involved in the study so that subjects can decide if they want to participate. Information on probability of the risks and the magnitude and reversibility of harmful effects is helpful to this process. Researchers should try to offer an estimate of the likelihood of a given risk, and should let subjects know what will be done to mitigate or address any injury or discomfort. Informing subjects of any safety procedures or how their distress will be handled is appropriate and beneficial in informed consent.

List any:
- Potential behavioral and psychological risks such as triggering bad memories, learning disturbing things about one's self, nervousness about being observed, etc.
- Legal and social risks, if any, as well as risks to confidentiality or privacy.
- Side effects for each drug, device or procedure. Specify if side effects are reversible and/or treatable, and what monitoring will occur to detect/control side effects. Indicate that all drugs have side effects and there is always the risk of previously unknown side effects occurring. If appropriate, you may state that the subjects may experience all, some or none of the side effects listed. Subjects should be told to report any side effects if they are experienced.

Other points to consider include:
- If the study involves blood draws, mention that this might cause pain and bruising at the site where the blood is taken, and sometimes it causes people to feel lightheaded or even to faint.
- If a sample consent form has been provided by a study sponsor/group, all the risks from the sample consent must be included in the consent form.

Mock Patients
Studies which plan to utilize mock participants during the training of study personnel should include theses participants in the application to IRB, indicating how this group may differ from inclusion/exclusion criteria (or other characteristics) of the research participants.

1. Mock patients receive the same protection from research risk as research subjects.
2. Any deviation from the frequency, duration, or intensity of the approved procedures or interventions must be approved by the IRB for the protection of the mock patients.
3. Mock patients who are subject to intervention procedures , risks, discomforts, or other burdens must sign an informed consent describing the procedures and modifications.

Number of Participants
This is actually an additional 'risk' consideration. If the total number of subjects to be studied is important for the subjects to consider before entering the study, the expected numbers should be stated. For example, a small number of study subjects may compromise confidentiality by making it easy to identify who the subjects are or, during the first 'phase 1' study of a new drug only a few subjects are permitted to be exposed. (This statement may also be placed in the Risk section above.)

Benefits of Participation
List any direct benefits to the subject or to others which may reasonably be expected from the research. Usually there is only a possibility of benefit or no benefit (so state). Benefits to others would include possible development of commercial products. It may be permissible to state that a project may yield results that could possibly benefit a sub-population (e.g., AIDS patients, low birth weight babies, students and so forth). Financial reimbursements or other compensations for participation such as discounts or coupons are not considered benefits of participation.

Making participation too attractive can be a form of coercion. An example of this is when studies imply that the benefits are guaranteed; when there is usually only a **possibility** the benefits will be obtained. Researchers must be careful not to promise or to imply endorsements. In fact, they should go out of their way to address potential misunderstandings.

New Study Findings
New findings developed during the course of the research may change subjects' willingness to continue to participate. If so, subjects need to be informed that these findings will be provided to them. This may require new consent forms or addenda.

Alternatives
Disclose appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject. Usually, clinical studies have alternatives, e.g., 'standard' treatment, no treatment, other research studies, etc. If a test drug/device is available "off protocol" (i.e., approved for use), that needs to be stated. Other types of studies may have alternative actions such as other options to earn course credit (e.g., reports and papers) or availability of non-research services.

For minimal risk studies that have no alternatives (e.g., some survey research), it may be stated that "the alternative is not to participate" or you may delete this section if it does not impact the information needed to decide about participation.

Costs
Any additional costs that may result from participation in the study must be listed. Examples include:
"There is no cost to you to participate in this research study" and "How much you will have to pay depends on whether or not you have insurance and what costs your insurance will cover. You or your insurance carrier will be responsible for the costs of clinic visits, any hospital admissions, laboratory tests, x-rays, and other tests. Insurance coverage cannot be guaranteed for tests and treatments related to this study."

Payments
If subjects are to be paid for participation or reimbursed for expenses, specify the amount, schedule of payment, and conditions for payment. Payment should be based on a prorated system. This means that payments are earned/given as the study progresses and subjects do not have to complete the entire study to receive a payment.

Note: For clarity, do not use the word "compensation" to refer to incentive payments or reimbursements for expenses (see Compensation for Injury below). Compensation amounts should do little more than cover the costs of transportation or other costs incurred by the subject or provide reasonable payment for the subject's time. Making participation too attractive can be a form of coercion. Note too, that advertisements may mention, but must not emphasize payments, and all advertisements must first be approved. If medications, tests and therapies are to be provided free as part of the study, specify this in the consent form.

Circumstances for Dismissal from the Study
List the circumstances, if any, under which the subject's participation may be terminated without their consent. The following are examples:

"You may be withdrawn….

- If you do not keep appointments for study visits or fail to complete study activities, e.g. taking study medications or completing forms."
- If you do not follow the instructions you are given". Note: do not use the phrase "fail to follow the protocol or research procedures" as subjects do not have this information.
- If your disease becomes worse or if your doctor feels that staying in the study is harmful to your health. Further treatment would be discussed at that time."
- If new scientific developments occur that indicate the study is not in your best interest."
- If the study sponsor decides to stop or cancel the study."

Compensation for Injury
All research involving greater than minimal risk must include statements about what NUHS will do for patients in the event of an injury or other negative event. For example, "The National University of Health Sciences will provide medical care for any emergency medical problem that you may experience as a direct result of your participation in this research. You will not be charged for this emergency care, but NUHS may seek reimbursement for this care from your health insurance carrier or the study sponsor. Decisions regarding care and compensation for any other research related injury will be made on a case-by-case basis."

Confidentiality of Records
The consent form must indicate that while NUHS will make every effort to maintain confidentiality, it cannot be absolutely guaranteed. Records which identify participants (including medical records) and the signed consent form, may be inspected by a regulatory agency [state which, e.g., DOH, FDA, NCI, etc.] and/or the Institutional Review Board. You may tell the subject, "the results of this research may be presented at meetings or in publications; however, your identity will not be disclosed".

Contact Persons
The consent form must address three areas for subjects' questions, namely, questions about the research itself, questions about research-related injury and questions about subjects' rights. For more information concerning the research, you might include the name and telephone number of the PI as the contact person. For Research Related Injury, you should specify that individuals should contact the PI or, if the PI is not a physician, some pre-arranged medical contact who will provide more information. For any questions about rights as a research subject, you could include the name and phone number of the IRB Chairman or the designee.

Voluntary Participation
Participation in research is completely voluntary and should be based on a complete understanding about the risks, benefits, goals, and procedures that are involved in the entire study. Participants must be free not to participate or to withdraw at any time for whatever reason. In the event that participants withdraw from a study, the study must guarantee that the information individuals have already provided will be kept in a confidential manner. For clinical studies, participants should understand that if they choose not to participate or withdraw from a study, they will not jeopardize present or future care that they would otherwise receive. For studies with students, they should understand that if they refuse to participate or withdraw from a study, that their decisions will not jeopardize grades nor risk loss of present or future faculty/school/University relationships.

Signatures / Dates
The signature of the subject and/or the subject's legal representative indicates an agreement to participate. The date (which should be in the subject's writing) is meant to indicate that consent was obtained prior to the subject being involved in any research procedures. With few exceptions, the subject's signature and date of signature are required by the federal regulations for human research subject protection and NUHS' research policy.

The signature of the subject's legal representative indicates permission to participate is granted by a person legally empowered to give consent to research. For some research, this is appropriate (e.g., coma studies) and for some it is not appropriate (e.g., survey research).

The signature of the person obtaining consent indicates that the form has been read by or read to the subject, that an appropriate explanation of the research was given, that questions from the subject were solicited and answered to the subject's satisfaction, and that, in this person's judgment, the subject demonstrated comprehension of the information. While this signature is not required by federal regulations, NUHS does require this signature for all research that presents greater than minimal risk to subjects. The date of signature should also be recorded when this signature line is used.

The signature of an auditor/witness attests to the fact that the form was read by or read to the subject, that an explanation of the research was given, that questions from the subject were

solicited and answered to the subject's satisfaction, and that, in this person's judgment, the subject voluntarily agreed to participate. This signature is not required by federal regulations; however, the IRB may require this signature for some research that presents greater than a minimal risk to subjects. The auditor-witness must be used when the 'short form' method is used to document consent. It should also be used when subjects may not completely understand the process (e.g. diminished capacity or decreased competency). This is both a protection for subjects as well as investigators. The date of signature should also be recorded when this signature line is used.

Sample consent forms and language are available from the Research Department.

VII. CONSENT ISSUES IN RESEARCH INVOLVING MINORS (SUBJECTS UNDER 18 YEARS OF AGE)

In all human subjects' research, the agreement of the subject to participate is an essential protection of the rights and welfare of subjects. Minors (children under age 18), by definition, can not give legal 'consent.' Therefore, a combination of 'assent' (agreement) of the minor subject and 'permission' of the parent or legal guardian is generally deemed an adequate substitute. Two forms may be used (an 'assent' with the child's signature line and a 'permission form' with the parent's signature line) or, if appropriate, one form with both signature lines. Note: Some research with children may require the permission of both parents. In this type of research, two parental signature lines would be needed for documentation. If either of the parents refuses permission or the minor subject refuses assent, the minor should not be enrolled.

The National University of Health Sciences requires the permission of parents for research that involves children. There are four exceptions to this general policy: 1) no-risk or minimal-risk research with older adolescents (e.g., anonymous surveys in high school juniors and seniors); 2) purely observational studies (no intervention) of public behavior (e.g., classroom activities); 3) studies of existing data and 4) research with 'emancipated' minors that is directly applicable to their condition(s).

VIII. GUIDANCE ON RECRUITMENT OF HUMAN RESEARCH SUBJECTS THROUGH ADVERTISING

Direct advertising for research subjects, i.e., advertising that is intended to be seen or heard by prospective subjects, is considered as part of the informed consent and subject selection processes. The aim of IRB review is to ensure that the information is not misleading to subjects. This is especially important when a study may involve subjects who are likely to be vulnerable to undue influence, such as financially constrained subjects.

When direct advertising is to be used, the IRB must review both the information contained in the advertisement and the mode of its communication. This is to determine that the procedure for recruiting subjects is not coercive and that the recruitment material does not state or imply certainty of a favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.

Generally, advertisements should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items should be included in advertisements:

- The name and address of the investigator and/or research facility (e.g., National University of Health Sciences) and the person or office to contact for further information;
- The purpose of the research (e.g., the condition under study or goal of the project);
- In summary form, the criteria that will be used to determine eligibility for the study;
- The time or other commitment required of the subjects; and
- A brief list of participation benefits, if any (e.g., a no-cost health examination).

Note: payments to subjects for participation are not benefits, they are inducements. Advertisements may state that subjects will be paid, but they should not emphasize the payment or the amount to be paid.